# 1-HETEROCYCLYL-1,5-DIHYDRO-PYRAZOLO[3,4-D]PYRIMIDIN-4-ONE DERIVATIVES AND THEIR USE AS PDE9A MODULATORS

The invention relates to novel 1,6-disubstituted pyrazolopyrimidinones, wherein i.) the nitrogen atom of the pyrazolo-group that is next to the pyrimidino-group is attached to a non-aromatic, organic heterocycle having at least one ring hetero atom selected from O, N and S and ii.) to the C-atom between the two nitrogen atoms of the pyrimidinone-ring a second substituent is bound via an optionally substituted methylene-bridge. According to one aspect of the invention the new compounds are for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. The new compounds are also for the manufacture of medicaments for the treatment of Alzheimer's disease. Further aspects of the present invention refer to a process for the manufacture of the compounds and their use for producing medicaments.

## BACKGROUND OF THE INVENTION

The inhibition of phosphodiesterase 9A (PDE9A) is one of the currents concepts to find new access paths to the treatment of cognitive impairments due to CNS disorders like Alzheimer's Disease or due to any other neurodegenerative process of the brain. With the present invention, new compounds are presented that follow this concept.

Phosphodiesterase 9A is one member of the wide family of phosphodiesterases. These kinds of enzymes modulate the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA), and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins, transcription factors). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides

are also able to act directly on effector molecules. Thus, it is known, for example, that cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, *56*, 37-64). The phosphodiesterases (PDE) are a control mechanism for controlling the activity of cAMP and cGMP and thus in turn for the corresponding physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. Currently, 11 PDE families have been defined on the basis of the sequence homology of the corresponding genes. Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, this is then indicated by an additional numbering after the letters (e.g. PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34 % (PDE8A) and is never less than 28 % (PDE5A). With a Michaelis-Menten constant (Km) of 170 nanomolar, PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (Km for cAMP=230 micromolar). PDE9A has no cGMP binding domain, suggesting that the enzyme activity is not regulated by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, kidney, prostate, colon, and spleen (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, *314*, 15-27). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21 exons. 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, *103*, 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 micromolar. An $IC_{50}$ of 35 micromolar has been demonstrated for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, *273* (25), 15559-15564).

Murine PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). This has, like the human form, high affinity for cGMP with a Km of 70 nanomolar. Particularly high expression was found in the

mouse kidney, brain, lung and liver. Murine PDE9A is not inhibited by IBMX in concentrations below 200 micromolar either; the $IC_{50}$ for zaprinast is 29 micromolar (Soderling *et al.*, *J. Biol. Chem.*, **1998**, *273* (19), 15553-15558). It has been found that PDE9A is strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, *21* (22), 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes.
As already mentioned above, PDE9A is distinguished by having particularly high affinity for cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (Km=10 micromolar; Martins *et al.*, *J. Biol. Chem.*, **1982**, *257*, 1973-1979), PDE5A (Km=4 micromolar; Francis *et al.*, *J. Biol. Chem.*, **1980**, *255*, 620-626), PDE6A (Km=17 micromolar; Gillespie and Beavo, *J. Biol. Chem.*, **1988**, *263* (17), 8133-8141) and PDE11A (Km=0.52 micromolar; Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, *97* (7), 3702-3707). In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, *29*, 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, *12*, 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

This outline will make it evident that PDE9A engages into specific physiological processes in a characteristic and unique manner, which distinguish the role of PDE9A characteristically from any of the other PDE family members.

WO04099210 discloses 6-arylmethyl-substituted pyrazolopyrimidinones which are PDE9 inhibitors. The compounds do not have a non-aromatic heterocyclic moiety in the 1 position of the pyrazolopyrimidine.

WO04096811 discloses heterocyclic bicycles as PDE9 inhibitors for the treatment of diabetes, including type 1 and type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, metabolic syndrome, and/or cardiovascular disease.
Other prior art is directed to chemically similar nucleoside derivatives. As examples it is referred to WO02057425, which discloses nucleosides derivatives, which are inhibitors of RNA-dependent RNA viral polymerase, or WO01060315, which discloses nucleoside derivatives for the treatment of hepatitis C infection or

EP679657, which discloses compounds that serve as ribonucleoside analogues or US2002058635, which discloses purine L-nucleoside compounds, in which both the purine rings and the sugar are either modified, functionalized, or both. So the sugar for example must show at least one esterified OH group.

WO06084281 discloses inhibitors of the E1 acitvation enzyme that have a sulfonamid moiety.
WO05051944 discloses oxetane-containing nucleosides, for the treatment of nucleoside analogue related disorders such as disorders involving cellular proliferation and infection.

WO9840384 discloses pyrazolopyrimidinones which are PDE1, 2 and 5 inhibitors and can be employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.
CH396 924, CH396 925, CH396 926, CH396 927, DE1147234, DE1149013, GB937726 describe pyrazolopyrimidinones which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.
US3732225 describes pyrazolopyrimidinones which have an anti-inflammatory and blood glucose-lowering effect.
DE2408906 describes styrylpyrazolopyrimidinones which can be employed as antimicrobial and anti-inflammatory agents for the treatment of, for example, oedema.

## OBJECTIVE OF THE INVENTION

The above cited prior art makes it evident that changes in the substitution pattern of pyrazolopyrimidinones result in interesting changes concerning biological activity, respectively changes in the affinity towards different target enzymes.

Therefore it is an objective of the present invention to provide compounds that effectively modulate PDE9A for the purpose of the development of a medicament, in particular in view of diseases, the treatment of which is accessible via PDE9A modulation.

It is another objective of the present invention to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

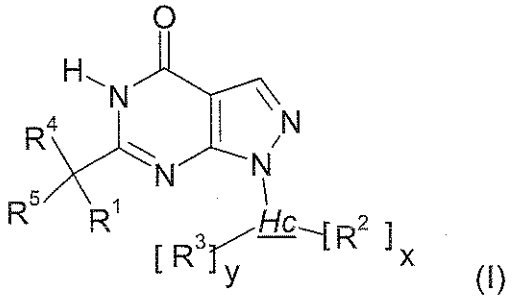
Yet another objective of the present invention is to provide compounds which show a better side effect profile compared to the compounds of the prior art.

Another objective of the present invention is to provide compounds that have a favourable selectively profile in favour for PDE9A inhibition over other PDE family members and by this may provide advantage over the prior art compounds.

Yet another objective is to provide such a medicament not only for treatment but also for prevention or modification of the corresponding disease.

## SUMMARY

In a first aspect, there is provided a compound according to general formula I,



(I)

wherein

***Hc*** is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

$\mathbf{R^1}$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1\text{-}6}$-alkyl-O-, $C_{1\text{-}6}$-alkyl-, $CF_3O$-, and $CF_3$- ;

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other $\mathbf{R^2}$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$\mathbf{R^3}$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$\mathbf{R^4}$ and $\mathbf{R^5}$ independently of one another being selected from the group of H-, fluorine, and methyl;

**x** is 0, 1, 2, 3 or 4;

**y** is 0 or 1;

and pharmaceutically acceptable salts thereof.

In a second aspect, there is provided a compound as defined herein for use as a medicament.

In a third aspect, there is provided a compound as defined herein for use in the treatment of a disease that is accessible by the inhibition of PDE9.

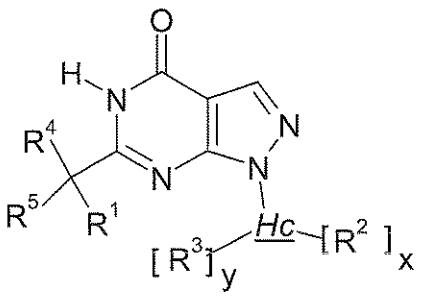
In a fourth aspect, there is provided a compound as defined herein for use in the treatment, amelioration or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In a fifth aspect, there is provided a pharmaceutical composition comprising a compound as defined herein and a pharmaceutical carrier.

In a sixth aspect, there is provided a combination of a compound as defined herein with another active agent for the treatment of Alzheimer's disease.

## DETAILED DESCRIPTION OF THE PRESENT INVENTION

The compounds of the present invention are characterised by general formula I:



(I),

with the following definitions (substituents may be printed in bold for better reading):

Substituent ***Hc*** is defined by the following definitions $\underline{\mathbf{Hc}}^{i}$, whereby the index i describes the order of preference, ascending from $\underline{\mathbf{Hc}}^{1}$ to more preferably (i.e. $\underline{\mathbf{Hc}}^{2}$), and so on:

$\underline{\mathbf{Hc}}^{1}$:

***Hc*** is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected

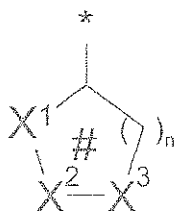
from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r-$ with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member.

Hc$^2$:

*Hc* is a heterocyclyl group according to any of formulae I.1 or I.2 or I.3:

formula I.1:



with

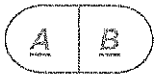
n = 1, 2, 3;

$X^1$, $X^2$, $X^3$, independently from each other being $CH_2$, $CHR^2$, $CHR^3$, $C(R^2)_2$, $CR^2R^3$, O, NH, $NR^2$, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of $X^1$, $X^2$, $X^3$ is O, NH, $NR^2$ or $S(O)_r$.

#: meaning that the ring is not aromatic while for n = 1, one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms. For each occasion the double bond preferably is a C-C double bond. Preferably the ring system is saturated.

The * represents the point of attachment to the nitrogen atom of the pyrazolo ring of formula I.

formula I.2:



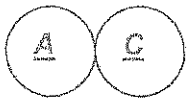

with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to A and that besides the two atoms and one bond it shares with A consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents $R^2$ and/or $R^3$ independently of each other and independently of each x, y, may be at ring A or ring B;

The two ring atoms that are shared by the two ring systems A and B both may be C-atoms, both may be N-atoms or one may be a C- and the other one may be a N-atom. Preferred are two C-atoms, or one C- and one N-atom, and more preferred are two C-atoms. The shared bond may be a single bond or a double bond.

formula I.3:



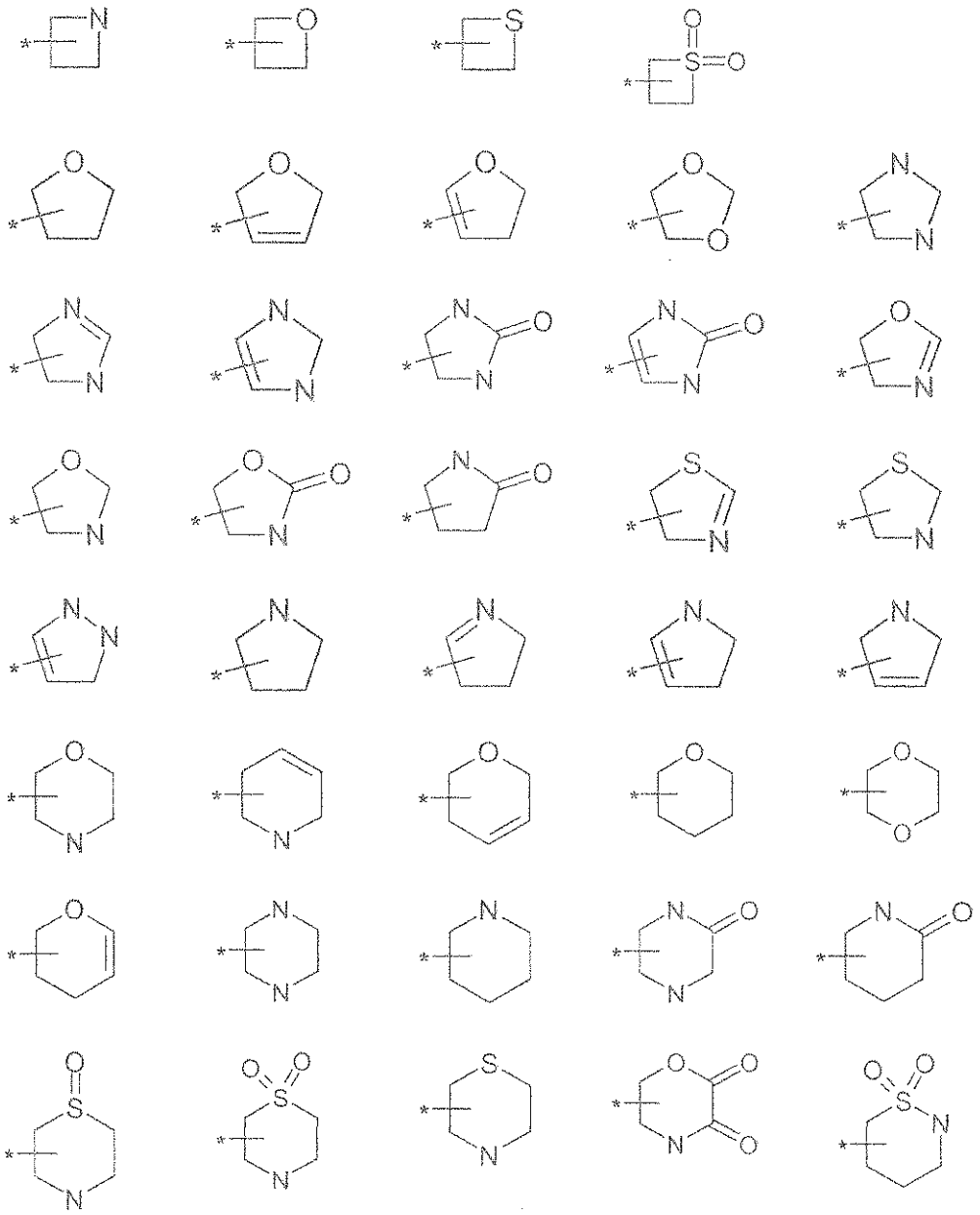

with

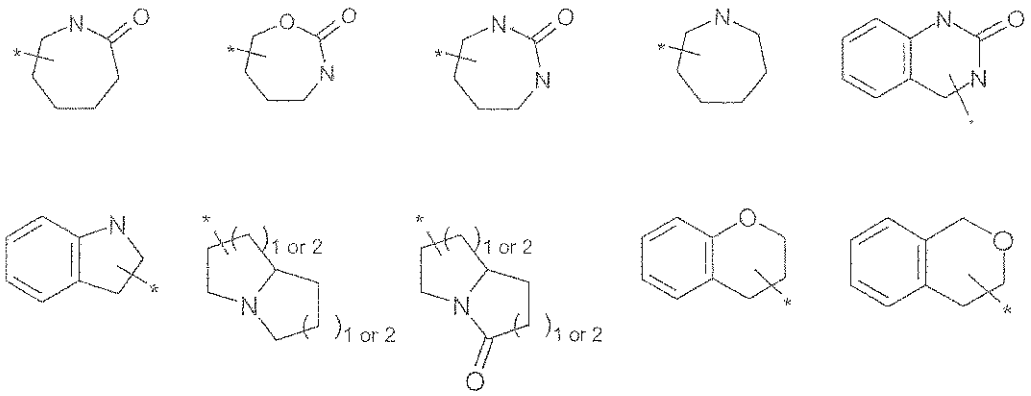
A, being the ring system of formula I.1;

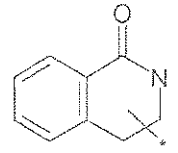
*C* being a 3, 4, 5 or 6 membered second ring system that is spiro fused to *A* and that besides the one atom it shares with *A* consists only of carbon atoms and that may be saturated or partially saturated; the substituents $R^2$ and/or $R^3$ independently of each other and independently of each x and y, may be at ring *A* or ring *C*.

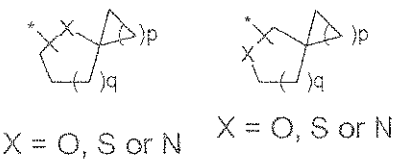
$Hc^3$:

*Hc* being a heterocyclyl group selected from the group of








$Hc^4$:

*Hc* being the heterocyclyl group according to formula I.1 as defined above for $Hc^2$.

$Hc^5$:

*Hc* being the heterocyclyl group according to formula I.2 as defined above for $Hc^2$.

$Hc^6$:

*Hc* being the heterocyclyl group according to formula I.3 as defined above for $Hc^2$.

$Hc^{7.0}$:

*Hc* is a monocyclic, non-aromatic, saturated heterocyclic group of 4 to 8, preferably 5, 6 or 7 ring atoms, whereby said ring atoms are carbon atoms and 1, 2 or 3 heteroatom(s), preferably 1 heteroatom, the heteroatom(s) being selected from oxygen, nitrogen and sulphur, the sulphur being in the form of $-S(O)_r-$ with r being 0, 1 or 2, preferably with r being 0 and whereby preferably said heterocyclic group being attached to the scaffold by a carbon ring atom which is not directly attached to said ring heteroatom.

$Hc^{7.1}$:

*Hc* is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl.

$Hc^{8}$:

*Hc* is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl and pyrrolidinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl.

$Hc^{9}$:

*Hc* is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl.

$Hc^{10}$:

*Hc* is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

Substituent $R^1$ is defined by the following definitions $R^{1.0.j}$, respectively $R^{1.j}$, whereby the index j describes the order of preference, ascending from $R^{1.0.1}$ to more preferred definitions like $R^{1.0.2}$, and so on to $R^{1.1}$, to $R^{1.2}$ and so on:

$R^{1.0.1}$:

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{2-8}$-alkenyl-, $C_{2-8}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, aryl-$C_{2-6}$-alkenyl-, aryl-$C_{2-6}$-alkynyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-$C_{2-6}$-alkenyl-, and heteroaryl-$C_{2-6}$-alkynyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-O-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-O-, heteroaryl-$C_{1-6}$-alkyl-O-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-O-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to O via one of its ring C-atoms, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to the $C_{1-6}$-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})N$-, $R^{10}$O-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})N$-, $R^{10}$-$SO_2$-$(R^{10})N$-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})N$-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and/or $C_{1-6}$-alkyl-$SO_2$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl-, heteroaryl-, N-linked-pyridine-2-one-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})$N-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and/or $C_{1-6}$-alkyl-$SO_2$-.

$R^{1.0.2}$.

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-

atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-.

$R^{1.0.3}$.

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-O-, $CF_3O$-, $CF_3$-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, HO-$C_{1-6}$-alkyl-, oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO- and/or phenyl,

whereby the oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $CH_3$-, $CF_3$-, $CH_3O$-, $CF_3O$-, $H_2NCO$-, NC-, morpholinyl and/or benzyl-O-.

$R^{1.0.4}$:

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $CH_3$-, $CH_3O$-, $H_2NCO$- and/or NC-.

$R^{1.1}$:

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{2-8}$-alkenyl-, $C_{2-8}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{3-}$

$_{7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-O-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-O-, heteroaryl-$C_{1-6}$-alkyl-O-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to O via one of its ring C-atoms, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to the $C_{1-6}$-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-$SO_2$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl-, heteroaryl-groups mentioned above may optionally be substituted by HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})$N-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, or $C_{1-6}$-alkyl-$SO_2$-.

$R^{1.2}$:

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$O-CO-O-, and $R^{10}$O-CO-$(R^{10})$N-;

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted by NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}$O-CO-, or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-.

$R^{1.3}$:

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of HO-, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-O-, $CF_3O$-, $CF_3$-, fluorine, chlorine, bromine, $C_{3-7}$-heterocycloalkyl- and $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-.

$R^{1.4}$:

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$- and halogen (the halogen preferably being selected from the group of fluorine, chlorine, and bromine).

Optional substituent $R^2$ is defined by the following definitions $R^{2.0.k}$, respectively $R^{2.k}$, whereby the index k describes the order of preference, ascending from $R^{2.0.1}$ to more preferred definitions (like $R^{2.2}$), and so on:

$R^{2.0.1}$:

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, carboxy-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, preferably $C_{1-6}$-alkyl-S-$C_{2-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, aryl-$C_{2-6}$-alkenyl-, aryl-$C_{2-6}$-alkynyl-, heteroaryl-, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl -$C_{2-6}$-alkenyl-, heteroaryl -$C_{2-6}$-alkynyl-, $R^{10}$-O-$C_{2-3}$-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, $R^{10}$-O-CO-$(R^{10})N$-, $R^{10}$-$SO_2$-$(R^{10})N$-, $C_{1-6}$-alkyl-$SO_2$- and oxo,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-,

and in case $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, $R^{10}$-$SO_2$-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-.

$R^{2.1}$:

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, carboxy-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{2-3}$-alkyl-, $(R^{10})_2N$-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, $R^{10}$-$SO_2$-$(R^{10})N$-, and $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-,

and in case $R^2$ is attached to a nitrogen which is a ring member of ***Hc***,
this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, $R^{10}$-$SO_2$-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-.

$R^{2.2}$:

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $(R^{10})_2N$-CO- and $R^{10}$-CO-$(R^{10})$N-,

where the above-mentioned members may optionally be substituted by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-,

$O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-,

and in case $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-.

$R^{2.3}$:

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $(R^{10})_2N$-CO- and $R^{10}$-CO-$(R^{10})N$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and $C_{1-6}$-alkyl-,

and in case $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, or $C_{1-6}$-alkyl-$SO_2$-,

where these substituents may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and $C_{1-6}$-alkyl-.

$R^{2.4}$:

$R^2$ independently of any other $R^2$ being selected from the group of

H- and $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl),

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, then $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, phenyl-CO- and phenyl-O-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and $C_{1-6}$-alkyl-.

$R^{2.5}$:

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$ H-, C1-6-alkyl-CO-, C1-6-alkyl-O-CO-, C1-6-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C1\text{-}6\text{-}alkyl)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents.

Optional substituent $R^3$ is defined by the following definitions $R^{3.l}$ whereby the index l describes the order of preference, ascending from (i.e. $R^{3.1}$) to preferably (i.e. $R^{3.2}$), and so on:

$R^{3.1}$:

$R^3$ being selected from the group of H-, hydroxy and $R^{10}$-O-.

$R^{3.2}$:

$R^3$ being selected from the group of H-, hydroxyl and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-.

$R^{3.3}$:

$R^3$ being H.

Substituents $R^4$ and $R^5$ are defined by the following definitions $R^{4/5.m}$ whereby the index m describes the order of preference, ascending from (i.e. $R^{4/5.1}$) to preferably (i.e. $R^{4/5.2}$), and so on:

$R^{4/5.1}$:

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, and $C_{1-3}$-alkyl-,

or

$R^4$ and $R^5$ together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O- and ($C_{1-6}$-alkyl-)$_2$N-CO-.

$R^{4/5.2}$:

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine and methyl.

$R^{4/5.3}$:

$R^4$ and $R^5$ being H-.

Substituent $R^{10}$ is defined by the following definitions $R^{10.0.n}$, respectively $R^{10.n}$, whereby the index n describes the order of preference. The preference ascends from $R^{10.0.1}$ to preferably $R^{10.0.2}$, and so on up to $R^{10.4}$:

$R^{10.0.1}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $F_3C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-3}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-3}$-alkyl-,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two $R^{10}$ together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl- and $C_{1-6}$-alkyl-O-.

$R^{10.0.2}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, aryl and heteroaryl,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)-

and preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two $R^{10}$ together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,

and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

$R^{10.0.3}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, aryl and heteroaryl, preferably aryl is phenyl and also preferably heteroaryl is selected from the group of oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, and pyrimidinyl;

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

$R^{10.0.4}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of $C_{1-6}$-alkyl-, phenyl and pyridyl and in case $R^{10}$ is a substituent of a nitrogen atom $R^{10}$ is selected from the group of H, $C_{1-6}$-alkyl-, phenyl and pyridyl;

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

$R^{10.0.5}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of methyl-, ethyl- and tert.-butyl, and in case $R^{10}$ is a substituent of a nitrogen atom $R^{10}$ is selected from the group of H, methyl-, ethyl- and tert.-butyl;

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine(s).

$R^{10.1}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $F_3C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, aryl, aryl-$C_{1-3}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-3}$-alkyl-,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -$CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two $R^{10}$ groups together with said nitrogen atom they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl, and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl- and $C_{1-6}$-alkyl-O-.

$R^{10.2}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, aryl and heteroaryl,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two $R^{10}$ together with said nitrogen they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

$R^{10.3}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, aryl and heteroaryl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

$R^{10.4}$:

$R^{10}$ independently from any other $R^{10}$ being selected from the group of $C_{1-6}$-alkyl-, phenyl and pyridyl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, more preferably x = 0, 1 and more preferably x = 0; if not specified otherwise in the context;

y = 0, or 1, preferably y = 0, if not specified otherwise in the context;

with the proviso for each applicable embodiment of formula I of the invention - such as for example embodiments that comprise $\underline{Hc}^1$ and $\underline{Hc}^3$ - that

if $\underline{Hc}$ is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

The values of x and y are independent from each other.

The index symbols i, j, k, l, m, n in $R^{1.j}$, $R^{2.k}$ etc. are indices, each of which shall have the meaning of an integer figure: 1, 2, 3, etc. so that each $R^{1.j}$, $R^{2.k}$ etc. represents a characterised, individual embodiment of the corresponding substituents for which $R^{1.j}$, $R^{2.k}$ etc. are the definitions.

So given the above definitions, a generic genius of compounds according to formula I is fully characterised by the term ($\underline{Hc}^i$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$) if for each letter i, j, k, l, m and n an individual figure is given whereby – if not indicated otherwise in a specific context - for each such embodiment ($\underline{Hc}^i$ $R^{1.j}$ $R^{2.k}$ $R^{3.l}$ $R^{4/5.m}$ $R^{10.n}$) x shall be 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2 and y shall be 0 or 1 and with the proviso for each applicable embodiment of formula I of the invention that if $\underline{Hc}$ is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ group.

In other words, each embodiment (Hc$^{i}$ R$^{1.j}$ R$^{2.k}$ R$^{3.l}$ R$^{4/5.m}$ R$^{10.n}$) represents a fully characterised genius or subset genius according to the general formula I, i.e. a generic genius of compounds that is subject of the present invention.

Such embodiment defines the variables *Hc*, R$^{1}$, R$^{2}$, R$^{3}$, R$^{4}$, R$^{5}$ and if applicable R$^{10}$ of formula I and wherein – if not in a specific context indicated otherwise - x shall be 0, 1, 2, 3 or 4, preferably being 0, 1 or 2 and y shall be 0 or 1 and with the proviso for each applicable embodiment of formula I of the invention that if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$- group.

In a **1st general aspect** of the present invention, the compound or compounds of the present invention is (are) defined by the following embodiment according to the general formula I characterised by

Hc$^{1}$R$^{1.0.1}$R$^{2.0.1}$R$^{3.1}$R$^{4/5.1}$R$^{10.0.1}$

with

x independently from of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2

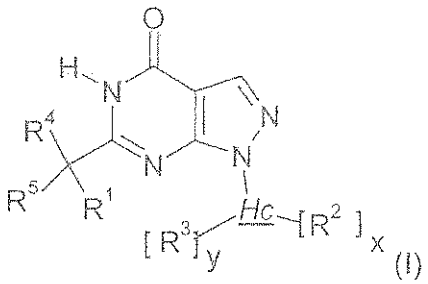
y independently of any x: y = 0 or 1,

and pharmaceutically acceptable salts and/or solvates and/or tautomeres etc. thereof;

with the proviso that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$- spacer.

According to the above, this means that the 1st aspect of the present invention is related to compounds according to general formula I



(I)

with

*Hc* as defined by Hc$^1$;

$R^1$ as defined by $R^{1.0.1}$;

$R^2$ as defined by $R^{2.0.1}$;

$R^3$ as defined by $R^{3.1}$;

$R^4$ and $R^{4'}$ as defined by $R^{4/5.1}$;

$R^{10}$ as defined by $R^{10.0.1}$;

x independently from of any y: x being 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2;

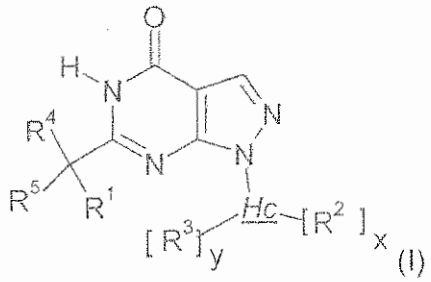
y independently of any x: y = 0 or 1;

and pharmaceutically acceptable salts and/or solvates and/or tautomeres etc. thereof;

with the proviso that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$- spacer.

Thus this **1st aspect** of the inventions is defined as a compound according to general formula I



(I)

with

*Hc* is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r$ - with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member;

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{2-8}$-alkenyl-, $C_{2-8}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, aryl-$C_{2-6}$-alkenyl-, aryl-$C_{2-6}$-alkynyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-$C_{2-6}$-alkenyl-, and heteroaryl-$C_{2-6}$-alkynyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-O-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-O-, heteroaryl-$C_{1-6}$-alkyl-O-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-O-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to O via one of its ring C-atoms, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to the $C_{1-6}$-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and/or $C_{1-6}$-alkyl-$SO_2$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl-, heteroaryl-, N-linked-pyridine-2-one-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})$N-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and/or $C_{1-6}$-alkyl-$SO_2$-;

$R^2$ independently of any other $R^2$ being selected from the group of:

H-, fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, carboxy-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, preferably $C_{1-6}$-alkyl-S-$C_{2-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, aryl-$C_{2-6}$-alkenyl-, aryl-$C_{2-6}$-alkynyl-, heteroaryl-, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl -$C_{2-6}$-alkenyl-, heteroaryl -$C_{2-6}$-alkynyl-, $R^{10}$-O-$C_{2-3}$-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, $R^{10}$-O-CO-$(R^{10})N$-, $R^{10}$-$SO_2$-$(R^{10})N$-, $C_{1-6}$-alkyl-$SO_2$- and oxo,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-,

and in case $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, $R^{10}$-$SO_2$-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-;

$R^3$ being selected from the group of

H-, hydroxy and $R^{10}$-O-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, and $C_{1-3}$-alkyl-,

or

**$R^4$ and $R^5$ together** with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O- and $(C_{1-6}$-alkyl-$)_2$N-CO-;

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $F_3C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-3}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-3}$-alkyl-,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -$CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)-, preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two $R^{10}$ together with said nitrogen atom they are bound to form a group selected

from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl- and $C_{1-6}$-alkyl-O-;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof,

with the proviso for each applicable embodiment of formula I of the invention that

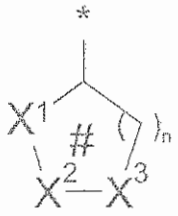
if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$-spacer*.

*This means that no substituent comprises a $CH_2$-group by which it is bound to oxetanyl.

A **2nd aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



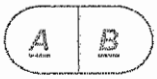
with

n = 1, 2, 3;

$X^1$, $X^2$, $X^3$, independently from each other being $CH_2$, $CHR^2$, $CHR^3$, $C(R^2)_2$, $CR^2R^3$, O, NH, $NR^2$, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of $X^1$, $X^2$, $X^3$ is O, NH, $NR^2$ or $S(O)_r$.;

#: meaning that the ring is not aromatic while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:




with

*A* being the ring system of formula I.1;

*B* being a 3, 4, 5 or 6 membered second ring system that is annelated to *A* and that besides the two atoms and one bond - which may be a single or a double bond - it shares with *A* consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents $R^2$ and/or $R^3$ independently of each other and

independently of each x or y may be at ring *A* or ring *B*; whereby the two ring atoms that are shared by the two ring systems *A* and *B* both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:




with

*A*, being the ring system of formula I.1;

*C* being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to *A* and that besides the one atom it shares with *A* consists only of carbon atoms and the substituents $R^2$ and/or $R^3$ independently of each other and independently of each x and y may be at ring *A* or ring *C*;

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-,

tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$O-CO-O-, and/or $R^{10}$O-CO-$(R^{10})$N-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}$O-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-;

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $(R^{10})_2N$-CO- and $R^{10}$-CO-$(R^{10})$N-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine and $C_{1-6}$-alkyl-,

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and $C_{1-6}$-alkyl-;

$R^3$ being selected from the group of

H-, hydroxy, $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl;

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

H- (but not in case it is part of a group being selected from $R^{10}$O-CO- or $R^{10}$-CO-), $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, aryl and heteroaryl,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -$CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)-, preferably, and in particular preferably in case of $(R^{10})_2$N-CO-, these two $R^{10}$ together with said nitrogen atom they are bound to form a group selected from the group of piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof.

A **3rd aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is a monocyclic, non-aromatic, saturated heterocyclic group of 4 to 8, preferably 5, 6 or 7 ring atoms, whereby said ring atoms are carbon atoms and 1, 2 or 3 heteroatom(s), preferably 1 heteroatom, the heteroatom(s) being selected from oxygen, nitrogen and sulphur, the sulphur being in the form of $-S(O)_r-$ with r being 0, 1 or 2, preferably with r being 0 and whereby preferably said heterocyclic group being attached to the scaffold by a carbon ring atom which is not directly attached to said ring heteroatom;

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-

$C_{1-6}$-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}O$-CO-, benzyl-O-, and/or $(R^{10})_2N$-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-;

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably both being H;

$R^{10}$ independently from any other $R^{10}$ selected from the group of $C_{1-6}$-alkyl-, phenyl and pyridyl and in case $R^{10}$ is a substituent of a nitrogen atom $R^{10}$ is selected from the group of H, $C_{1-6}$-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof,

with the proviso that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$-group*.

*This means that no substituent comprises a $CH_2$-group by which it is bound to oxetanyl.

A **4th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl; more preferably *Hc* is tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, N-linked-pyridine-2-one, N-linked-pyridine-2-one-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-$(R^{10})N$-$C_{1-6}$-alkyl-, $R^{10}O$-CO-O-, and/or $R^{10}O$-CO-$(R^{10})N$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, N-linked-pyridine-2-one, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl- groups mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of

fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $C_{3-7}$-heterocycloalkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}$O-CO-, benzyl-O-, and/or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-;

$R^2$ independently of any other potential $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

$R^{10}$ independently from any other $R^{10}$ being selected from the group of $C_{1-6}$-alkyl-, phenyl and pyridyl and in case $R^{10}$ is a substituent of a nitrogen atom $R^{10}$ is selected from the group of H, $C_{1-6}$-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof.

A **5th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl and piperazinyl, whereby preferably the tetrahydropyranyl is 3- or 4-tetrahydropyranyl, the tetrahydrofuranyl is 3-tetrahydrofuranyl, and the piperidinyl is 3- or 4-piperidinyl; more preferably *Hc* is tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably , 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine,

bromine, iodine, oxo, HO-, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-O-, $CF_3O$-, $CF_3$-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, HO-$C_{1-6}$-alkyl-, oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO- and/or phenyl,

whereby the oxadiazolyl, oxazolyl, isoxazolyl, triazolyl, thiazolyl, pyrrolyl, furanyl, pyrazolyl, pyridyl, pyridazinyl, pyrimidinyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $CH_3$-, $CF_3$-, $CH_3O$-, $CF_3O$-, $H_2NCO$-, NC-, morpholinyl and/or benzyl-O-;

$R^2$ independently of any other potential $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}$-alkyl$)_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxyl and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

$R^{10}$ independently from any other $R^{10}$ is selected from the group of H, $C_{1-6}$-alkyl-, phenyl and pyridyl,

where the above-mentioned members may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

x independently from each other x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2. preferably x = 0 or 1, more preferably x = 0;

y independently from each other y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof.

A 6th aspect of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, piperazinyl, preferably tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl, and thereof preferably, 3- and 4-tetrahydropyranyl, 3- and 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $CH_3$-, $CH_3O$-, $H_2NCO$- and/or NC-;

$R^2$ independently of any other $R^2$ being selected from the group of H- or $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof.

A **7th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents

independently of one another selected from the group consisting of fluorine, $CH_3$-, $CH_3O$-, $H_2NCO$- and/or NC-;

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently of any x: y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salts thereof.

A **8th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of piperidinyl and pyrrolidinyl, preferably 3- or 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^4$ and $R^5$ both being H

x = 0 or 1;

y = 0;

and pharmaceutically acceptable salts thereof.

An **9th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$-, oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl, and/or phenyl,

whereby the oxadiazolyl, triazolyl, pyrazolyl, furanyl, pyridyl and phenyl group mentioned above may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, $CH_3$-, $CH_3O$-, $H_2NCO$- and/or NC-;

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

where the above-mentioned $C_{1-6}$-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, most preferably x = 0;

y independently of any x: y = 0, or 1, most preferably y = 0;

and pharmaceutically acceptable salts thereof.

A **10th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

where the above-mentioned $C_{1-6}$-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl, preferably $R^4$ and $R^5$ both being H;

x independently of any y: x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, most preferably x = 0;

y independently of any x: y = 0, or 1, most preferably y = 0;

and pharmaceutically acceptable salts thereof.

An **11th aspect** of the inventions concerns a compound according to general formula I of the 1st aspect of the invention, wherein

*Hc* is selected from the group of tetrahydropyranyl and tetrahydrofuranyl, preferably 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of each other selected from the group consisting of NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$- and halogen, the halogen preferably being selected from fluorine, chlorine and bromine.

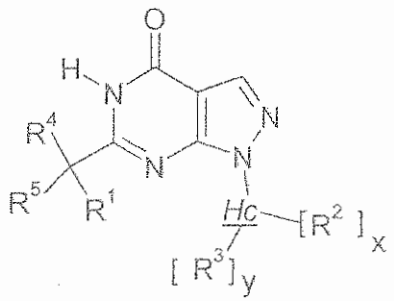
$R^4$ and $R^5$ both being H

x = 0;

y = 0;

and pharmaceutically acceptable salts thereof.

A **12th aspect** of the inventions concerns a compound according to general formula I



(I),

wherein;

*Hc* is a mono-, bi- or tricyclic heterocyclyl group, the ring members of which are carbon atoms and at least 1, preferably 1, 2 or 3, heteroatom(s), which are selected from the group of nitrogen, oxygen and sulphur, which is in the form of $-S(O)_r$ - with r being 0, 1 or 2, and

- said heterocyclyl group is or comprises 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member and
- said heterocyclyl group is bound to the scaffold by said 1 non-aromatic, saturated, or partly unsaturated monocyclic ring which comprises at least 1 heteroatom as ring member.

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{2-8}$-alkenyl-, $C_{2-8}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-6}$-alkyl-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-,

$HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-O-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, heteroaryl-O-, heteroaryl-$C_{1-6}$-alkyl-O-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to O via one of its ring C-atoms, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-O- with $C_{3-7}$-heterocycloalkyl being bound to the $C_{1-6}$-alkyl- via one of its ring-C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-$SO_2$-,

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl-, heteroaryl-groups mentioned above may optionally be substituted preferably independently of each other by HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $R^{10}$-S-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-S-, $R^{10}$-CO-, $R^{10}$O-CO-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-CO-O-, $R^{10}$O-CO-O-, $R^{10}$O-CO-O-$C_{1-6}$-alkyl-, $R^{10}$O-CO-$(R^{10})$N-, $R^{10}$O-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-O-, $(R^{10})_2N$-CO-$(R^{10})$N-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-, $(R^{10})_2N$-CO-O-$C_{1-6}$-alkyl-, $(R^{10})_2N$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$-$SO_2$-$(R^{10})$N-, $R^{10}$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-$(R^{10})$N-$C_{1-6}$-alkyl-, $(R^{10})_2N$-$SO_2$-, $(R^{10})_2N$-$SO_2$-$C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-$SO_2$-;

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, carboxy-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-

$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{2-3}$-alkyl-, $(R^{10})_2N$-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-$(R^{10})N$-, $R^{10}$-CO-, $(R^{10})_2N$-CO-$(R^{10})N$-, $R^{10}$-$SO_2$-$(R^{10})N$-, and $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-,

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{2-6}$-alkynyl-, $C_{1-6}$-alkyl-S-$C_{1-3}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-$C_{2-6}$-alkynyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkenyl-, $C_{3-7}$-heterocycloalkyl-$C_{2-6}$-alkynyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}O$-CO-, $(R^{10})_2N$-CO-, $R^{10}$-CO-, $R^{10}$-$SO_2$-, or $C_{1-6}$-alkyl-$SO_2$-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-3}$-alkyl-, and $(R^{10})_2N$-CO-;

$R^3$ independently being selected from the group of H-, hydroxy and $R^{10}$-O-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, and $C_{1-3}$-alkyl-,

or

$R^4$ and $R^5$ together with the carbon atom to which they are bound form a 3- to 6-membered cycloalkyl group,

where the above-mentioned members including the carbocyclic ring formed may optionally be substituted independently of one another by one or more substituents selected from the group consisting of
fluorine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-O- and ($C_{1-6}$-alkyl-)$_2$N-CO-;

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

H- (but not in case it is part of a group being selected from $R^{10}$O-CO-, $R^{10}$-$SO_2$- or $R^{10}$-CO-), $F_3C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{2-6}$-alkenyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, aryl, aryl-$C_{1-3}$-alkyl-, heteroaryl, and heteroaryl-$C_{1-3}$-alkyl-,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the -$CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -S-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)- preferably, and in particular preferably in case of ($R^{10}$)$_2$N-CO-, these two $R^{10}$ groups together with said nitrogen atom they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, HO-$C_{1-6}$-alkyl-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl- and $C_{1-6}$-alkyl-O-;

x independently from each other x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently from each other y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salt forms or solvates thereof,

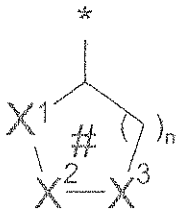
with the proviso that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

A **13th aspect** of the inventions concerns a compound according to general formula I of the 12th aspect of the invention, wherein

*Hc* is a heterocyclyl group according to a formula being selected from the group of formulae I.1, I.2 and I.3:

formula I.1:



with

n = 1, 2, 3;

$X^1$, $X^2$, $X^3$, independently from each other being $CH_2$, $CHR^2$, $CHR^3$, $C(R^2)_2$, $CR^2R^3$, O, NH, $NR^2$, or $S(O)_r$ with r = 0, 1, 2, whereby at least one of $X^1$, $X^2$, $X^3$ is O, NH, $NR^2$ or $S(O)_r$.;

#: meaning that the ring is not aromatic, while for n = 1 one bond within the ring system optionally may be a double bond and for n = 2 or n = 3 one bond or two bonds within the ring system optionally may be (a) double bond(s), thereby replacing ring-member bound hydrogen atoms, whereby such double bond(s) preferably being a C-C double bond, more preferably the ring being saturated;

formula I.2:

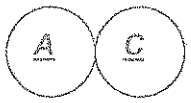



with

A being the ring system of formula I.1;

B being a 3, 4, 5 or 6 membered second ring system that is annelated to A and that besides the two atoms and one bond - which may be a single or a double bond - it shares with A consists only of carbon atoms and that may be saturated, partially saturated or aromatic; the substituents $R^2$ and/or $R^3$ independently of each other and independently of each x or y may be at ring A or ring B; whereby the two ring atoms that are shared by the two ring systems A and B both may be carbon atoms, both may be nitrogen atoms or one may be a carbon and the other one may be a nitrogen atom, whereby two carbon atoms or one carbon and one nitrogen atom are preferred and two carbon atoms are more preferred;

formula I.3:



with

*A*, being the ring system of formula I.1;

*C* being a 3, 4, 5 or 6 membered saturated or partially saturated second ring system that is spiro fused to *A* and that besides the one atom it shares with *A* consists only of carbon atoms and the substituents $R^2$ and/or $R^3$ independently of each other and independently of each x and y may be at ring *A* or ring *C*;

$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$O-CO-O-, and $R^{10}$O-CO-$(R^{10})$N-;

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above may optionally be substituted preferably independently of each other by NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-

O-, $R^{10}$-CO-, $R^{10}$O-CO-, or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-;

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $(R^{10})_2$N-CO-, $R^{10}$-CO-($R^{10}$)N-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and $C_{1-6}$-alkyl-,

and in case $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2$N-CO-, $R^{10}$-CO-, or $C_{1-6}$-alkyl-$SO_2$-,

where where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and $C_{1-6}$-alkyl-;

$R^3$ independently of any other $R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-; preferably $R^3$ being H;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being H- or fluorine, more preferably $R^4$ and $R^5$ being H;

$R^{10}$ independently from any other potential $R^{10}$ being selected from the group of

$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, aryl and heteroaryl,

and in case where two $R^{10}$ groups both are bound to the same nitrogen atom they may together with said nitrogen atom form a 3 to 7 membered heterocycloalkyl ring, and wherein one of the $-CH_2$-groups of the heterocycloalkyl ring formed may be replaced by -O-, -NH-, -N($C_{3-6}$-cycloalkyl)-, -N($C_{3-6}$-cycloalkyl-$C_{1-4}$-alkyl)- or -N($C_{1-4}$-alkyl)- preferably, and in particular preferably in case of $(R^{10})_2N$-CO-, these two $R^{10}$ together with said nitrogen they are bound to form a group selected from piperidinyl, piperazinyl, pyrrolidinyl, morpholinyl and thiomorpholinyl,
and

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, NC-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

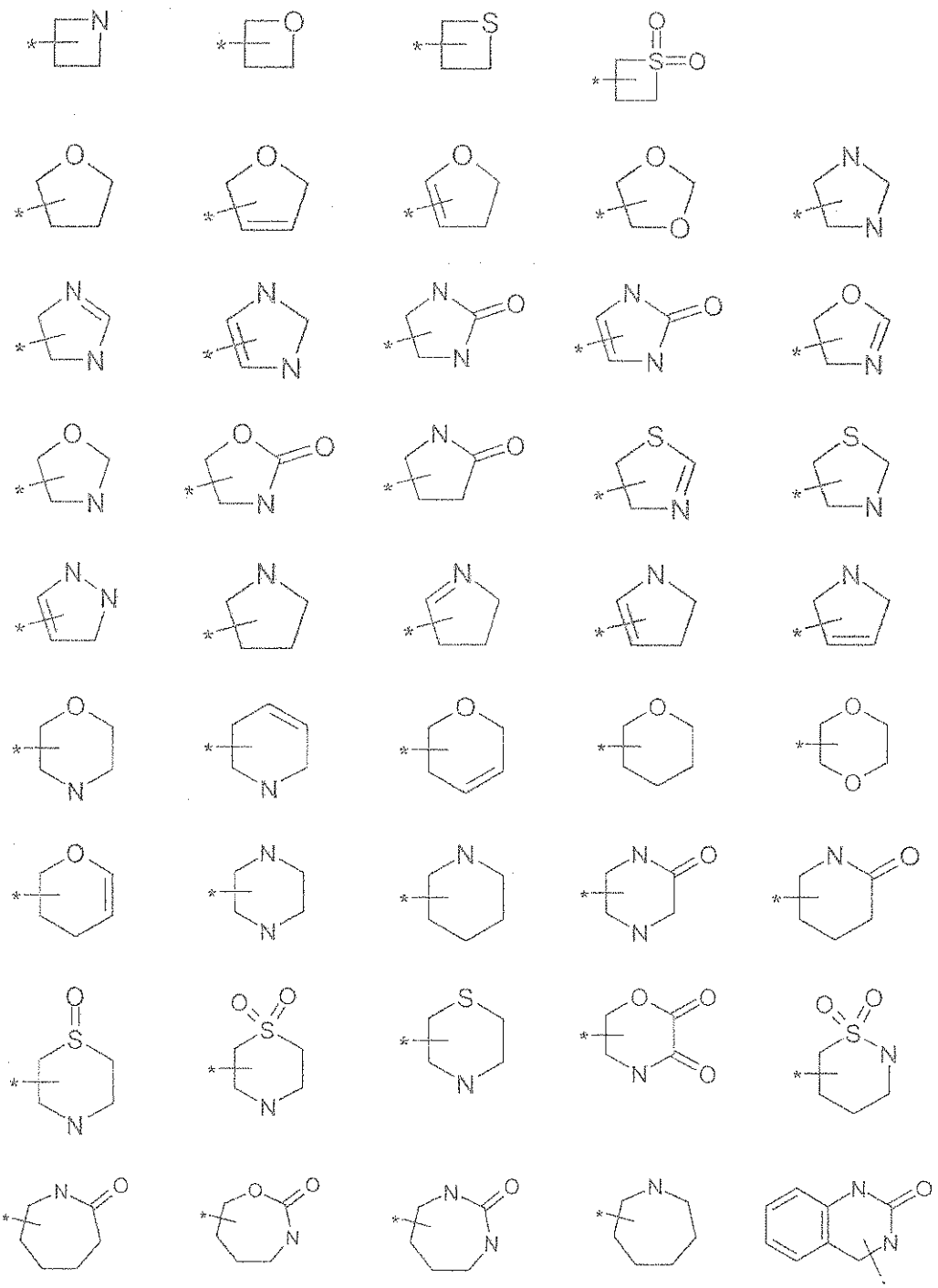
x independently from each other x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

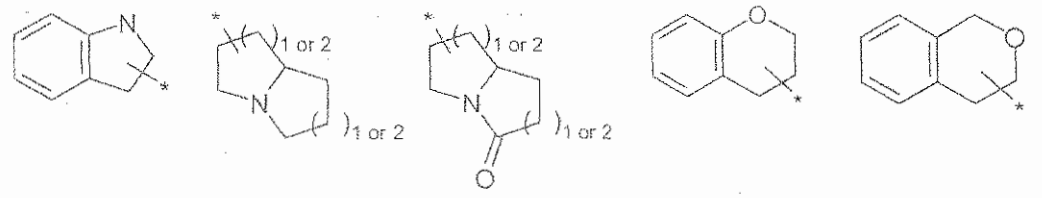
y independently from each other y = 0, or 1, more preferably y = 0;

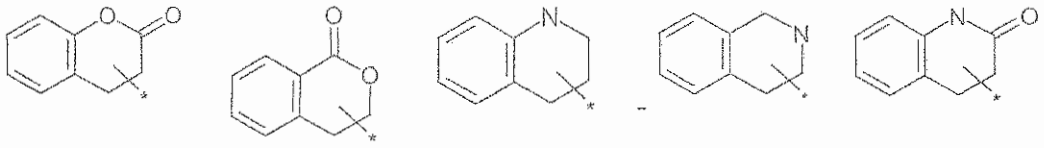
and pharmaceutically acceptable salt forms or solvates thereof.

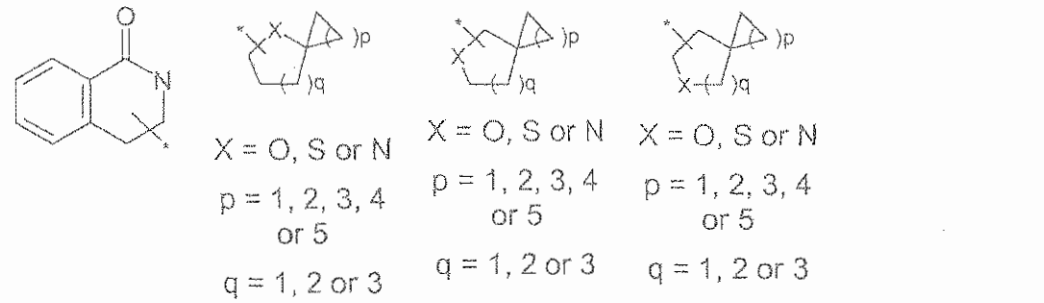
An 14th aspect of the inventions concerns a compound according to general formula I of the 12th aspect of the invention, wherein

*Hc* being a heterocyclyl group selected from the group of








$R^1$ being selected from the group of

$C_{1-8}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, aryl and heteroaryl,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine, HO-, NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, HO-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, tetrahydrofuranyl-O-, tetrahydropyranyl-O-, piperidinyl-O- with piperidinyl being bound to O via one of its ring C-atoms, pyrrolidinyl-O- with pyrrolidinyl being bound to O via one of its ring C-atoms, $(R^{10})_2N$-, $(R^{10})_2N$-$C_{1-6}$-alkyl-, $R^{10}$-O-, $(R^{10})_2N$-CO-, $(R^{10})_2N$-CO-$C_{1-6}$-alkyl-, $R^{10}$-CO-$(R^{10})$N-, $R^{10}$-CO-$(R^{10})$N-$C_{1-6}$-alkyl-, $R^{10}$O-CO-O-, and $R^{10}$O-CO-$(R^{10})$N-;

whereby any of the $C_{3-7}$-cycloalkyl-, $C_{3-7}$-heterocycloalkyl-, aryl, heteroaryl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, pyrrolidinyl-groups mentioned above

may optionally be substituted preferably independently of each other by NC-, $O_2N$-, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $F_3C$-O-, $HF_2C$-O-, $R^{10}$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, $R^{10}$-O-, $R^{10}$-CO-, $R^{10}$O-CO-, or $(R^{10})_2$N-CO-, whereby piperidinyl or pyrrolidinyl preferably are substituted by $R^{10}$-CO-;

$R^2$ independently of any other $R^2$ being selected from the group of

H-, fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $C_{1-6}$-alkyl- (preferably $C_{2-6}$-alkyl), $(R^{10})_2$N-CO-, $R^{10}$-CO-($R^{10}$)N-,

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, chlorine, bromine and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $F_3C$-$CH_2$-, $HF_2C$-$CH_2$-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, $C_{3-7}$-cycloalkyl-$C_{1-6}$-alkyl-, $C_{3-7}$-heterocycloalkyl-, $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-, aryl, aryl-$C_{1-6}$-alkyl-, heteroaryl, heteroaryl-$C_{1-6}$-alkyl-, $R^{10}$-O-$C_{1-3}$-alkyl-, $R^{10}$O-CO-, $(R^{10})_2$N-CO-, $R^{10}$-CO-, or $C_{1-6}$-alkyl-$SO_2$-,

where where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine and C1-6-alkyl-;

$R^3$ independently of any other $R^3$ being selected from the group of

H-, hydroxyl and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl; preferably independently of one another being selected from the group of H- and fluorine, more preferably $R^4$ and $R^5$ being H;

$R^{10}$ independently from any other $R^{10}$ being selected from the group of

$C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-, aryl and heteroaryl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-;

x independently from each other x = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2, preferably x = 0 or 1, more preferably x = 0;

y independently from each other y = 0, or 1, more preferably y = 0;

and pharmaceutically acceptable salt forms or solvates thereof

with the proviso that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a -$CH_2$- spacer.

A **15th aspect** of the inventions concerns a compound according to the 13th aspect of the invention, wherein

*Hc* being selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

and

$R^2$ independently of any other $R^2$ being H- or $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of *Hc*, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

and

$R^4$ and $R^5$ being H

and

$R^{10}$ independently from any other $R^{10}$ being selected from the group of $C_{1-6}$-alkyl-, phenyl, and pyridyl

where the above-mentioned members may optionally be substituted independently of one another by one or more substituents selected from the group consisting of fluorine, $F_3C$-, $HF_2C$-, $FH_2C$-, $F_3C$-$CH_2$-, $CH_3$-O-$C_{1-6}$-alkyl-, $C_{1-6}$-alkyl-, and $C_{1-6}$-alkyl-O-.

A **16th aspect** of the inventions concerns a compound according to the 15th aspect of the invention, wherein

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl, pyrimidinyl, pyrazolyl, thiazolyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1-and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents selected from the group consisting of HO-, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $C_{3-7}$-cycloalkyl-O-, $C_{3-7}$-cycloalkyl-$C_{1-3}$-alkyl-O-, $CF_3O$-, $CF_3$-, fluorine, chlorine, bromine, $C_{3-7}$-heterocycloalkyl- and $C_{3-7}$-heterocycloalkyl-$C_{1-6}$-alkyl-.

A **17th aspect** of the inventions concerns a compound with all features according to the 16th aspect of the invention, except in that

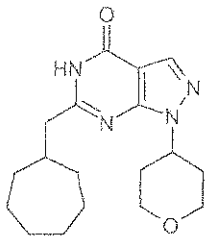
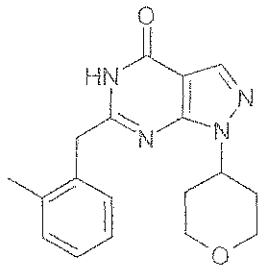
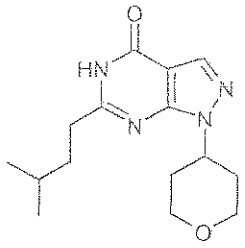
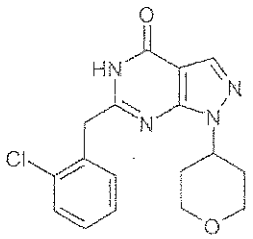
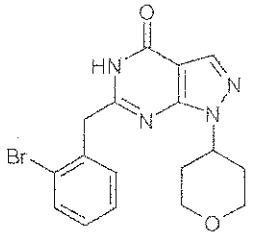
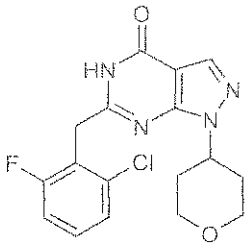
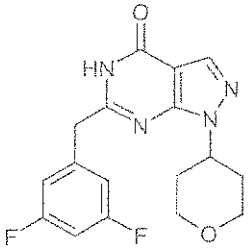
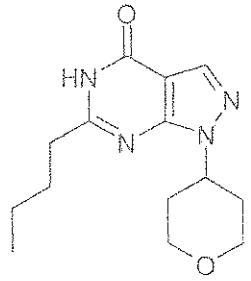
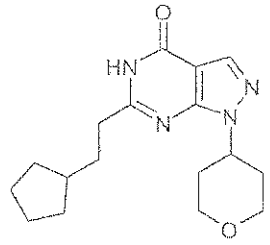
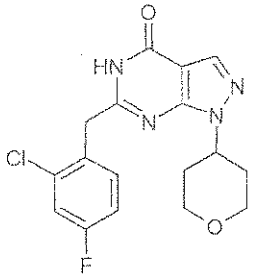
$R^1$ being selected from the group of

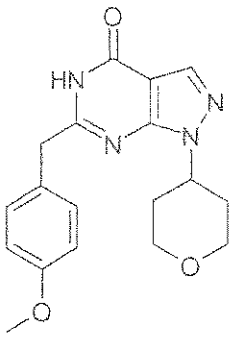
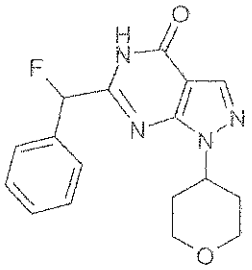
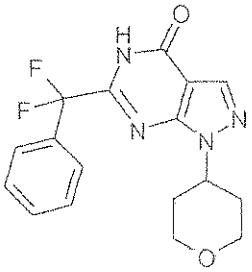
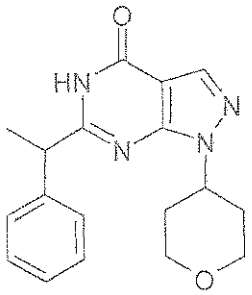
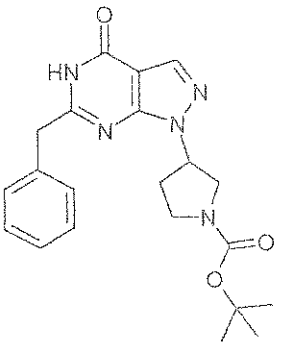
phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl, ethyl, propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl, and tetrahydropyranyl,

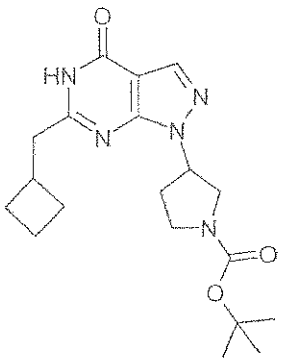
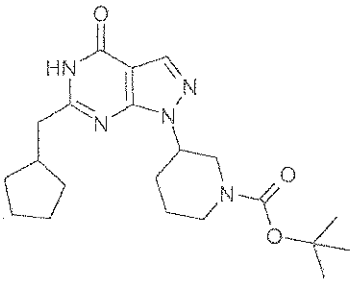
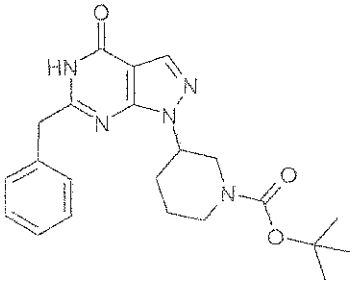
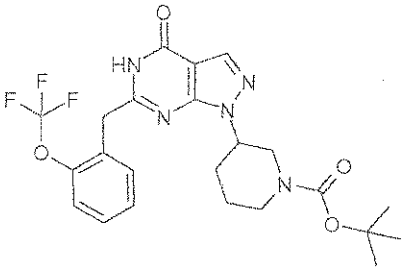
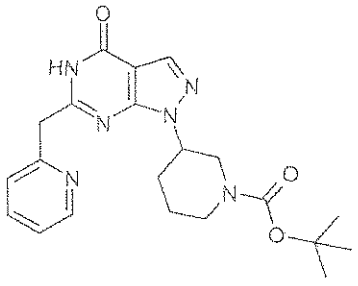
where these groups may optionally be substituted by one or more substituents selected from the group consisting of NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$- and halogen, the halogen preferably being selected from the group of fluorine, chlorine and bromine.

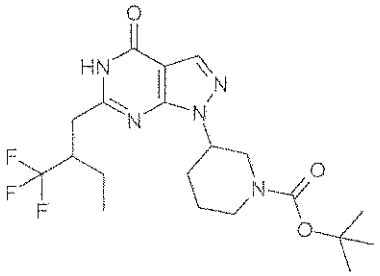
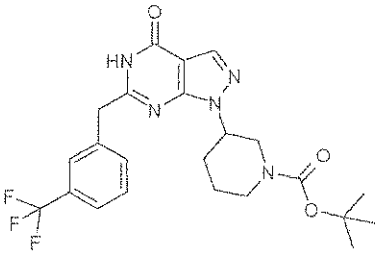
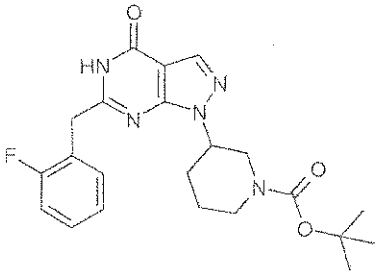
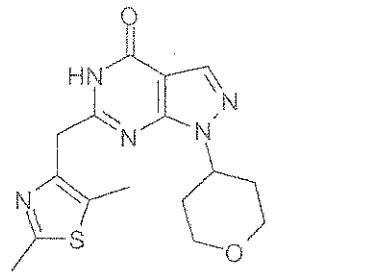
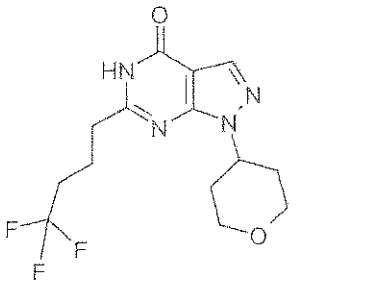
A **specific aspect** of the inventions **(18th aspect)** concerns - independently of each other and separable therefrom - each of the following compounds and/or wherever applicable each specific stereoisomer thereof and/or tautomer thereof and/or a pharmaceutically acceptable salt thereof. Each compound is represented and considered in form of the neutral compound without indicating the stereochemistry thereof if any. The left hand column indicates the example the compound derives from. Specific information concerning stereochemical properties can be taken from the experimental section, section **Exemplary embodiments**. In case the final compounds according to said section **Exemplary embodiments** are salts forms,

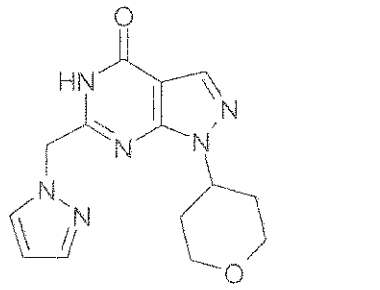
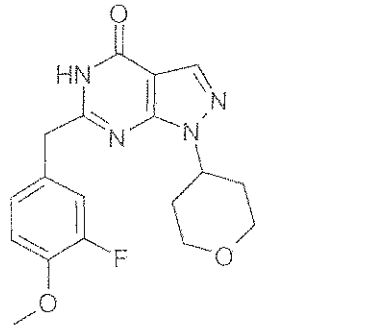
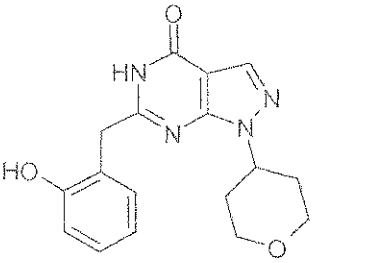
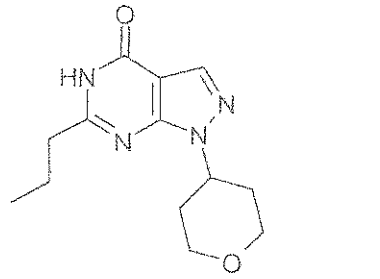
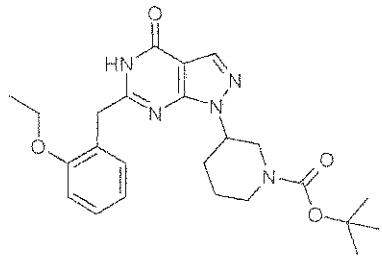
they can be converted into the neutral compound (free base or acid) by conventional methods.

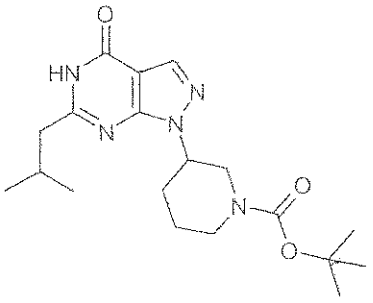
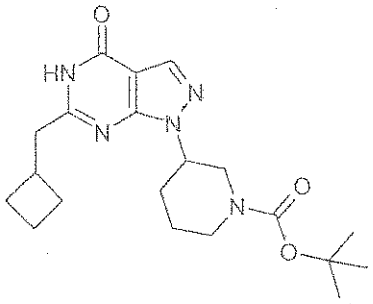
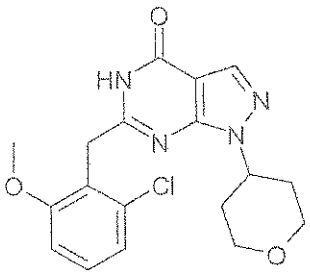
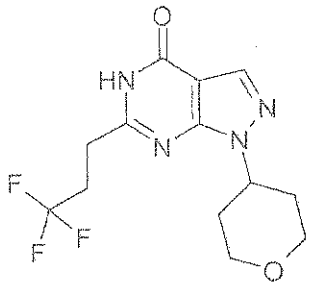
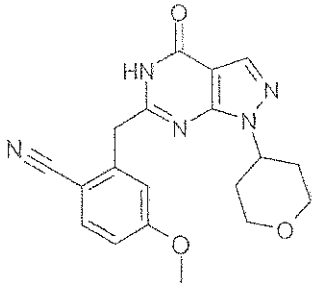
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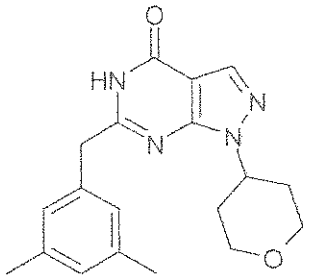
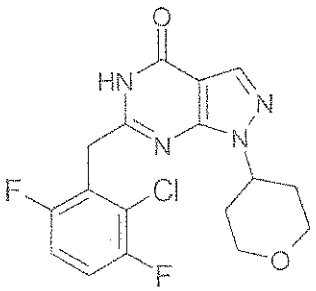
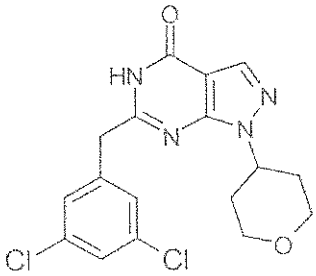
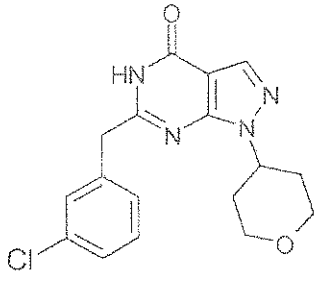
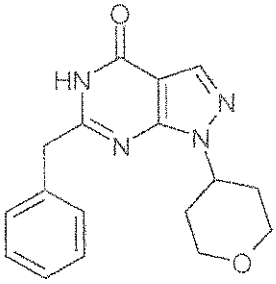
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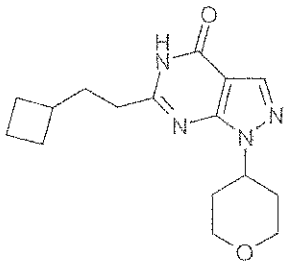
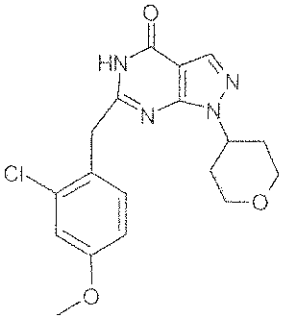
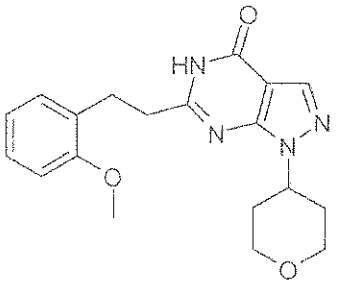
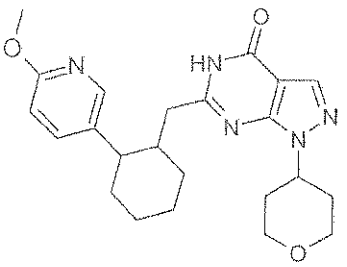
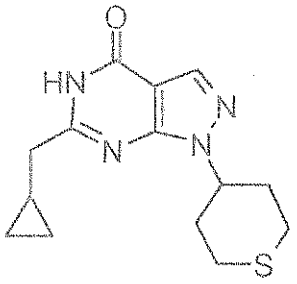
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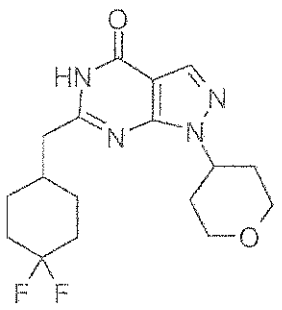
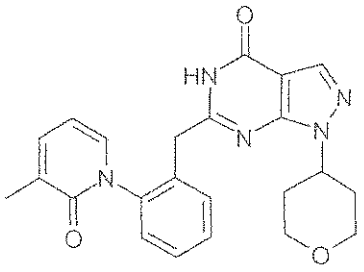
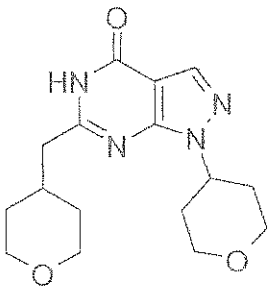
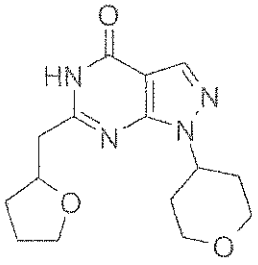
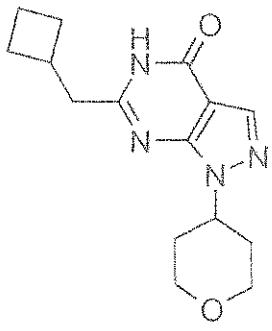
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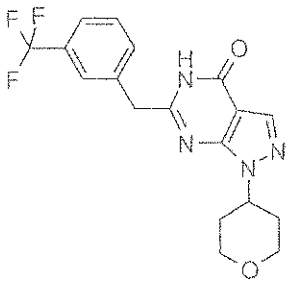
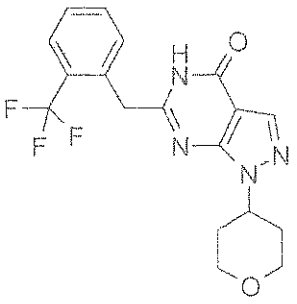
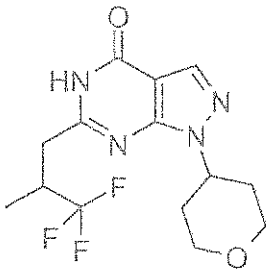
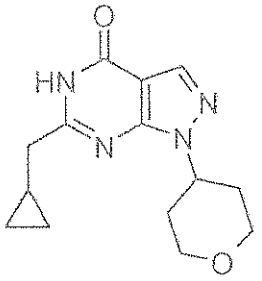
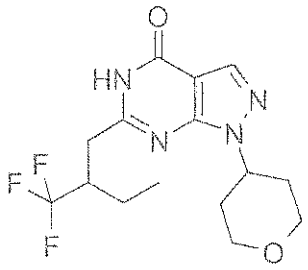
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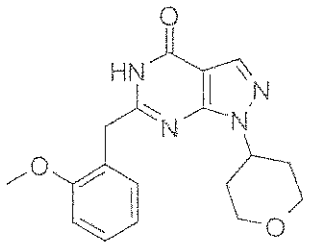
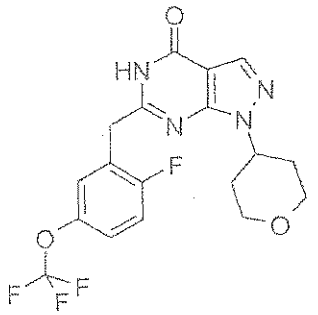
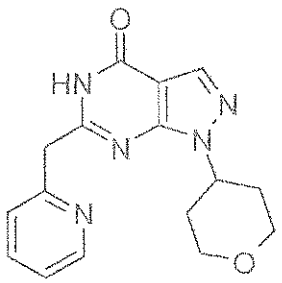
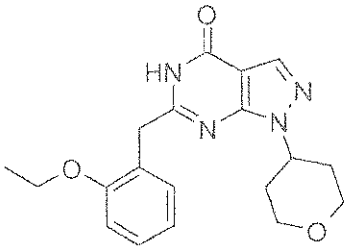
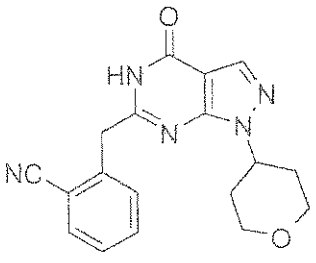
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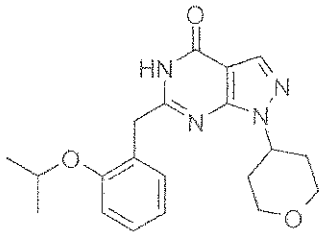
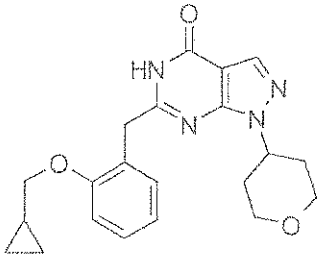
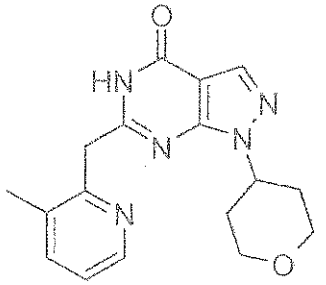
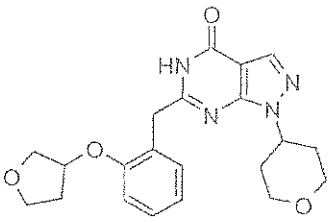
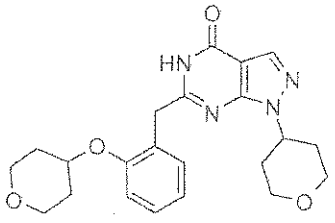
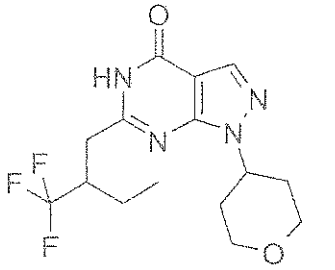
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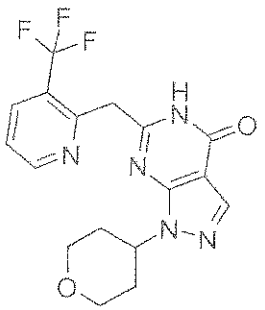
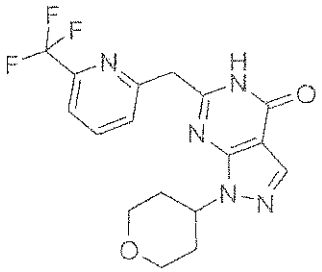
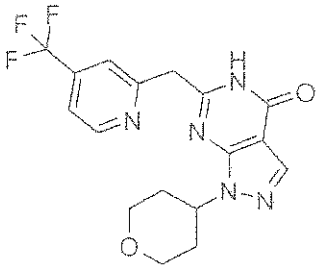
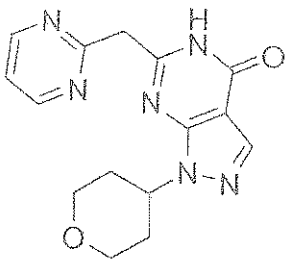
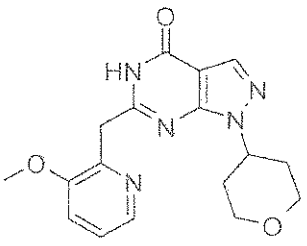
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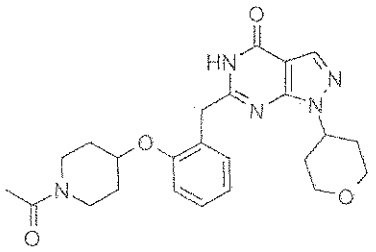
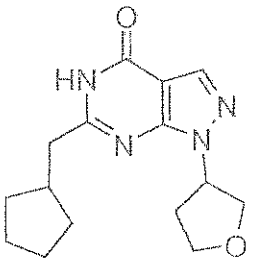
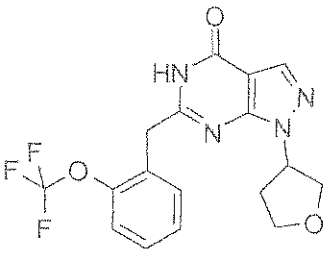
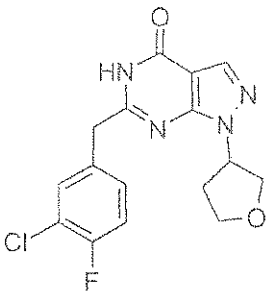
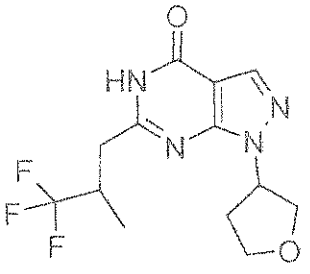
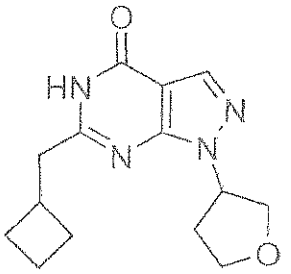
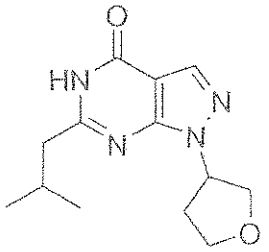
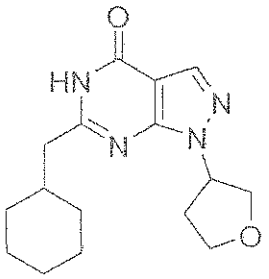
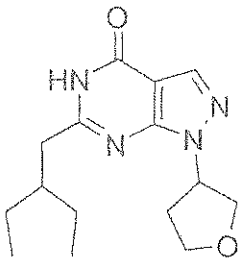
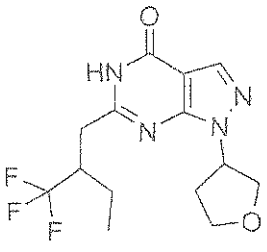
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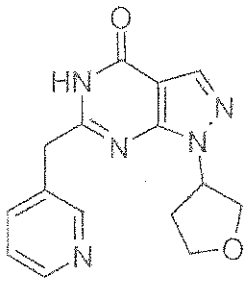
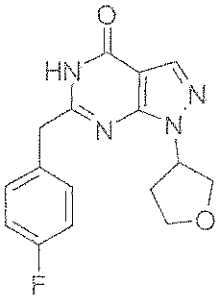
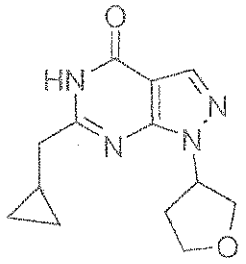
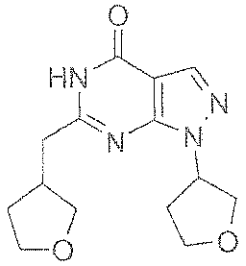
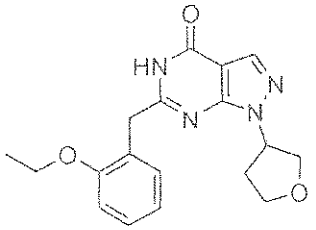
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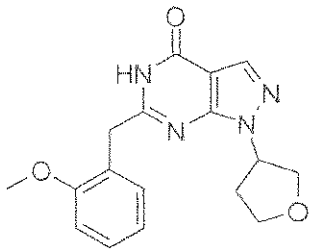
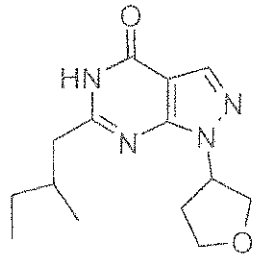
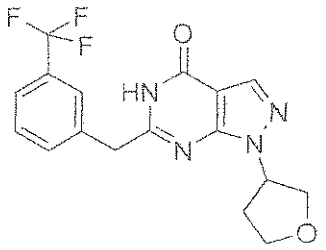
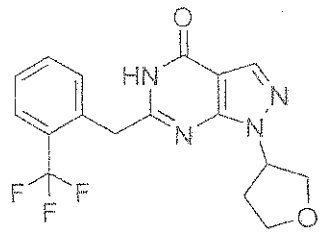
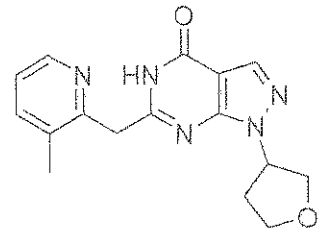
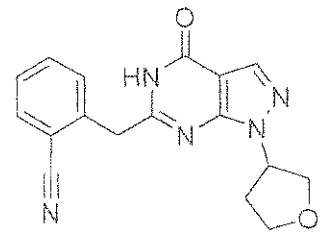
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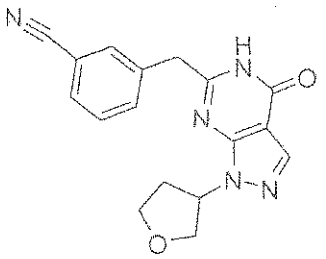
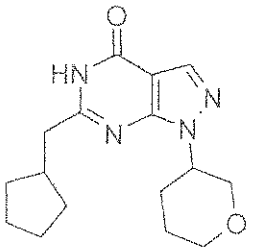
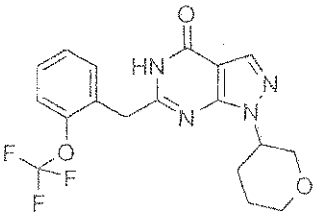
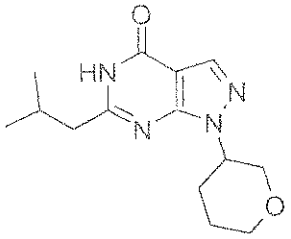
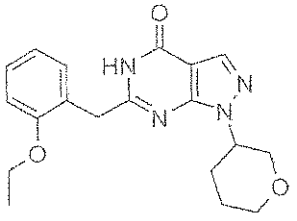
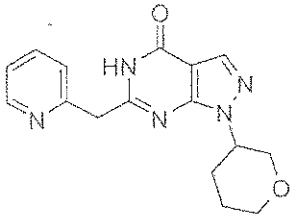
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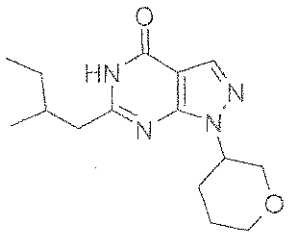
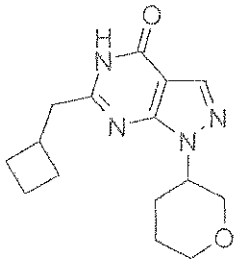
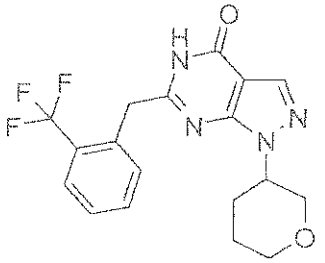
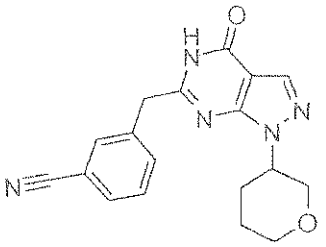
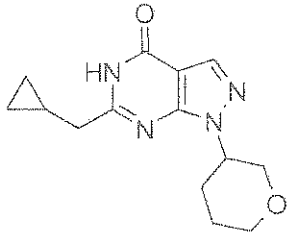
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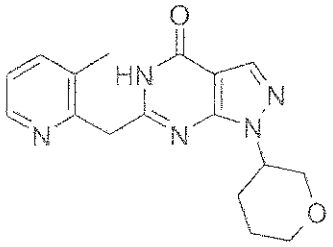
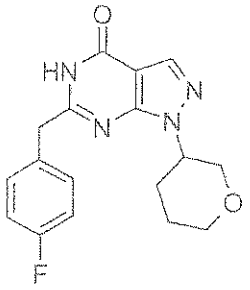
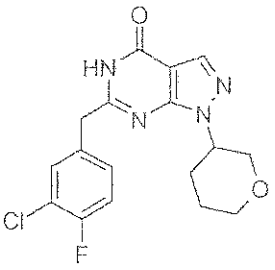
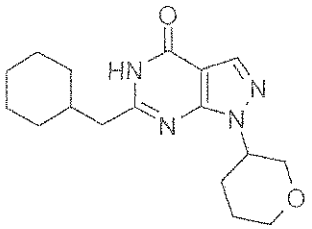
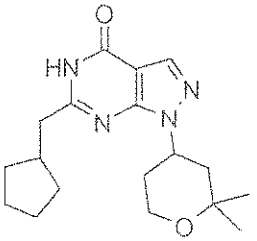
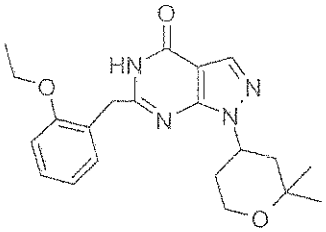
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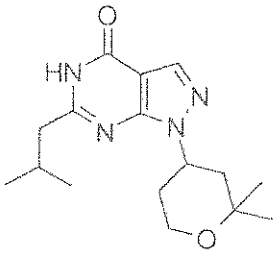
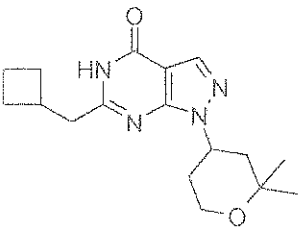
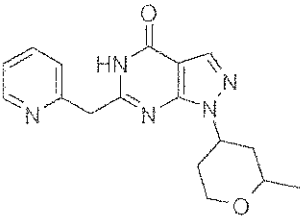
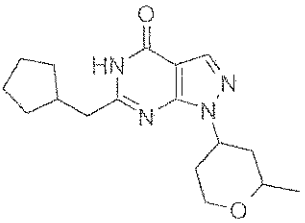
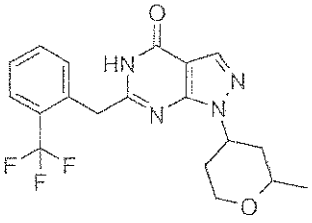
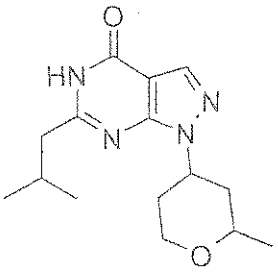
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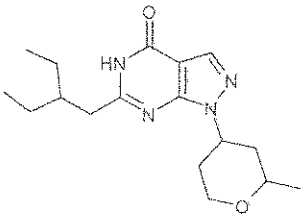
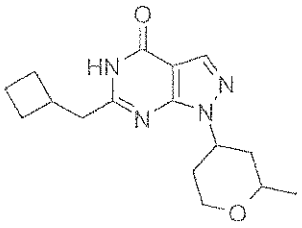
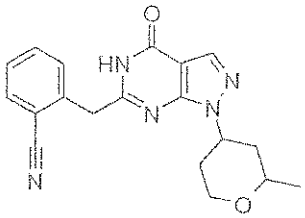
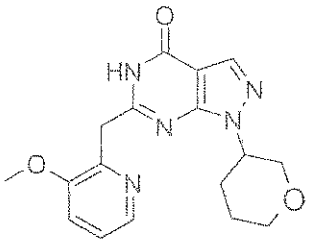
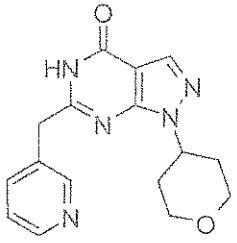
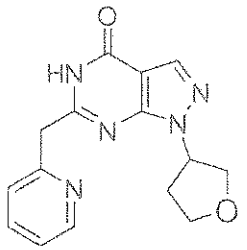
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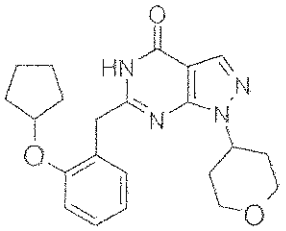
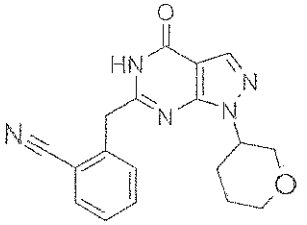
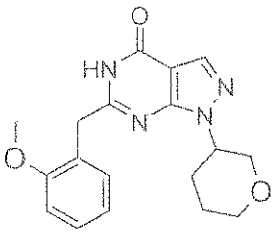
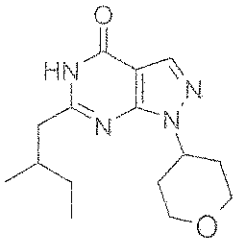
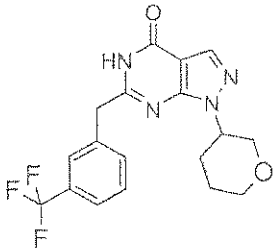
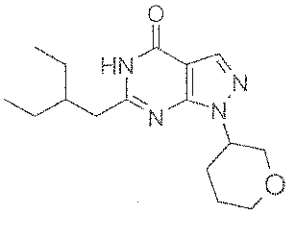
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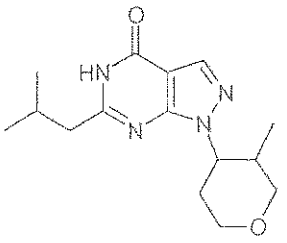
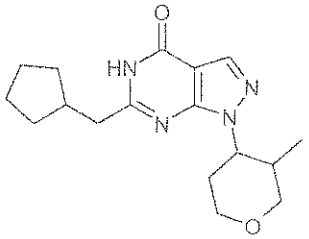
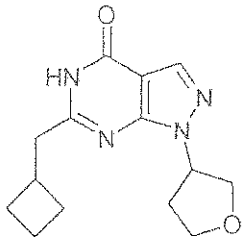
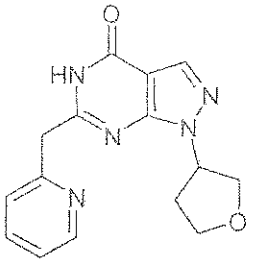
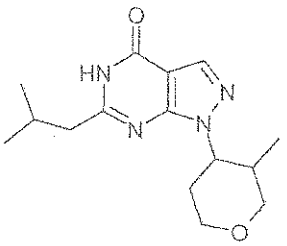
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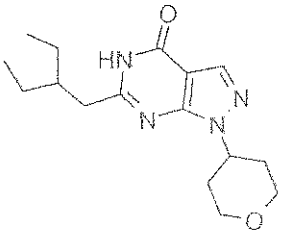
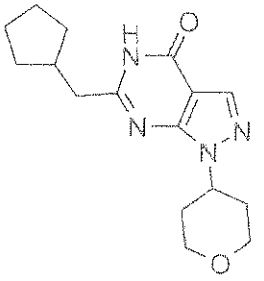
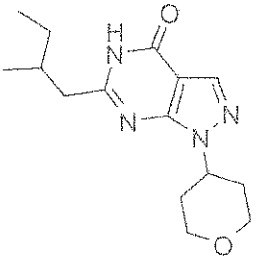
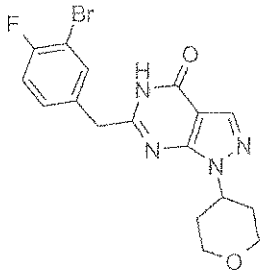
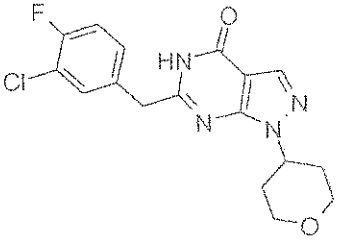
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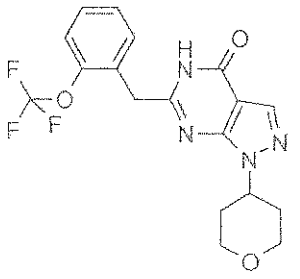
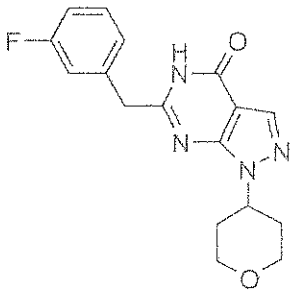
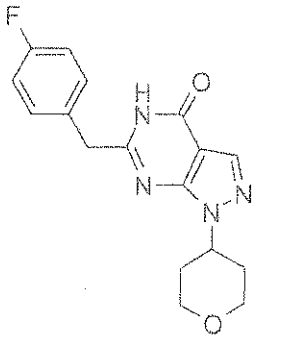
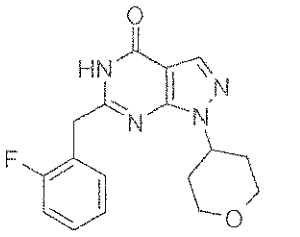
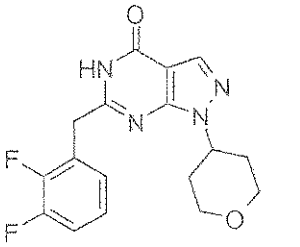
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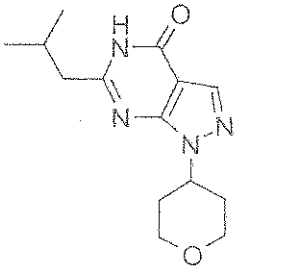
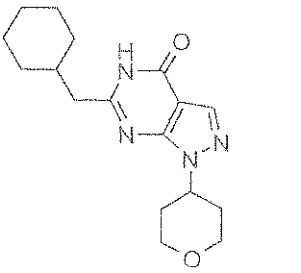
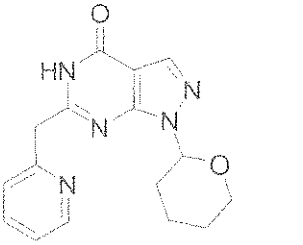
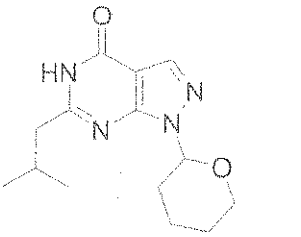
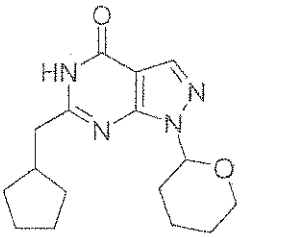
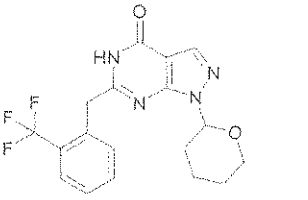
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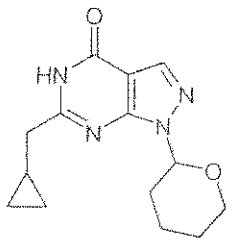
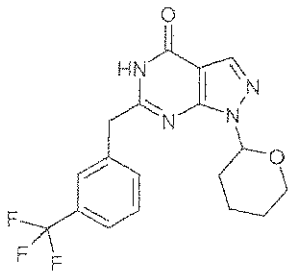
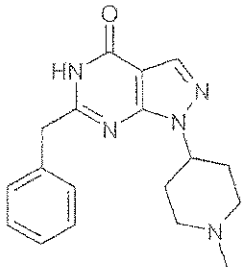
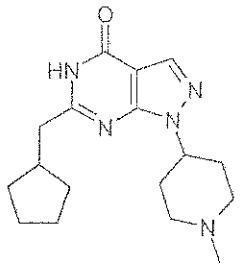
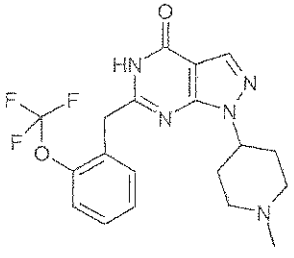
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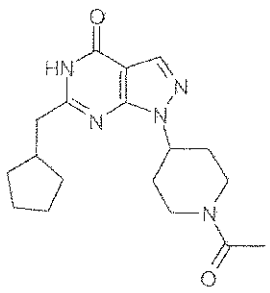
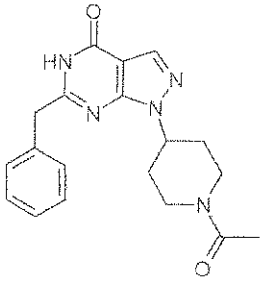
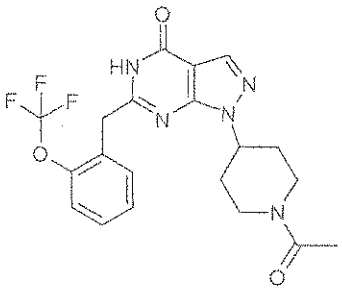
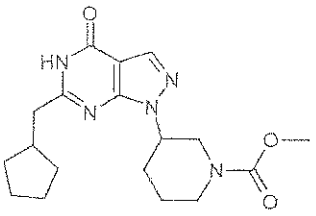
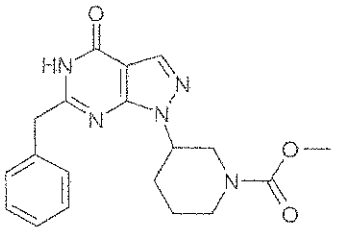
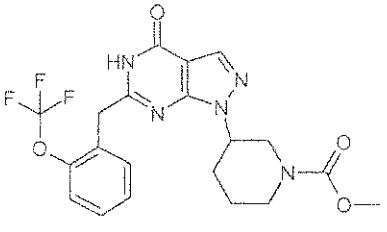
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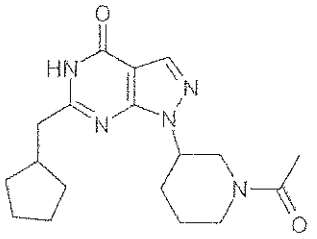
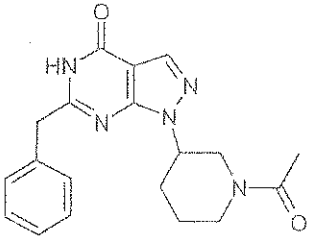
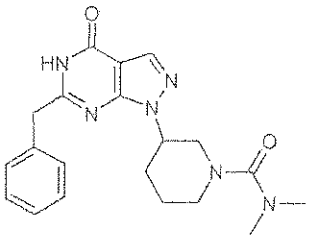
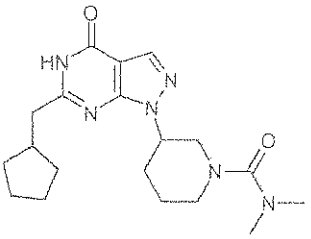
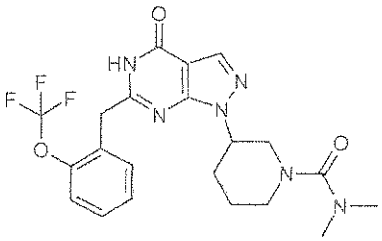
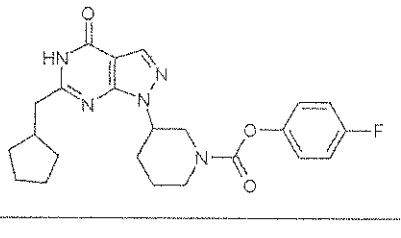
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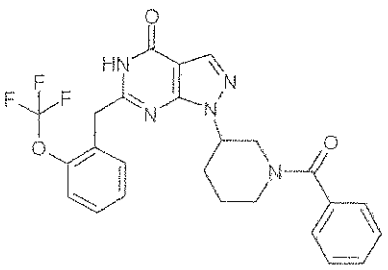
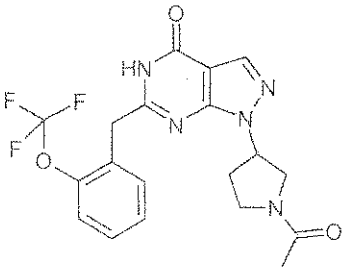
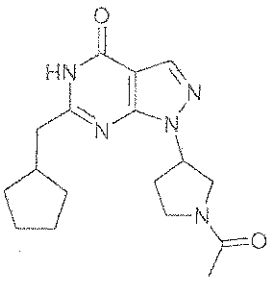
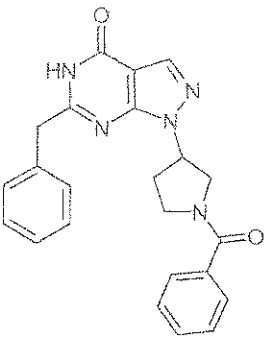
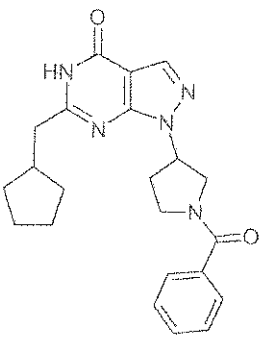
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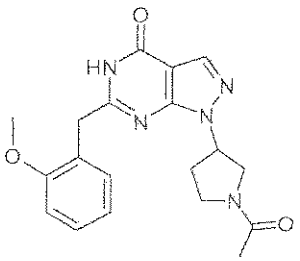
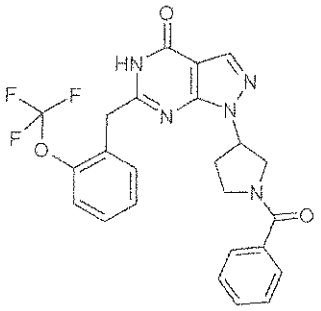
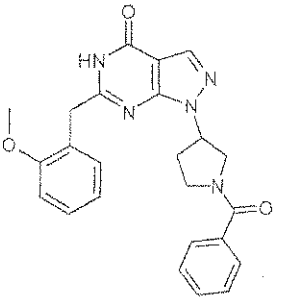
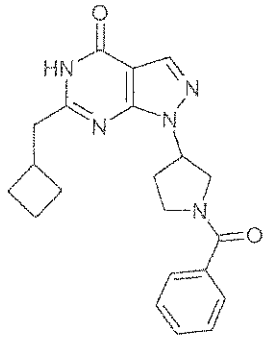
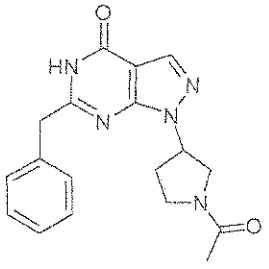
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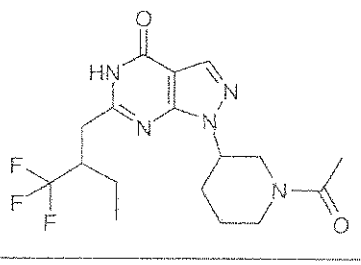
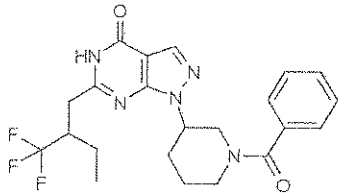
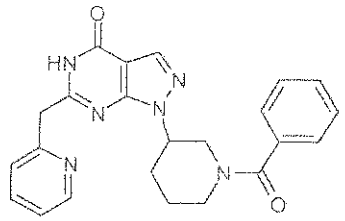
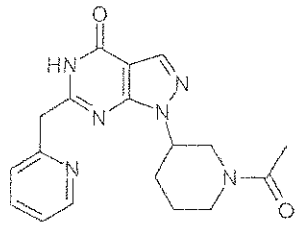
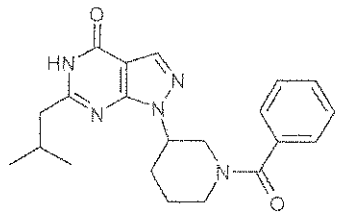
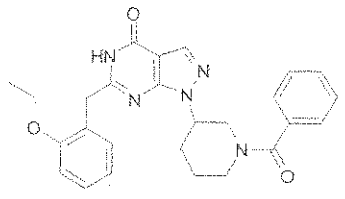
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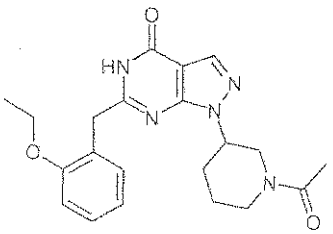
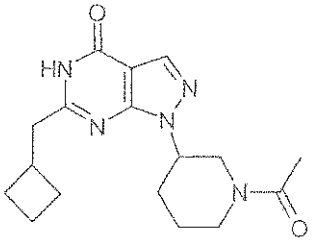
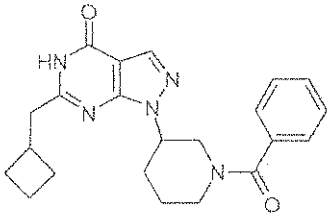
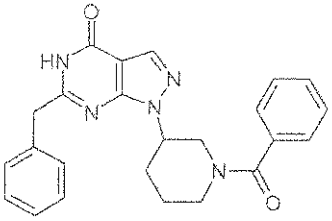
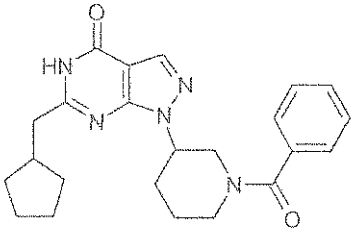
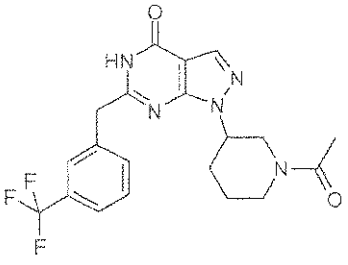
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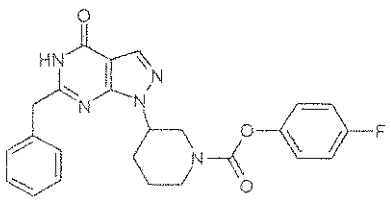
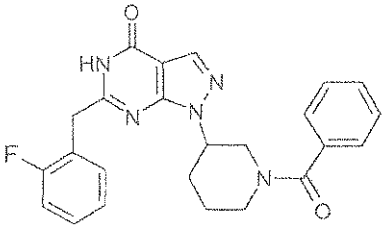
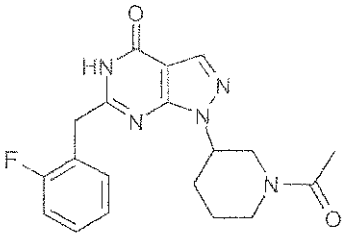
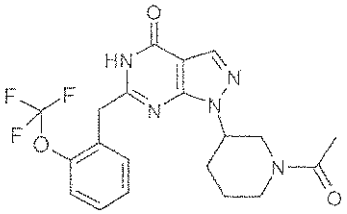
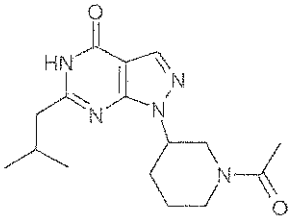
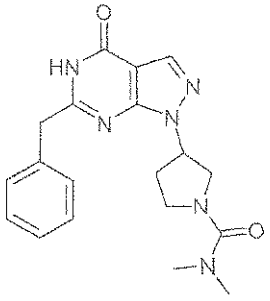
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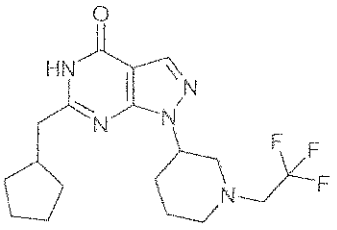
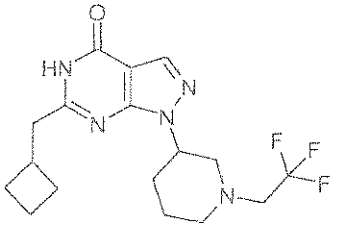
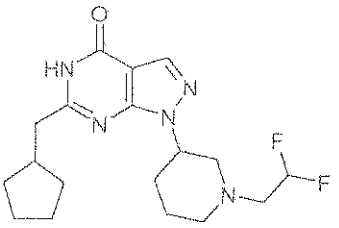
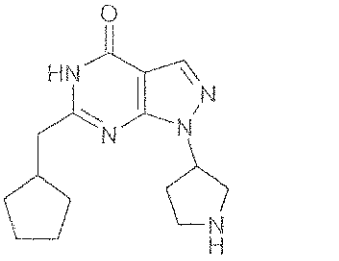
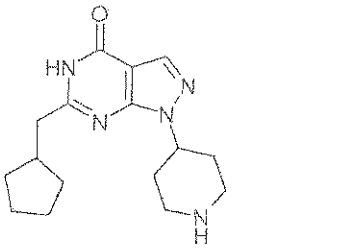
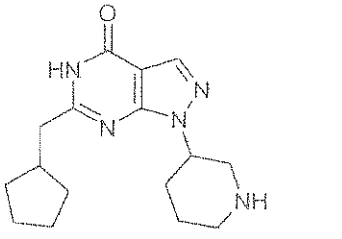
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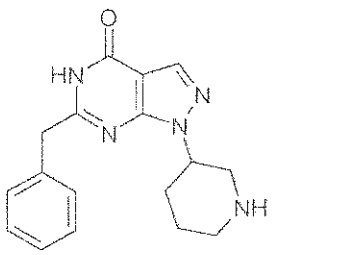
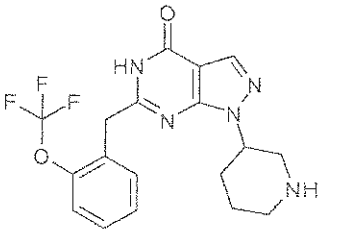
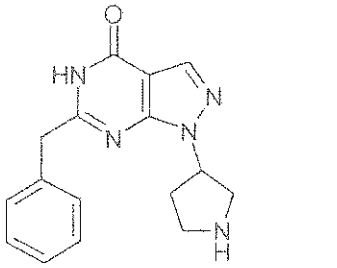
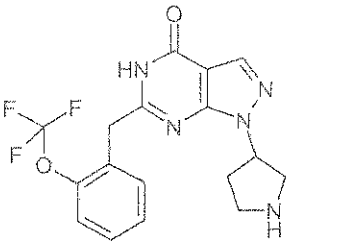
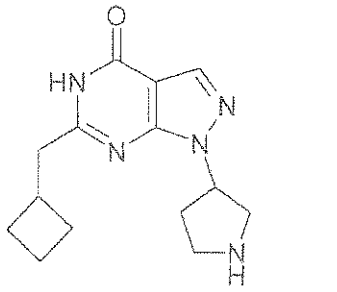
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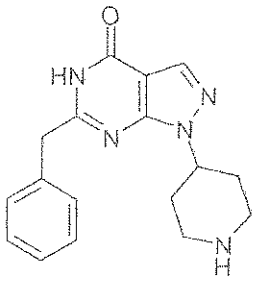
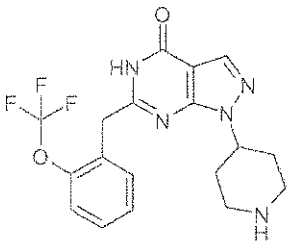
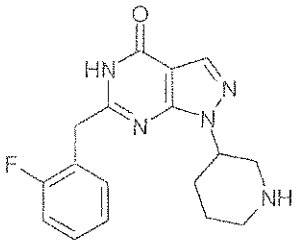
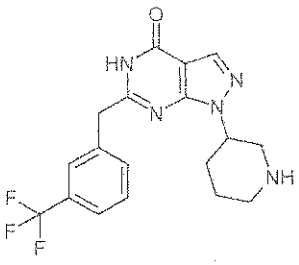
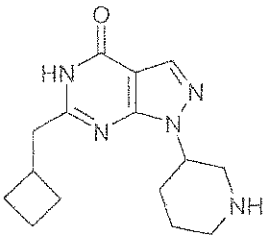
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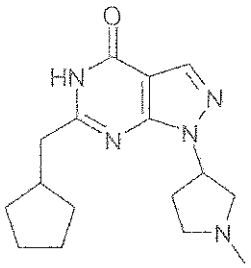
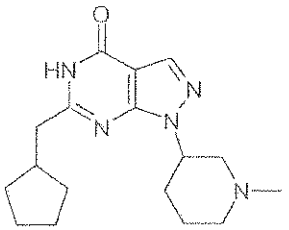
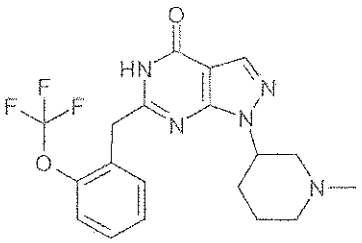
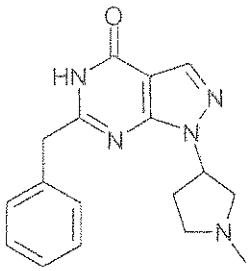
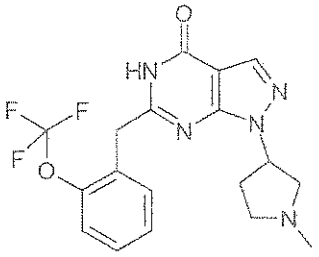
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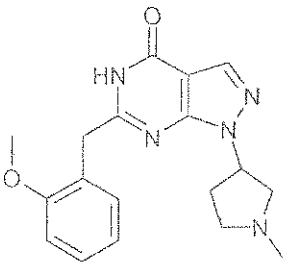
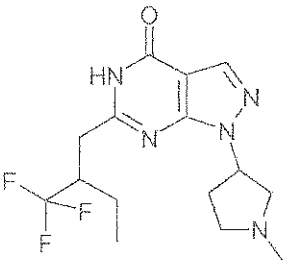
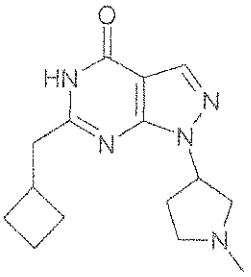
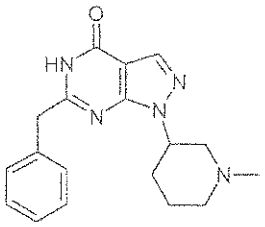
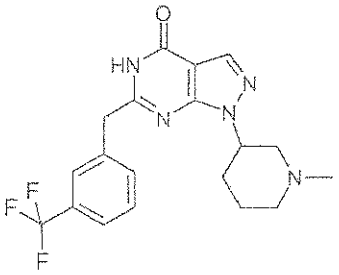
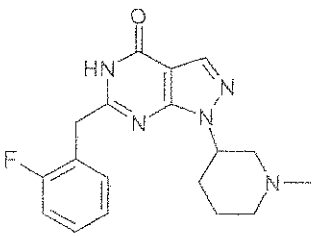
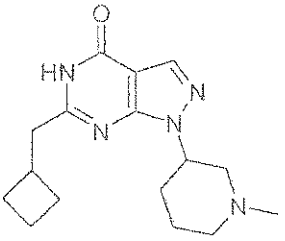
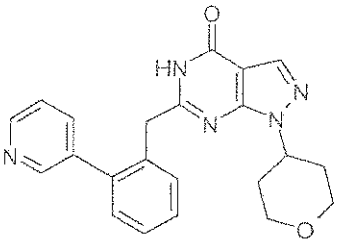
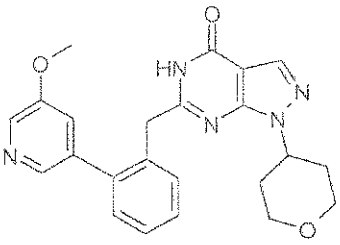
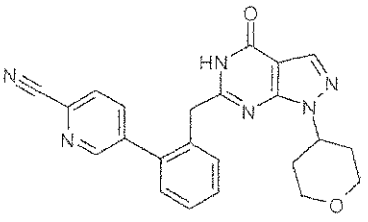
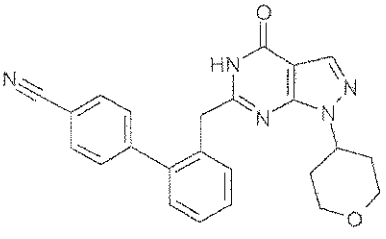
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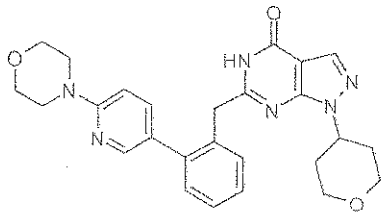
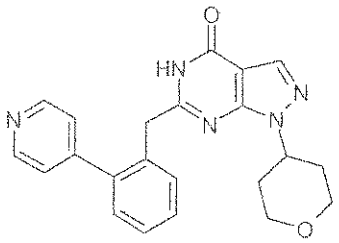
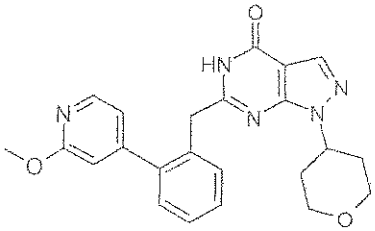
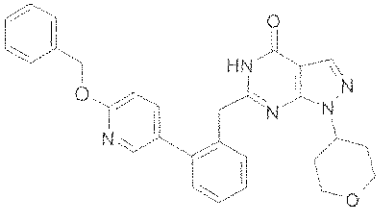
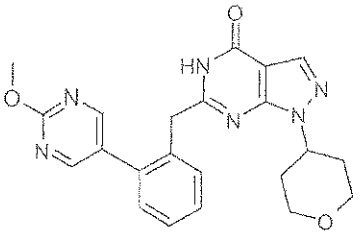
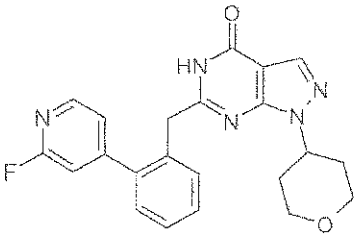
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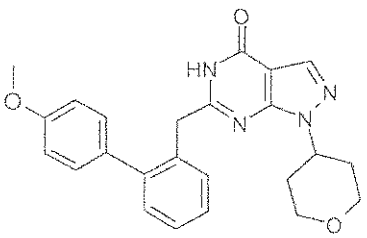
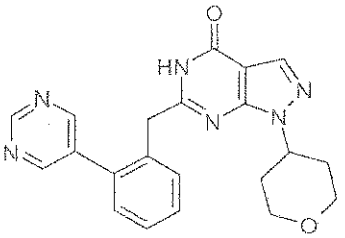
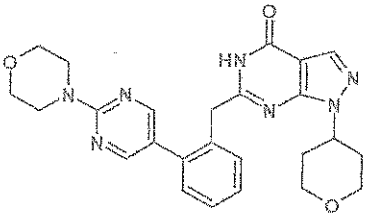
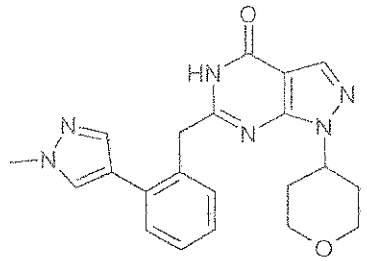
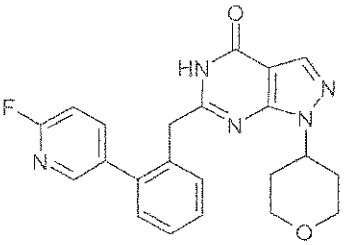
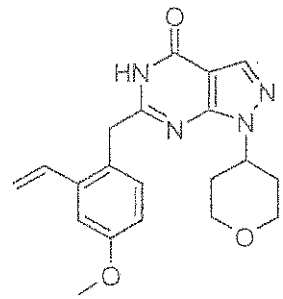
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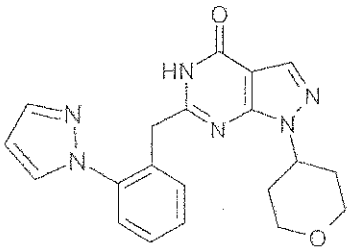
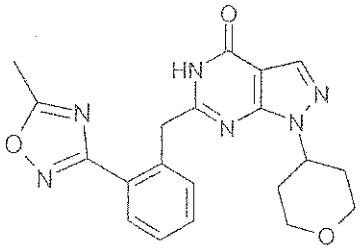
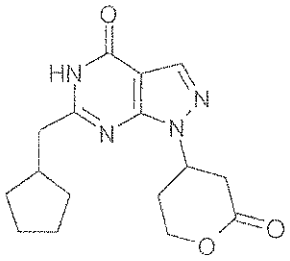
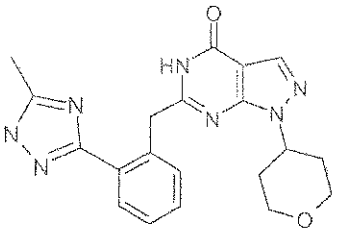
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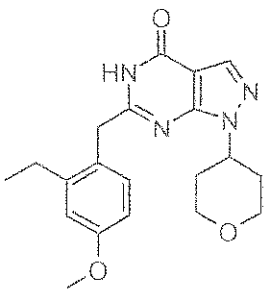
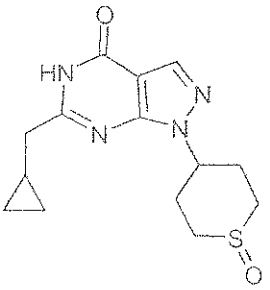
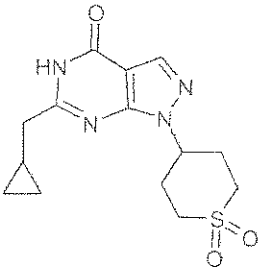
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These 18 main aspects of the inventions, subgroups thereof and some further other aspects of the invention are listed as elements of the following matrix 0 and matrix I which make reference to the notation ($\underline{Hc}^{i}\ R^{1.j}\ R^{2.k}\ R^{3.l}\ R^{4/5.m}\ R^{10.n}$), the reading of which is as defined above, i.e. together with general formula I and the remaining features like x, y, as outlined directly below said matrix 0 or matrix I.

Matrix 0 and matrix I show in the right hand column the embodiments ($\underline{Hc}^{i}\ R^{1.j}\ R^{2.k}\ R^{3.l}\ R^{4/5.m}\ R^{10.n}$) of the invention according to general formula I that are considered preferred, independent and separable of each other, i.e. individual aspects of the invention. The left hand column provides a reference number to such embodiments. The embodiments or elements are listed in the order from less preferred to most preferred, the preference of the embodiments is ascending with the reference number. This means that the embodiment, which is presented by the matrix element in the last row, last entry of matrix 0 or matrix I is the most preferred embodiment, while the embodiments of matrix I are preferred over the embodiments of matrix 0.

Aspects 1 to 18 are the main aspects of the invention.

Matrix 0

The first embodiment of this matrix 0 represents the first general aspect of the invention. The following embodiments are subsets thereof.

| No. | Embodiment |
|---|---|
| M0-001 | $\underline{Hc}^{1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-002 | $\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-003 | $\underline{Hc}^{2}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.0.2}$ |
| M0-004 | $\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.0.3}$ |
| M0-005 | $\underline{Hc}^{3}R^{1.0.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.0.3}$ |
| M0-006 | $\underline{Hc}^{7.0}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-007 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.1}R^{3.1}R^{4/5.2}R^{10.0.2}$ |
| M0-008 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-009 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-010 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.4}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-011 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-012 | $\underline{Hc}^{7.0}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-013 | $\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-014 | $\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-015 | $\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$ |
| M0-016 | $\underline{Hc}^{7.0}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$ |
| M0-017 | $\underline{Hc}^{7.0}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-018 | $\underline{Hc}^{7.1}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-019 | $\underline{Hc}^{7.1}R^{1.0.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-020 | $\underline{Hc}^{7.1}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-021 | $\underline{Hc}^{7.1}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |

| | |
|---|---|
| M0-022 | $Hc^{7.1}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-023 | $Hc^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-024 | $Hc^{7.1}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$ |
| M0-025 | $Hc^{7.1}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$ |
| M0-026 | $Hc^{7.1}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-027 | $Hc^{7.1}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| M0-028 | $Hc^{8}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-029 | $Hc^{8}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-030 | $Hc^{8}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-031 | $Hc^{8}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-032 | $Hc^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-033 | $Hc^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-034 | $Hc^{8}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$ |
| M0-035 | $Hc^{8}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$ |
| M0-036 | $Hc^{8}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-037 | $Hc^{8}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| M0-038 | $Hc^{9}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-039 | $Hc^{9}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-040 | $Hc^{9}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-041 | $Hc^{9}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-042 | $Hc^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-043 | $Hc^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-044 | $Hc^{9}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$ |
| M0-045 | $Hc^{9}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$ |
| M0-046 | $Hc^{9}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-047 | $Hc^{9}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| M0-048 | $Hc^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}R^{10.4}$ |
| M0-049 | $Hc^{9}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| M0-050 | $Hc^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}R^{10.4}$ |
| M0-051 | $Hc^{9}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| M0-052 | $Hc^{10}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$ |
| M0-053 | $Hc^{10}R^{1.0.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.0.2}$ |
| M0-054 | $Hc^{10}R^{1.0.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-055 | $Hc^{10}R^{1.0.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-056 | $Hc^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.4}$ |
| M0-057 | $Hc^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.4}$ |
| M0-058 | $Hc^{10}R^{1.0.3}R^{2.5}R^{3.2}R^{4/5.3}R^{10.0.5}$ |
| M0-059 | $Hc^{10}R^{1.0.3}R^{2.5}R^{3.3}R^{4/5.3}R^{10.0.5}$ |
| M0-060 | $Hc^{10}R^{1.0.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-061 | $Hc^{10}R^{1.0.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| M0-062 | $Hc^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.2}$ |
| M0-063 | $Hc^{10}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}$ |
| M0-064 | $Hc^{10}R^{1.4}R^{2.4}R^{3.3}R^{4/5.2}$ |
| M0-065 | $Hc^{10}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| M0-066 | $Hc^{10}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| | |

whereby for each matrix embodiment of matrix 0:

x independently from each other = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2; preferably being 0 or 1, more preferably x= 0:

y independently from each other y = 0, or 1; more preferably y= 0, whereby specific definitions with the embodiments of the matrix prevail;

and pharmaceutically acceptable salts and/or solvates thereof.

and with the proviso - for each embodiment of matrix 0 for that this proviso is applicable - such as for embodiments which comprise *Hc* as defined by $Hc^1$ or $Hc^3$ - that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

It will be evident, that if x and/or y = 0 then *Hc* is unsubstituted, i. e. the corresponding valences of the ring member atoms are saturated by hydrogen.

In case $R^{10}$ is not sufficiently defined in matrix 0 it shall be $R^{10.0.4}$ or $R^{10.0.5}$, preferably $R^{10.0.5}$.

matrix I:

| No. | Embodiment |
|---|---|
| MI-001 | $Hc^1R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-002 | $Hc^2R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-003 | $Hc^2R^{1.2}R^{2.3}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-004 | $Hc^2R^{1.2}R^{2.3}R^{3.3}R^{4/5.2}R^{10.2}$ |
| MI-005 | $Hc^3R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-006 | $Hc^3R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-007 | $Hc^3R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-008 | $Hc^3R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-009 | $Hc^3R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-010 | $Hc^3R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |

| | |
|---|---|
| MI-011 | $\underline{Hc}^{3}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-012 | $\underline{Hc}^{3}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-013 | $\underline{Hc}^{3}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-014 | $\underline{Hc}^{3}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-015 | $\underline{Hc}^{3}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-016 | $\underline{Hc}^{3}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-017 | $\underline{Hc}^{3}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-018 | $\underline{Hc}^{3}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-019 | $\underline{Hc}^{3}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-020 | $\underline{Hc}^{3}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-021 | $\underline{Hc}^{3}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-022 | $\underline{Hc}^{3}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-023 | $\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-024 | $\underline{Hc}^{3}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-025 | $\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-026 | $\underline{Hc}^{3}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-027 | $\underline{Hc}^{4}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-028 | $\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-029 | $\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-030 | $\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-031 | $\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-032 | $\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-033 | $\underline{Hc}^{4}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-034 | $\underline{Hc}^{4}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-035 | $\underline{Hc}^{4}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-036 | $\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-037 | $\underline{Hc}^{4}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-038 | $\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-039 | $\underline{Hc}^{4}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-040 | $\underline{Hc}^{4}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-041 | $\underline{Hc}^{4}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-042 | $\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-043 | $\underline{Hc}^{4}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-044 | $\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-045 | $\underline{Hc}^{4}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-046 | $\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-047 | $\underline{Hc}^{4}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-048 | $\underline{Hc}^{4}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-049 | $\underline{Hc}^{4}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-050 | $\underline{Hc}^{4}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-051 | $\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-052 | $\underline{Hc}^{4}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-053 | $\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-054 | $\underline{Hc}^{4}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-055 | $\underline{Hc}^{7.1}R^{1.1}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-056 | $\underline{Hc}^{7.1}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |

| | |
|---|---|
| MI-057 | $\underline{Hc}^{7.1}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-058 | $\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-059 | $\underline{Hc}^{7.1}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-060 | $\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-061 | $\underline{Hc}^{7.1}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-062 | $\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-063 | $\underline{Hc}^{7.1}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-064 | $\underline{Hc}^{7.1}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-065 | $\underline{Hc}^{7.1}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-066 | $\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-067 | $\underline{Hc}^{7.1}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-068 | $\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-069 | $\underline{Hc}^{7.1}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-070 | $\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-071 | $\underline{Hc}^{7.1}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-072 | $\underline{Hc}^{7.1}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-073 | $\underline{Hc}^{7.1}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-074 | $\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-075 | $\underline{Hc}^{7.1}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-076 | $\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-077 | $\underline{Hc}^{7.1}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-078 | $\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.2}R^{4/5.34}$ |
| MI-079 | $\underline{Hc}^{7.1}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$ |

| | |
|---|---|
| MI-080 | $\underline{Hc}^{8}R^{1.2}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-081 | $\underline{Hc}^{8}R^{1.2}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-082 | $\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-083 | $\underline{Hc}^{8}R^{1.2}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-084 | $\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-085 | $\underline{Hc}^{8}R^{1.2}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-086 | $\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-087 | $\underline{Hc}^{8}R^{1.2}R^{2.5}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-088 | $\underline{Hc}^{8}R^{1.3}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-089 | $\underline{Hc}^{8}R^{1.3}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-090 | $\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-091 | $\underline{Hc}^{8}R^{1.3}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-092 | $\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-093 | $\underline{Hc}^{8}R^{1.3}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-094 | $\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.2}R^{4/5.3}$ |
| MI-095 | $\underline{Hc}^{8}R^{1.3}R^{2.5}R^{3.3}R^{4/5.3}$ |
| MI-096 | $\underline{Hc}^{8}R^{1.4}R^{2.1}R^{3.1}R^{4/5.1}R^{10.1}$ |
| MI-097 | $\underline{Hc}^{8}R^{1.4}R^{2.2}R^{3.2}R^{4/5.2}R^{10.2}$ |
| MI-098 | $\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.2}R^{4/5.3}R^{10.3}$ |
| MI-099 | $\underline{Hc}^{8}R^{1.4}R^{2.3}R^{3.3}R^{4/5.3}R^{10.3}$ |
| MI-100 | $\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.2}R^{4/5.3}R^{10.4}$ |
| MI-101 | $\underline{Hc}^{8}R^{1.4}R^{2.4}R^{3.3}R^{4/5.3}R^{10.4}$ |
| MI-102 | $\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.2}R^{4/5.3}$ |

| | |
|---|---|
| MI-103 | $\underline{Hc}^{8}R^{1.4}R^{2.5}R^{3.3}R^{4/5.3}$ |

whereby for each embodiment of matrix I:

x independently from each other = 0, 1, 2, 3 or 4, preferably x = 0, 1 or 2;

y independently from each other y = 0 or 1;

and pharmaceutically acceptable salts and/or solvates thereof

and with the proviso - for each embodiment of matrix 0 for that this proviso is applicable - such as for embodiments which comprise *Hc* as defined by $\underline{Hc}^{1}$ or $\underline{Hc}^{3}$ - that

if *Hc* is oxetanyl, which is bound via the carbon atom next to the oxygen of the oxetanyl, there is no substituent attached to said carbon atom via a $-CH_2-$ spacer.

It will be evident, that if x and/or y = 0 then *Hc* is unsubstituted, i. e. the corresponding valences of the ring member atoms are saturated by hydrogen.

In case $R^{10}$ is not sufficiently defined in matrix I it shall be $R^{10.4}$.

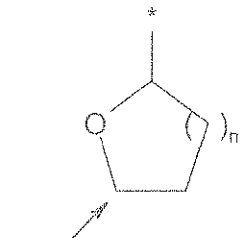
**Additional embodiments according to the invention and subset of the aspects 1 to 17 and the embodiments of matrix 0 or matrix I**

In the following further embodiments of the invention are presented. Each one is independent and separable, i.e. individual aspect of the invention.

Additionally mentioned are the embodiments ($\underline{Hc}^{5}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$) and ($\underline{Hc}^{6}R^{1.0.1}R^{2.0.1}R^{3.1}R^{4/5.1}R^{10.0.1}$), with the remaining features as outlined for the elements of matrix I.

**a.) subset of aspects 1 – 17 and embodiments of matrix 0 or I with respect to $R^2$**

(a.1.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* within the group *Hc*$[R^2]_x[R^3]_y$ may be a group defined by the following formula D1

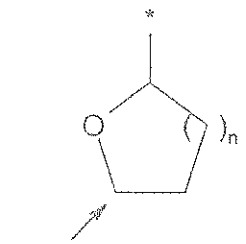



(D1),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 0, 1, 2 or 3, except that in this subset for no embodiment at the position ** there is an $R^2$ that comprises a -$CH_2$- group by which $R^2$ is bound at said position **:

This subset is called "subset a.1.1".

(a.1.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* within the group *Hc*$[R^2]_x[R^3]_y$ may be a group defined by the following formula D1

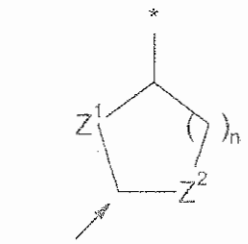



(D1),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 0, 1, 2 or 3; except that in this subset for no embodiment at the position ** there is an $R^2$ or $R^3$ other than H.

This subset is called "subset a.1.2".

(a.2.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* within the group $Hc[R^2]_x[R^3]_y$ may be a group defined by the following formula D1-2



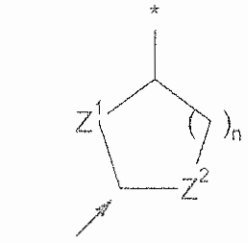

(D1-2),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 1, 2 or 3 and wherein $Z^1$ is selected from the group of N, O and $S(O)_r$, with r = 0, 1, 2 and $Z^2$ is selected from the group of C, N, O and $S(O)_r$, with r = 0, 1, 2, in all cases with eventually remaining valences of $Z^1$ or $Z^2$ being saturated by H or as the case may be by $R^2$ or $R^3$,

except that within this subset for no embodiment at the position ** there is an $R^2$ that comprises an optionally substituted $-CH_2-$ group by which this $R^2$ is bound at said position **:

This subset is called "subset a.2.1".

(a.2.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* within the group $Hc[R^2]_x[R^3]_y$ may be a group defined by the following formula D1-2




(D1-2),

whereby the * is the attachment point to the pyrazolo-group in general formula I and n = 1, 2 or 3 and wherein $Z^1$ is selected from the group of N, O and $S(O)_r$, with r = 0, 1, 2 and $Z^2$ is selected from the group of C, N, O and $S(O)_r$, with r = 0, 1, 2, in all cases with eventually remaining valences of $Z^1$ or $Z^2$ being saturated by H or as the case may be by $R^2$ or $R^3$,

except that within this subset for no embodiment at the position ** there is an $R^2$ or $R^3$ other than H:

This subset is called "subset a.2.2".

(a.3) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydrofuranyl, except that within this subset for no embodiment $R^2$ is a $CH_3$-group that is bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.3".

(a.4) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydrofuranyl, except that within this subset for no embodiment $R^2$ is a $R^{10}$-O- $C_{2-6}$-alkyl-group having a $CH_2$-group by which it is bound to a C-atom of the tetrahydrofuranyl, which is at the alpha position to the ring oxygen atom.
This subset is called "subset a.4".

(a.5.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydrofuranyl, except that within this subset for no embodiment $R^2$ is a $C_{1-6}$-alkyl-group-being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.1".

(a.5.2) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that within this subset for no embodiment $R^2$ is a $C_{2-6}$-alkenyl-group-being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.2".

(a.5.3) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrofuranyl, except that in this subset for no embodiment $R^2$ is a $C_{2-6}$-alkynyl-group-being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.5.3".

(a.6) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment $R^2$ is a $CH_3$-group being bound at the alpha position to the ring sulphur atom.
This subset is called "subset a.6".

(a.7) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment $R^2$ is a $R^{10}$-O- $C_{2-6}$-alkyl-group having a $CH_2$-group by which it is bound to a C-atom of the tetrahydrothiophenyl, which is at the alpha position to the ring sulphur atom.
This subset is called "subset a.7".

(a.8) In one individual and independent subset of embodiments according to the present invention the embodiments correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be tetrahydrothiophenyl, except that in this subset for no embodiment $R^2$ is a $C_{1-}$

$_6$-alkyl-group having a $CH_2$-group by which it is bound at the alpha position to the ring sulphur atom.
This subset is called "subset a.8".

(a.9) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment $R^2$ is a $CH_3$-group being bound to the alpha position of the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.9".

(a.10) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment $R^2$ is a $R^{10}$-O-$C_{2-6}$-alkyl-group having a $CH_2$-group by which it is bound to a C-atom of the tetrahydropyranyl or tetrahydrothiopyranyl which C-atom is at the alpha position to the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.10".

(a.11) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* is or may be tetrahydropyranyl or a tetrahydrothiopyranyl, except that in this subset for no embodiment $R^2$ is a $C_{1-6}$-alkyl-group having a $CH_2$-group by which it is bound at the alpha position to the ring oxygen atom or the sulphur atom respectively.
This subset is called "subset a.11".

(a.12) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which *Hc* may be an

oxetanyl group, except that in this subset for no embodiment ***Hc*** is an oxetanyl-group.
This subset is called "subset a.12".

(a.13) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other group, except that in this subset for no embodiment $R^2$ is a $CH_3$-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.13".

(a.14) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other group, except that in this subset for no embodiment $R^2$ is a $C_{1-6}$-alkyl-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.14".

(a.15) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 and matrix I in which ***Hc*** is or may be a cyclic hexanosyl sugar group in which for any of the hydroxy groups the hydrogen optionally may be replaced by any other group and / or ***Hc*** is or may be a cyclic mono-desoxy or di-desoxy hexanosyl sugar group in which for any of the remaining hydroxy groups the hydrogen optionally may be replaced by any other

group, except that in this subset for no embodiment $R^2$ is a $R^{10}$-O-$C_{2-6}$-alkyl-group being bound at the alpha position to the ring oxygen atom.
This subset is called "subset a.15".

(a.16) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of aspects 1 – 17 and each of the embodiments of matrix 0 or I in which $R^2$ is defined such that it may comprise a group selected from $(R^{10})_2N$- and $(R^{10})_2N$-$C_{1-3}$-alkyl-, except that in this subset for no embodiment $R^2$ shall be $(R^{10})_2N$- or $(R^{10})_2N$-$C_{1-3}$-alkyl-, while all remaining definitions of $R^2$ remain unchanged.
This subset is called "subset a.16".

**b.) subset of embodiments of matrix 0 or matrix I with respect to $R^{4/5}$**

(b.1) In one individual and independent subset of embodiments according to the present invention the embodiments thereof correspond with each of the embodiments of matrix 0 or matrix I in which $R^{4/5}$ is $R^{4/5.2}$, whereby for the embodiments of this subset

$R^{4/5.2-2}$ shall mean that $R^4$ and $R^5$ independently of one another are H- or fluorine.

This subset is called "subset b.1".

**c.) subset of embodiments of matrix I with respect to $R^{10}$**

(c.1) In one individual and independent subset of embodiments according to the present invention concerns each embodiment selected from the group of matrix I with $R^{10}$ being defined by $R^{10.2}$, $R^{10.3}$or $R^{10.4}$: for the embodiments of this subset each of the definitions $R^{10.2}$, $R^{10.3}$and $R^{10.4}$ is extended so that $R^{10}$ also may be H, in case this $R^{10}$ is bound to a nitrogen atom.
This subset is called "subset c.1".

It will be evident that the subsets as defined under a.) and b.) within this section "Additional embodiments according to the invention / subset of aspects 1 – 17 and

the embodiments of matrix 0 or matrix I" correspond with embodiments of aspects 1 – 17 and matrix 0, matrix I respectively, whereby the scope of specific definitions is changed. In case these changes are limitations the new definitions can be considered to include provisos. Therefore these embodiments are considered to be only "subsets" of aspects 1 – 17 and the embodiments of matrix 0, matrix I respectively.

Each embodiment of general formula I defined by aspects 1 – 18 and any of the elements of matrix 0, matrix I, or each embodiment defined by the above subsets a.), b.) or c.) is considered an independent and separable aspect of the invention, i.e. an individual aspect of the invention.

## USED TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by a person skilled in the art in light of the disclosure and the context. Examples include that specific substituents or atoms are presented with their 1 or 2 letter code, like H for hydrogen, N for nitrogen, C for carbon, O for oxygen, S for sulphur and the like. Optionally but not mandatorily the letter is followed by a hyphen to indicate a bond. As used in the specification, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often specified preceding the group, for example, $C_{1-6}$-alkyl means an alkyl group or alkyl radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "thioalkyl" means a monovalent radical of the formula HS-alkyl-. If the term of a substituent starts or ends with a minus sign or hyphen, i.e. -. This sign emphasises the attachment point like in the aforementioned example HS-alkyl-, where the "alkyl" is linked to the group of which the HS-alkyl- is a substituent. Unless otherwise specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

In general, all "**tautomeric forms and isomeric forms and mixtures**", whether individual geometric isomers or optical isomers or racemic or non-racemic mixtures of isomers, of a chemical structure or compound are intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure.

The term "**substituted**" as used herein explicitly or implicitly, means that any one or more hydrogen(s) on the designated atom is replaced with a member of the indicated group of substituents, provided that the designated atom's normal valence is not exceeded. In case a substituent is bound via a double bond, e.g. an oxo substituent, such substituent replaces two hydrogen atoms on the designated atom. The substitution shall result in a stable compound. "Stable" in this context preferably means a compound that from a pharmaceutical point of view is chemically and physically sufficiently stable in order to be used as an active pharmaceutical ingredient of a pharmaceutical composition.
If a substituent is not defined, it shall be hydrogen.

By the term "**optionally substituted**" is meant that either the corresponding group is substituted or it is not. Accordingly, in each occasion where this term is used, the non-substituted variation is a more pronounced aspect of the invention, i.e. preferably there are no such optional substituents.

The phrase "**pharmaceutically acceptable**" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "**pharmaceutically acceptable salt(s)**" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the

quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, and the like; and the salts prepared from organic acids such as acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isothionic acid, and the like. As the compounds of the present invention may have both, acid as well as basic groups, those compounds may therefore be present as internal salts too.

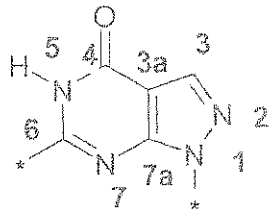
The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

"Prodrugs" are considered compounds that release an active parent drug of the present invention in vivo when such prodrug is administered to a mammalian subject. Prodrugs according to the present invention are prepared by modifying functional groups present in the compound in such a way that these modifications are retransformed to the original functional groups under physiological conditions. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bound to any group that, when the prodrug of the present invention is administered to a mammalian subject, is retransformed to free said hydroxyl, amino, or sulfhydryl group. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

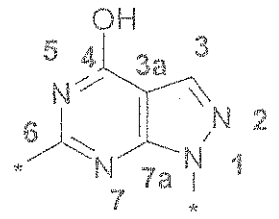
"**Metabolites**" are considered as derivatives of the compounds according to the present invention that are formed in vivo. Active metabolites are such metabolites that cause a pharmacological effect. It will be appreciated that metabolites of the compounds according to the present inventions are subject to the present invention as well, in particular active metabolites.

Some of the compounds may form "**solvates**". For the purposes of the invention the term "solvates" refers to those forms of the compounds which form, in the solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water. According to the present invention, the term preferably is used for solid solvates, such as amorphous or more preferably crystalline solvates.

"**Scaffold**": The scaffold of the compounds according to the present invention is represented by the following core structure, the numeration of which is indicated in bold:

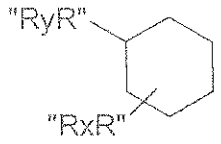



It will be evident for the skilled person in the art, that this scaffold can be described by its tautomeric "enol" form



In the context of the present invention both structural representations of the scaffold shall be considered the subject of the present invention, even if only one of the two representatives is presented. It is believed that for the majority of compounds under ambient conditions and therewith under conditions which are the relevant conditions for a pharmaceutical composition comprising said compounds, the equilibrium of the tautomeric forms lies on the side of the pyrazolopyrimdin-4-one representation. Therefore, all embodiments are presented as pyrazolopyrimdin-4-one-derivatives or more precisely as pyrazolo[3,4-d]pyrimidin-4-one derivatives.

"**Bonds**": If within a chemical formula of a ring system or a defined group a substituent is directly linked to an atom or a group like "RyR" in below formula this shall mean that the substituent is only attached to the corresponding atom. If however from another substituent like "RxR" a bond is not specifically linked to an atom of the ring system but drawn towards the centre of the ring or group this means that this substituent "RxR" may be linked to any meaningful atom of the ring system / group unless stated otherwise.




The bond symbol "-" (= minus sign) or the symbol "- *" (= minus sign followed by an asterisk sign) stands for the bond through which a substituent is bound to the corresponding remaining part of the molecule / scaffold. In cases in that minus sign does not seem to be sufficiently clear, an asterisk is added to the bond symbol "-" in order to determine the point of attachment of said bond with the corresponding main part of the molecule / scaffold.

In general, the bond to one of the herein defined heterocycloalkyl, heterocyclyl or heteroaryl groups may be effected via a C atom or optionally an N atom.

The term "**aryl**" used in this application denotes a phenyl, biphenyl, indanyl, indenyl, 1,2,3,4-tetrahydronaphthyl or naphthyl group, preferably it denotes a phenyl or

naphtyl group, more preferably a phenyl group. This definition applies for the use of "**aryl**" in any context within the present description in the absence of a further definition.

The term "**$C_{1-n}$-alkyl**" denotes a saturated, branched or unbranched hydrocarbon group with 1 to n C atoms, wherein n is a figure selected from the group of 2, 3, 4, 5, 6, 7, 8, 9, or 10, preferably from the group of 2, 3, 4, 5, or 6, more preferably from the group of 2, 3, or 4. Examples of such groups include methyl, ethyl, *n*-propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl etc. As will be evident from the context, such **$C_{1-n}$-alkyl** group optionally can be substituted.

This definition applies for the use of "**alkyl**" in any reasonable context within the present description in the absence of a further definition.

In cases in which the term "**$C_{1-n}$-alkyl**" is used in the middle of two other groups / substituents, like for example in "**$C_{1-n}$-cylcoalkyl-$C_{1-n}$-alkyl-O-**", this means that the "$C_{1-n}$-alkyl"-moiety bridges said two other groups. In the present example it bridges the $C_{1-n}$-cylcoalkyl with the oxygen like in "cyclopropyl-methyl-oxy-". It will be evident, that in such cases "$C_{1-n}$-alkyl" has the meaning of a "$C_{1-n}$-alkylene" spacer like methylene, ethylene etc. The groups that are bridged by "$C_{1-n}$-alkyl" may be bound to "$C_{1-n}$-alkyl" at any position thereof. Preferably the right hand group is located at the distal right hand end of the alkyl group and left hand group at the distal left hand side of the alkyl group. The same applies for other substituents.

The term "**$C_{2-n}$-alkenyl**" denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C=C group (i.e. carbon – carbon double bond), wherein n preferably has a value selected from the group of 3, 4, 5, 6, 7, or 8, more preferably 3, 4, 5, or 6, more preferably 3 or 4. Examples of such groups include ethenyl, 1-propenyl, 2-propenyl, *iso*-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl etc. As will be evident from the context, such **$C_{2-n}$-alkenyl** group optionally can be substituted.

This definition applies for the use of "**alkenyl**" in any reasonable context within the present description in the absence of a further definition if no other definition.
In cases in which the term "**$C_{2-n}$-alkenyl**" is used in the middle of two other groups / substituents, the analogue definition as for $C_{1-n}$-alkyl applies.

The term "**$C_{2-n}$-alkynyl**" denotes a branched or unbranched hydrocarbon group with 2 to n C atoms and at least one C≡C group (i.e. a carbon-carbon triple bond), wherein n preferably has a value selected from the group of 3, 4, 5, 6, 7, or 8, more preferably 3, 4, 5, or 6, more preferably 3 or 4. Examples of such groups include ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl, 5-hexynyl etc. As will be evident from the context, such **$C_{2-n}$-alkynyl** group optionally can be substituted.
This definition applies for the use "**alkynyl**" in any reasonable context within the present description in the absence of a further definition.
In cases in which the term "**$C_{2-n}$-alkynyl**" is used in the middle of two other groups / substituents, the analogue definition as for $C_{1-n}$-alkyl applies.

The term "**$C_{3-n}$-cycloalkyl**" denotes a saturated monocyclic group with 3 to n C ring atoms. n preferably has a value of 4 to 8 (= 4, 5, 6, 7, or 8), more preferably 4 to 7, more preferably such $C_{3-n}$-cycloalkyl is 5 or 6 membered. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl etc.. This definition applies for "**cycloalkyl**" in any reasonable context within the present description in the absence of a further definition.

The term "**halogen**" denotes an atom selected from among F, Cl, Br, and I.

The term "**heteroaryl**" used in this application denotes a heterocyclic, mono- or bicyclic aromatic ring system which includes within the ring system itself in addition to at least one C atom one or more heteroatom(s) independently selected from N, O, and/or S. A monocyclic ring system preferably consists of 5 to 6 ring members, a bicyclic ring system preferably consists of 8 to 10 ring members. Preferred are

heteroaryls with up to 3 heteroatoms, more preferred up to 2 heteroatoms, more preferred with 1 heteroatom. Preferred heteroatom is N. Examples of such moieties are benzimidazolyl, benzisoxazolyl, benzo[1,4]-oxazinyl, benzoxazol-2-onyl, benzofuranyl, benzoisothiazolyl, 1,3-benzodioxolyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzoxadiazolyl, benzoxazolyl, chromanyl, chromenyl, chromonyl, cinnolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, 2,3-dihydrobenzofuranyl, 3,4-dihydrobenzo[1,4]oxazinyl, 2,3-dihydroindolyl, 1,3-dihydroisobenzofuranyl, 2,3-dihydroisoindolyl, 6,7-dihydropyrrolizinyl, dihydroquinolin-2-onyl, dihydroquinolin-4-onyl, furanyl, imidazo[1,2-*a*]pyrazinyl, imidazo[1,2-*a*]pyridyl, imidazolyl, imidazopyridyl, imidazo[4,5-d]thiazolyl, indazolyl, indolizinyl, indolyl, isobenzofuranyl, isobenzothienyl, isochromanyl, isochromenyl, isoindoyl, isoquinolin-2-onyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, 1,2,4-oxadiazoyl, 1,3,4-oxadiazoyl, 1,2,5-oxadiazoyl, oxazolopyridyl, oxazolyl, 2-oxo-2,3-dihydrobenzimidazolyl, 2-oxo-2,3-dihydroindolyl, 1-oxoindanyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolo[1,5-*a*]pyridyl, pyrazolo[1,5-*a*]pyrimidinyl, pyrazolyl, pyridazinyl, pyridopyrimidinyl, pyridyl (pyridinyl), pyridyl-*N*-oxide, pyrimidinyl, pyrimidopyrimidinyl, pyrrolopyridyl, pyrrolopyrimidinyl, pyrrolyl, quinazolinyl, quinolin-4-onyl, quinolinyl, quinoxalinyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, tetrazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, thiazolyl, thieno[2,3-*d*]imidazolyl, thieno[3,2-*b*]pyrrolyl, thieno[3,2-*b*]thiophenyl, thienyl, triazinyl, or triazolyl.

Preferred heteroaryl groups are furanyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, thienyl, and thiazolyl.

More preferred heteroaryl groups are oxadiazolyl, triazolyl, pyrazolyl, furanyl, and pyridyl, more preferred is pyrazolyl and pyridyl.

The definition pyrazole includes the isomers 1H-, 3H- and 4H-pyrazole. Preferably pyrazolyl denotes 1H-pyrazolyl.

The definition imidazole includes the isomers 1H-, 2H- and 4H-imidazole. A preferred definition of imidazolyl is 1H-imidazolyl.

The definition triazole includes the isomers 1H-, 3H- and 4H-[1,2,4]-triazole as well as 1H-, 2H- and 4H-[1,2,3]-triazole. The definition triazolyl therefore includes 1H-[1,2,4]-triazol-1-, -3- and -5-yl, 3H-[1,2,4]-triazol-3- and -5-yl, 4H-[1,2,4]-triazol-3-, -4- and -5-yl, 1H-[1,2,3]-triazol-1-, -4- and -5-yl, 2H-[1,2,3]-triazol-2-, -4- and -5-yl as well as 4H-[1,2,3]-triazol-4- and -5-yl.

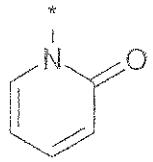
The term tetrazole includes the isomers 1H-, 2H- and 5H-tetrazole. The definition tetrazolyl therefore includes 1H-tetrazol-1- and -5-yl, 2H-tetrazol-2- and -5-yl and 5H-tetrazol-5-yl.

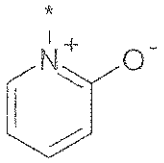
The definition indole includes the isomers 1H- and 3H-indole. The term indolyl preferably denotes 1H-indol-1-yl.

The term isoindole includes the isomers 1H- and 2H-isoindole.

This definition applies for "**heteroaryl**" in any reasonable context within the present description in the absence of a further definition.

The term "**N-linked-pyridine-2-one**" used in this application denotes:




and its tautomeric form 

.

The term "**heterocycloalkyl**" within the context of the present invention denotes a saturated 3 to 8 membered, preferably 5-, 6- or 7-membered ring system or a 5-12 membered bicyclic ring system, which include 1, 2, 3 or 4 heteroatoms, selected from N, O, and/or S. Preferred are 1, 2, or 3 heteroatoms.
The preferred number of carbon atoms is 3 to 7 with 1, 2, 3 or 4 heteroatoms selected from N, O, and/or S. Such heterocycloalkyl groups are addressed as $C_{3-7}$-heterocycloalkyl.
Preferred are saturated heterocycloalkyl rings with 5, 6, or 7 ring atoms, of which 1 or 2 are heteroatoms and the remaining are C-atoms.

Wherever $C_{3-7}$-heterocycloalkyl- substituents are mentioned, the preferred embodiments thereof are 5-, 6-,- or 7-membered cycles, more preferably monocycles. They include 1, 2, 3, or 4 heteroatoms, selected from N, O, and/or S, whereby 1 or 2 such heteroatoms are preferred, more preferably 1 such heteroatom.

Preferred example for heterocycloalkyl include morpholinyl, piperidinyl, piperazinyl, thiomorpholinyl, oxathianyl, dithianyl, dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dioxolanyl, oxathiolanyl, imidazolidinyl, tetrahydropyranyl, pyrrolinyl, tetrahydrothienyl, oxazolidinyl, homopiperazinyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, azetidinyl, 1,3-diazacyclohexanyl or pyrazolidinyl group.

This definition applies for "**heterocycloalkyl**" in any reasonable context within the present description in the absence of a further specific definition.

The term "**heterocyclyl**" specifically is used to define the group ***Hc*** in formula I and formulae which are derived thereof and therefore will be independently used from the definition of "heterocycloalkyl". However, the definitions for "heterocycloalkyl" shall be comprised within the definition for "heterocyclyl". ***Hc*** is a group which is or at least comprises a non-aromatic heterocycloalkyl group which is bound to the scaffold.

Within the context of the present invention and as used herein, specifically within the context of ***Hc***, "**heterocyclyl**" means a non-aromatic monocyclic, bicyclic or tricyclic ring system, whereby the ring members are carbon atoms and at least one, preferably one to three heteroatom(s) selected from the group of nitrogen, oxygen, or sulphur, the sulphur being part the group $-S(O)_r$ - with r being 0, 1 or 2. Such ring system may further be bridged. Such systems also will be called heteromonocyclic, heterobicyclic, or heterotricyclic ring system within the present context.

This heterocyclyl group may be saturated or partly unsaturated, whereby in systems with more than one ring system, at least one of them is not aromatic. This at least one non aromatic ring system comprises said at least one heteroatom.

This heterocyclyl group may be bound to the scaffold in more than one way. If no particular bonding arrangement is specified, then all possible arrangements are

intended. For example, the term "tetrahydropyranyl" includes 2-, 3-, or 4-tetrahydropyranyl and the like. In cases with more than one ring system, the bonding to the scaffold is via at least one ring atom of the non aromatic ring system comprising at least one heteroatom. Preferably this heterocyclyl-group is bound to the scaffold via a nitrogen atom or one of the saturated carbon atoms in said ring system. More preferably it is attached to the scaffold via a carbon atom of the non-aromatic heterocyclic ring system.

Such heterocyclyl group may be fused, respectively annelated, with a cycloalkyl, another heterocyclic group, an aromatic ring system, such as phenyl or may be part of a spirocyclic system. In a fused or annelated system, the two ring systems share a bond between two adjacent ring atoms. In the spiro variation, the two ring systems have one ring atom in common.

The monoheterocyclic ring systems within this definition are non-aromatic monocyclic ring systems, in which at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2 comprises preferably 4 to 8 ring atoms. Within this context preferred are 5-, 6- or 7-membered, saturated or at least partly unsaturated heterocyclic rings

The heterobicyclic ring systems within this definition are bicyclic ring systems with at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2; the ring system has at least one non-aromatic ring, which comprises said at least one heteroatom, and the bicyclic ring system comprises preferably 7 to 12 ring atoms. Within this context preferred are 8-, 9- or 10-membered, saturated or at least partly unsaturated heterocyclic rings.

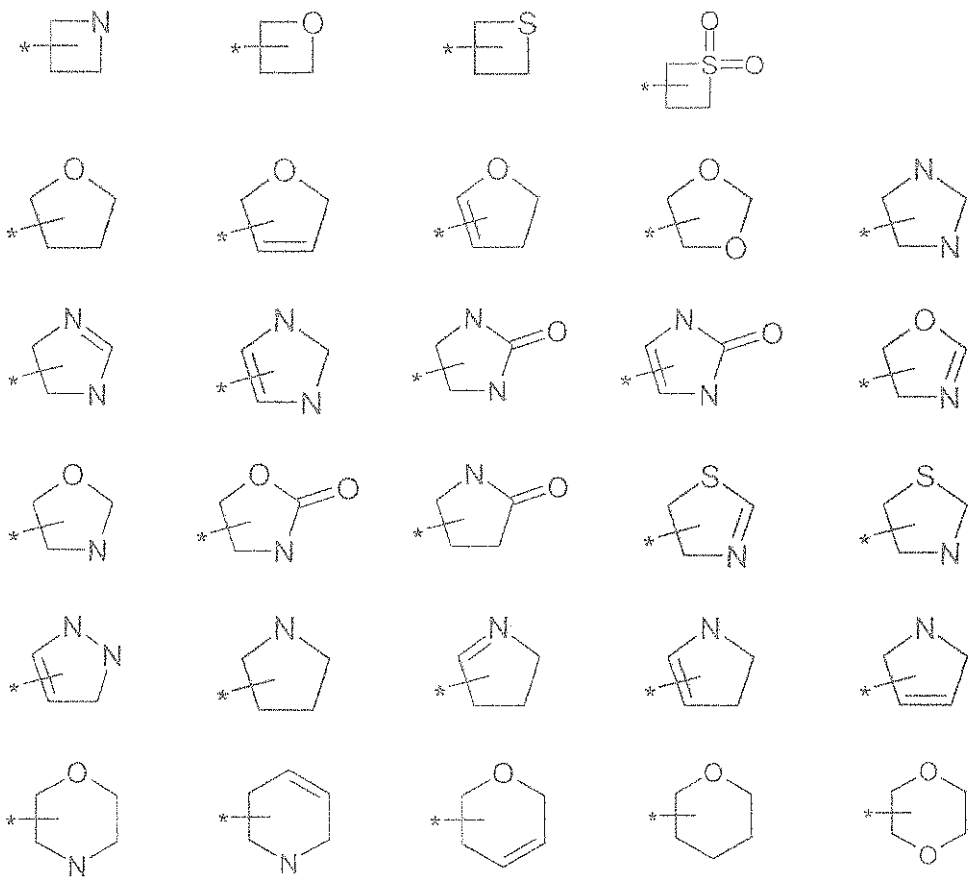
The heterotricyclic ring systems within this definition are tricyclic systems of annelated monocycles, in which at least one, preferably one to three, of the carbon atoms have been replaced with a heteroatom such as nitrogen, oxygen, or sulphur, the sulphur being part the group – $S(O)_r$ - with r being 0, 1 or 2; the ring system has

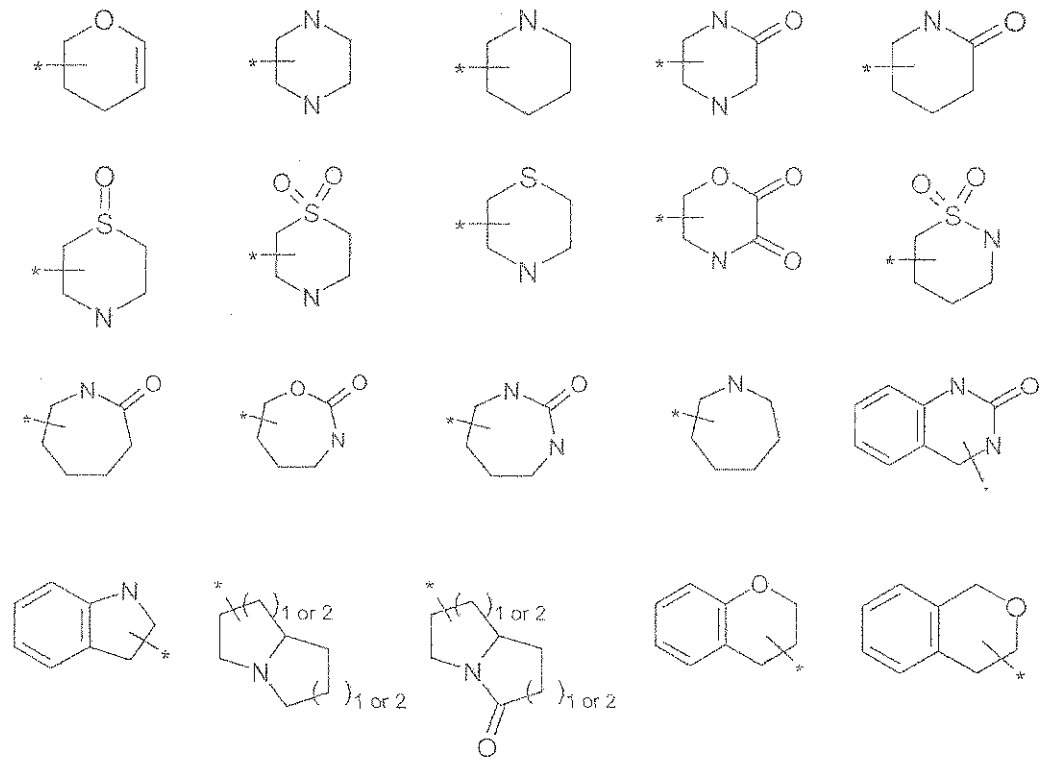
at least one non-aromatic ring, which comprises said at least one heteroatom, and the tricyclic ring system comprises preferably 7 to 14 ring atoms.

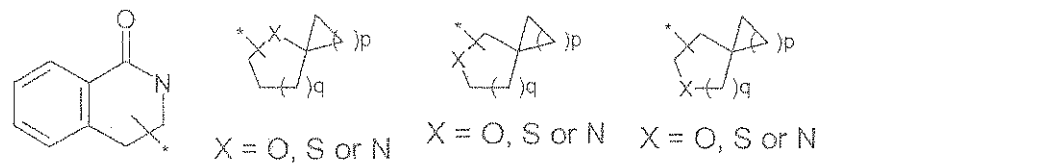
By the term spirocyclic system as mentioned within this definition, are meant preferably 5-10 membered, spirocyclic rings which may optionally contain 1, 2 or 3 heteroatoms, selected from among oxygen, sulphur, and nitrogen. Such systems optionally may be annelated with an aromatic ring system such as phenyl.

The order of preference of heterocyclic ring systems is: monocyclic ring systems are more preferred than bicyclic ring systems, which are more preferred than tricyclic ones.

Examples for such heterocyclic *Hc* groups according to the present invention are the following groups:





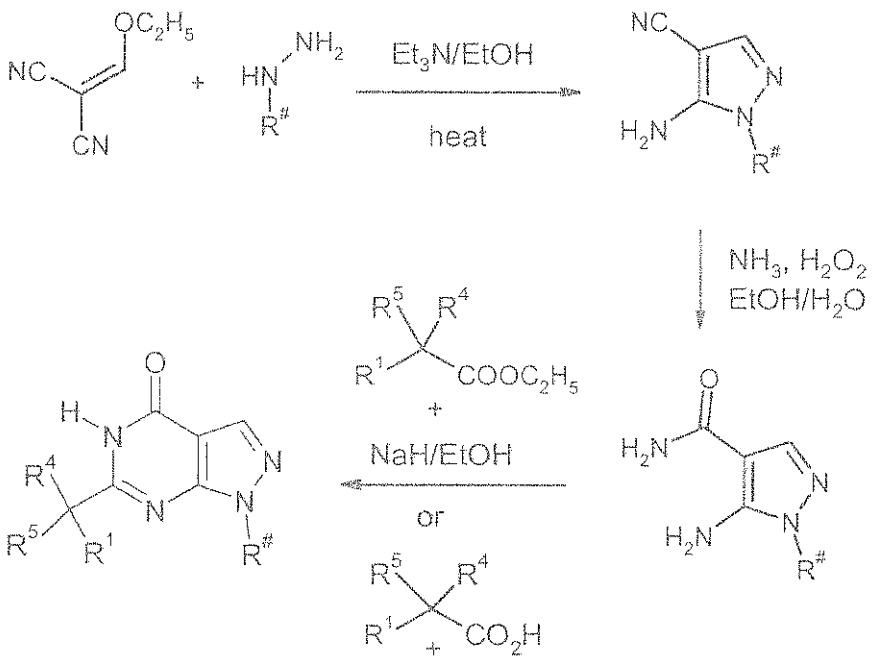

, wherein → stands for the bond by which said group is bound to the nitrogen atom of the scaffold, that is numbered as 1.

The above definition applies for "**heterocyclyl**" in any reasonable context within the present description in the absence of a further definition.

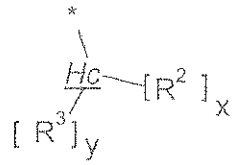
The term "oxo" denotes an oxygen atom as substituent that is bonded by a double bond, preferably it is bonded to a C-atom. In case oxo is used as a substituent, the oxo replaces two hydrogen atoms of the corresponding atom of the unsubstituted compound.

The following schemes shall illustrate a process to manufacture the compounds of the present invention by way of example:

Scheme 1




with

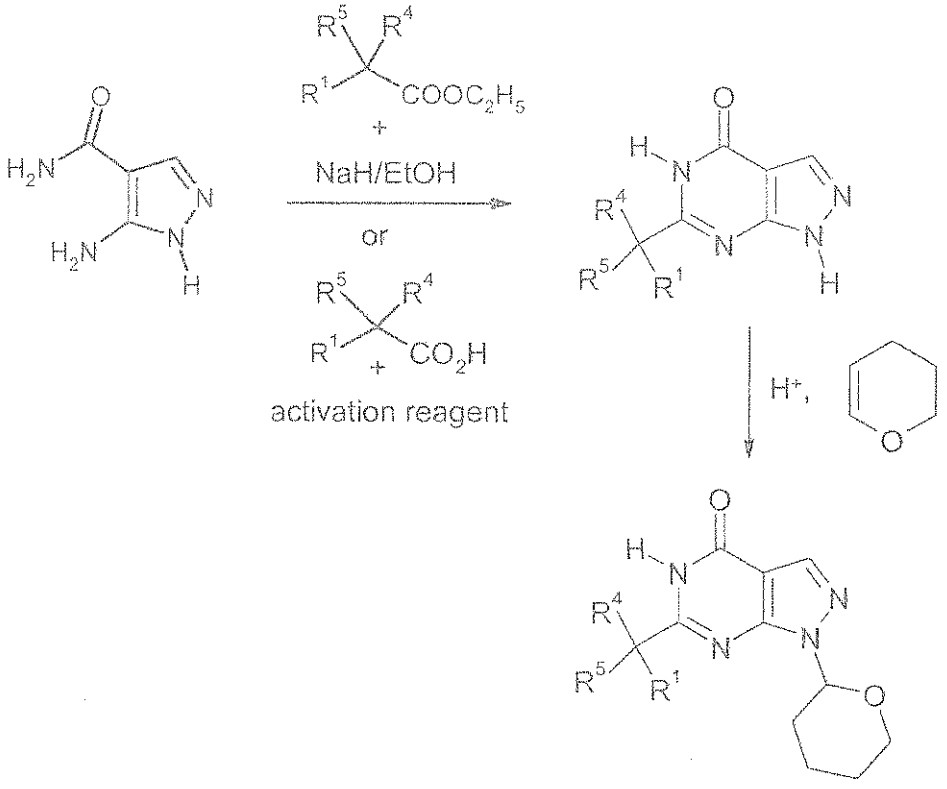
$R^{\#} =$ 

Scheme 1: In a first step 2-ethoxymethylene-malononitrile is condensed with mono-substituted hydrazines by heating in an appropriate solvent like ethanol in the presence of a base (e.g. triethylamine) to form 5-amino-1H-pyrazole-4-carbonitriles.

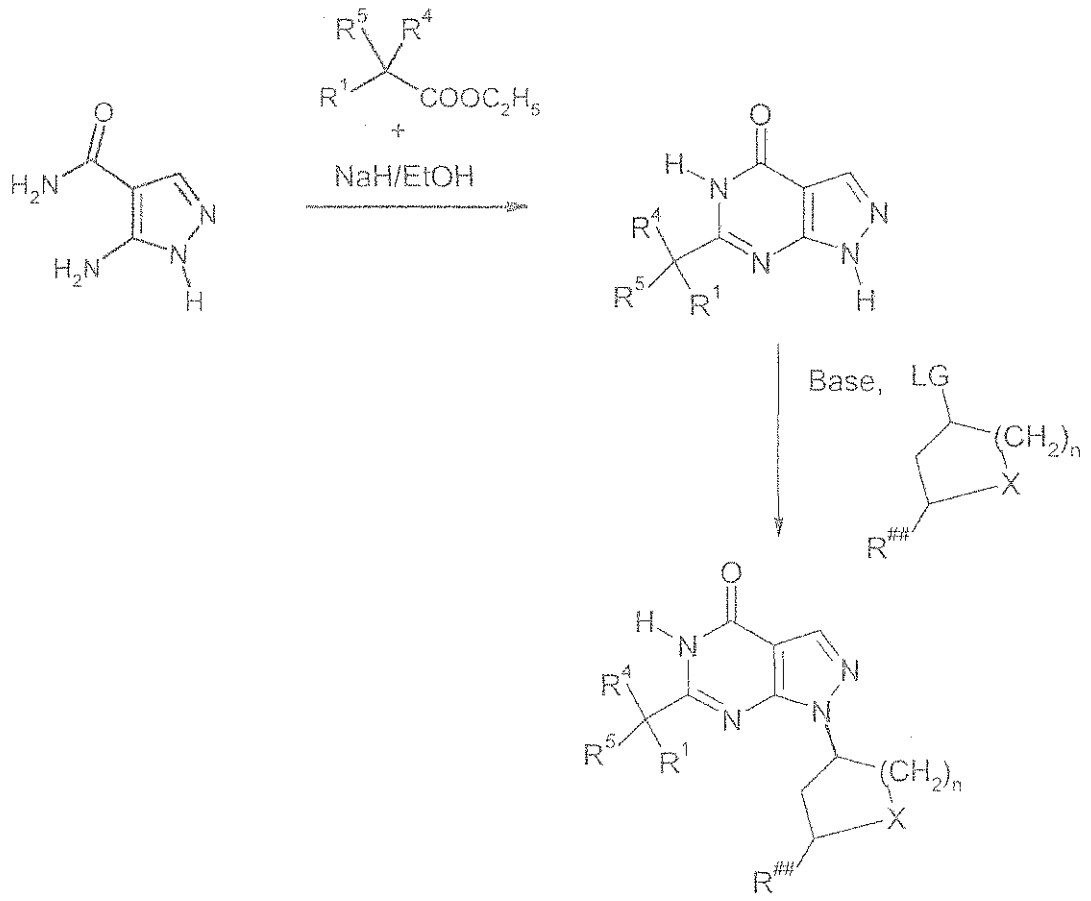
These compounds are converted in a second step to the corresponding amides, e.g. by treatment of an ethanolic solution with ammonia (25 % in water) and hydrogen peroxide (35 % in water). In a third step, heating with carboxylic esters under basic conditions (e.g sodium hydride in ethanol) or carboxylic acids with an activation reagent (e.g. polyphosporic acid) leads to pyrazolo[3,4-d]pyrimidin-4-ones as final products [cf., for example, A. Miyashita *et al.*, *Heterocycles* **1990**, *31*, 1309ff].

Schemes 2 and 3 illustrate alternative methods to prepare the final compounds: in these exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with an appropriate ester derivative followed in a second step by alkylation with suitable electrophiles.

Scheme 2



Scheme 3




X = O, NH, $NR^2$, S, SO or $SO_2$

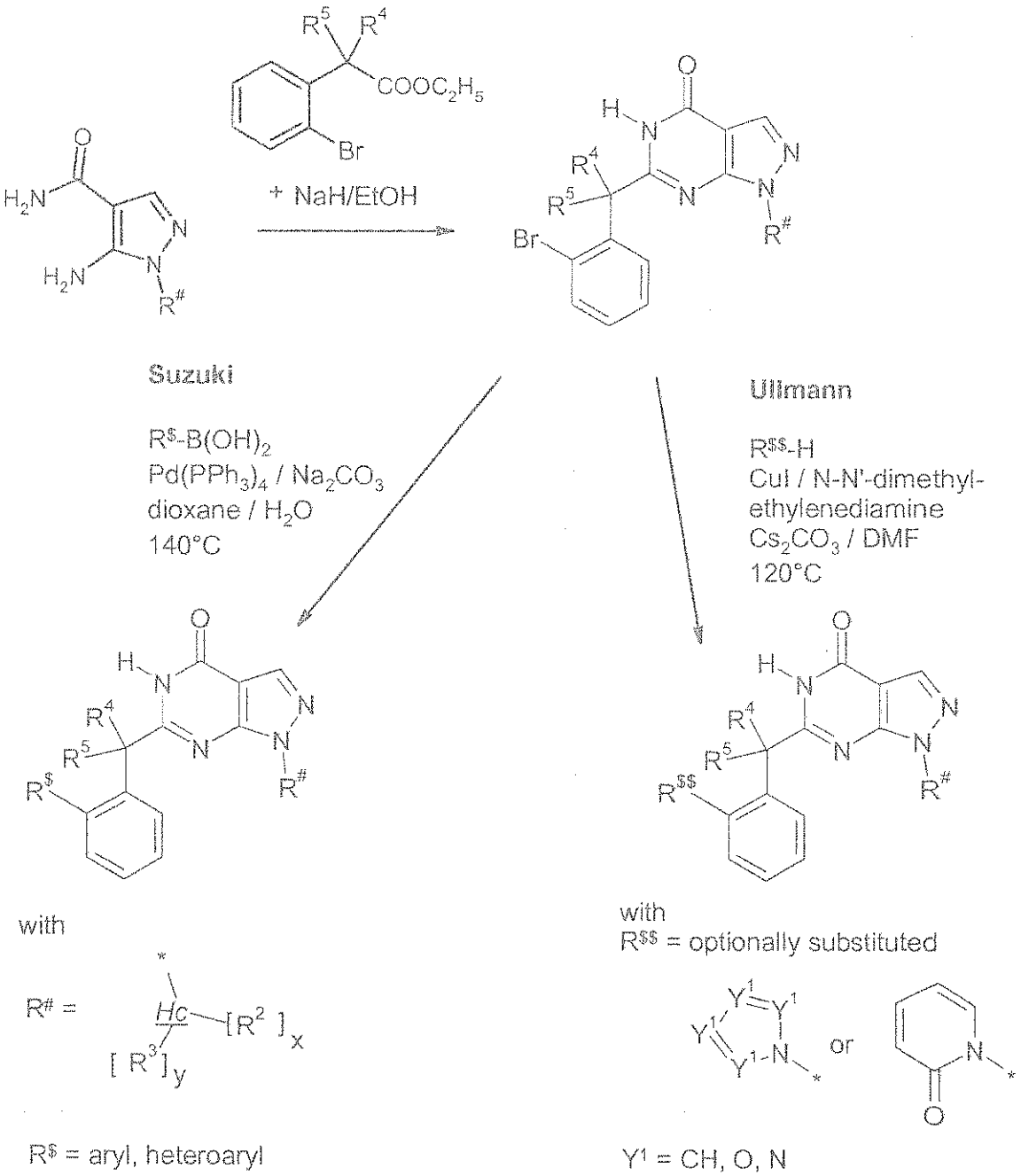
$R^{\#\#}$ = $R^2$ or $R^3$

LG = Br-, Cl-, I-, $CH_3$-$SO_2$-O-, p-toluenesulphonyl-

n = 1,2

Scheme 4 illustrates alternative methods to prepare the final compounds: in the exemplified manufacturing methods 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-bromo-phenyl)-acetic acid ester derivatives followed in a second step by substitution of the bromine atom by an aromatic or heteroaromatic residue e.g. using Suzuki or Ullmann type reaction conditions.

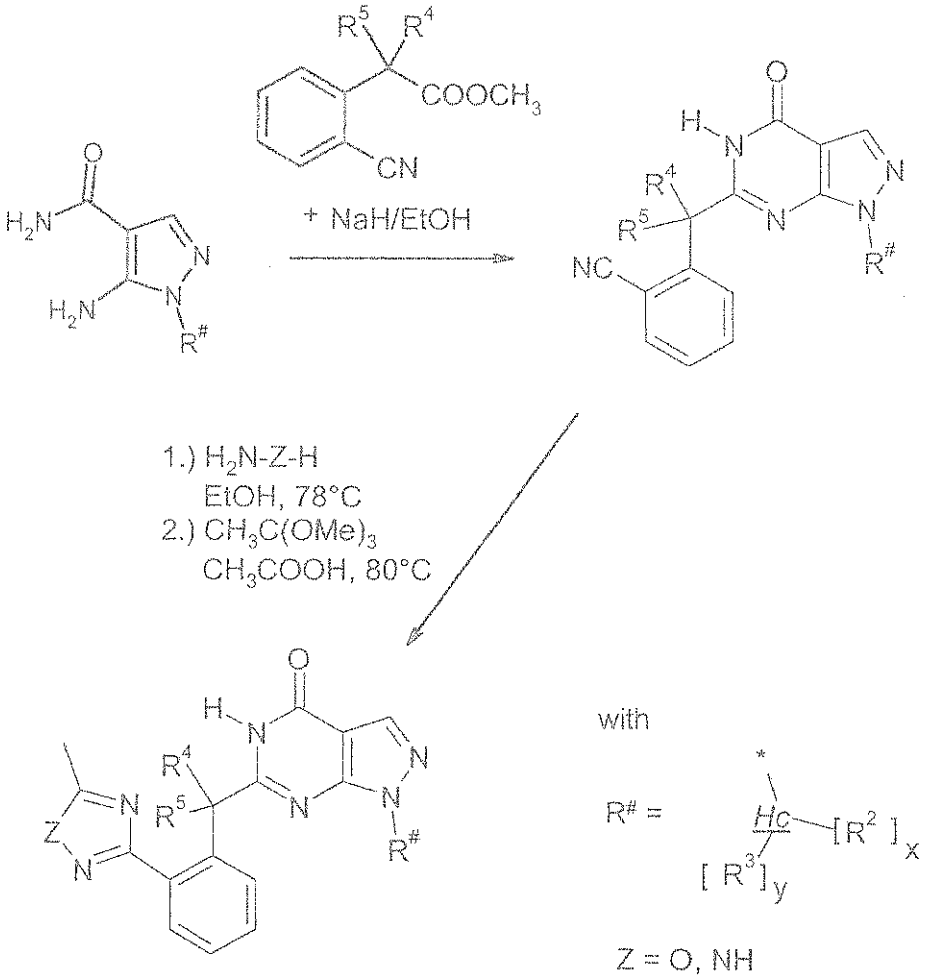
Scheme 4




Scheme 5 illustrates an alternative method to prepare the final compounds: in the exemplified manufacturing method 5-amino-1H-pyrazole-4-carboxylic acid amides are condensed in a first step with (2-cyano-phenyl)-acetic acid ester derivatives followed in

a second step by transformation of the nitrile group into a 5-membered heteroaromatic group.

Scheme 5

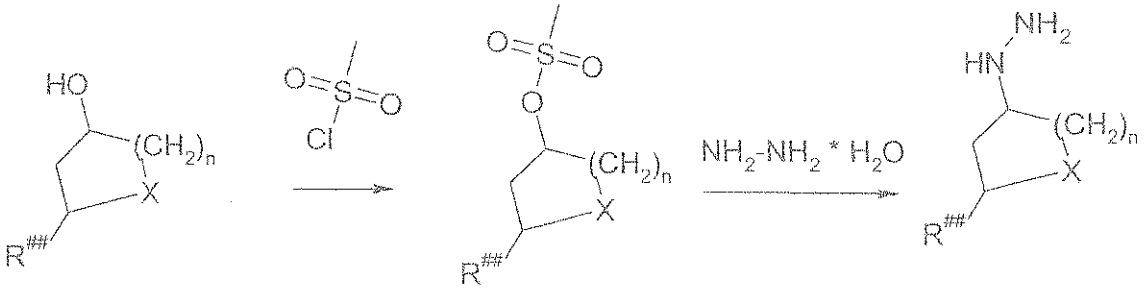



Further alternative processes for preparing pyrazolo[3,4-d]pyrimidin-4-ones are known in the art and can likewise be employed for synthesizing the compounds of the invention (see, for example: P. Schmidt *et al.*, *Helvetica Chimica Acta* **1962**, *189*, 1620ff.).

The mono-substituted hydrazine derivatives, that are used in step 1 of scheme 1 can be prepared either by nucleophilic displacement on the corresponding mesylate derivative (scheme 6) or by reduction of the hydrazone intermediate as depicted in scheme 7 [cf.,

for example, J.W. Timberlake *et al.*, "*Chemistry of Hydrazo-,Azo-, and Azoxy Groups*"; *Patai,S.,Ed.;* 1975, *Chapter 4*; S. C. Hung *et al.*, *Journal of organic Chemistry 1981*, 46, 5413-5414].

**Scheme 6**

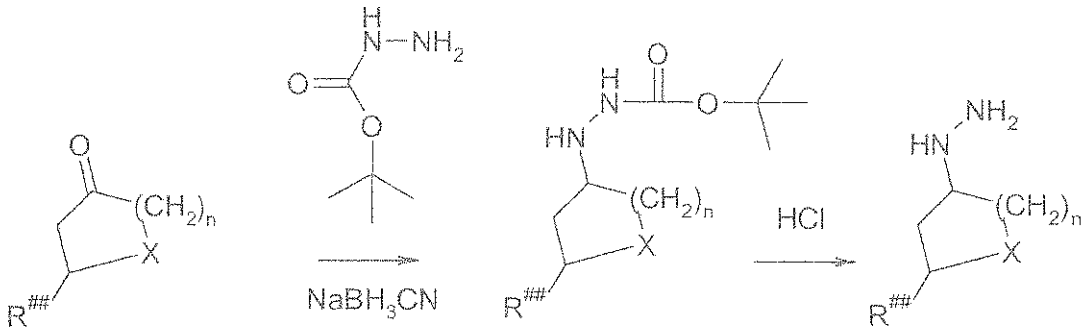



X = O, NH, $NR^2$, S, SO or $SO_2$

$R^{##}$ = $R^2$ or $R^3$

n = 1,2

**Scheme 7**




X = O, NH, $NR^2$, S, SO or $SO_2$

$R^{##}$ = $R^2$ or $R^3$

n = 1,2

Further information also can be found in WO04099210 (in particular page 9, last paragraph to page 14, line 8, incorporated by reference).

The compounds of the invention show a valuable range of pharmacological effects which could not have been predicted. They are characterised in particular by inhibition of PDE9A.

Preferably the compounds according to the present invention show a high selectivity profile in view of inhibiting or modulating specific members within the PDE9 family or other PDE families, with a clear preference (selectivity) towards PDE9A inhibition.

The compounds of the present invention are supposed to show a favourable safety profile.

## METHOD OF TREAMENT

The present invention refers to compounds, which are considered effective and selective inhibitors of phosphodiesterase 9A and can be used for the development of medicaments. Such medicaments shall preferably be used for the treatment of diseases in which the inhibition of PDE9A can evolve a therapeutic, prophylactic or disease modifying effect. Preferably the medicaments shall be used to improve perception, concentration, cognition, learning or memory, like those occurring in particular in situations/diseases/syndromes such as mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

Another aspect of the present invention concerns the treatment of a disease which is accessible by PDE9A modulation, in particular sleep disorders like insomnia or narcolepsy, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, including

type 1 or type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Thus the medical aspect of the present invention can be summarised in that it is considered that a compound according to any of the genius embodiments of the invention as outlined herein, in particular the one according to formula I as defined by each of the aspects 1 – 17, each of the elements/embodiments of matrix 0 or matrix I or a compound selected from the group of the exemplified final compounds (see aspect 18 or chapter exemplary embodiments) is used as a medicament.

Such a medicament preferably is for the treatment of a CNS disease.

In an alternative use, the medicament is for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment of a disease that is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

In an alternative use, the medicament is for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

In an alternative use, the medicament is for the treatment of Alzheimer's disease.

In an alternative use, the medicament is for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetis mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

## PHARMACEUTICAL COMPOSITIONS

Medicaments for administration comprise a compound according to the present invention in a therapeutically effective amount. By "therapeutically effective amount" it is meant that if the medicament is applied via the appropriate regimen adapted to the patient's condition, the amount of said compound of formula (I) will be sufficient to effectively treat, to prevent or to decelerate the progression of the corresponding disease, or otherwise to ameliorate the estate of a patient suffering from such a disease. It may be the case that the "therapeutically effective amount" in a mono-therapy will differ from the "therapeutically effective amount" in a combination therapy with another medicament.

The dose range of the compounds of general formula (I) applicable per day is usually from 0.1 to 5000 mg, preferably 0.1 to 1000 mg, preferably from 2 to 500 mg, more preferably from 5 to 250 mg, most preferably from 10 to 100 mg. A dosage unit (e.g. a tablet) preferably contains between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age, weight, gender or other condition of the patient, route of administration, severity of disease, and the like.

The compounds according to the invention may be administered by oral, parenteral (intravenous, intramuscular etc.), intranasal, sublingual, inhalative, intrathecal, topical or rectal route. Suitable preparations for administering the compounds according to the present invention include for example patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions,

suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.- %, preferably 0.1 to 50 wt.- % of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

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

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylenediaminetetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as diluent, for example, organic solvents may optionally be used as solubilisers or dissolving aids, and the solutions may be transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

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

For oral use the tablets may obviously contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin and the like. Lubricants such as magnesium stearate, sodium laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated. When administered by inhalation the compounds of formula (I) are characterised by a high potency even at doses in the microgram range. The compounds of formula (I) may also be used effectively above the microgram range. The dosage may then be in the gram range, for example.

COMBINATIONS WITH OTHER ACTIVE SUBSTANCES

In another aspect the present invention relates to the above-mentioned pharmaceutical formulations as such which are characterised in that they contain a compound according to the present invention.

A further aspect of the present invention refers to a combination of each of the compounds of the present invention, preferably at least one compound according to the present invention with another compound selected from the group of for example beta-secretase inhibitors; gamma-secretase inhibitors; gamma-secretase modulators; amyloid aggregation inhibitors such as e.g. alzhemed; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants, such as e.g. vitamin E , ginko biloba or ginkolide; anti-inflammatory substances, such as e.g. Cox inhibitors, NSAIDs additionally or exclusively having Aß lowering properties; HMG-CoA reductase inhibitors, such as statins; acetylcholine esterase inhibitors, such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines - monoamine receptor reuptake inhibitors; substances modulating the concentration or release of neurotransmitters; substances inducing the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocyclin or rifampicin; PDE1, PDE2, PDE4, PDE5 and / or PDE10 inhibitors, GABAA receptor inverse agonists; GABAA receptor antagonists; nicotinic receptor agonists or partial agonists; alpha4beta2 nicotinic receptor agonists or partial agonists; alpha7 nicotinic receptor agonists or partial agonists; histamine receptor H3 antagonists; 5-HT4 receptor agonists or partial agonists; 5-HT6 receptor antagonists; alpha2-adrenoreceptor antagonists, calcium antagonists; muscarinic receptor M1 agonists or positive modulators; muscarinic receptor M2 antagonists; muscarinic receptor M4 antagonists; metabotropic glutamate receptor 5 positive modulators; metabotropic glutamate receptor 2 antagonists, and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

This invention further relates to pharmaceutical compositions containing one or more, preferably one active substance, which is selected from the compounds according to

the invention and/or the corresponding salts, as well as one or more, preferably one active substance selected from among alzhemed, vitamin E, ginkolide, donepezil, rivastigmine, tacrine, galantamine, memantine, ibutamoren mesylate, capromorelin, minocyclin and/or rifampicin, optionally together with one or more inert carriers and/or diluents.

The compounds according to the invention may also be used in combination with immunotherapies such as e.g. active immunisation with Abeta or parts thereof or passive immunisation with humanised anti-Abeta antibodies or antibodyfragments or nanobodies for the treatment of the above-mentioned diseases and conditions.

The combinations according to the present invention may be provided simultaneously in one and the same dosage form, i.e. in form of a combination preparation, for example the two components may be incorporated in one tablet, e. g. in different layers of said tablet. The combination may be also provided separately, in form of a free combination, i.e the compounds of the present invention are provided in one dosage form and one or more of the above mentioned combination partners is provided in another dosage form. These two dosage forms may be equal dosage forms, for example a co-administration of two tablets, one containing a therapeutically effective amount of the compound of the present invention and one containing a therapeutically effective amount of the above mentioned combination partner. It is also possible to combine different administration forms, if desired. Any type of suitable administration forms may be provided.

The compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may be used simultaneously or at staggered times, but particularly close together in time. If administered simultaneously, the two active substances are given to the patient together; if administered at staggered times the two active substances are given to the patient successively within a period of less than or equal to 12, particularly less than or equal to 6 hours.

The dosage or administration forms are not limited, in the frame of the present invention any suitable dosage form may be used. Exemplarily the dosage forms may

be selected from solid preparations such as patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like.

The dosage forms are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of each active component being present. Depending from the administration route and dosage form the ingredients are selected accordingly.

The dosage for the above-mentioned combination partners is expediently 1/5 of the normally recommended lowest dose up to 1/1 of the normally recommended dose.

The dosage forms are administered to the patient for example 1, 2, 3, or 4 times daily depending on the nature of the formulation. In case of retarding or extended release formulations or other pharmaceutical formulations, the same may be applied differently (e.g. once weekly or monthly etc.). It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily.

## EXAMPLES

### PHARMACEUTICAL COMPOSITIONS

The following pharmaceutical formulations may illustrate the present invention without restricting its scope:

Some examples of formulations will now be described, wherein the term "active substance" denotes one or more compounds according to the invention including the salts thereof. In the case of one of the aforementioned combinations with one or more other active substances the term "active substance" also includes the additional active substances.

Example A

Tablets containing 100 mg of active substance

Composition:

1 tablet contains:

| | |
|---|---|
| active substance | 100.0 mg |
| lactose | 80.0 mg |
| corn starch | 34.0 mg |
| polyvinylpyrrolidone | 4.0 mg |
| magnesium stearate | 2.0 mg |
| | 220.0 mg |

Diameter: 10 mm, biplanar, facetted on both sides and notched on one side.

Example B

Tablets containing 150 mg of active substance

Composition:

1 tablet contains:

| | |
|---|---|
| active substance | 150.0 mg |
| powdered lactose | 89.0 mg |
| corn starch | 40.0 mg |
| colloidal silica | 10.0 mg |
| polyvinylpyrrolidone | 10.0 mg |
| magnesium stearate | 1.0 mg |
| | 300.0 mg |

Diameter: 10 mm, flat

Example C

Hard gelatine capsules containing 150 mg of active substance

1 capsule contains:

| | |
|---|---|
| active substance | 150.0 mg |
| corn starch (dried) | approx. 80.0 mg |
| lactose (powdered) | approx. 87.0 mg |
| magnesium stearate | 3.0 mg |
| | approx. 320.0 mg |

Capsule shell: size 1 hard gelatine capsule.

Example D

Suppositories containing 150 mg of active substance

1 suppository contains:

| | |
|---|---|
| active substance | 150.0 mg |
| polyethyleneglycol 1500 | 550.0 mg |
| polyethyleneglycol 6000 | 460.0 mg |
| polyoxyethylene sorbitan monostearate | 840.0 mg |
| | 2,000.0 mg |

Example E

Ampoules containing 10 mg active substance

Composition:

| | | |
|---|---|---|
| active substance | | 10.0 mg |
| 0.01 N hydrochloric acid | q.s. | |
| double-distilled water | ad | 2.0 mL |

Example F

Ampoules containing 50 mg of active substance

Composition:

| | | |
|---|---|---|
| active substance | | 50.0 mg |
| 0.01 N hydrochloric acid | q.s. | |
| double-distilled water | ad | 10.0 mL |

The preparation of any the above mentioned formulations can be done following standard procedures.

BIOLOGICAL ASSAY

The in vitro effect of the compounds of the invention can be shown with the following biological assays.

PDE9A2 assay protocol:

The PDE9A2 enzymatic activity assay was run as scintillation proximity assay (SPA), in general according to the protocol of the manufacturer (Amersham Biosciences, product number: TRKQ 7100).

As enzyme source, lysate (PBS with 1 % Triton X-100 supplemented with protease inhibitors, cell debris removed by centrifugation at 13.000 rpm for 30 min) of SF 9 cell expressing the human PDE9A2 was used. The total protein amount included in the assay varied upon infection and production efficacy of the SF9 cells and lay in the range of 0.1 – 100 ng.

In general, the assay conditions were as follows:

- total assay volume: 40 microliter
- protein amount: 0.1 – 50 ng
- substrate concentration (cGMP): 20 naomolar; ~1 mCi/l
- incubation time: 60 min at room temperature
- final DMSO concentration: 0.2 - 1 %

The assays were run in 384-well format. The test reagents as well as the enzyme and the substrate were diluted in assay buffer. The assay buffer contained 50 mM

Tris, 8.3 mM MgCl2, 1.7 mM EGTA, 0.1 % BSA, 0.05 % Tween 20; the pH of assay buffer was adjusted to 7.5. The reaction was stopped by applying a PDE9 specific inhibitor (e.g. compounds according to WO04099210) in excess.

Determination of % inhibition:

The activity of the positive control (minus the negative control = background) is set to 100 % and activity in the presence of test compound is expressed relative to these 100 %. Within this setting, an inhibition above 100 % might be possible due to the nature of the variation of the positive control within the assay, however, in this case the reported % inhibition had been adjusted to 100 %.

Determination of $IC_{50}$:

$IC_{50}$ can be calculated with GraphPadPrism or other suited software setting the positive control as 100 and the negative control as 0. For calculation of $IC_{50}$ dilutions of the test compounds (substrates) are to be selected and tested following the aforementioned protocol.

Data

In the following, % inhibition data will illustrate that the compounds according to the present invention are suited to inhibit PDE9 and thus provide useful pharmacological properties. The examples are not meant to be limiting. The table also provides $IC_{50}$ values. The values are presented as being within a nanomolar range (nM), i.e. within the range of either 1 nanomolar to 100 nanomolar or within the range of 101 nanomolar to 1200 nanomolar. The specific $IC_{50}$ value is within said range. The example number refer to the final examples as outlined in the section **Exemplary embodiments** (see also aspect 18 of the invention).

All data are measured according to the procedure described herein.

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 1 | 100 | 1 - 100 |
| 2 | 99 | 1 - 100 |
| 3 | 99 | 1 - 100 |
| 4 | 98 | 1 - 100 |
| 5 | 99 | 1 - 100 |
| 6 | 98 | 1 - 100 |
| 7 | 98 | 1 - 100 |
| 8 | 100 | 1 - 100 |
| 9 | 99 | 1 - 100 |
| 10 | 98 | 1 - 100 |
| 11 | 98 | 1 - 100 |
| 12 | 97 | 1 - 100 |
| 13 | 90 | 101 - 1200 |
| 14 | 96 | 101 - 1200 |
| 15 | 92 | 101 - 1200 |
| 16 | 86 | 101 - 1200 |
| 17 | 100 | 1 - 100 |
| 18 | 99 | 1 - 100 |
| 19 | 99 | 1 - 100 |
| 20 | 98 | 1 - 100 |
| 21 | 97 | 101 - 1200 |
| 22 | 98 | 1 - 100 |
| 23 | 99 | 1 - 100 |
| 24 | 86 | 101 - 1200 |
| 25 | 96 | 1 - 100 |
| 26 | 91 | 101 - 1200 |
| 27 | 99 | 1 - 100 |
| 28 | 98 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 29 | 96 | 1 - 100 |
| 30 | 100 | 1 - 100 |
| 31 | 98 | 1 - 100 |
| 32 | 100 | 1 - 100 |
| 33 | 97 | 1 - 100 |
| 34 | 93 | 101 - 1200 |
| 35 | 100 | 101 - 1200 |
| 36 | 100 | 1 - 100 |
| 37 | 97 | 1 - 100 |
| 38 | 99 | 1 - 100 |
| 39 | 99 | 1 - 100 |
| 40 | 99 | 1 - 100 |
| 40-1 | 100 | 1 - 100 |
| 40-2 | 100 | 1 - 100 |
| 40-3 | 100 | 101 - 1200 |
| 40-4 | 92 | 101 - 1200 |
| 40-5 | 98 | 1 - 100 |
| 40-6 | 97 | 1 - 100 |
| 40-7 | 95 | 101 - 1200 |
| 41 | 92 | 101 - 1200 |
| 42 | 92 | 101 - 1200 |
| 43 | 98 | 1 - 100 |
| 44 | 99 | 1 - 100 |
| 45 | 98 | 1 - 100 |
| 46 | 100 | 1 - 100 |
| 47 | 97 | 1 - 100 |
| 48 | 96 | 1 - 100 |
| 49 | 98 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 50 | 97 | 1 - 100 |
| 51 | 96 | 1 - 100 |
| 52 | 100 | 1 - 100 |
| 53 | 99 | 1 - 100 |
| 54 | 97 | 1 - 100 |
| 55 | 97 | 1 - 100 |
| 56 | 95 | 1 - 100 |
| 57 | 100 | 1 - 100 |
| 58 | 96 | 1 - 100 |
| 60 | 97 | 1 - 100 |
| 61 | 97 | 1 - 100 |
| 62 | 95 | 1 - 100 |
| 63 | 92 | 101 - 1200 |
| 64 | 97 | 1 - 100 |
| 65 | 97 | 1 - 100 |
| 66 | 91 | 101 - 1200 |
| 67 | 95 | 101 - 1200 |
| 68 | 97 | 1 - 100 |
| 69 | 99 | 1 - 100 |
| 70 | 99 | 1 - 100 |
| 71 | 99 | 1 - 100 |
| 72 | 91 | 101 - 1200 |
| 73 | 97 | 1 - 100 |
| 74 | 95 | 1 - 100 |
| 75 | 98 | 1 - 100 |
| 76 | 98 | 1 - 100 |
| 77 | 89 | 101 - 1200 |
| 78 | 99 | 101 - 1200 |
| 79 | 99 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 80 | 94 | 1 - 100 |
| 81 | 78 | 101 - 1200 |
| 82 | 100 | 1 - 100 |
| 83 | 96 | 1 - 100 |
| 84 | 97 | 1 - 100 |
| 85 | 99 | 1 - 100 |
| 86 | 95 | 101 - 1200 |
| 87 | 86 | 101 - 1200 |
| 88 | 96 | 1 - 100 |
| 89 | 95 | 101 - 1200 |
| 90 | 100 | 1 - 100 |
| 91 | 99 | 1 - 100 |
| 92 | 98 | 1 - 100 |
| 93 | 97 | 1 - 100 |
| 94 | 96 | 101 - 1200 |
| 95 | 98 | 1 - 100 |
| 96 | 99 | 1 - 100 |
| 97 | 98 | 1 - 100 |
| 98 | 97 | 1 - 100 |
| 99 | 96 | 1 - 100 |
| 100 | 93 | 101 - 1200 |
| 101 | 98 | 1 - 100 |
| 102 | 100 | 1 - 100 |
| 103 | 99 | 1 - 100 |
| 104 | 95 | 101 - 1200 |
| 105 | 84 | 101 - 1200 |
| 106 | 87 | 101 - 1200 |
| 108 | 89 | 101 - 1200 |
| 111 | 88 | 101 - 1200 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 112 | 97 | 1 - 100 |
| 113 | 92 | 101 - 1200 |
| 114 | 89 | 101 - 1200 |
| 115 | 92 | 101 - 1200 |
| 116 | 93 | 101 - 1200 |
| 117 | 97 | 1 - 100 |
| 118 | 89 | 101 - 1200 |
| 119 | 95 | 1 - 100 |
| 120 | 95 | 1 - 100 |
| 121 | 94 | 101 - 1200 |
| 122 | 85 | 101 - 1200 |
| 123 | 91 | 101 - 1200 |
| 124 | 95 | 101 - 1200 |
| 125 | 95 | 1 - 100 |
| 126 | 98 | 1 - 100 |
| 127 | 97 | 1 - 100 |
| 128 | 99 | 1 - 100 |
| 129 | 99 | 1 - 100 |
| 130 | 99 | 1 - 100 |
| 131 | 97 | 1 - 100 |
| 132 | 90 | 101 - 1200 |
| 132-1 | 97 | 1 - 100 |
| 132-2 | 100 | 1 - 100 |
| 132-3 | 89 | 101 - 1200 |
| 132-4 | 98 | 1 - 100 |
| 132-5 | 100 | 1 - 100 |
| 132-6 | 99 | 1 - 100 |
| 132-7 | 94 | 1 - 100 |
| 132-8 | 94 | 101 - 1200 |
| 132-9 | 95 | 101 - 1200 |
| 133 | 98 | 1 - 100 |
| 134 | 99 | 1 - 100 |
| 135 | 98 | 1 - 100 |
| 136 | 100 | 1 - 100 |
| 137 | 99 | 1 - 100 |
| 138 | 100 | 1 - 100 |
| 139 | 99 | 1 - 100 |
| 140 | 100 | 1 - 100 |
| 141 | 99 | 1 - 100 |
| 142 | 98 | 1 - 100 |
| 143 | 100 | 1 - 100 |
| 144 | 100 | 1 - 100 |
| 145 | 84 | 101 - 1200 |
| 146 | 91 | 101 - 1200 |
| 147 | 99 | 1 - 100 |
| 147-1 | 86 | 101 - 1200 |
| 147-2 | 87 | 101 - 1200 |
| 147-3 | 95 | 1 - 100 |
| 148 | 86 | 101 - 1200 |
| 149 | 95 | 101 - 1200 |
| 150 | 90 | 101 - 1200 |
| 151 | 92 | 101 - 1200 |
| 152 | 93 | 101 - 1200 |
| 153 | 90 | 101 - 1200 |
| 154 | 100 | 1 - 100 |
| 155 | 100 | 1 – 100 |
| 156 | 99 | 1 – 100 |
| 157 | 97 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 158 | 97 | 1 - 100 |
| 159 | 100 | 1 - 100 |
| 160 | 96 | 1 - 100 |
| 161 | 95 | 101 - 1200 |
| 162 | 98 | 1 - 100 |
| 163 | 97 | 101 - 1200 |
| 164 | 98 | 101 - 1200 |
| 165 | 99 | 101 - 1200 |
| 166 | 92 | 101 - 1200 |
| 167 | 93 | 101 - 1200 |
| 168 | 90 | 101 - 1200 |
| 169 | 86 | 101 - 1200 |
| 170 | 75 | 101 - 1200 |
| 171 | 100 | 101 - 1200 |
| 172 | 100 | 1 - 100 |
| 173 | 86 | 101 - 1200 |
| 174 | 89 | 101 - 1200 |
| 175 | 88 | 101 - 1200 |
| 176 | 85 | 101 - 1200 |
| 177 | 93 | 101 - 1200 |
| 178 | 92 | 101 - 1200 |
| 179 | 91 | 101 - 1200 |
| 180 | 96 | 101 - 1200 |
| 181 | 96 | 1 - 100 |
| 182 | 100 | 1 - 100 |
| 183 | 99 | 1 - 100 |
| 184 | 97 | 1 - 100 |
| 185 | 100 | 1 - 100 |
| 186 | 97 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 187 | 96 | 1 - 100 |
| 188 | 96 | 1 - 100 |
| 189 | 90 | 101 - 1200 |
| 190 | 82 | 101 - 1200 |
| 191 | 92 | 101 - 1200 |
| 192 | 100 | 101 - 1200 |
| 193 | 99 | 101 - 1200 |
| 194 | 97 | 101 - 1200 |
| 195 | 88 | 101 - 1200 |
| 196 | 91 | 101 - 1200 |
| 197 | 91 | 101 - 1200 |
| 198 | 100 | 101 - 1200 |
| 199 | 88 | 101 - 1200 |
| 200 | 91 | 101 - 1200 |
| 201 | 85 | 101 - 1200 |
| 202 | 83 | 101 - 1200 |
| 203 | 84 | 101 - 1200 |
| 204 | 87 | 101 - 1200 |
| 205 | 100 | 1 - 100 |
| 206 | 82 | 101 - 1200 |
| 207 | 100 | 1 - 100 |
| 208 | 100 | 101 - 1200 |
| 209 | 89 | 101 - 1200 |
| 210 | 97 | 1 - 100 |
| 211 | 99 | 1 - 100 |
| 212 | 92 | 101 - 1200 |
| 213 | 86 | 101 - 1200 |
| 214 | 98 | 1 - 100 |
| 215 | 93 | 101 - 1200 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 216 | 96 | 1 - 100 |
| 217 | 97 | 101 - 1200 |
| 218 | 88 | 101 - 1200 |
| 219 | 100 | 1 - 100 |
| 220 | 100 | 1 - 100 |
| 221 | 100 | 1 - 100 |
| 222 | 100 | 1 - 100 |
| 223 | 100 | 1 - 100 |
| 224 | 100 | 1 - 100 |
| 225 | 100 | 1 - 100 |
| 226 | 100 | 1 - 100 |
| 227 | 100 | 1 - 100 |
| 228 | 100 | 1 - 100 |

| Example No. | % inhibition of PDE9A2 (at 10 micromolar concentration) | $IC_{50}$ within range [nanomolar (nM)] |
|---|---|---|
| 229 | 99 | 1 - 100 |
| 230 | 100 | 1 - 100 |
| 230-1 | 98 | 1 - 100 |
| 230-2 | 100 | 1 - 100 |
| 230-3 | 99 | 1 - 100 |
| 230-4 | 98 | 101 - 1200 |
| 231 | 95 | 1 - 100 |
| 232 | 99 | 1 - 100 |
| 233 | 100 | 1 - 100 |
| 234 | 100 | 1 - 100 |
| 235 | 98 | 101 - 1200 |
| 236 | 93 | 101 - 1200 |
| 237 | 89 | 101 - 1200 |

In vivo effect:

The in vivo effect of the compounds of this invention can be tested in the Novel Object Recognition test according to the procedure of Prickaerts *et al.* (*Neuroscience*, **2002**, *113*, 351-361).

For further information concerning biological testing of the compounds of the present invention see also *Neuropharmacology*, **2008**, *55*, 908-918.

CHEMICAL MANUFACTURE

Abbreviations:

*APCI* *Atmospheric pressure chemical ionization*

*DAD* *diode array detector*

*DMSO* *dimethyl sulphoxide*

*ESI* *electrospray ionization (in MS)*

*Exp.* *example*

*Fp.* *melting point*

*h* *hour(s)*

*HPLC* *high performance liquid chromatography*

*HPLC-MS* *coupled high performance liquid chromatography with mass spectrometric detection*

*GC-MS* *gas chromatography with mass spectrometric detection*

*MPLC* *medium pressure liquid chromatography*

*mL* *millilitre*

*µL* *microlitre*

*min* *minutes*

*MS* *mass spectrometry*

*racem.* *racemic*

*rt* *room temperature*

$R_t$ *retention time (in HPLC)*

*Rf* *retardation factor (in TLC)*

*TBTU* *2-(1 H-Benzotriazole-1-yl)-1,1,3,3-Tetramethyluronium tetrafluoroborate*

*TFA* *trifluoroacetic acid*

*TLC* *thin-layer chromatography*

**LC-MS methods:**

**Method A**

Instrument: HPLC/MS ThermoFinnigan. HPLC Surveyor DAD, LCQduo Ion trap.; column: Sunryse MS-C18, 5 um, 4.6x100 mm; eluent A: water + 20 mM ammonium formate; eluent B: acetonitrile + 20 mM ammonium formate; gradient: A/B (95:5) for 1 min, then to A/B (5:95) in 7 min for 1.5 min; flow rate: 0.85 mL/min; UV detection: 254 nm; ion source: ESI

**Method 1**

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 3.0 µm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.18 min 5 % B → 2.0 min 98 % B → 2.2 min 98 % B → 2.3 min 5 % B → 2.5 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

**Method 2**

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695, Waters 2996 diode array detector; column: Merck Chromolith Performance RP18e, 100 x 1 mm; eluent A: water + 0.13 % TFA, eluent B: acetonitrile; gradient: 0.0 min 5 % B → 0.2 min 5 % B → 1.6 min 98 % B → 1.9 min 98 % B → 2.0 min 5 % B → 2.2 min 5 % B; flow rate: 3.5 mL/min; UV detection: 210-380 nm.

**Method 1D**

Instrument:HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Sunryse MS-C18, 5 um, 4.6 x 100 mm; eluent A: 90 % water +10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % water + ammonium formate 10 mM; gradient:A (100) for 1 min, then to B (100) in 7 min for 1 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI.

**Method 1E**

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Symmetry C8, 5 µm, 3 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % $H_2O$ + ammonium formate 10 mM; gradient: A (100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

**Method 1E fusion**

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Fusion-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10mM; eluent B: acetonitrile 90 % + 10 % $H_2O$ + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

**Method 1E hydro**

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, MSQ Quadrupole; column: Synergi Hydro-RP80A, 4 µm, 4.60 x 100 mm; eluent A: 90 % water + 10 % acetonitrile + ammonium formate 10 mM; eluent B: acetonitrile 90 % + 10 % $H_2O$ + ammonium formate 10 mM; gradient: A (100 %) for 1.5 min, then to B (100 %) in 10 min for 1.5 min; flow rate: 1.2 mL/min; UV detection: 254 nm; ion source: APCI

**Method 2F**

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap; column: Symmetry-C18, 5 um, 3 x 150 mm; eluent A: 95 % water + 5 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 95 % + 5 % water + formic acid 0.1 %; gradient: A/B (95/5) for 1.5 min, then to A/B (5/95) in 10 min for 1.5 min; flow rate: 1 mL/min; UV detection: 254 nm; ion source: ESI

**Method 2L**

Instrument: HPLC-MS ThermoFinnigan. HPLC Surveyor DAD, Finnigan LCQduo Ion trap;
column: Symmetry Shield, 5 um, 4,6 x 150 mm; eluent A: 90 % water + 10 % acetonitrile + formic acid 0.1 %; eluent B: acetonitrile 90 % + 10 % water + formic acid 0.1 %; flow rate: 0,85 mL/min; UV detection: 254 nm; ion source: ESI

**Method Grad_C8_acidic**

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI

**Method Grad_C18_acidic**

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Sunfire MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A/B (80:20), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

**Method Grad_90_10_C8_acidic**

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100 %), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

**Method Grad_90_10_C18_acidic**

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole; column: Xterra MS-C18, 3.5 µm, 4.6 x 50 mm; eluent A: water + 0.1 % TFA + 10 % acetonitrile; eluent B: acetonitrile; gradient: A (100), then to A/B (10:90) in 3.25 min for 0.75 min; flow rate:1.3 mL/min; UV detection: 254 nm; ion source: ESI.

**Method Grad_C8_$NH_4COOH$**

Instrument: HPLC-MS Waters. HPLC Alliance 2695 DAD, ZQ Quadrupole. Column: Xterra MS-C8, 3.5 µm, 4.6 x 50 mm; eluent A: water + ammonium formate 5 mM + 10 % acetonitrile; eluent B: acetonitrile; gradient: A 100 %, then to A/B (10:90) in 3.25 min for 0.75 min; flow rate: 1.3 mL/min; UV detection: 254 nm; ion source: ESI.

**Chiral HPLC Methods**

Instrument: Agilent 1100. Column: Chiralpak AS-H Daicel, 4.6 µm, 4.6 x 250 mm;

Method Chiral 1: eluent: hexane/ethanol 97/3 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm.
Method Chiral 2: eluent: hexane/ethanol 98/2 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm
Method Chiral 3: eluent: hexane/ethanol 80/20 (isocratic); flow rate: 1.0 mL/min; UV detection: 254 nm

**GC/MS methods**

**Method 3A**

Instrument: GC/MS Finnigan. Trace GC, MSQ quadrupole. Column: DB-5MS, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace MSQ, quadrupole
ion source: IE scan range: 50-450 u.

**Method 3A.1**

Instrument: GC/MS Finnigan Thermo Scientific. Trace GC Ultra, DSQ II single quadrupole. Column: DB-5MS UI, 25 m x 0.25 mm x 0.25 µm; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace DSQ, single quadrupole

**Microwave heating:**

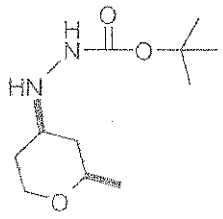
Microwave apparatus types:

- Discover® CEM instruments, equipped with 10 and 35 mL vessels;
- Microwave apparatus type: Biotage Initiator Sixty.

**General comment concerning the presentation of the structures**

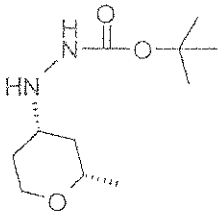
Some compounds have one or more chiral centres. The depicted structure will not necessarily show all the possible stereochemical realisation of the compound but only one. However, in such cases a term like "cis-racemic mixture" is depicted next to the structure in order to point to the other stereochemical options.

An example is given for Example 7D, below. The presented structural formula is



Cis - racemic mixture

The added term "cis - racemic mixture" points to the second stereochemical option:



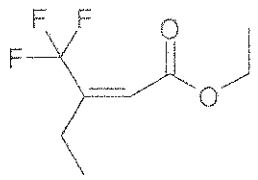
This principle applies to other depicted structures as well.

Synthesis

In the following the manufacture of compounds which exemplify the present invention is described. In case the process of manufacture of a specific compound has not been disclosed literally, the skilled person in the art will find a description of analogue procedures within these descriptions which he can follow in principle. At some places it is said, the examples can be prepared in analogy to another example. If reference should be made to such an "analogue process" the reactions conditions are about the same, even if molar ratios of reagents and educts might to be adjusted. It also will be evident that starting materials within a described process can be varied chemically to achieve the same results, i.e. if a condensation reaction of an ester is described, in that the alcoholic component is a leaving group but not subject of the product, this alcoholic component may vary without significant changes of the procedure as such.

Starting compounds:

Example 1A



A solution of 70 g (201 mmol) carbethoxymethylene triphenylphosphorane in 300 mL diethyl ether was cooled to 0°C and 25 g (198 mmol) 1.,1,1-trifluorobutanone was added. The solution was warmed to room temperature and stirred over night. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure (700 mbar and 40°C bath temperature). The residue was purified by vacuum distillation (170 mbar and 130°C bath temperature, main fraction: 95-96°C). 29 g (75 %) of the product were obtained as colourless oil.

HPLC-MS (Method 1): $R_t$: 1.77 min

MS (ESI pos): m/z = 196 $(M+H)^+$

Example 1AA

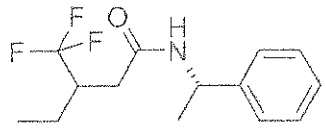


400 mg (10.0 mmol) sodium hydride (60 % in mineral oil) was suspended in 10 ml THF and cooled to 4°C. While being stirred, a solution of 1.3 ml (8.99 mmol) trimethylphosphono acetate in 10 ml THF was added. The mixture was stirred for 1 h at the same temperature. After this, a solution of 4,4-difluorocyclohexanone in 10 ml THF was added at 0°C. The mixture was allowed to warm to room temperature and stirred for 14 h. THF and water was added and the THF evaporated. The remainder was diluted with ethyl acetate, washed with water and saturated sodium hydrogen carbonate solution and evaporated to yield 1.49 g (95 %) of the product.

MS (EI): m/z = 190 $(M)^+$

The following examples 1B, 1C, 1D, 1E, 2A, 2B, 2C and 2D show how the racemic acids 3-trifluoromethyl-pentanoic acid and 3-trifluoromethyl-butyric acid can be transferred into the two enantiomeric forms of the free acid. The resolution can be done via separation of diastereomeric intermediates. The two pure enantiomeric forms of the free acid will be called enantiomer A, enatiomer B respectively. The corresponding diastereomeric intermediates will be called diastereomer A, diastereomer B respectively.
The same principle may be applied for enantiomeric resolution of other racemic mixtures if appropriate.

Example 1B



Diastereoisomer A

A solution of racemic 3-trifluoromethyl-pentanoic acid (8 g, 47 mmol), TBTU (16.6 g, 52 mmol) and diisopropylethylamine (24.1 mL, 141 mmol) in dimethylformamide (80 mL) was stirred at 20°C for 1h then (*S*)-(−)-1-phenylethylamine (10 g, 82 mmol) was added and the mixture was stirred for 16 h at 20°C. The solvent was removed and dichloromethane (200 mL) was added. The resulting mixture was washed with citric acid 10 % in water (200 mL), $K_2CO_3$ 20 % in water (100 mL) and dried over sodium sulphate. Evaporation of the solvent gave a crude solid that was mixed with methanol (10 mL) and filtered through a pad of activated basic alumina. Separation of diastereoisomers was obtained by flash chromatography on $SiO_2$ eluting with a mixture of cyclohexane/ethyl acetate 85/15.

4.5 g (35.8 %) of the title compound were obtained as white solid.

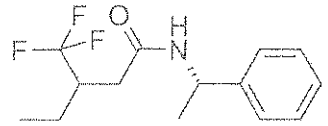
Rf: 0.25 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

HPLC-MS (Method 1E hydro): $R_t$: 9.35 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): $R_t$: 5.58 min de: >99 %

Example 1C



Diastereoisomer B

4.4 g (34.2 %) of a white solid were obtained as second product from flash chromatography of Example 1B.

Rf: 0.20 (cyclohexane/ethyl acetate 85/15, stained with basic $KMnO_4$)

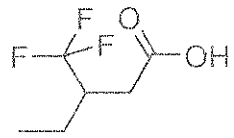
HPLC-MS (Method 1E hydro): $R_t$: 9.33 min

MS (APCI pos): m/z = 274 $(M+H)^+$.

Chiral HPLC (Method Chiral 1): $R_t$: 6.18 min de: >99 %

Example 1D

3-Trifluoromethyl-pentanoic acid, Enantiomer A



Enantiomer A

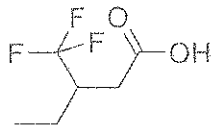
A solution of Example 1B (4.6 g, 17 mmol) in dioxane (15 mL) was treated with $H_2SO_4$ 70 % in water (25 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with

dichloromethane (2x 200 mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 500 mL) and the combined organic phases were dried. Evaporation of solvent afforded 2.47 g (86.3 %) of a brown oil.

Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)
Chiral HPLC (Method Chiral 1): $R_t$ 5.58 min ee: >99 %

Example 1E

3-Trifluoromethyl-pentanoic acid, Enantiomer B

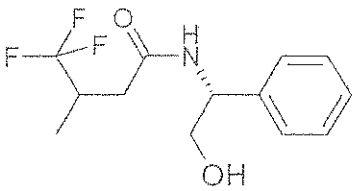


Enantiomer B

In analogy to the preparation of Example 1D, the title compound was obtained using Example 1C as starting material.
Yield: 80.3 %
Rf: 0.66 (dichloromethane/methanol 9/1, stained with Bromocresol Green)
Chiral HPLC (Method Chiral 1): $R_t$: 5.08 min ee: >99 %

Example 2A

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide, Diastereoisomer A



A solution of 3-(trifluoromethyl)butyric acid (10 g, 64 mmol) in dimethylformamide (100mL) was treated with N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (14.7 g, 77 mmol), 4-dimethyl-amino pyridine (11 g, 89.7 mmol) and

(R)-(-)-phenylglycinol (9.9 g, 70.5 mmol). The mixture was stirred at 20°C for 16h, then concentrated to reduce the volume and treated with 10 % citric acid in water (300 mL). The mixture was extracted with ethyl ether (2x 200mL) and the separated organic phase were washed with 10 % $NaHCO_3$ (150 mL) and brine (150 mL). The organic phase was dried and evaporated to give 13.1 g of a crude white solid.

Separation of diastereoisomers was achieved by flash chromatography on $SiO_2$ eluting with a mixture of ethyl acetate/hexane 6/4.

5.32g (30.2 %) of the title compound were obtained as white solid.

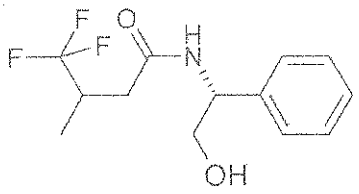
Rf: 0.23 (ethyl acetate/hexane 6/4)

HPLC-MS (1E hydro): $R_t$: 6.97 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Example 2B

4,4,4-Trifluoro-N-((R)-2-hydroxy-1-phenyl-ethyl)-3-methyl-butyramide,
Diastereoisomer B



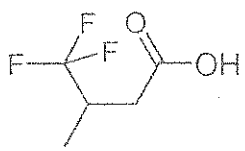
3.08 g (17.5 %) of a white solid were obtained as second product from flash chromatography of Example 2A.

Rf: 0.16 (ethyl acetate/hexane 6/4)

HPLC-MS (1E hydro): $R_t$: 6.92 min

MS (APCI pos): m/z = 276 $(M+H)^+$.

Example 2C, Enantiomer A



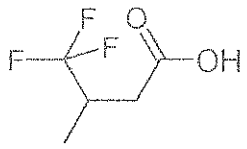
A solution of Example 2A (2 g, 7.26 mmol) in tetrahydrofuran (10 mL) was treated with $H_2SO_4$ 70 % in water (10 mL) and refluxed for 16 h. The mixture was cooled, basified to pH 14 with NaOH 32 % in water, diluted with water (50 mL) and extracted with dichloromethane (2x 50mL). The resulting solution was acidified to pH 1 with 9N HCl, extracted with dichloromethane (3x 50 mL) and the combined organic phases were dried. Evaporation of solvent afforded 0.84 g (74.1 %) of a brown oil.

HPLC-MS (1E hydro): $R_t$: 1.73 min

MS (APCI neg): m/z = 155 $(M-H)^-$.

Chiral HPLC (Method Chiral 2): $R_t$: 6.92 min ee: 99 %

Example 2D, Enantiomer B



In analogy to the preparation of Example 2C, the title compound was obtained using Example 2B as starting material. Obtained 1.4 g (8.96 mmol)

Yield: 82.3 %

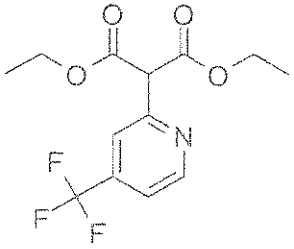
HPLC-MS (1E hydro): $R_t$: 1.30 min

MS (APCI neg): m/z = 155 $(M-H)^-$.

Chiral HPLC (Method Chiral 2): $R_t$: 6.49 min ee: 98.6 %

Example 3A

2-(4-Trifluoromethyl-pyridin-2-yl)-malonic acid diethyl ester



A suspension of sodium hydride 60 % in mineral oil (1.65 g, 41 mmol) in anhydrous dioxane (36 mL) was treated with diethylmalonate (6.3 mL, 41 mmol) at 25°C and heated to 60°C for 30 min. Cuprous chloride (1.63 g, 17 mmol) was added, the mixture was heated to 80°C and 2-chloro-4-(trifluoromethyl)-pyridine was added and the was heating increased to 100°C for 16h.

After cooling to 20°C the mixture was acidified with 37 % HCl, diluted with water (120 mL) and extracted with dichloromethane (2 x 60 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate from 95/5 to 60/40.

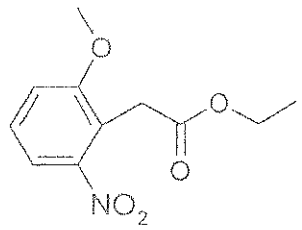
1.9 g (38 %) were obtained as a colourless oil.

HPLC-MS (2F): $R_t$: 12.24 min

MS (ESI pos): m/z = 306 $(M+H)^+$.

Example 4A

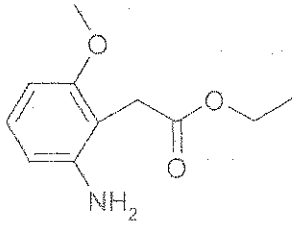
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid (Sinova Inc., Bethesda, MD 20814, USA) as starting material.



HPLC-MS (Method 1): $R_t$: 1.47 min

MS (ESI pos): m/z = 194 $(M+H-EtOH)^+$

Example 4B



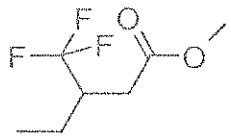
2.0 g (8.6 mmol) of Example 4A was dissolved in 40 mL ethanol, Pd (10 % on charcoal) was added, and the mixture was hydrogenated at room temperature (2h, 50 psi). The reaction mixture was filtered and the residue washed with ethanol. The solvent was evaporated by reduced pressure.1.80 g (100 %) of the product were obtained.

HPLC-MS (Method 1): $R_t$: 0.91 min

MS (ESI pos): m/z = 210 $(M+H)^+$

Example 5A

3-Trifluoromethyl-pentanoic acid methyl ester, Enantiomer A



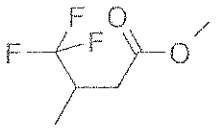
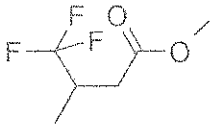
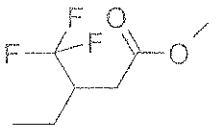
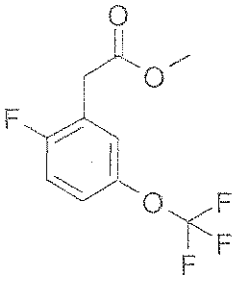
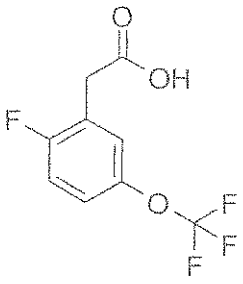
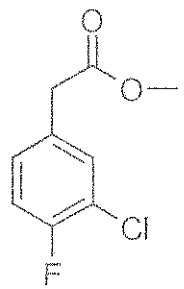
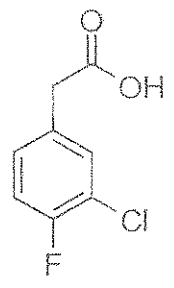
Enantiomer A

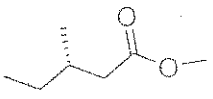
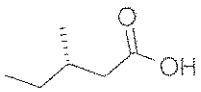
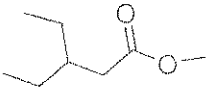
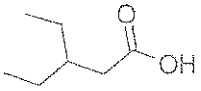
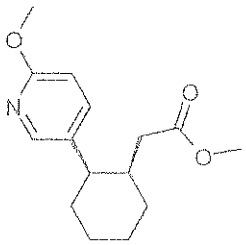
To a stirred solution of Example 1D (250 mg, 1.47 mmol) in dichloromethane (10 mL) and methanol (0.25 mL), under nitrogen atmosphere, trimethylsilyldiazomethane (2.0 M solution in diethyl ether) (2.1 mL, 4.19 mmol) was added drop wise at 0°C. The reaction mixture was stirred keeping the temperature below 5°C for 1h. The solvent was removed (40°C, 25 bar) yielding 250 mg (75.4 %) of a yellow oil that was used in the next step without further purification.

GC (Method 3A): $R_t$: 3.29 min

MS (EI): m/z: 165 $(M-19)^+$,155 $(M-29)^+$, 153 $(M-31)^+$

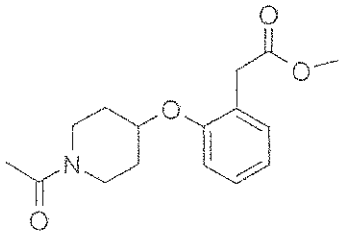
The following examples were synthesized in analogy to the preparation of Example 5A, using the corresponding acids as starting materials:

| | structure | starting material: carboxylic acid | $R_t$ [min] | MS *m/z* |
|---|---|---|---|---|
| Example 5B Enantiomer A |  | Example 2C | 8.01 (Method 3A) | 170 [EI] |
| Example 5 C Enantiomer B |  | Example 2D | 8.01 (Method 3A) | 170 [EI] |
| Example 5D Enantiomer B |  | Example 1E | 3.29 (Method 3A) | 165(M-19)$^+$, 155(M-29)$^+$, 153(M-31)$^+$ [EI] |
| Example 5E |  |  | 7.82 (Method 3A) | 252 [EI] |
| Example 5F |  |  | 9.53 (Method 3A) | 202 [EI] |

| | structure | starting material: carboxylic acid | $R_t$ [min] | MS *m/z* |
|---|---|---|---|---|
| Example 5G Enantiomer S |  |  | 3.92 (Method 3A) | 130 [EI] |
| Example 5H |  |  | 5.09 Method 3A | 115 $(M-29)^+$ [EI] |
| Example 5HA cis, racem. mixture |  | Example 18A | 1.22 (Method 1) | 264 [ESI, $(M+H)^+$] |

Example 5I

[2-(1-Acetyl-piperidin-4-yloxy)-phenyl]-acetic acid methyl ester



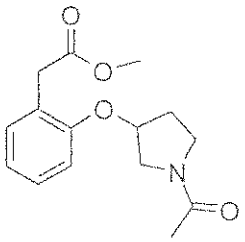
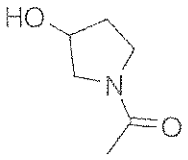
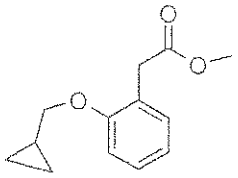
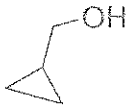
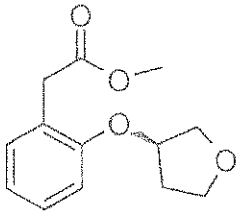
Di-tert-butylazodicarboxylate (305 mg, 1.32 mmol) was dropped to a solution of 1-(4-hydroxy-piperidin-1-yl)-ethanone (259 mg, 1.8 mmol) in tetrahydrofuran (4 mL) under nitrogen atmosphere. Then (2-hydroxy-phenyl)-acetic acid methyl ester (200 mg, 1.2 mmol) and triphenylphosphine (347 mg, 1.3 mmol) were added. The yellow mixture was stirred at 20°C for 16h. The solvent was evaporated and the residue was purified

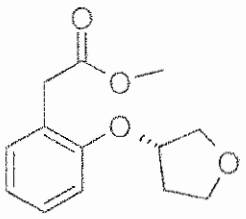
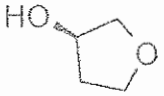
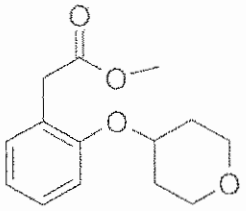
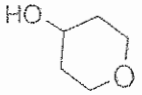
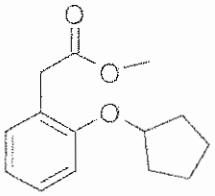
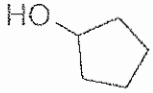
on silica using hexane/ethyl acetate mixture of increasing polarity (from 70 % to 100 % ethyl acetate) as eluent to give 195 mg (55.6 %) of a colourless oil.

HPLC-MS (Method Grad_C8_$NH_4COOH$): $R_t$: 2.67 min

MS (ESI pos): m/z = 292 $(M+H)^+$.

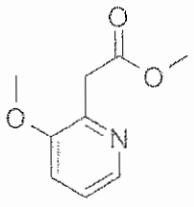
The following examples were synthesized in analogy to the preparation of Example 5G, using the corresponding alcohols as starting materials:

| | Structure | starting material: Alcohol | Rf | $R_t$ [min] | MS m/z |
|---|---|---|---|---|---|
| Example 5J racem. mixture |  |  | | 2.53 (Method Grad_C8_ $NH_4COOH$ ) | 292 $(M+H)^+$ |
| Example 5K |  |  | 0.35 (hexane/ethyl acetate 8/2) | | |
| Example 5L |  |  | 0.2 (hexane/ethyl acetate 7/3) | | |

| | Structure | starting material: Alcohol | Rf | $R_t$ [min] | MS m/z |
|---|---|---|---|---|---|
| Example 5M |  |  | 0.2 (hexane/ethyl acetate 7/3) | | |
| Example 5O |  |  | 0.25 (hexane/ethyl acetate 7/3) | | |
| Example 5P |  |  | 0.35 (hexane/ethyl acetate) | | |

Example 5Q

(3-Methoxy-pyridin-2-yl)-acetic acid methyl ester



A mixture of (3-methoxy-2-pyridin-2-yl) acetonitrile (400 mg, 2.7 mmol) in 2 mL of methanol and 96 % sulphuric acid (1.8 mL, 32 mmol) was heated in a microwave oven at 120°C for 1h. The mixture was cooled to 0°C, basified with solid $NaHCO_3$,

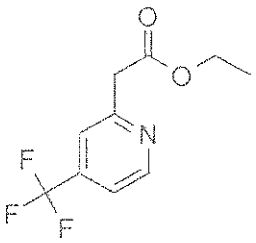
diluted with water (2mL) and extracted with dichloromethane. The separated organic phase was dried and evaporated to give 450 mg (92 %) of a dark yellow oil that was used in the next step without further purification.

HPLC-MS (Method Grad_C8_$NH_4COOH$): $R_t$: 1.92 min

MS (ESI pos): m/z = 182 $(M+H)^+$.

Example 5R

(4-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



A solution of Example 3A (1.0 g, 3.27 mmol) in anhydrous DMSO (8 mL) was treated with water (60 microL, 3.27 mmol) and lithium chloride (347 mg, 8.2 mmol). The resulting mixture was heated at 120°C for 16h. After cooling to 20°C the mixture was treated with brine (12 mL) and extracted with ethyl acetate (3x 20 mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl acetate 8/2.

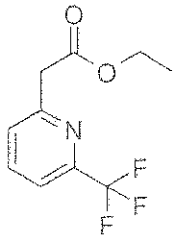
390 mg (51 %) were obtained as a colourless oil.

HPLC-MS (Method 2F): $R_t$: 11.09 min

MS (ESI pos): m/z = 234 $(M+H)^+$

Example 5S

(6-Trifluoromethyl-pyridin-2-yl)-acetic acid ethyl ester



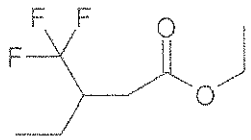
A mixture of caesium carbonate (1.87g, 5.75 mmol) and tri-t-butylphosphine (107 µL, 0.44 mmol) in dry 1,2 dimethoxyethane (10 mL) was treated with tris-(dibenzylideneacetone)di-palladium (81 mg, 0.09 mmol), 2-Bromo-6-(trifluoromethyl)pyridine (1g, 4.42 mmol) and diethylmalonate (0.8 mL, 5.3 mmol) under nitrogen atmosphere. The mixture was heated to 150°C for 30 min in a microwave oven. After cooling to 20°C the mixture was treated with a saturated solution of ammonium chloride (120 mL) and extracted with ethyl ether (3x 80mL). The organic phase was dried and evaporated to give a crude oil that was purified by flash chromatography eluting with n-hexane/ethyl ether 6/1.

460 mg (81 %) were obtained as a colourless oil.

GC (Method 3A): $R_t$: 8.28 min

MS (EI): m/z = 233 $(M)^+$

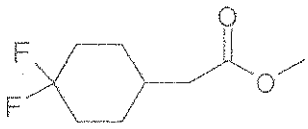
Example 5T, racemic mixture



29 g (148 mmol) of Example 1A was combined with 2 g Pd/C (10 %) and hydrogenated at room temperature (6h, 15 psi). The reaction mixture was filtered and washed with diethyl ether. The solvent was evaporated under reduced pressure (500 mbar, 40°C bath temperature). 27.6 g (94 %) of the product were obtained as a colourless liquid.

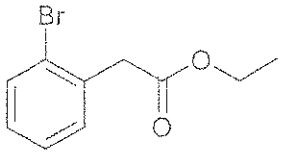
HPLC-MS (Method 1): $R_t$: 1.65 min

Example 5TA



1.49 g (95 %, 7.43 mmol) was dissolved in 20 ml ethanol and hydrogenated over 150 mg Pd/C (10 %) at atmospheric pressure for 14 h. The mixture was filtered and the solvent removed to yield 1.27 g (89 %) of the product.

Example 5U

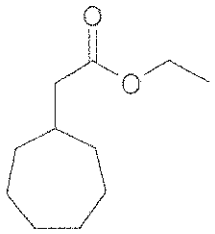
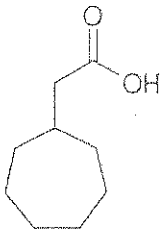
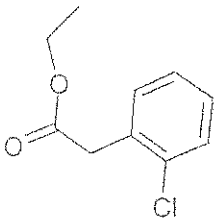
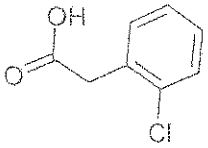
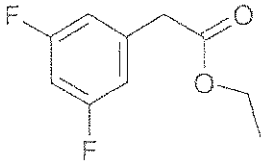
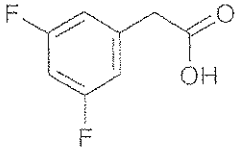
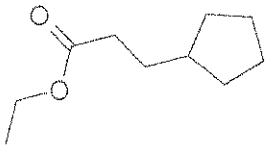
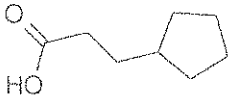
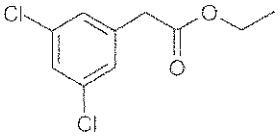
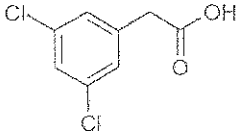
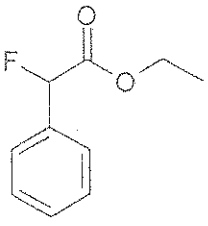
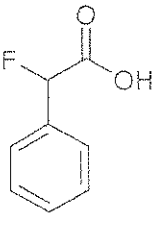


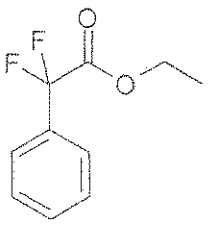
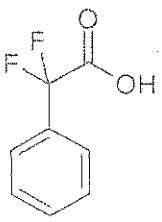
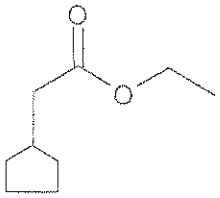
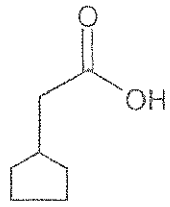
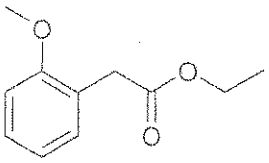
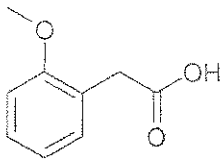
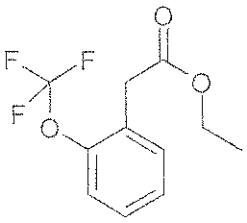
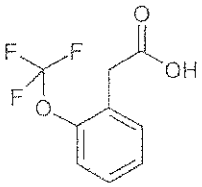
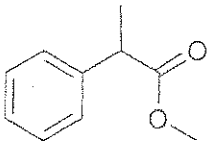
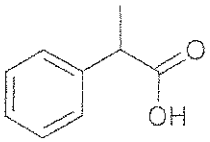
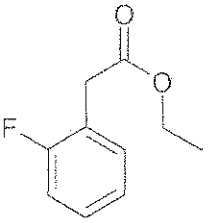
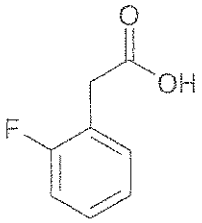
A solution of 15 g (69.8 mmol) of (2-bromo-phenyl)-acetic acid in 50 mL ethanol was cooled to 0°C and 8 mL (110 mmol) thionylchloride was added drop wise. The reaction mixture was heated to 50°C over night. After cooling to room temperature the solvent was removed under reduced pressure. The residue was mixed with ethyl acetate and filtered over 30 g basic aluminium oxide. The filtrate was evaporated under reduced pressure. 18 g (92 %) of the product were obtained.

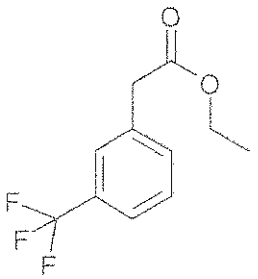
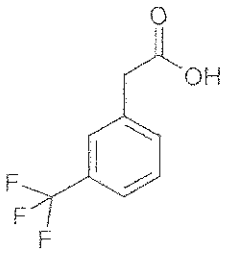
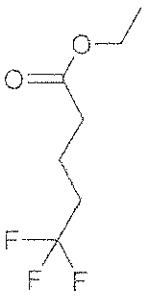
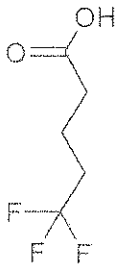
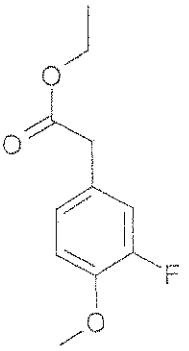
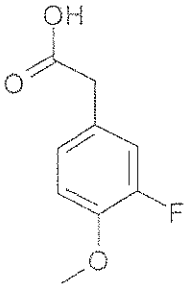
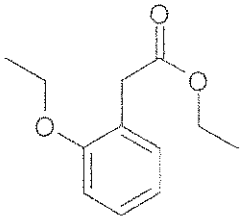
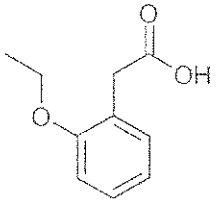
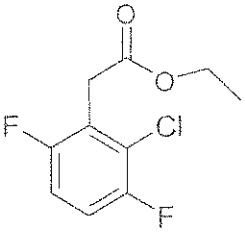
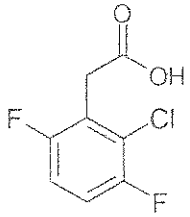
HPLC-MS (Method1): $R_t$: 1.62 min

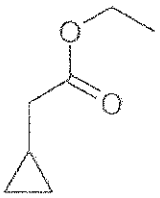
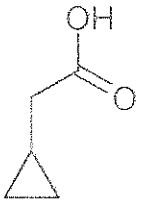
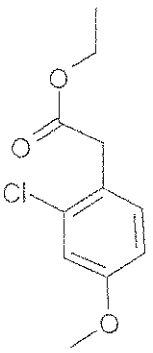
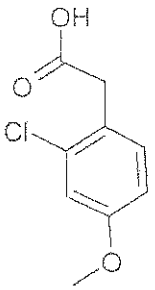
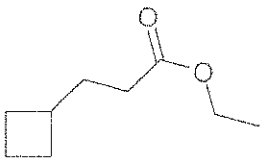
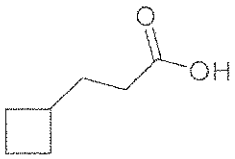
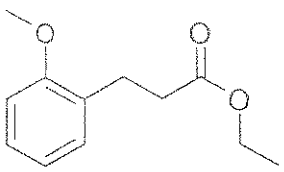
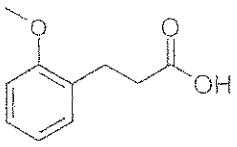
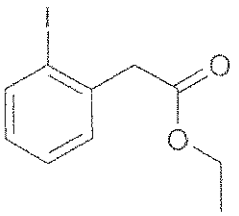
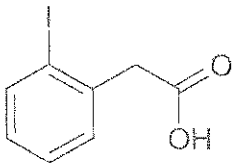
MS ( ESI pos ): m/z = 243/45 (Br) $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 5U, using the corresponding acids as starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI m/z) |
|---|---|---|---|---|
| Exp. 5V |  |  | | 185 $(M+H)^+$ |
| Exp. 5Y |  |  | 1.56 (Method 1) | 199/201 (Cl) $(M+H)^+$ |
| Exp. 5W |  |  | 1.53 (Method 1) | 201 $(M+H)^+$ |
| Exp. 5X |  |  | | 171 $(M+H)^+$ |
| Exp. 5Z |  |  | 1.74 (Method 1) | 233/235/237 (2Cl) $(M+H)^+$ |
| Exp. 5AA racem. mixture |  |  | | 133 $(M+H)^+$ |

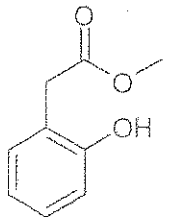
| | | | | |
|---|---|---|---|---|
| Exp. 5AB |  |  | | 201 $(M+H)^+$ |
| Exp. 5AC |  |  | 1.65 (Method 1) | 157/58 $(M+H)^+$ |
| Exp. 5AD |  |  | 1.36 (Method 1) | 195 $(M+H)^+$ |
| Exp. 5AE |  |  | 1.69 (Method 1) | 249/50 $(M+H)^+$ |
| Exp. 5AF racem. mixture |  |  | | commerciall y available |
| Exp. 5AG |  |  | 1.46 (Method 1) | |

| | | | | |
|---|---|---|---|---|
| Exp. 5AH |  |  | 1.63 (Method 1) | |
| Exp. 5AI |  |  | | 185 $(M+H)^+$ |
| Exp. 5AJ |  |  | 1.43 (Method 1) | 213 $(M+H)^+$ |
| Exp. 5AK |  |  | | |
| Exp. 5AL |  |  | 1.58 (Method 1) | 235/237 (Cl) $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 5ALA |  |  | 1.29 (Method 1) | 129 $(M+H)^+$ |
| Exp. 5ALB |  |  | 1.54 (Method 1) | 229/231 (Cl) $(M+H)^+$ |
| Exp. 5ALC |  |  | 1.62 (Method 1) | 157 $(M+H)^+$ |
| Exp. 5ALD |  |  | 1.56 (Method 1) | 209 $(M+H)^+$ |
| Exp. 5ALE |  |  | 1.59 (Method 1) | 291 $(M+H)^+$ |

Example 5AM

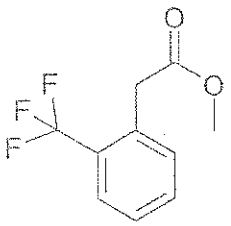
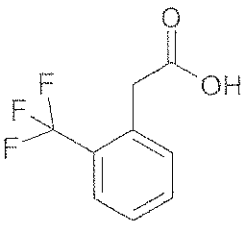
The following example was synthesized in analogy to the preparation of Example 5U, using the corresponding acid as starting material and methanol as solvent.



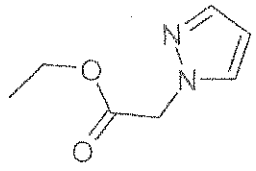
HPLC-MS (Method 1): $R_t$: 1.04 min

MS ( ESI pos ): m/z = 167 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 5AM, using the corresponding acids as starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 5AMA |  |  | 1.52 (Method 1) | 236 $(M+NH_4)^+$ |

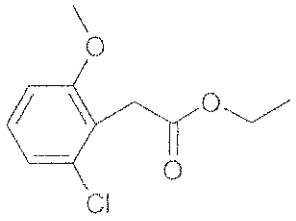
Example 5AN



6.0 g (88.5 mmol) pyrazole was dissolved in 60 mL DMSO and 10.4 g (93 mmol) potassium-tert-butylate was added in portions, keeping the temperature between 20-25°C. The reaction mixture stirred 10 min at room temperature. 10.8 mL (93 mmol) ethyl bromacetate was added drop wise, keeping the temperature between 25-35°C. The reaction mixture was stirred for 2h at room temperature. The reaction mixture was added to a saturated aqueous solution of NaCl and extracted with ethyl acetate. The organic layer was dried, filtered, and the filtrate was evaporated under reduced

pressure. The residue was purified by preparative MPLC ($SiO_2$, eluent dichloromethane / methanol 95/5).10.4 g (38 %) of the product were obtained.

Example 5AO

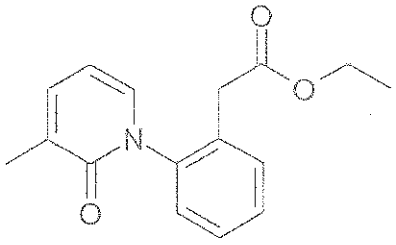


1.83 g ( 7.7 mmol) of Example 4B was mixed with in 60 mL 4N HCl and cooled with an ice bath. A solution of 1.15 g (16.4 mmol) sodium nitrite in 13.5 mL water was added drop wise. After 10 min a solution of 3.9 g (39.5 mmol) copper(I)chloride in 20 mL conc. HCl was added drop wise. The reaction mixture was allowed to turn to room temperature and stirred for 30 min. The mixture was extracted with ethyl acetate. The organic layer was neutralized with potassium carbonate, filtered over celite and the filtrate extracted with water. The organic layer was dried, filtered and the filtrate was evaporated under reduced pressure. 1.24 g (62 %) of the product were obtained.

HPLC-MS (Method 1): $R_t$: 1.60 min

MS ( ESI pos ): m/z = 229/231 (Cl) $(M+H)^+$

Example 5AP



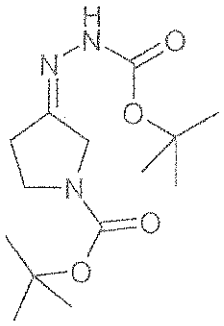
Under argon 1.00 g (4.11 mmol) of example 5U, 540 mg (4.95 mmol) 3-methylpyridone and 80 mg ( 0.42 mmol) copper-(I) iodide were mixed with 5 ml DMSO and 1.14 g (8.25 mmol) potassium carbonate and 120 mg (0.82 mmol) 8-hydroxyquinoline were added. The mixture was stirred for 48 h at 120°C. After

cooling to room temperature the mixture was dissolved in ethyl acetate and washed with 1 M HCl and saturated sodium chloride solution. The organic phase was separated, dried and evaporated. The residue was purified by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). The acetonitrile was evaporated and the remainder extracted with ethyl acetate. The organic phase was dried and evaporated to yield 633 mg (57 %) of the desired product.

HPLC-MS (Method 1): $R_t$: 1.56 min

MS ( ESI pos ): m/z = 272 $(M+H)^+$

Example 6A



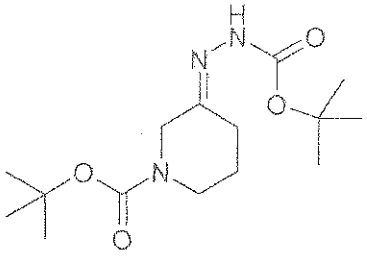
10 g (54 mmol) 1-N-Boc-3-pyrrolidinone was dissolved in 50 mL ethanol and 7.3 g (55.2 mmol) tert-butyl carbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was purified by preparative MPLC ($SiO_2$, eluent dichloromethane / methanol 95/5). 18 g (89 %) of the product were obtained as oil.

HPLC-MS (Method 1): $R_t$: 1.35 min

MS (ESI neg.): m/z = 298 $(M-H)^-$

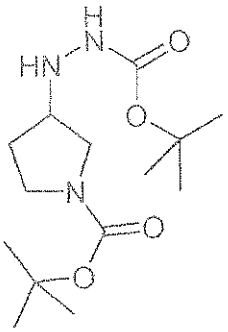
Example 6B

The following example was synthesized in analogy to the preparation of Example 6A, using 1-N-Boc-3-piperidone as starting material.



HPLC-MS (Method 1): $R_t$: 1.45 min

Example 7A, racemic mixture

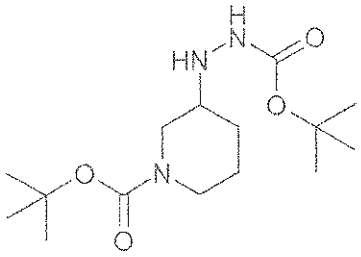


18 g (48 mmol) of Example 6A was dissolved in 300 mL methanol, 2.5 g Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue washed with methanol. The solvent was evaporated by reduced pressure. 16 g of product were obtained as a colourless oil and used without further purification.

HPLC-MS (Method 1): $R_t$: 1.36 min

Example 7B, racemic mixture

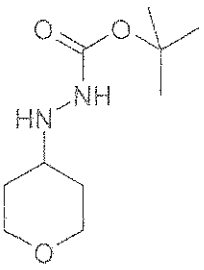
The following example was synthesized in analogy to the preparation of Example 7A, using Example 6B as starting material.



HPLC-MS (Method 1): $R_t$: 1.42 min

MS ( ESI pos ): m/z = 316 $(M+H)^+$

Example 7C

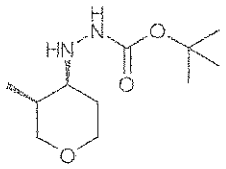
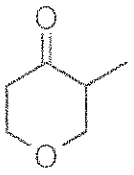
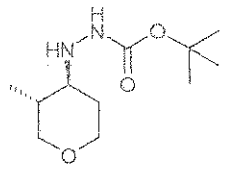
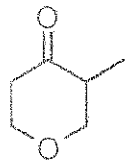
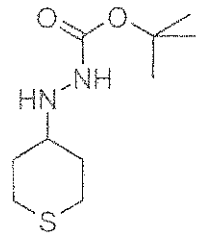
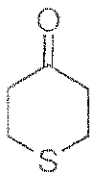


10 g (100 mmol) of tetrahydropyran-4-one was dissolved in 100 mL methanol and 14.5 g (110 mmol) tert-butylcarbazate was added. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated by reduced pressure. The residue was mixed with 140 mL acetic acid (50 %), 6.9 g (110 mmol) sodium cyanoborohydride was added and the mixture was stirred at room temperature over night. The reaction mixture was neutralized with 4M NaOH and extracted with dichloromethane. The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and a saturated aqueous solution of sodium chloride.

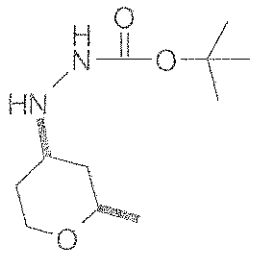
The organic layer was dried over sodium sulphate, filtered, and the filtrate was concentrated under reduced pressure. 19 g (88 %) of the product were obtained as a white solid.

MS ( ESI pos ): m/z = 217 $(M+H)^+$

The following example was synthesized in analogy to the preparation of Example 7C using the corresponding keton as starting material.

| | Structure | starting material: keton | $R_t$ [min] | MS m/z |
|---|---|---|---|---|
| Example 7CA cis, racem. mixture |  |  | 11.12 (Method 3A) | 174 [EI, $(M-56)^+$] |
| Example 7CB trans, racem. mixture |  |  | 11.22 – (Method 3A) | 174 [EI, $(M-56)^+$] |
| Example 7CC |  |  | 0.99 (Method 1) | 177 [ESI, $(M-56+H)^+$] |

Example 7D



Cis - racemic mixture

A solution of 2-methyl-tetrahydro-pyran-4-one (2.2 g, 19.7 mmol) in methanol (30 mL) was treated with tert-butyl carbazate (2.6 g, 19.7 mmol) and stirred for 3h at 20°C. Evaporation of solvent affords a white solid that was mixed with 30 mL acetic acid (50 % in water), and treated with sodium cyanoborohydride (1.2 g, 19.7 mmol) portion wise. The mixture was stirred at 20°C for 16h then neutralized with 5N NaOH and extracted with dichloromethane. The organic phase was washed with a saturated solution of $NaHCO_3$ and brine, dried, filtered and evaporated to give a crude solid. Separation of diastereoisomers was obtained by flash chromatography on $SiO_2$ eluting with a mixture of cyclohexane/ethyl acetate mixture of increasing polarity (from 7/3 to 1/1) to give 1.85 g (41 %) of a white solid.

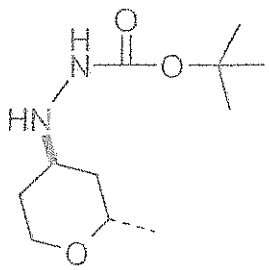
Rf: 0.29 (hexane/ethyl acetate 1:1)

HPLC-MS (Method Grad_90_10_C8_acidic): $R_t$: 1.79 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

The cis configuration between methyl and carbazyl group was implied by the ROESY correlation for H-2/H-4.

Example 7E



Trans - Racemic mixture

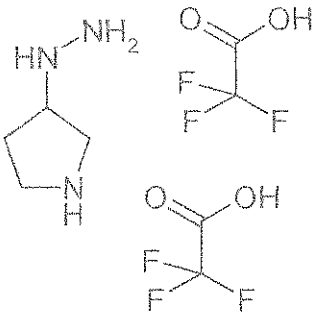
0.7 g (16 %) of a colourless oil were obtained as the second product from flash chromatography of Example 7D

Rf: 0.29 (hexane/ethyl acetate 1:1 stained with Pancaldi's reagent)

HPLC-MS (Method Grad_90_10_C8_acidic): $R_t$: 1.96 min

MS (ESI pos): m/z = 131 $(M-100+H)^+$

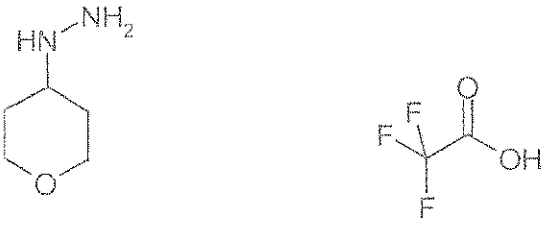
Example 8A, racemic mixture



14 g (46.5 mmol) of Example 7A were dissolved in 50 mL dichloromethane, cooled with an ice bath and 25 mL (325 mmol) trifluoroacetic acid was added. The reaction mixture was stirred 3h at room temperature. The solvent was evaporated under reduced pressure. The residue was purified by preparative MPLC ($SiO_2$, eluent dichloromethane / methanol 8/2). 12 g (78 %) of the product were obtained.

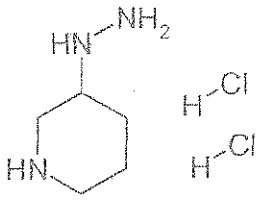
Example 8B

The following example was synthesized in analogy to the preparation of Example 8A, using Example 7C as starting material.



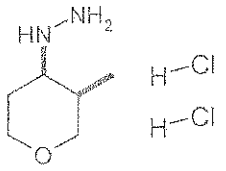
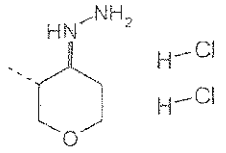
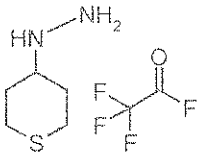
MS (ESI pos): m/z = 117 $(M+H)^+$

Example 8C, racemic mixture

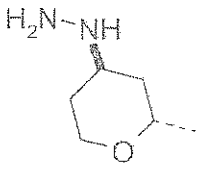


13.0 g (37.1 mmol) of Example 7B were dissolved in 5 mL dioxane and 93 mL (371 mmol) of hydrochloride acid in dioxane (4 M) were added. The reaction mixture was stirred over night at room temperature. 40 mL diethyl ether were added and the mixture stirred 15 min at room temperature. The reaction mixture was filtered. 7.0 g (100 %) of the product were obtained as white solid.

The following examples were synthesized in analogy to the preparation of example 8C using the corresponding Boc-hydrazine as starting material.

| | Structure | starting material: Boc-hydrazine | MS m/z |
|---|---|---|---|
| Example 8CA cis, racem. mixture |  | Example 7CA | 131 $(M+H)^+$ |
| Example 8CB trans, racem. mixture |  | Example 7CB | 131 $(M+H)^+$ |
| Example 8CC |  | Example 7CC | 133 $(M+H)^+$ |

Example 8D



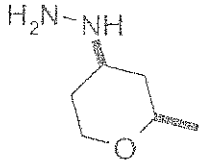
trans - racemic mixture

A solution of Example 7E (700mg, 3 mmol) in dioxane (5 mL) was treated with 4N HCl in dioxane (15 mL, 60 mmol) and the mixture stirred at 20°C for 18h. The solvent was evaporated to give 560 mg (91 %) of a sticky solid that was used in the next step without further purification.

HPLC-MS (Grad_C8_$NH_4COOH$_Lowmass): $R_t$: 0.67 min

MS (ESI pos): m/z = 131 $(M+H)^+$

Example 8E



cis -racemic mixture

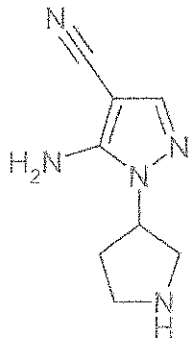
In analogy to the preparation of Example 8D, the title compound was obtained using Example 7D as starting material.

Yield: 68.3 %

HPLC-MS (Method Grad_C8_$NH_4COOH$_Lowmass): $R_t$: 0.70 min

MS (ESI pos): m/z = 131 $(M+H)^+$

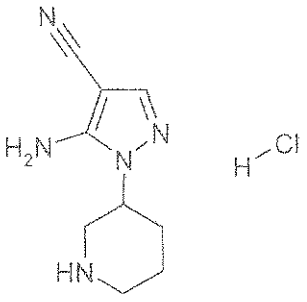
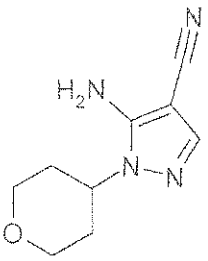
Example 9A, racemic mixture

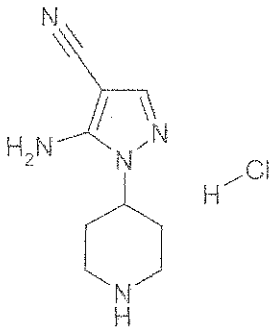
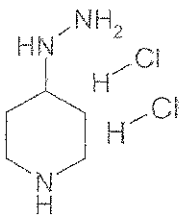
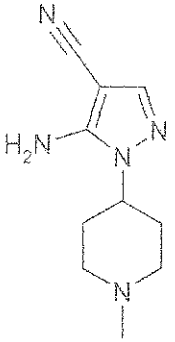
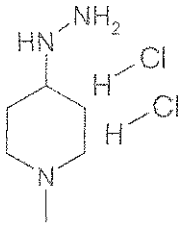
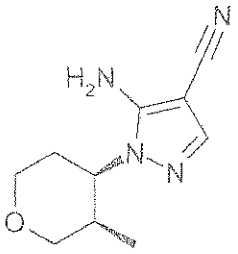
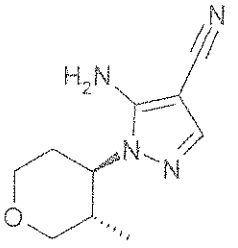
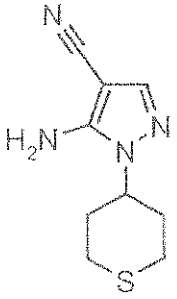


32.0 g (77.8 mmol) of Example 8A was mixed with with 12.0 g (98.3 mmol) of ethoxymethylene-malonodinitrile in 250 mL ethanol, and 40 mL (288 mmol) of triethylamine were added. The reaction mixture was heated to 50°C for 2h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC ($SiO_2$, eluent dichloromethane / methanol 8/2).

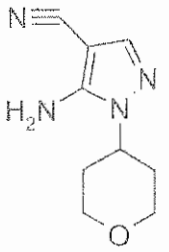
HPLC-MS (Method 1): $R_t$: 0.29 min

The following examples were synthesized in analogy to the preparation of Example 9A, using the corresponding hydrazines as starting materials.

| | structure | starting material | $R_t$[min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 9B racem. mixture |  | Example 8C | 0.59 (Method1) | 192 $(M+H)^+$ |
| Exp. 9C |  | Example 8B | 0.76 (Method1) | 193 $(M+H)^+$ |

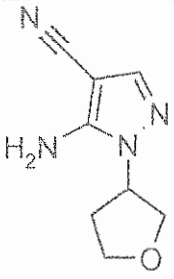
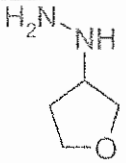
| | | | | |
|---|---|---|---|---|
| Exp. 9D |  |  | 0.32 (Method1) | 192 $(M+H)^+$ |
| Exp. 9E |  |  | 0.40 (Method1) | 206 $(M+H)^+$ |
| Example 9EA cis, racem. mixture |  | Example 8CA | 1.90 Grad C8-$NH_4CCOH$ | 207 $(M+H)^+$ |
| Example 9EB trans, racem. mixture |  | Example 8CB | 1.87 Grad C8-$NH_4CCOH$ | 207 $(M+H)^+$ |
| Example 9EC |  | Example 8CC | 1.01 (Method1) | 209 $(M+H)^+$ |

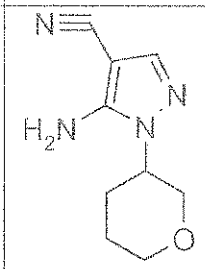
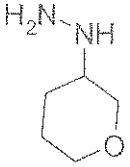
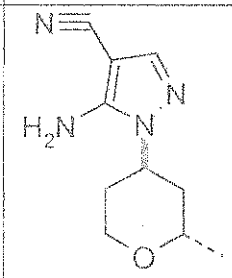
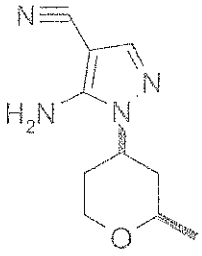
Example 9F



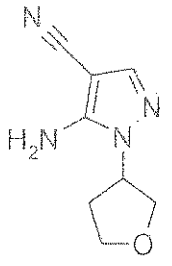
A mixture of 4.4 g (38 mmol) of (tetrahydro-pyran-4-yl)-hydrazine and 4.7 g (38 mmol) of ethoxymethylene-malononitrile in 90 mL of ethanol and 10.5 mL (103 mmol) of triethylamine was stirred at 50°C for 30 min. After cooling to 20°C the solvent was removed under reduced pressure and the residue was treated with a mixture of water / dichloromethane = 1/1. The resulting suspension was stirred for 15 min and then filtered to give a yellow solid that was washed subsequently with dichloromethane, water and dichloromethane. The solid was dried at 45°C under reduced pressure. 2.7 g (37 %) of the title compound were obtained as yellow solid and used in the next step without further purification.

The following examples were synthesized in analogy to the preparation of Example 9F, using the corresponding hydrazines as starting materials:

| | Structure | starting material: hydrazine | $R_t$ [min] | MS m/z |
|---|---|---|---|---|
| Example 9G racem. mixture |  |  | 1.31 (Method Grad_90_10_C8_acidic) | 179 $(M+H)^+$ |

| | Structure | starting material: hydrazine | $R_t$ [min] | MS m/z |
|---|---|---|---|---|
| Example 9H racem. mixture |  |  | 4.97 (Method 1E hydro) | 193 $(M+H)^+$ |
| Example 9I trans; racem. mixture |  | Example 8D | 2.14 (Method Grad_10_90_C8_acidic) | 207 $(M+H)^+$ |
| Example 9J cis; racem. mixture |  | Example 8E | 1.91 (Method Grad_10_90_C8_acidic) | 207 $(M+H)^+$ |

Example 9GA (Enantiomer A)



Enantiomer A

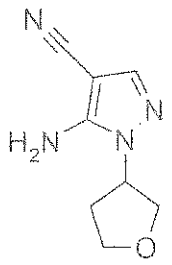
Example 9G was submitted for chiral separation to isolate its enantiomers. The enantiomer labeled A, of unknown but single stereochemistry was isolated using the following conditions.

| | |
|---|---|
| Amount supplied | 5g |
| Chiral Column | Daicel Chiralpak AD 50 x 300 mm |
| Mobile phase | n-Hexane (60%)/methyl-tert-butyl ether (40%) /Ethanol (5 %) v/v |
| Flow rate | 20 mL/min |
| Detection | UV at 254 nm |
| Injection mode | continuous |

Obtained 1g of enantiomer A.

Enantiomeric excess 99.3%; retention time 27.83 min; (analytical method: Chiral 3)

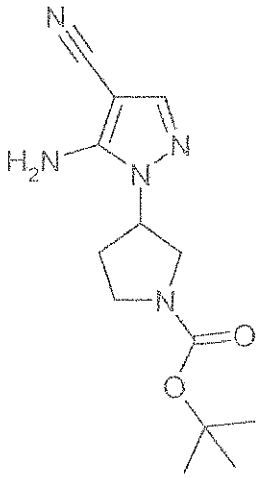
Example 9GB (Enantiomer B)



Enantiomer B

Isolated using the same conditions as enantiomer A, obtaining 0.5 g ; enantiomeric excess 96.7%; $R_t$:30.94 min; (analytical method: Chiral 3).

Example 10A, racemic mixture

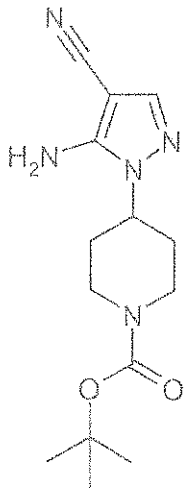
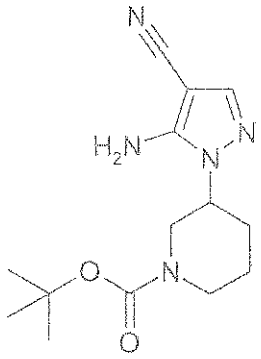


4.0 g (22.6 mmol) of Example 9A were mixed with in 60 mL tetrahydrofuran, and 5.7 g (30 mmol) di-tert-butyl-dicarbamate was added. The reaction mixture was heated to 60°C for 5h. After cooling to room temperature the solvent was removed under reduced pressure. The residue was purified by preparative MPLC ($SiO_2$, eluent dichloromethane/methanol 9/1).

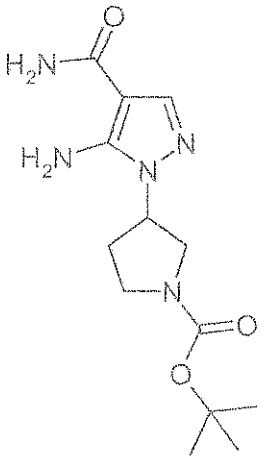
HPLC-MS (Method 1): $R_t$: 1.28 min

MS ( ESI pos ): m/z = 278 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 10A, using the corresponding pyrazoles as starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 10B |  | Example 9D | 1.30 (Method 1) | 292 $(M+H)^+$ |
| Exp. 10C racem. mixture |  | Example 9B | 1.33 (Method 1) | 292 $(M+H)^+$ |

Example 11A, racemic mixture

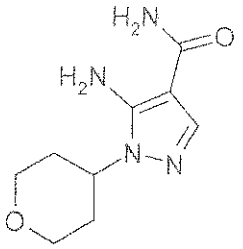
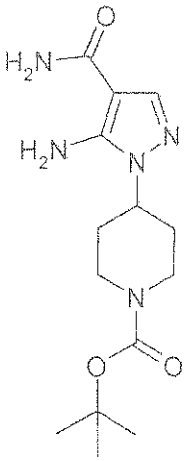


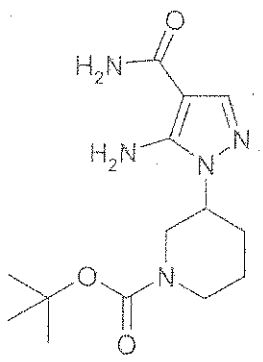
2.4 g (8.96 mmol) of Example 10A were dissolved in 30 mL ethanol. At room temperature a solution of 10 mL (120 mmol) hydrogen peroxide (35 % in water) and 50 mL ammonia (25 % in water) was added slowly over a period of 10 min. The reaction mixture was stirred at room temperature for 2h. The solution was carefully concentrated to a volume of 50 mL under reduced pressure. A precipitate formed and was collected by filtration. 1.3 g (50 %) of the product were obtained as a solid.

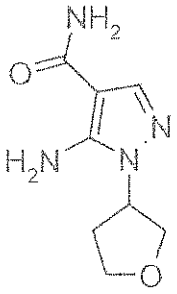
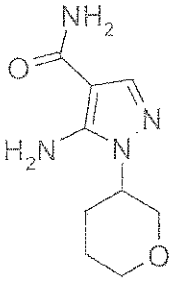
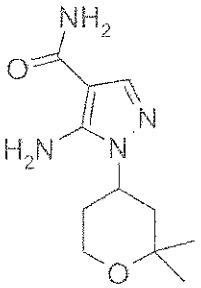
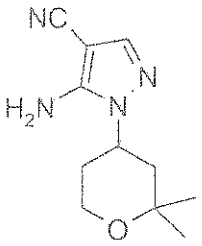
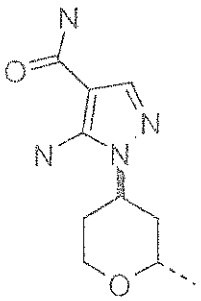
HPLC-MS (Method 1): $R_t$: 1.08 min

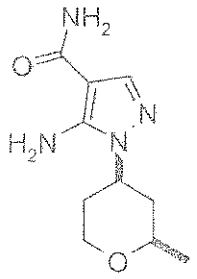
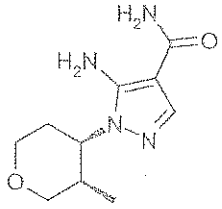
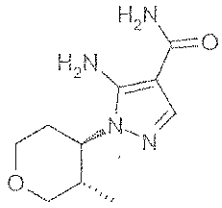
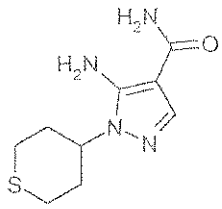
MS ( ESI pos ): m/z = 296 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 11A, using the corresponding pyrazoles as starting materials.

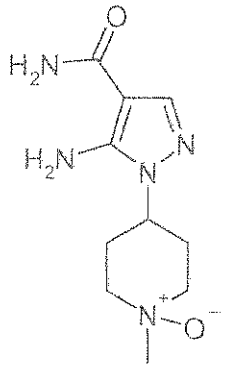
| | structure | starting material | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|
| Exp. 11B |  | Example 9C | 0.44 (Method 1) | 211 $(M+H)^+$ |
| Exp. 11C |  | Example 10B | 1.12 (Method 1) | 308 $(M-H)^-$ |

| | | | | |
|---|---|---|---|---|
| Exp. 11D racem. mixture |  | Example 10C | 1.13 (Method 1) | 310/311 $(M+H)^+$ HPLC-MS |

| | | | | |
|---|---|---|---|---|
| Exp. 11E racem. mixture |  | Example 9G | 2.39 (Method 2F) | 197 $(M+H)^+$ |
| Exp. 11F racem. mixture |  | Example 9H | 0.95 (Method Grad_C8_NH$_4$COOH) | 211 $(M+H)^+$ |
| Exp. 11G racem. mixture |  |  | 1.57 (Method Grad_C8_NH$_4$COOH) | 339 $(M+H)^+$ |
| Exp. 11H trans, racem. mixture |  | Example 9I | 1.27 (Method Grad_90_10_C8_acidic) | 225 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 11I cis, racem. mixture |  | Example 9J | 1.27 (Method Grad_90_10 _C8_acidic) | 225 $(M+H)^+$ |
| Example 11IA cis, racem. mixture |  | Example 9EA | 1.11 (Method Grad_C8_NH 4COOH) | 225 $(M+H)^+$ |
| Example 11IB trans, racem. mixture |  | Example 9EB | 1.14 (Method Grad_C8_NH 4COOH) | 225 $(M+H)^+$ |
| Example 11IC |  | Example 9EC | | 227 $(M+H)^+$ |

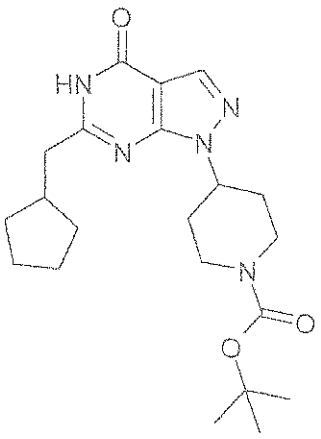
Example 11J, racemic mixture



2.30 g (11.2 mmol) of Example 9E were dissolved in 6 mL dimethylsulfoxide. Under ice cooling 8 mL (77.6 mmol) hydrogen peroxide and 1.7 g (12.3 mmol) potassium carbonate were added. Then the reaction mixture was stirred 15 min at room temperature. The reaction mixture was cooled with an ice bath, 100 mL of water were added and extracted with dichloromethane. The water phase was evaporated under reduced pressure. The residue was mixed with in dichloromethane and filtered. 2.8 g (52 %) of the product were obtained as a white solid.

HPLC-MS (Method1): $R_t$: 0.24 min

Example 12A



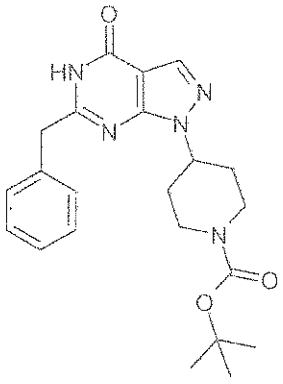
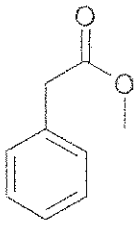
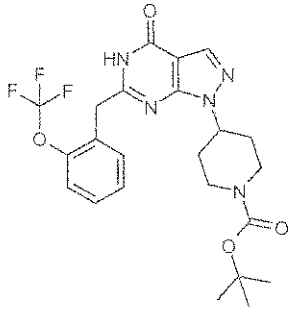
660 mg (2.13 mmol) of Example 11C were dissolved in 15 mL of absolute ethanol. 1.85 g (10.7 mmol) of Example 5AC and 430 mg (10.7 mmol) of sodium hydride (60

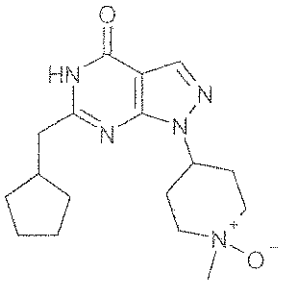
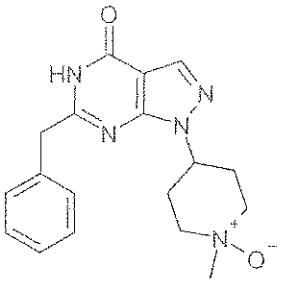
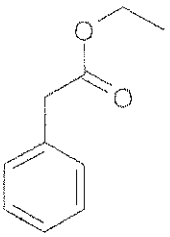
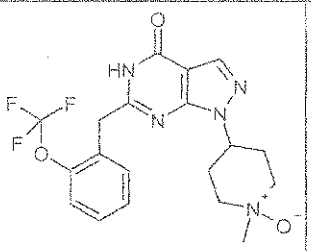
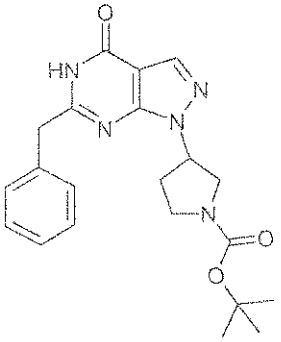
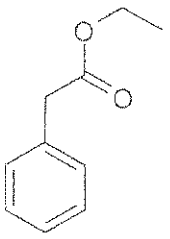
% suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 320 mg (38 %) of the product were obtained as a white solid.

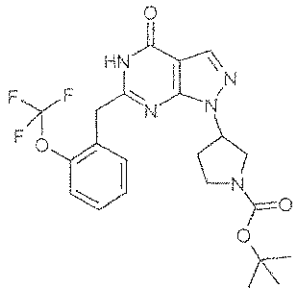
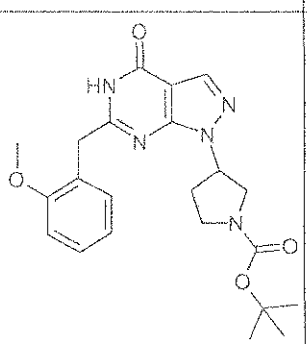
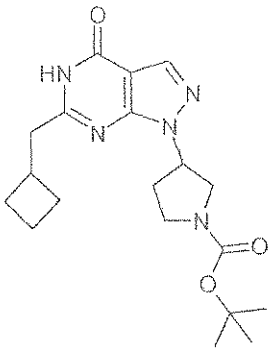
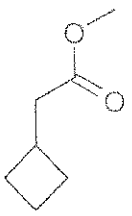
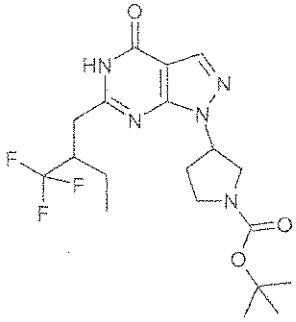
HPLC-MS (Method1): $R_t$: 1.61 min

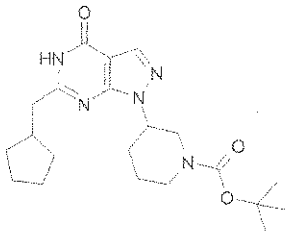
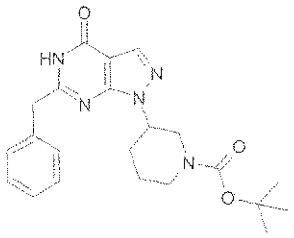
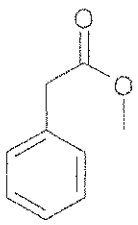
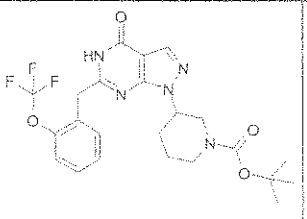
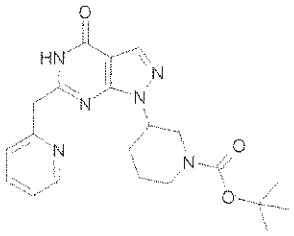
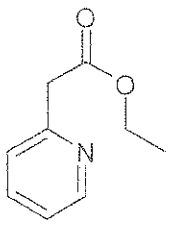
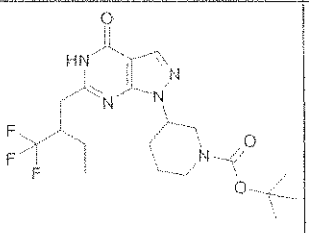
MS ( ESI pos ): m/z = 402 $(M+H)^+$

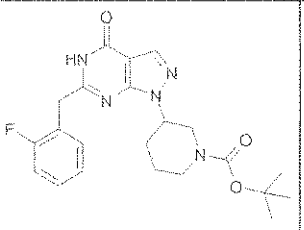
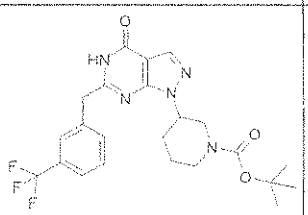
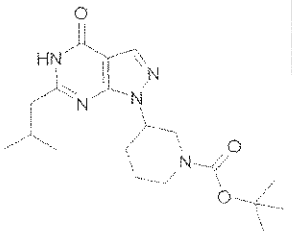
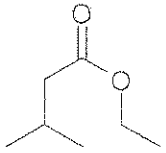
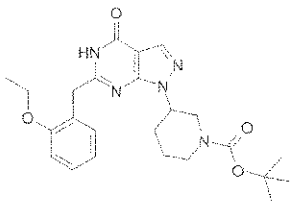
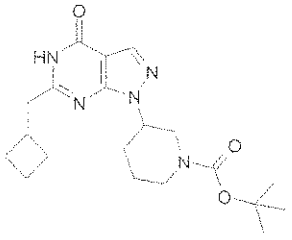
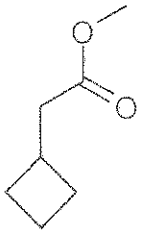
The following examples were synthesized in analogy to the preparation of Example 12A, using the corresponding pyrazoles and esters as starting materials.

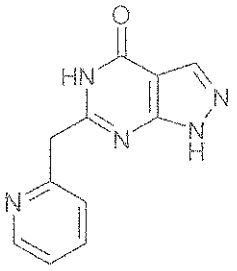
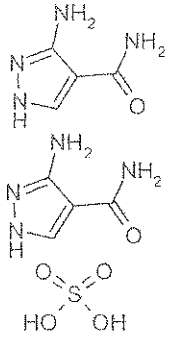
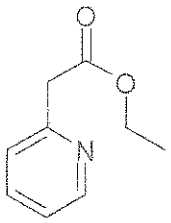
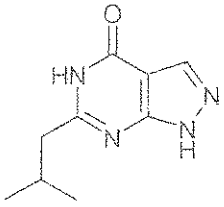
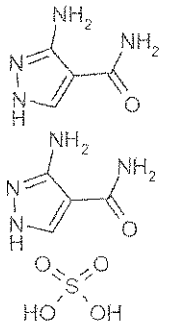
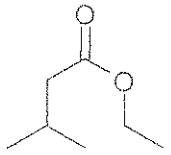
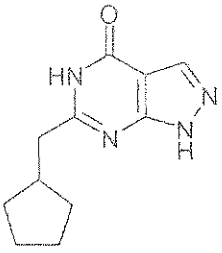
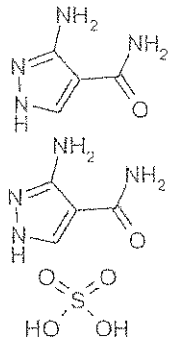
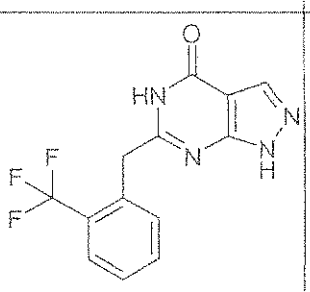
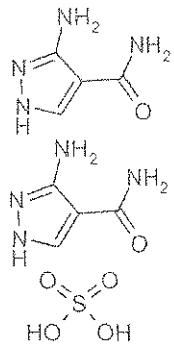
| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12B |  | Exp. 11C |  | 1.52 (Method 1) | 410 $(M+H)^+$ |
| Exp. 12C |  | Exp. 11C | Example 5AE | 1.66 (Method 1) | 492 $(M-H)^-$ |

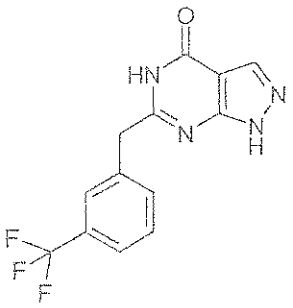
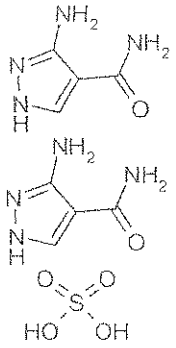
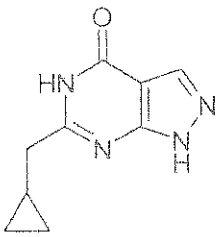
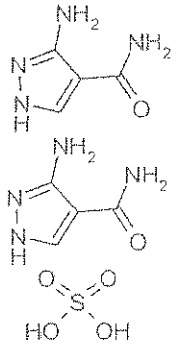
| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12D mixture of stereoisomers |  | Exp. 11J | Example 5AC | 1.02 (Method 1) | 332 $(M+H)^+$ |
| Exp. 12E mixture of stereoisomers |  | Exp. 11J |  | 0.96 (Method 1) | 340 $(M+H)^+$ |
| Exp. 12F mixture of stereoisomers |  | Exp. 11J | Example 5AE | 1.12 (Method 1) | 424 $(M+H)^+$ |
| Exp. 12G racem. mixture |  | Exp. 11A |  | 1.49 (Method 1) | 396 $(M+H)^+$ |

| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12H racem. mixture |  | Exp. 11A | Example 5AE | 1.62 (Method 1) | 480 $(M+H)^+$ |
| Exp. 12I racem. mixture |  | Exp. 11A | Example 5AD | 1.52 (Method 1) | 426 $(M+H)^+$ |
| Exp. 12J racem. mixture |  | Exp. 11A |  | 1.49 (Method 1) | 374 $(M+H)^+$ |
| Exp. 12K mixture of stereoisomers |  | Exp. 11A | Example 5T | 1.58 (Method 1) | 428 $(M-H)^-$ |

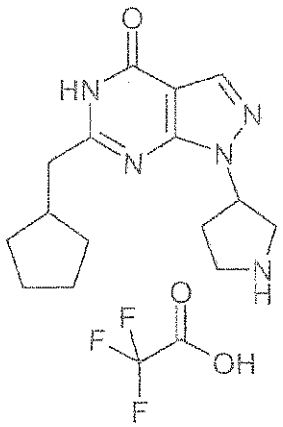
| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12L racem. mixture |  | Exp. 11D | Example 5AC | 1.65 (Method 1) | 402 $(M+H)^+$ |
| Exp. 12M racem. mixture |  | Exp. 11D |  | 1.55 (Method 1) | 408 $(M+H)^+$ |
| Exp. 12N racem. mixture |  | Exp. 11D | Example 5AE | 1.67 (Method 1) | 494 $(M+H)^+$ |
| Example 12O racem. mixture |  | Exp. 11D |  | 1.13 (Method 1) | 411 $(M+H)^+$ |
| Exp. 12P mixture of stereoisomers |  | Exp. 11D | Example 5T | 1.63 (Method 1) | 444 $(M+H)^+$ |

| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12Q racem. mixture |  | Exp. 11D | Example 5AG | 1.53 (Method 1) | 428 $(M+H)^+$ |
| Exp. 12R racem. mixture |  | Exp. 11D | Example 5AH | 1.66 (Method 1) | 478 $(M+H)^+$ |
| Exp. 12S racem. mixture |  | Exp. 11D |  | 1.51 (Method 1) | 376 $(M+H)^+$ |
| Exp. 12T racem. mixture |  | Exp. 11D | Example 5AK | 1.63 (Method 1) | 454 $(M+H)^+$ |
| Exp. 12U racem. mixture |  | Exp. 11D |  | 1.56 (Method 1) | 388 $(M+H)^+$ |

| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 12V |  |  |  | 1.77 (Method 2F) | 228 $(M+H)^+$ |
| Exp. 12W |  |  |  | 6.96 (Method 2F) | 193 $(M+H)^+$ |
| Exp. 12X |  |  | Example 5AC | 8.28 (Method 2F) | 219 $(M+H)^+$ |
| Exp. 12Y |  |  | Example 5AMA | 9.15 (Method 2F) | 295 $(M+H)^+$ |

| | Structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| | | | | | |
| Example 12Z |  |  | Example 5AH | 9.54 (Method 2F) | 295 $(M+H)^+$ |
| Example 12AA |  |  | Example 5ALA | 6.48 (Method 2F) | 191 $(M+H)^+$ |

Example 13A, racemic mixture

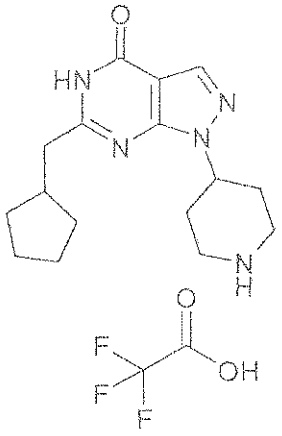


400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): $R_t$: 0.93 min

MS ( ESI pos ): m/z = 288 $(M+H)^+$

Example 13B



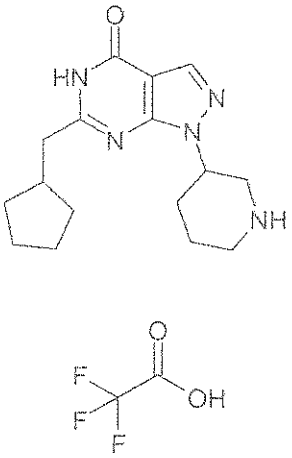
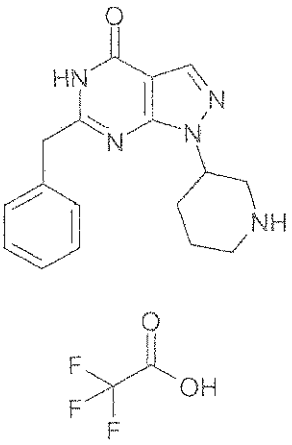
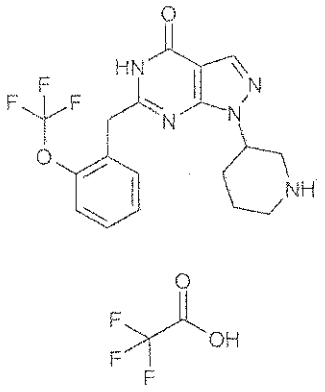
330 mg (0.82 mmol) of Example 12A was dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The remaining product was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

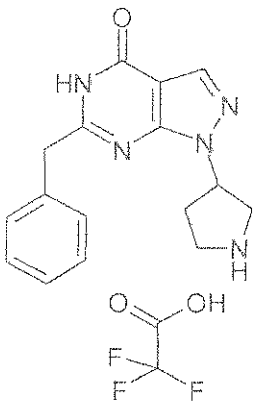
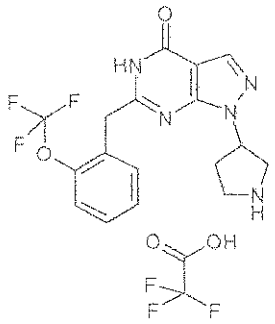
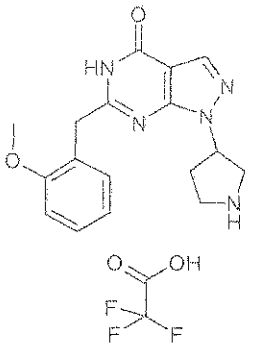
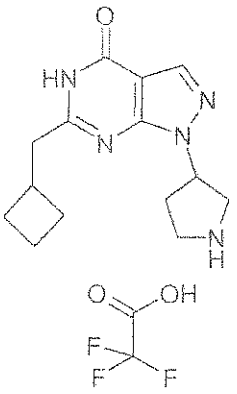
HPLC-MS (Method 1): $R_t$: 0.96 min

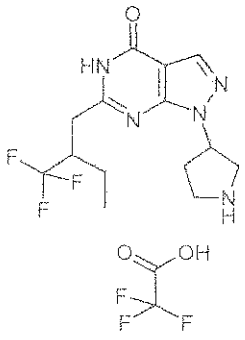
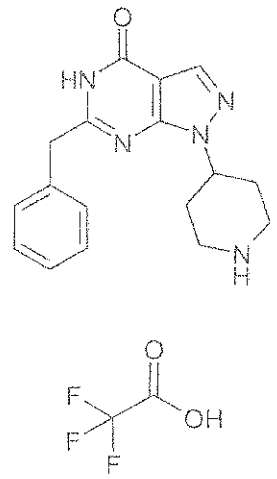
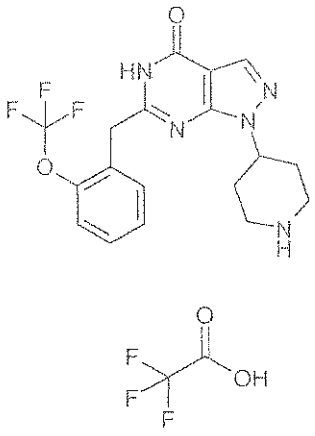
MS ( ESI pos ): m/z = 302 $(M+H)^+$

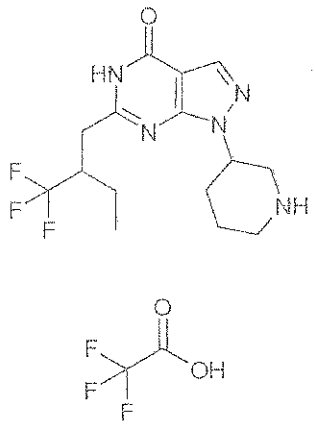
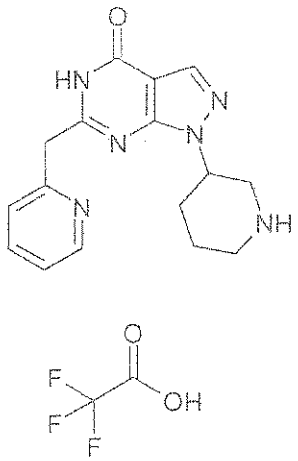
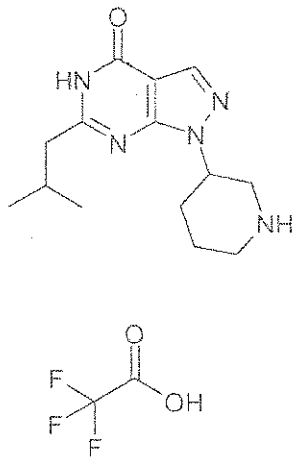
The following examples were synthesized in analogy to the preparation of Example 13B, using the corresponding Boc-protected amines as starting materials

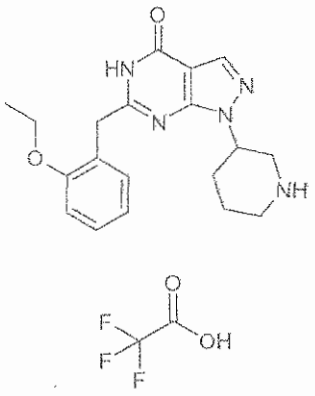
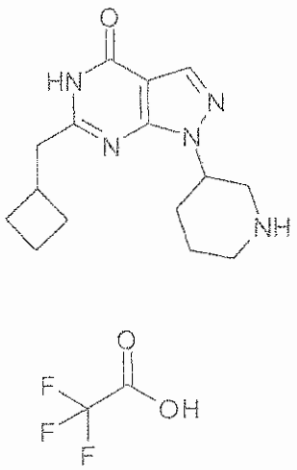
| | Structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Exp. 13C<br>racem.<br>mixture |  | Exp. 12L | 1.01<br>(Method 1) | 302 $(M+H)^+$ |
| Exp. 13D<br>racem.<br>mixture |  | Exp.<br>12M | 0.93<br>(Method 1) | 310 $(M+H)^+$ |
| Exp. 13E<br>racem.<br>mixture |  | Exp.<br>12N | 1.09<br>(Method 1) | 394 $(M+H)^+$ |

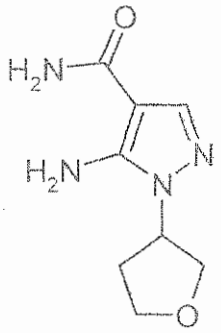
| | | | | |
|---|---|---|---|---|
| Exp. 13F racem. mixture |  | Exp. 12G | 0.92 (Method 1) | 296 $(M+H)^+$ |
| Exp. 13G racem. mixture |  | Exp. 12H | 1.08 (Method 1) | 380 $(M+H)^+$ |
| Exp. 13H racem. mixture |  | Exp. 12I | 0.96 (Method 1) | 326 $(M+H)^+$ |
| Exp. 13I racem. mixture |  | Exp. 12J | 0.89 (Method 1) | 274 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 13J racem. mixture |  | Exp. 12K | 1.0 (Method1) | 330 $(M+H)^+$ |
| Exp. 13K |  | Exp. 12B | 0.92 (Method1) | 310 $(M+H)^+$ |
| Exp. 13L |  | Exp. 12C | 1.07 (Method1) | 394 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 13M mixture of stereoisomers |  | Exp. 12P | 1.04 (Method 1) | 344 $(M+H)^+$ |
| Exp. 13N racem. mixture |  | Exp. 12O | 0.37 (Method 1) | 319 $(M+H)^+$ |
| Exp. 13O racem. mixture |  | Exp. 12S | 0.89 (Method 1) | 276 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 13P<br>racem.<br>mixture |  | Exp. 12T | 1.04<br>(Method 1) | 354 $(M+H)^+$ |
| Exp. 13Q<br>racem.<br>mixture |  | Exp.<br>12U | 0.94<br>(Method 1) | 288 $(M+H)^+$ |

Example 15A:



Enantiomer A

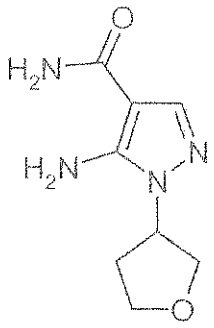
200 mg (1.12 mmol) of Example 9GA was mixed with 4.5 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave

oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 180 mg (82 %) of the product were obtained.

GC-MS (Method 3A. 1): $R_t$: 12.62 min

$[M]^+$ = 196

Example 16A:



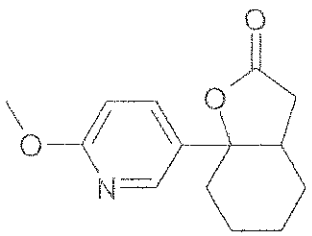
Enantiomer B

150 mg (0.84 mmol) of Example 9GB were mixed with 2.10 mL ammonia solution (30 % in water). The reaction mixture was heated to 130°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. 100 mg (60 %) of the product were obtained.

GC-MS (Method 3A. 2): $R_t$: 12.59 min

$[M]^+$ = 196

Example 17A, mixture of stereoisomers

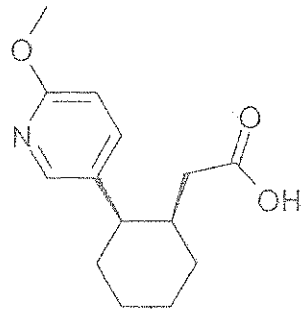


A solution of 1.00 g (5.32 mmol) 2-methoxy-5-bromopyridine in 10 mL anhydrous THF was cooled to -78°C and n-BuLi (3.66 mL, 5.85 mmol, 1.6 M in hexane) was added. After 10 min at -78°C 1.18 g (6.38 mmol) 2-oxo-cyclohexyl-acetic acid ethyl ester was added and the mixture was warmed to 25 °C. Water was added (1 mL) and the mixture was concentrated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 370 mg (28 %) of the product were obtained as an oil.

HPLC-MS (Method 1): $R_t$: 1.23 min

MS (ESI pos): m/z = 248 $(M+H)^+$

Example 18A, cis, racemic mixture



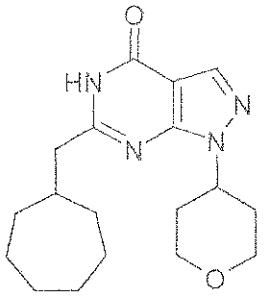
380 mg (1.54 mmol) of Example 17A was mixed with 5 mL methanol, 50 mg Pd/C (10 %) was added, and the mixture was hydrogenated at room temperature (8h, 50 psi). The reaction mixture was filtered and the residue was washed with methanol. The solvent was evaporated under reduced pressure. 340 mg (89 %) of product were obtained as colourless oil and used without further purification.

HPLC-MS (Method 1): $R_t$: 1.01 min

MS ( ESI pos ): m/z = 250 $(M+H)^+$

Exemplary embodiments:

Example1



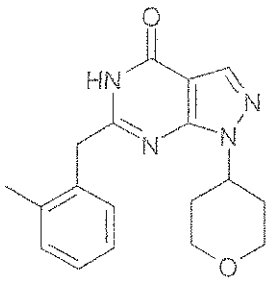
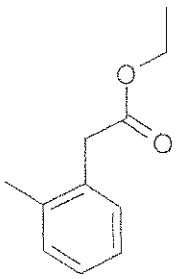
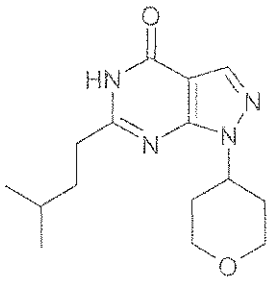
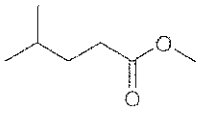
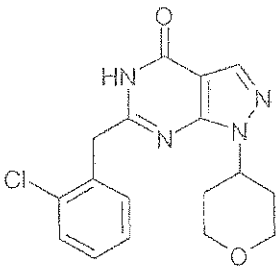
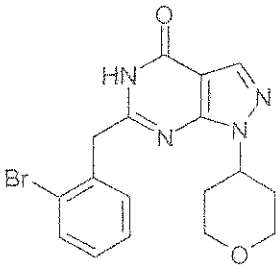
100 mg (0.48 mmol) of Example 11B were dissolved in 5 mL of absolute ethanol, 400 mg (2.17 mmol) of Example 5V and 100 mg (2.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. Cooling to room temperature was followed by evaporation of the solvent under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 29 mg (18 %) of the product were obtained as a white solid.

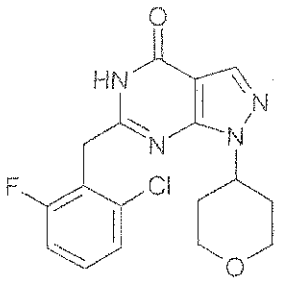
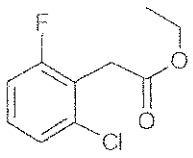
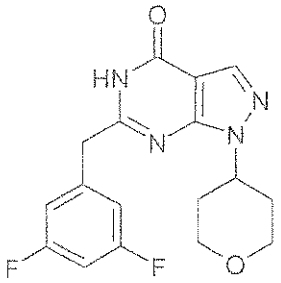
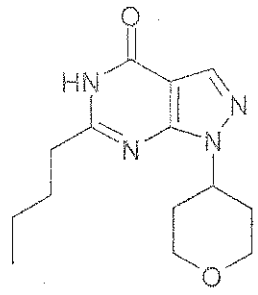
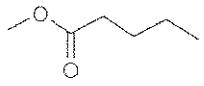
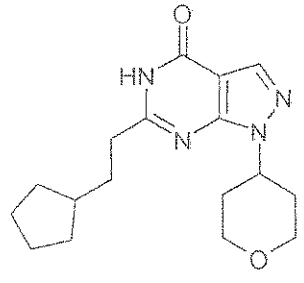
HPLC-MS (Method1): $R_t$: 1.08 min

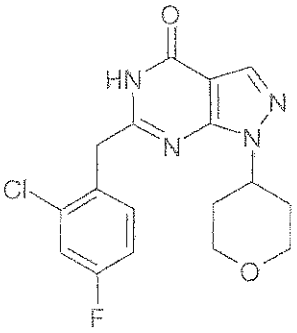
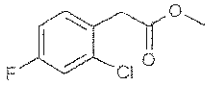
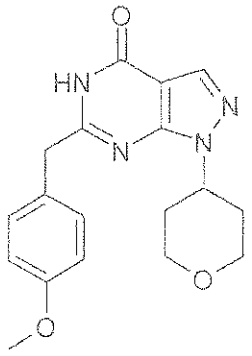
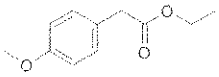
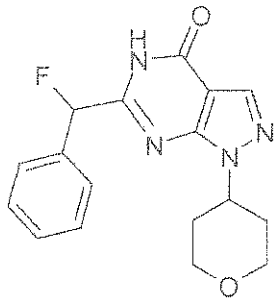
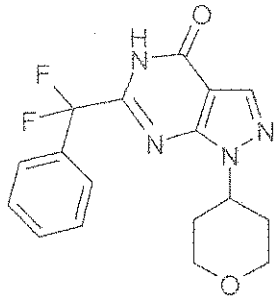
MS ( ESI pos ): m/z = 331 $(M+H)^+$

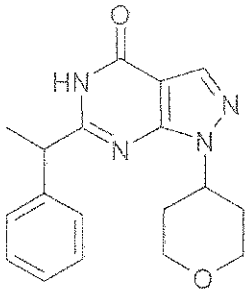
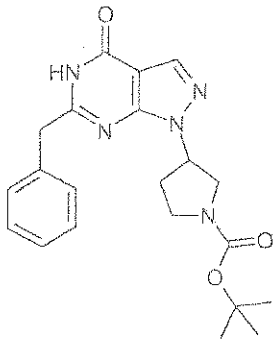
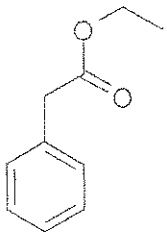
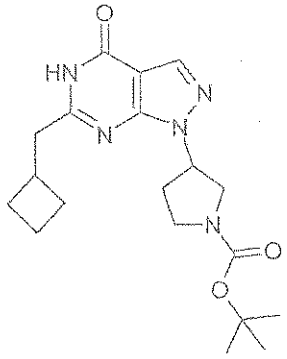
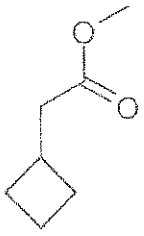
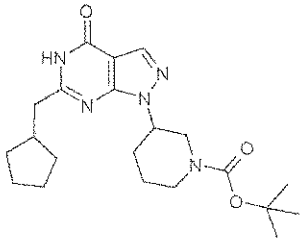
The following examples were synthesized in analogy to the preparation of Example 1, using the corresponding pyrazoles and esters as starting materials

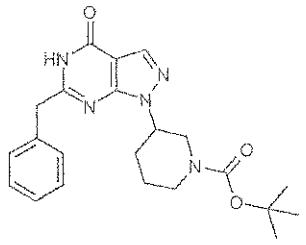
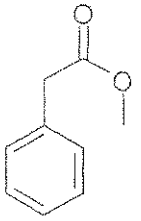
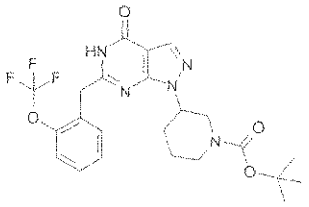
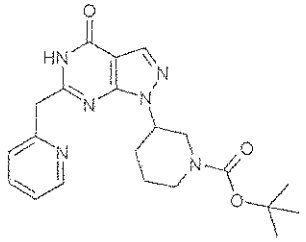
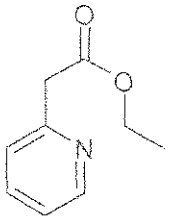
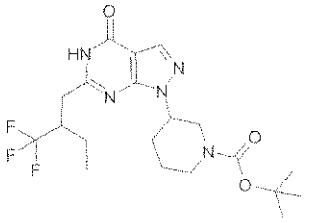
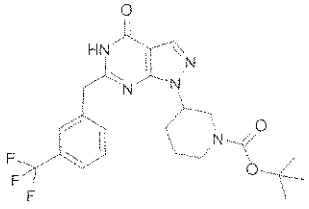
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|

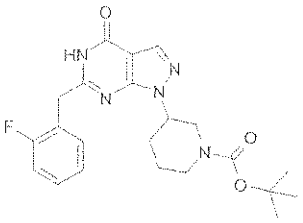
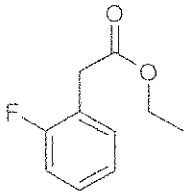
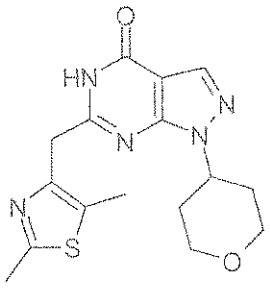
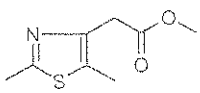
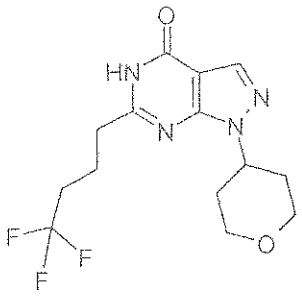
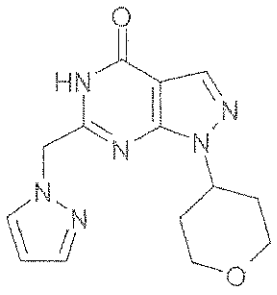
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 2 |  | Example 11B |  | 1.27 (Method 1) | 325 $(M+H)^+$ |
| Exp. 3 |  | Example 11B |  | 1.22 (Method 1) | 291 $(M+H)^+$ |
| Exp. 4 |  | Example 11B | Example 5Y | 1.23 (Method 1) | 345/347 (Cl) $(M+H)^+$ |
| Exp. 5 |  | Example 11B | Example 5U | 1.29 (Method 1) | 389/91 (Br) $(M+H)^+$ |

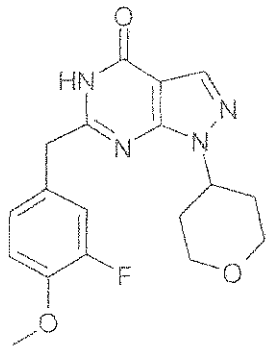
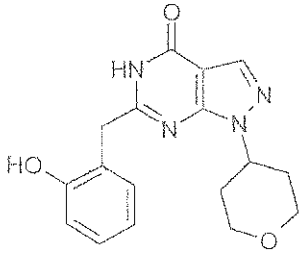
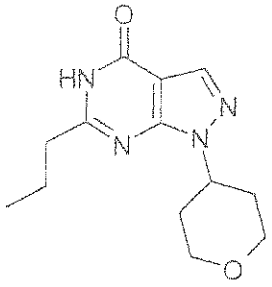
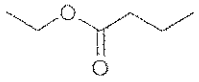
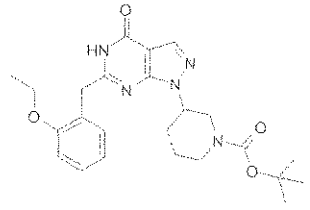
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 6 |  | Example 11B |  | 1.28 (Method 1) | 363/65 (Cl) $(M+H)^+$ |
| Exp. 7 |  | Example 11B | Example 5W | 1.22 (Method 1) | 345 $(M-H)^-$ |
| Exp. 8 |  | Exp. 11B |  | 1.14 (Method 1) | 277 $(M+H)^+$ |
| Exp. 9 |  | Exp. 11B | Example 5X | 1.37 (Method 1) | 317 $(M+H)^+$ |

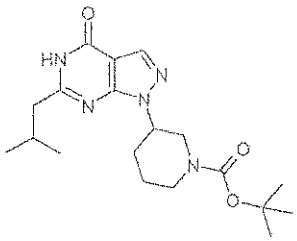
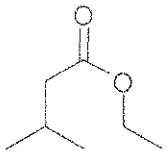
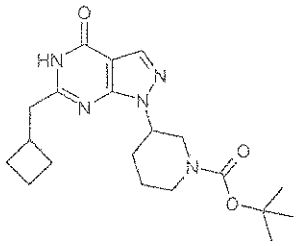
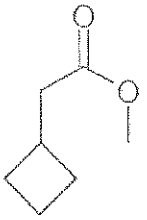
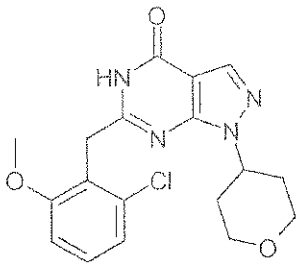
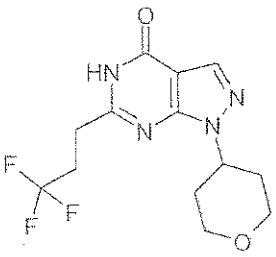
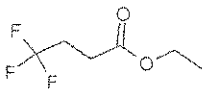
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 10 |  | Exp. 11B |  | 1.30 (Method 1) | 361/63 (Cl) $(M+H)^+$ |
| Exp. 11 |  | Exp. 11B |  | 1.18 (Method 1) | 341 $(M+H)^+$ |
| Exp. 12 racem. mixture |  | Exp. 11B | Example 5AA | 1.44 (Method 1) | 329 $(M+H)^+$ |
| Exp. 13 |  | Exp. 11B | Example 5AB | 1.26 (Method 1) | 347 $(M+H)^+$ |

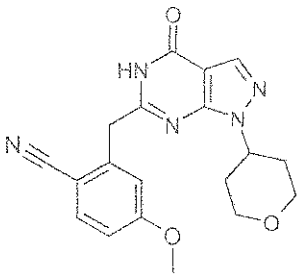
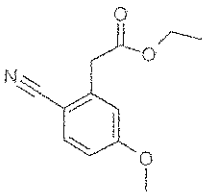
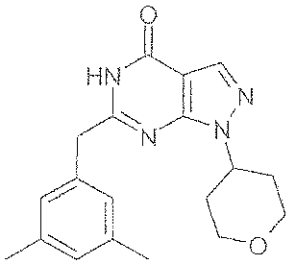
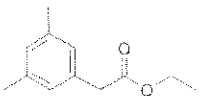
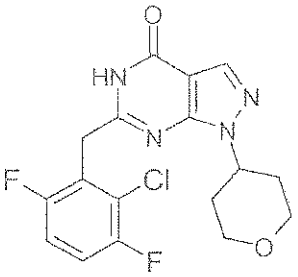
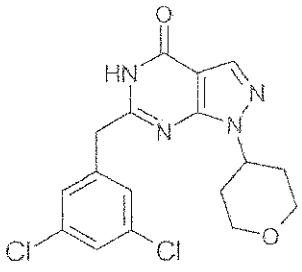
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 14 racem. mixture |  | Exp. 11B | Example 5AF | 1.28 (Method 1) | 325 $(M+H)^+$ |
| Exp. 15 racem. mixture |  | Exp. 11A |  | 1.49 (Method1) | 396 $(M+H)^+$ |
| Exp. 16 racem. mixture |  | Exp. 11A |  | 1.49 (Method 1) | 374 $(M+H)^+$ |
| Exp. 17 racem. mixture |  | Exp. 11D | Example 5AC | 1.65 (Method 1) | 402 $(M+H)^+$ |

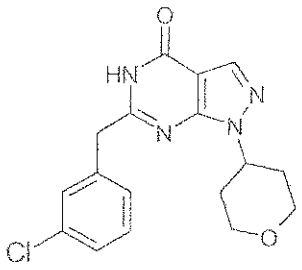
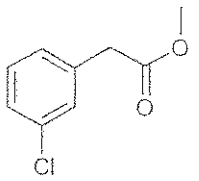
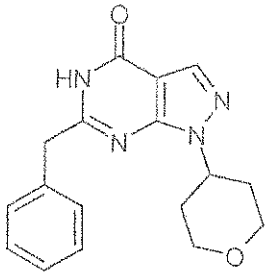
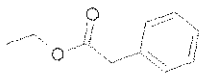
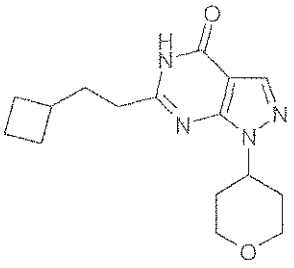
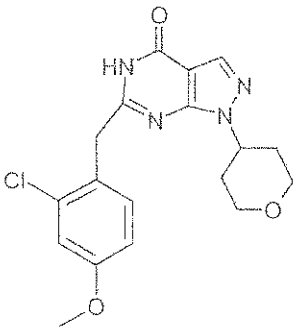
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 18 racem. mixture |  | Exp. 11D |  | 1.55 (Method 1) | 408 $(M+H)^+$ |
| Exp. 19 racem. mixture |  | Exp. 11D | Example 5AE | 1.67 (Method1) | 494 $(M+H)^+$ |
| Exp. 20 racem. mixture |  | Exp. 11D |  | 1.13 (Method 1) | 411 $(M+H)^+$ |
| Exp. 21 racem. mixture |  | Exp. 11D | Example 5T | 1.63 (Method 1) | 444 $(M+H)^+$ |
| Exp. 22 racem. mixture |  | Exp. 11D | Example 5AH | 1.66 (Method 1) | 478 $(M+H)^+$ |

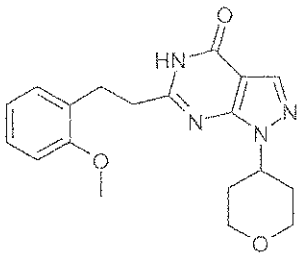
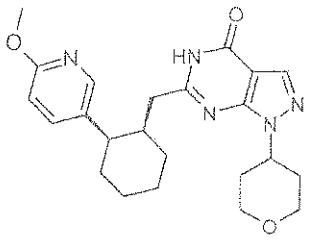
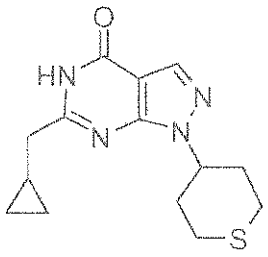
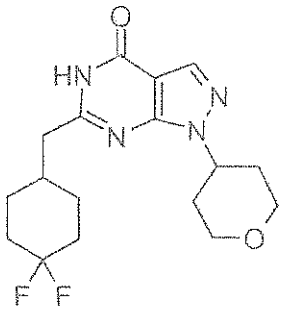
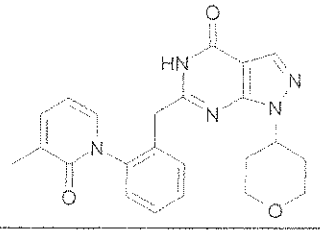
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 23 racem. mixture |  | Exp. 11D |  | 1.53 (Method 1) | 428 $(M+H)^+$ |
| Exp. 24 |  | Exp. 11B |  | 0.91 (Method 1) | 346 $(M+H)^+$ |
| Exp. 25 |  | Exp. 11B | Example 5AI | 1.17 (Method 1) | 331 $(M+H)^+$ |
| Exp. 26 |  | Exp. 11B | Example 5AN | 0.87 (Method 1) | 301 $(M+H)^+$ |

| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 27 |  | Exp. 11B | Example 5AJ | 1.17 (Method 1) | 359 $(M+H)^+$ |
| Exp. 28 |  | Exp. 11B | Example 5AM | 1.08 (Method 1) | 327 $(M+H)^+$ |
| Exp. 29 |  | Exp. 11B |  | 1.02 (Method 1) | 263 $(M+H)^+$ |
| Exp. 30 racem. mixture |  | Exp. 11D | Example 5AK | 1.63 (Method 1) | 454 $(M+H)^+$ |

| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 31 racem. mixture |  | Exp. 11D |  | 1.51 (Method 1) | 376 $(M+H)^+$ |
| Exp. 32 racem. mixture |  | Exp. 11D |  | 1.56 (Method 1) | 388 $(M+H)^+$ |
| Exp. 33 |  | Exp. 11B | Example 5AO | 1.29 (Method 1) | 375/377 (Cl) $(M+H)^+$ |
| Exp. 34 |  | Exp. 11B |  | 1.11 (Method 1) | 317 $(M+H)^+$ |

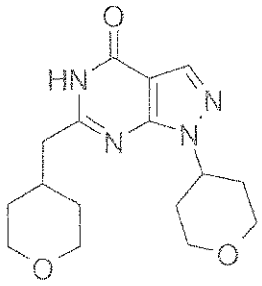
| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 35 |  | Exp. 11B |  | 1.17 (Method 1) | 366 $(M+H)^+$ |
| Exp. 36 |  | Exp. 11B |  | 1.36 (Method 1) | 339 $(M+H)^+$ |
| Exp. 37 |  | Exp. 11B | Example 5AL | 1.3 (Method 1) | 381/383 (Cl) $(M+H)^+$ |
| Exp. 38 |  | Exp. 11B | Example 5Z | 1.44 (Method 1) | 379/381/383 ($Cl_2$) $(M+H)^+$ |

| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 39 |  | Exp. 11B |  | 1.28 (Method 1) | 345/347 (Cl) $(M+H)^+$ |
| Exp. 40 |  | Exp. 11B |  | 1.16 (Method 1) | 311 $(M+H)^+$ |
| Exp. 40-1 |  | Exp. 11B | Exp. 5ALC | 1.30 (Method 1) | 303 $(M+H)^+$ |
| Exp. 40-2 |  | Exp. 11B | Example 5ALB | 1.31 (Method 1) | 375 $(M+H)^+$ |

| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| Exp. 40-3 |  | Exp. 11B | Example 5ALD | 1.25 (Method 1) | 355 $(M+H)^+$ |
| Exp. 40-4 cis, racem. mixture |  | Exp. 11B | Exp. 5HA | 1.18 (Method 1) | 424 $(M+H)^+$ |
| Exp. 40-5 |  | Exp. 11IC | Exp. 5ALA | 1.24 (Method 1) | 291 $(M+H)^+$ |
| Exp. 40-6 |  | Exp. 11B | Example 5TA | 1.22 (Method 1) | 353 $(M+H)^+$ |
| Exp. 40-7 |  | Exp. 11B | Example 5AP | 1.35 (Method 1) | 418 $(M+H)^+$ |

| | structure | starting material: pyrazole | starting material: ester | $R_t$ [min] | MS (ESI pos/neg, m/z) |
|---|---|---|---|---|---|
| | | | | | |

Example 41

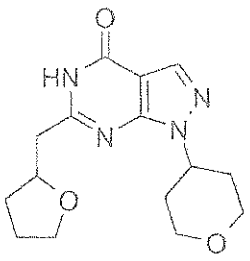
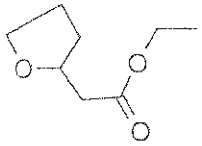
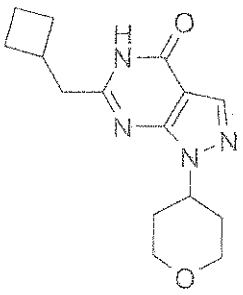
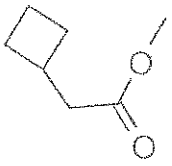
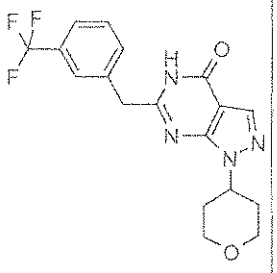
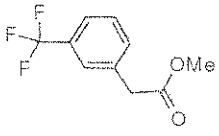
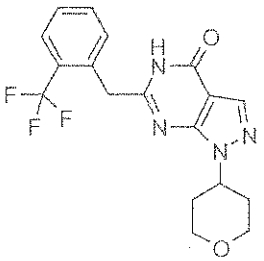
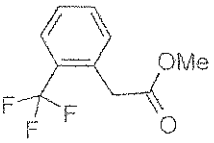


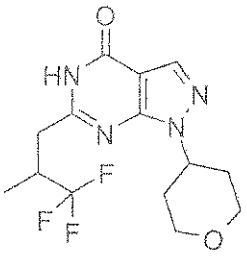
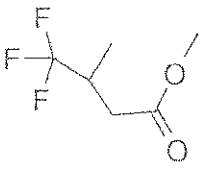
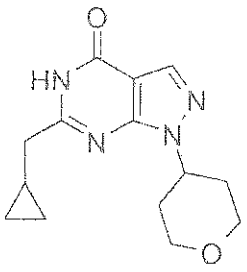
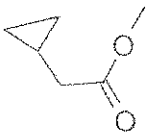
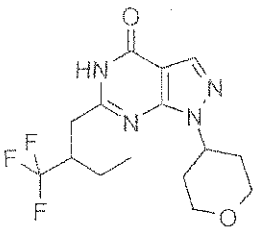
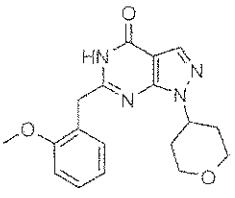
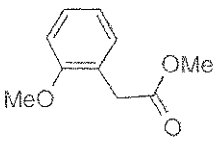
80 mg (0.38 mmol) of Example 11B were dissolved in 1 mL of absolute ethanol, 262 mg (1.52 mmol) of ethyl tetrahydropyran-4-yl-acetate, and 45.1 mg (1.10 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 40 min in a microwave oven. Cooling to 20°C was followed by evaporation of the solvent under reduced pressure. The residue was treated with water (10 mL), acidified with HCl (10 % in water) and extracted two times with dichloromethane (2 mL). The organic layer was dried over sodium sulphate, filtered and the filtrate was concentrated under reduced pressure. The residue was triturated with ether to give 65 mg (53.7 %) of the product as a white solid.

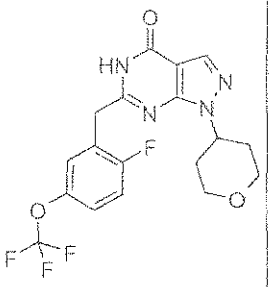
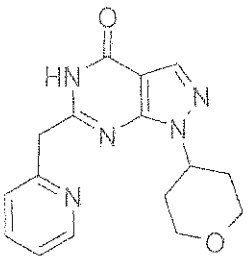
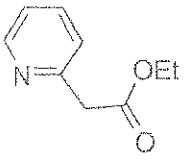
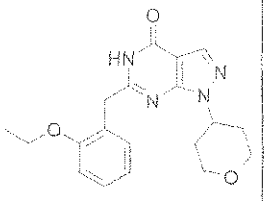
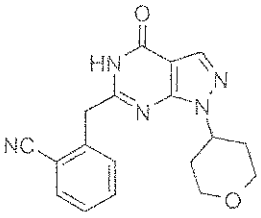
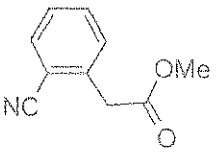
HPLC-MS (Method Grad_C8_$NH_4COOH$): $R_t$: 1.89 min

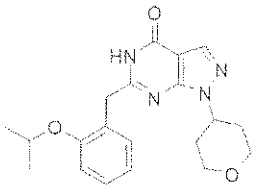
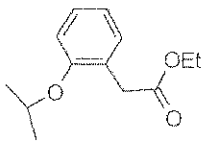
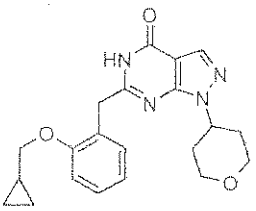
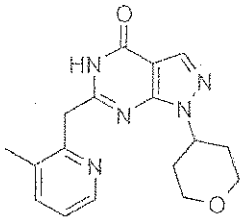
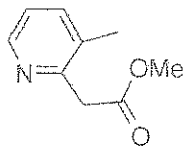
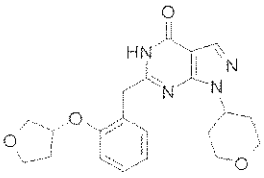
MS (ESI pos): m/z = 319 $(M+H)^+$.

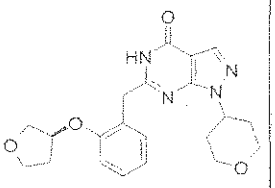
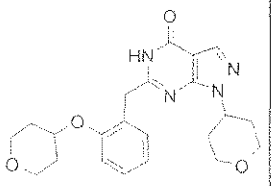
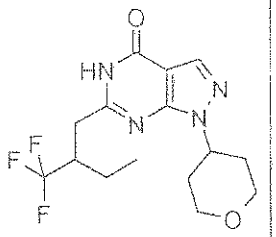
The following examples were synthesized in analogy to the preparation of Example 41, using the corresponding pyrazolyl-carboxamides and esters as starting materials.

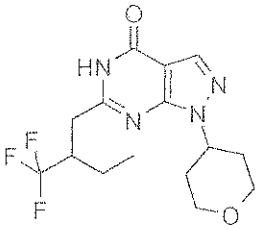
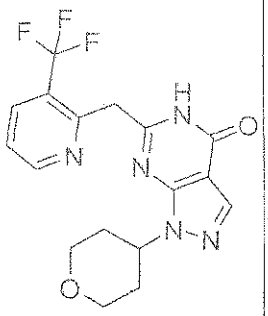
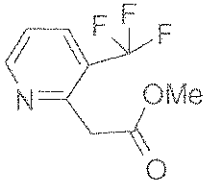
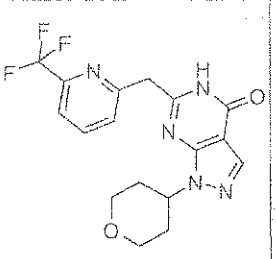
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 42 racem. mixture |  | Exp. 11B |  | 2.02 (Method Grad_C8_ $NH_4COOH$ ) | 305 $(M+H)^+$ |
| Exp. 43 |  | Exp. 11B |  | 2.40 (Method Grad_C8_ $NH_4COOH$ ) | 289 $(M+H)^+$ |
| Exp. 44 |  | Exp. 11B |  | 3.06 (Method Grad_C8_ $NH_4COOH$ ) | 379 $(M+H)^+$ |
| Exp. 45 |  | Exp. 11B |  | 3.04 (Method Grad_C8_ $NH_4COOH$ ) | 379 $(M+H)^+$ |

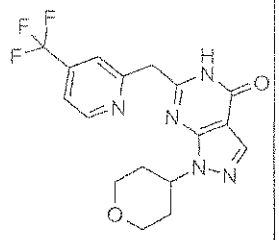
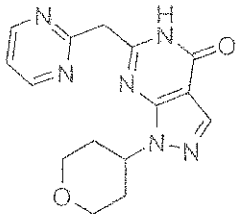
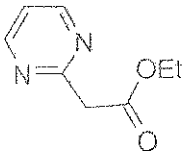
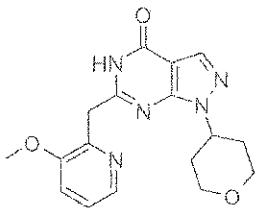
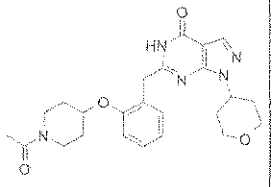
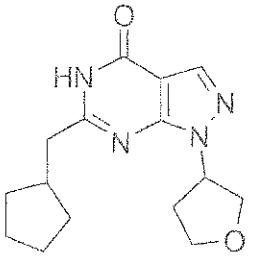
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 46 racem. mixture |  | Exp. 11B |  | 2.77 (Method Grad_C8_ $NH_4COOH$ ) | 331 $(M+H)^+$ |
| Exp. 47 |  | Exp. 11B |  | 2.21 (Method Grad_C8_ $NH_4COOH$ ) | 275 $(M+H)^+$ |
| Exp. 48 racem. mixture |  | Exp. 11B | Exp. 5T | 2.84 (Method Grad_C8_ $NH_4COOH$ ) | 345 $(M+H)^+$ |
| Exp. 49 |  | Exp. 11B |  | 2.57 (Method Grad_C8_ $NH_4COOH$ ) | 341 $(M+H)^+$ |

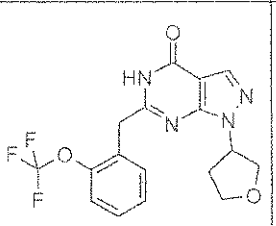
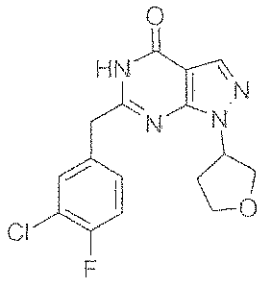
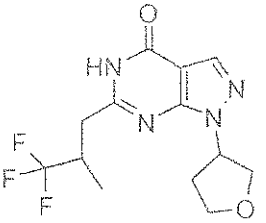
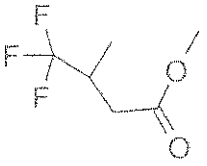
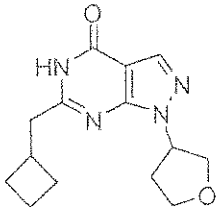
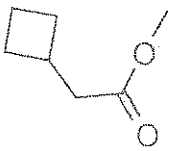
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 50 |  | Exp. 11B | Exp. 5E | 3.02 (Method Grad_C8_ $NH_4COOH$ ) | 413 $(M+H)^+$ |
| Exp. 51 |  | Exp. 11B |  | 5.97 (Method 1E hydro) | 312 $(M+H)^+$ |
| Exp. 52 |  | Exp. 11B | Exp. 5AK | 2.75 (Method Grad_C8_ $NH_4COOH$ ) | 355 $(M+H)^+$ |
| Exp. 53 |  | Exp. 11B |  | 2.75 (Method Grad_C8_ $NH_4COOH$ ) | 336 $(M+H)^+$ |

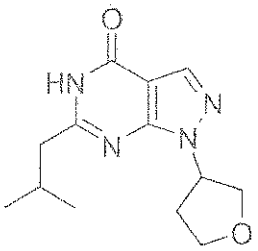
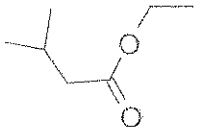
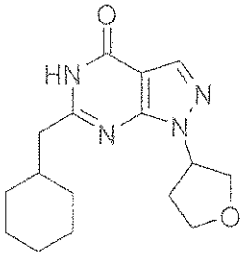
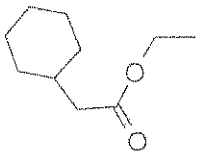
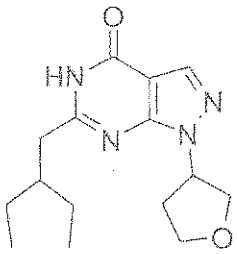
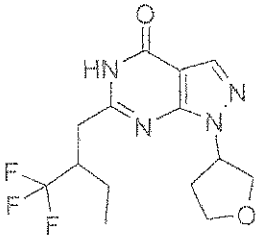
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 54 |  | Exp. 11B |  | 3.15 (Method Grad_C8_ $NH_4COOH$ ) | 369 $(M+H)^+$ |
| Exp. 55 |  | Exp. 11B | Exp. 5K | 3.21 (Method Grad_C8_ $NH_4COOH$ ) | 381 $(M+H)^+$ |
| Exp. 56 |  | Exp. 11B |  | 6.52 (Method 1E hydro) | 326 $(M+H)^+$ |
| Exp. 57 Enantio -mer R |  | Exp. 11B | Exp. 5M | 2.64 (Method Grad_C8_ $NH_4COOH$ ) | 397 $(M+H)^+$ |

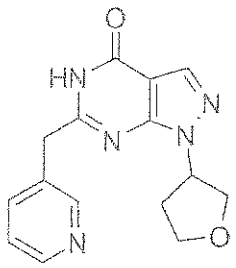
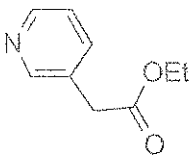
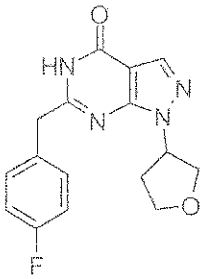
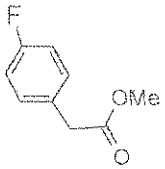
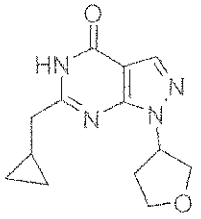
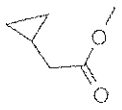
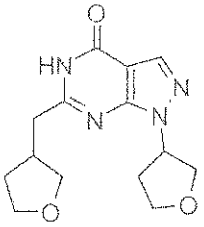
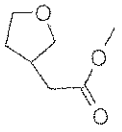
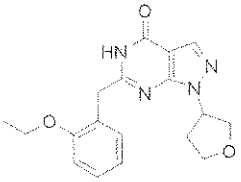
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 58 Enantio -mer S |  | Exp. 11B | Exp. 5L | 2.64 (Method Grad_C8_ $NH_4COOH$ ) | 397 $(M+H)^+$ |
| Exp. 60 |  | Exp. 11B | Exp. 5O | 2.78 (Method Grad_C8_ $NH_4COOH$ ) | 411 $(M+H)^+$ |
| Exp. 61 Enantio -mer A |  | Exp. 11B | Exp. 5A | 2.68 (Method Grad_C8_ $NH_4COOH$ ) 15.32 (Chiral 1) | 345 $(M+H)^+$ |

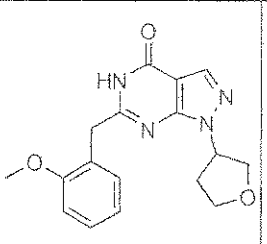
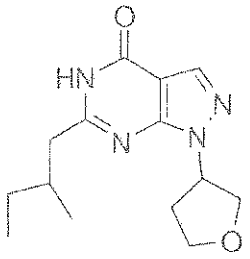
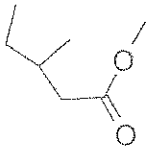
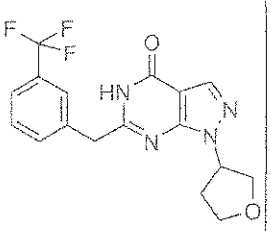
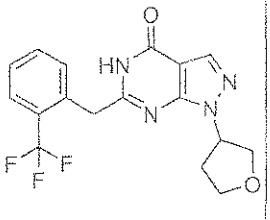
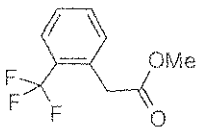
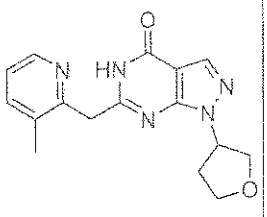
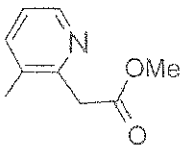
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 62<br>Enantio-mer B |  | Exp. 11B | Exp. 5D | 2.68<br>(Method Grad_C8_ $NH_4COOH$ )<br>18.74<br>(Chiral 1) | 345<br>$(M+H)^+$ |
| Exp. 63 |  | Exp. 11B |  | 9.37<br>(Method 2F) | 380<br>$(M+H)^+$ |
| Exp. 64 |  | Exp. 11B | Exp. 5S | 6.75<br>(Method 1E hydro) | 380<br>$(M+H)^+$ |

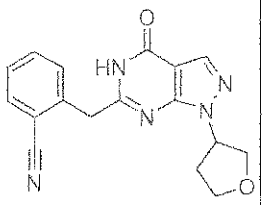
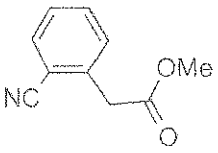
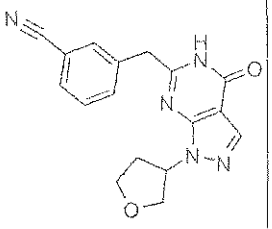
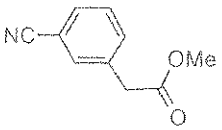
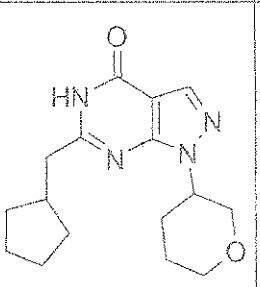
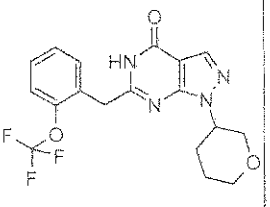
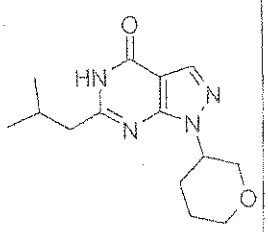
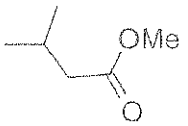
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 65 |  | Exp. 11B | Exp. 5R | 9.45 (Method 2F) | 380 $(M+H)^+$ |
| Exp. 66 |  | Exp. 11B |  | 6.70 (Method 2F) | 313 $(M+H)^+$ |
| Exp. 67 |  | Exp. 11B | Exp. 5Q | 2.38 (Method Grad_C8_ $NH_4COOH$ ) | 342 $(M+H)^+$ |
| Exp. 68 |  | Exp. 11B | Exp. 5I | 1.95 (Method Grad_C8_ $NH_4COOH$ ) | 452 $(M+H)^+$ |
| Exp. 69 racem. mixture |  | Exp. 11E | Exp. 5AC | 7.30 (Method 1E ) | 289 $(M+H)^+$ |

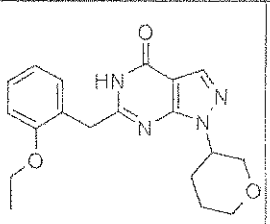
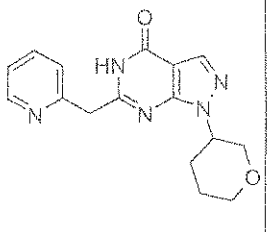
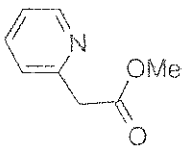
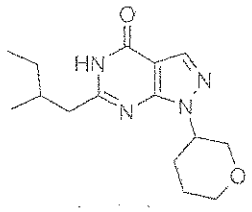
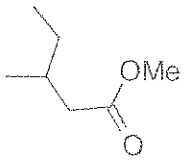
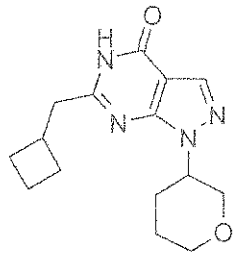
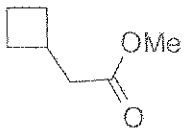
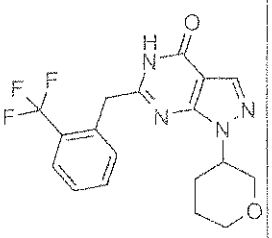
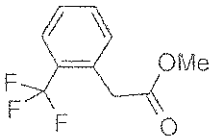
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| | | | | | |
| Exp. 70 racem. mixture |  | Exp. 11E | Exp. 5AE | 7.70 (Method 1E fusion) | 381 $(M+H)^+$ |
| Exp. 71 racem. mixture |  | Exp. 11E | Exp. 5F | 7.68 (Method 1E fusion) | 349 $(M+H)^+$ |
| Exp. 72 mixture of stereoisomers |  | Exp. 11E |  | 9.82 (Method 2F) | 317 $(M+H)^+$ |
| Exp. 73 racem. mixture |  | Exp. 11E |  | 9.44 (Method 2F) | 275 $(M+H)^+$ |

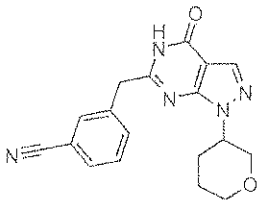
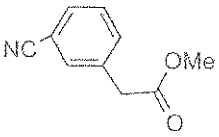
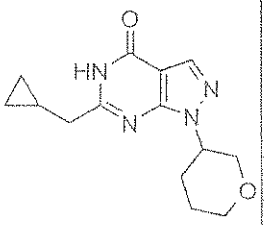
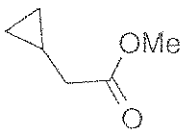
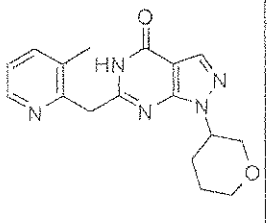
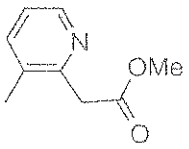
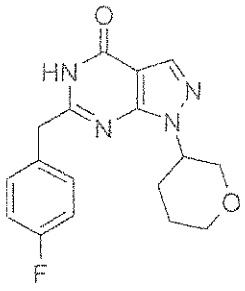
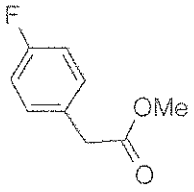
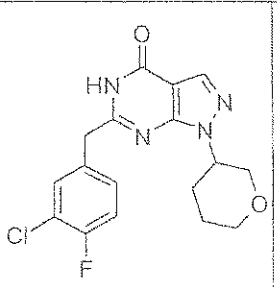
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 74 racem. mixture |  | Exp. 11E |  | 8.89 (Method 2F) | 263 $(M+H)^+$ |
| Exp. 75 racem. mixture |  | Exp. 11E |  | 10.69 (Method 2F) | 303 $(M+H)^+$ |
| Exp. 76 racem. mixture |  | Exp. 11E | Exp. 5H | 10.57 (Method 2F) | 291 $(M+H)^+$ |
| Exp. 77 mixture of stereoisomers |  | Exp. 11E | Exp. 5T | 10.55 (Method 2F) | 331 $(M+H)^+$ |

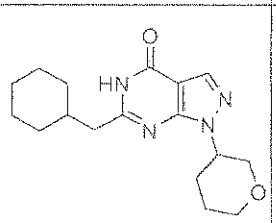
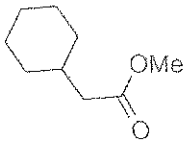
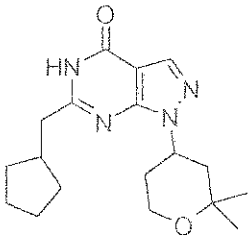
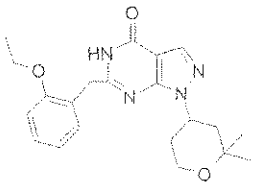
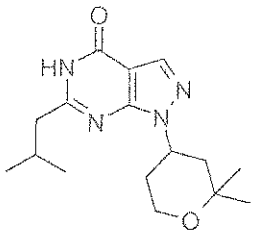
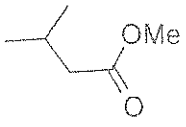
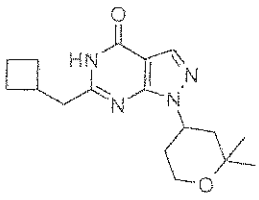
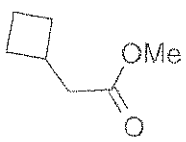
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 78 racem. mixture |  | Exp. 11E |  | 4.83 (Method 1E Hydro) | 298 $(M+H)^+$ |
| Exp. 79 racem. mixture |  | Exp. 11E |  | 7.10 (Method 1E fusion) | 315 $(M+H)^+$ |
| Exp. 80 racem. mixture |  | Exp. 11E |  | 5.97 (Method 1E fusion) | 261 $(M+H)^+$ |
| Exp. 81 mixture of stereoisomers |  | Exp. 11E |  | 4.73 (Method 1E hydro) | 291 $(M+H)^+$ |
| Exp. 82 racem. mixture |  | Exp. 11E | Exp. 5AK | 7.37 (Method 1E hydro) | 341 $(M+H)^+$ |

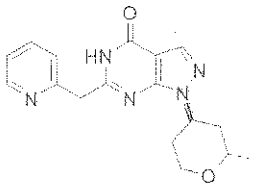
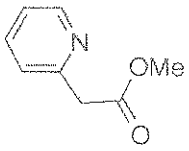
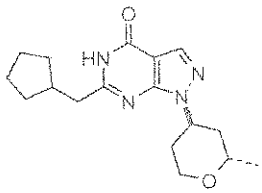
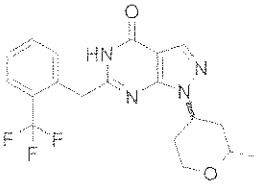
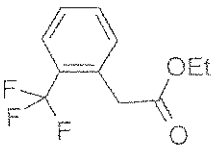
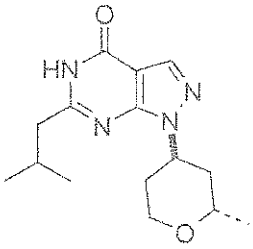
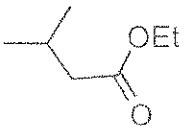
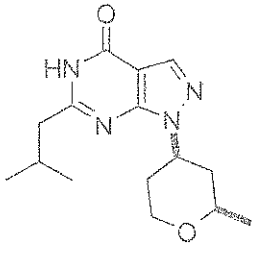
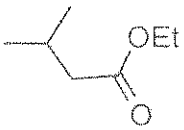
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 83 racem. mixture |  | Exp. 11E | Exp. 5AD | 6.85 (Method 1E hydro) | 327 $(M+H)^+$ |
| Exp. 84 mixture of stereoisomers |  | Exp. 11E |  | 6.88 (Method 1E hydro) | 277 $(M+H)^+$ |
| Exp. 85 racem. mixture |  | Exp. 11E | Exp. 5AH | 7.93 (Method 1E hydro) | 365 $(M+H)^+$ |
| Exp. 86 racem. mixture |  | Exp. 11E |  | 10.93 (Method 2F) | 365 $(M+H)^+$ |
| Exp. 87 racem. mixture |  | Exp. 11E |  | 5.43 (Method 1E hydro) | 312 $(M+H)^+$ |

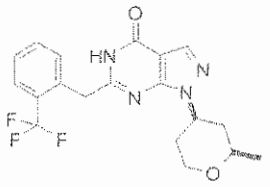
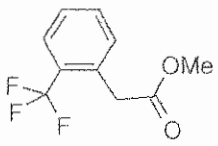
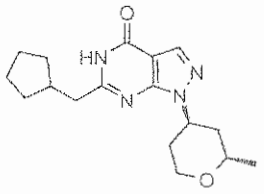
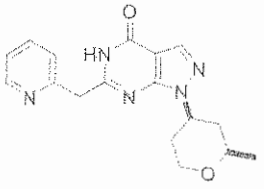
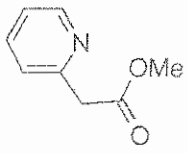
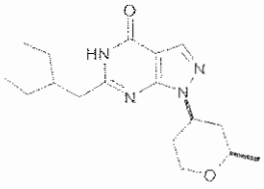
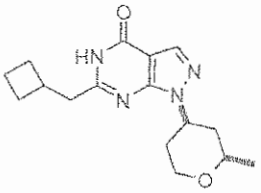
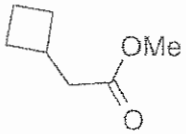
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 88 racem. mixture |  | Exp. 11E |  | 5.43 (Method 1E hydro) | 312 $(M+H)^+$ |
| Exp. 89 racem. mixture |  | Example 11E |  | 5.28 (Method 1E hydro) | 322 $(M+H)^+$ |
| Exp. 90 racem. mixture |  | Exp. 11F | Exp. 5AC | 8 (Method 1E hydro) | 303 $(M+H)^+$ |
| Exp. 91 racem. mixture |  | Exp. 11F | Exp. 5AE | 8.45 (Method 1E hydro) | 395 $(M+H)^+$ |
| Exp. 92 racem. mixture |  | Exp. 11F |  | 6.93 (Method 1E hydro) | 277 $(M+H)^+$ |

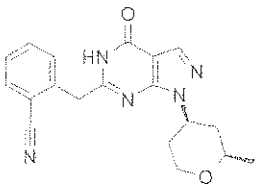
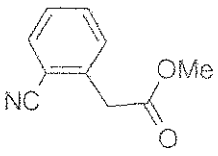
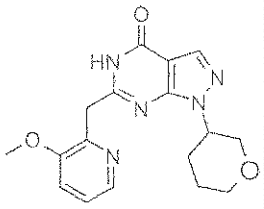
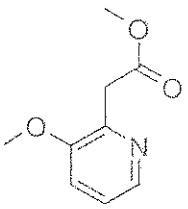
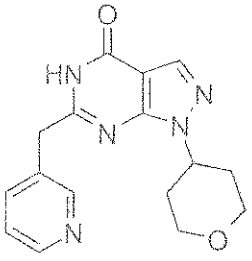
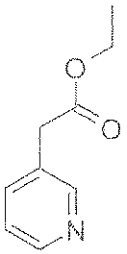
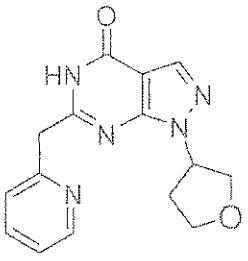
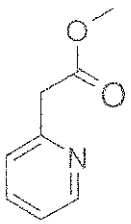
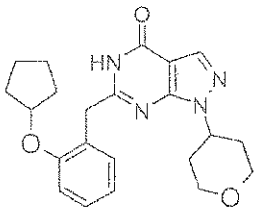
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 93 racem. mixture |  | Exp. 11F | Exp. 5AK | 8.20 (Method 1E hydro) | 355 $(M+H)^+$ |
| Exp. 94 racem. mixture |  | Exp. 11F |  | 6.28 (Method 1E hydro) | 312 $(M+H)^+$ |
| Exp. 95 mixture of stereois omers |  | Exp. 11F |  | 7.70 (Method 1E hydro) | 291 $(M+H)^+$ |
| Exp. 96 racem. mixture |  | Exp. 11F |  | 7.33 (Method 1E hydro) | 289 $(M+H)^+$ |
| Exp. 97 racem. mixture |  | Exp. 11F |  | 8.17 (Method 1E hydro) | 379 $(M+H)^+$ |

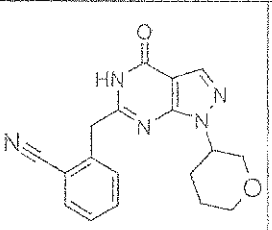
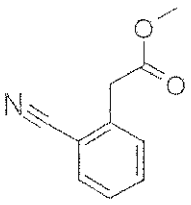
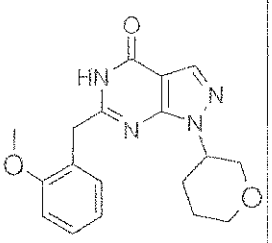
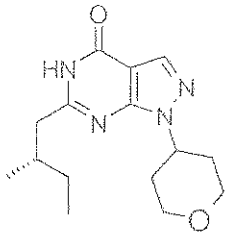
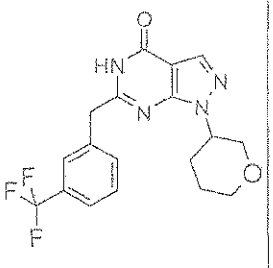
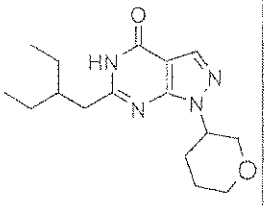
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 98 racem. mixture |  | Exp. 11F |  | 6.80 (Method 1E hydro) | 336 $(M+H)^+$ |
| Exp. 99 racem. mixture |  | Exp. 11F |  | 6.43 (Method 1E hydro) | 275 $(M+H)^+$ |
| Exp. 100 racem. mixture |  | Exp. 11F |  | 2.38 (Method 2F) | 326 $(M+H)^+$ |
| Exp. 101 racem. mixture |  | Exp. 11F |  | 7.52 (Method 1E hydro) | 329 $(M+H)^+$ |
| Exp. 102 racem. mixture |  | Exp. 11F | Exp. 5F | 8.28 (1E hydro) | 363 $(M+H)^+$ |

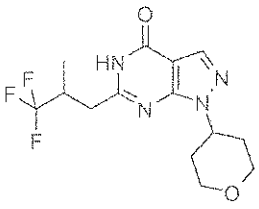
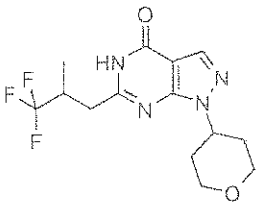
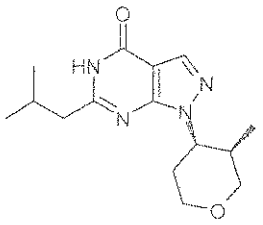
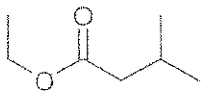
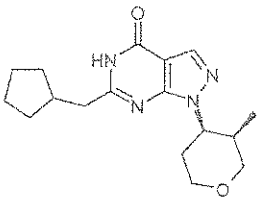
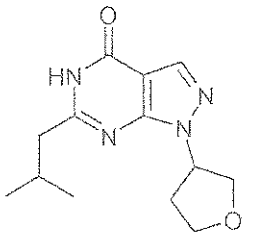
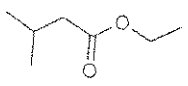
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 103 racem. mixture |  | Exp. 11F |  | 8.70 (Method 1E hydro) | 317 $(M+H)^+$ |
| Exp. 104 racem. mixture |  | Exp. 11G | Exp. 5AC | 8.57 (Method 1E hydro) | 331 $(M+H)^+$ |
| Exp. 105 racem. mixture |  | Exp. 11G | Exp. 5AK | 8.62 (Method 1E hydro) | 383 $(M+H)^+$ |
| Exp. 106 racem. mixture |  | Exp. 11G | Methyliso-valerate  | 7.58 (Method 1E hydro) | 305 $(M+H)^+$ |
| Exp. 108 racem. mixture |  | Exp. 11G | Cyclobutyl-acetic acid methyl ester  | 7.93 (Method 1E) | 317 $(M+H)^+$ |

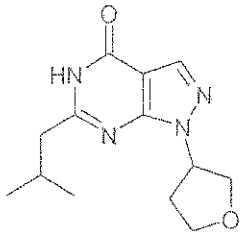
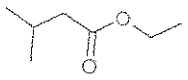
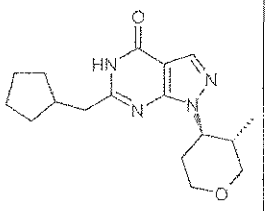
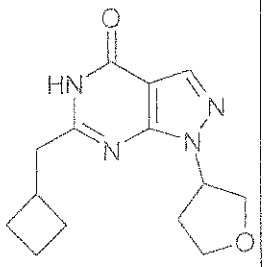
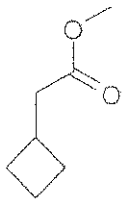
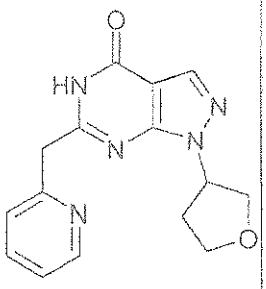
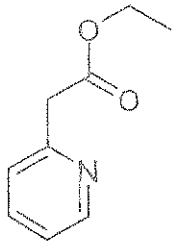
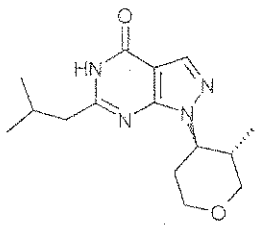
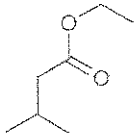
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 111 trans; racem. mixture |  | Exp. 11H |  | 2.05 (Method 2F) | 326 $(M+H)^+$ |
| Exp. 112 trans; racem. mixture |  | Exp. 11H | Exp. 5AC | 8.25 (Method 2F) | 317 $(M+H)^+$ |
| Exp. 113 trans; racem. mixture |  | Exp. 11H |  | 8.42 (Method 1E hydro) | 393 $(M+H)^+$ |
| Exp. 114 trans; racem. mixture |  | Exp. 11H |  | 7.15 (Method 1E hydro) | 291 $(M+H)^+$ |
| Exp. 115 cis; racem. mixture |  | Exp. 11I |  | 9.90 (Method 2F) | 291 $(M+H)^+$ |

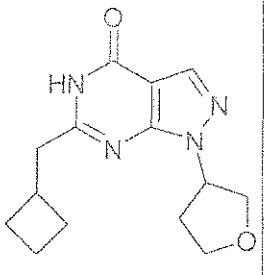
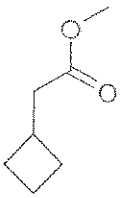
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 116 cis; racem. mixture |  | Exp. 11l |  | 8.18 (Method 1E hydro) | 393 $(M+H)^+$ |
| Exp. 117 cis; racem. mixture |  | Exp. 11l | Exp. 5AC | 7.98 (Method 1E hydro) | 317 $(M+H)^+$ |
| Exp. 118 cis; racem. mixture |  | Exp. 11l |  | 5.80 (Method 1E hydro) | 326 $(M+H)^+$ |
| Exp. 119 cis; racem. mixture |  | Exp. 11l | Exp. 5H | 8.42 (Method 1E hydro) | 319 $(M+H)^+$ |
| Exp. 120 cis; racem. mixture |  | Exp. 11l |  | 7.33 (Method 1E hydro) | 303 $(M+H)^+$ |

| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 121 cis; racem. mixture |  | Exp. 11I |  | 9.91 (Method 2F) | 350 $(M+H)^+$ |
| Exp. 122 racem. mixture |  | Exp. 11F |  | 6.95 (Method 2F) | 342 (M+H)+ |
| Exp. 123 |  | Exp. 11B |  | 2.12 (Method Grad_C8_ $NH_4COOH$ ) | 312 $(M+H)^+$ |
| Exp. 124 racem. mixture |  | Exp. 11E |  | 4.98 (Method 1E hydro) | 298 $(M+H)^+$ |
| Exp. 125 |  | Exp. 11B | Exp. 5P | 8.72 (Method 1E hydro) | 395 $(M+H)^+$ |

| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 126 racem. mixture |  | Exp. 11F |  | 9.72 (Method 2F) | 336 $(M+H)^+$ |
| Exp. 127 racem. mixture |  | Exp. 11F | Exp. 5AB | 7.62 (Method 1E hydro) | 341 $(M+H)^+$ |
| Exp. 128 Enantio-mer S |  | Exp. 11B | Exp. 5G | 9.83 (Method 2F) | 291 $(M+H)^+$ |
| Exp. 129 racem. mixture |  | Exp. 11F | Exp. 5AF | 11.56 (Method 2F) | 379 $(M+H)^+$ |
| Exp. 130 racem. mixture |  | Exp. 11F | Exp. 5H | 8.38 (Method 1E hydro) | 305 $(M+H)^+$ |

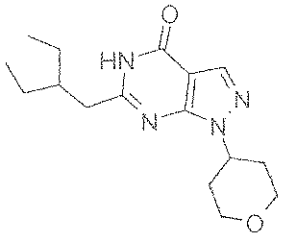
| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 131 Enantio-mer A |  | Exp. 11B | Exp. 5B | 9.93 (Method 2F) | 331 $(M+H)^+$ |
| Exp. 132 Enantio-mer B |  | Exp. 11B | Exp. 5C | 9.93 (Method 2F) | 331 $(M+H)^+$ |
| Exp. 132-1 cis, racem. mixture |  | Exp. 11IA |  | 9.83 (Method 2F) | 291 $(M+H)^+$ |
| Exp. 132-2 cis, racem. mixture |  | Exp. 11IA | Exp. 5AC | 10.96 (Method 2F) | 317 $(M+H)^+$ |
| Exp. 132-3 Enantio-mer A |  | Exp. 15A |  | 8.84 (Method 2F) | 263 $(M+H)^+$ |

| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 132-4 Enantio-mer B |  | Exp. 16A |  | 8.96 (Method 2F) | 263 $(M+H)^+$ |
| Exp. 132-5 trans, racem. mixture |  | Exp. 11IB | Exp. 5AC | 10.21 (Method 2F) | 317 $(M+H)^+$ |
| Exp. 132-6 Enantio-mer B |  | Exp. 16A |  | 7.15 (Method 1E Hydro) | 275 $(M+H)^+$ |
| Exp. 132-7 Enantio-mer B |  | Exp. 16A |  | 5.68 (Method 1E Hydro) | 298 $(M+H)^+$ |
| Exp. 132-8 trans, racem. mixture |  | Exp. 11IB |  | 9.23 (Method 2F) | 291 $(M+H)^+$ |

| | Structure | pyrazolyl-carbox-amide | Ester | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|---|
| Exp. 132-9 Enantio -mer A |  | Exp. 15A |  | 8.83 (Method 2L) | 275 $(M+H)^+$ |

Example 133

6-(2-Ethyl-butyl)-1-(tetrahydro-pyran-4-yl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one



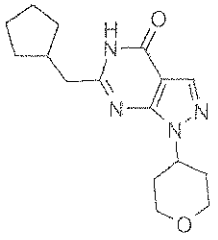
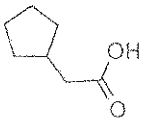
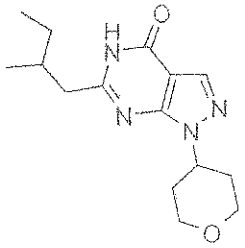
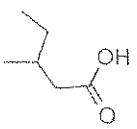
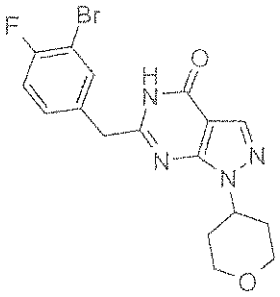
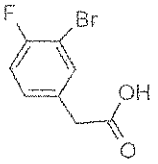
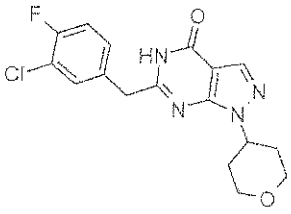
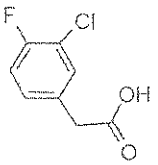
Example 11B (0.1 g, 0.48 mmol) was mixed with polyphosphoric acid (1.0 g) and 2-(trifluoromethoxy)phenylacetic acid (248 mg, 1.9 mmol) was added. The mixture was heated to 120°C during 16 hours. Temperature was lowered to 20°C and the pH value was adjusted to 7 by addition of ammonia (30 % solution in water). The aqueous phase was extracted with dichloromethane (2 x 20 mL) and the organic phase was dried over sodium sulphate. The crude mixture was purified by flash chromatography. Eluent: hexane/ethyl acetate 40/60.

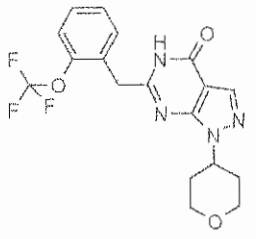
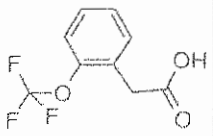
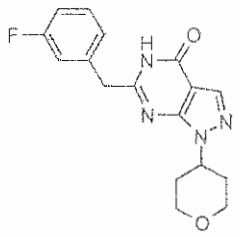
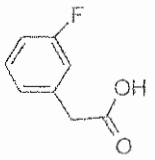
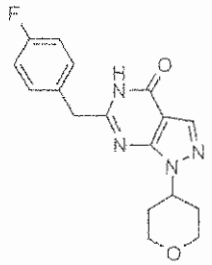
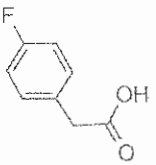
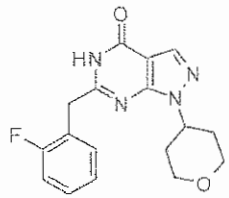
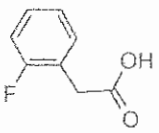
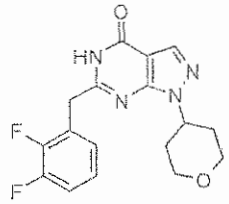
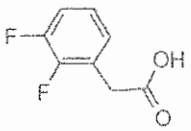
Obtained 23.5 mg (16 %) as a white solid

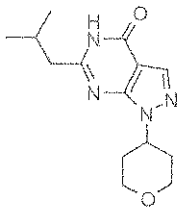
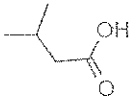
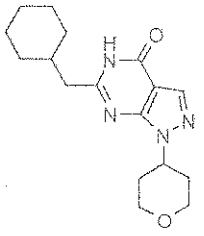
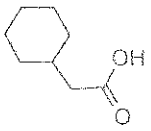
HPLC-MS (1E ) $R_t$: 6.77 min

MS (APCI pos): m/z = 305 $(M+H)^+$

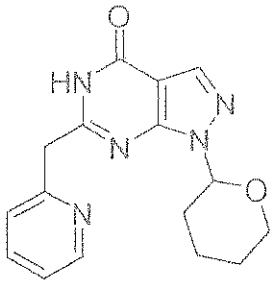
The following examples were synthesized in analogy to the preparation of Example 133, using the corresponding carboxylic acids as starting materials:

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 134 |  |  | 6.37 (Method 1E ) | 303 $(M+H)^+$ |
| Example 135 racem. mixture |  |  | 5.95 (Method 1E ) | 291 $(M+H)^+$ |
| Example 136 |  |  | 6.57 (Method 1E ) | 407 $(M+H)^+$ |
| Example 137 |  |  | 6.48 (Method 1E ) | 363 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 138 |  |  | 6.72 (Method 1E ) | 395 $(M+H)^+$ |
| Example 139 |  |  | 2.71 (Method Grad_C8_$NH_4COOH$) | 329 $(M+H)^+$ |
| Example 140 |  |  | 2.77 (Method Grad_C8_$NH_4COOH$) | 329 $(M+H)^+$ |
| Example 141 |  |  | 2.90 (Method Grad_C8_$NH_4COOH$) | 329 $(M+H)^+$ |
| Example 142 |  |  | 3.07 (Method Grad_C8_$NH_4COOH$) | 347 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 143 |  |  | 2.71 (Method Grad_C8_$NH_4COOH$) | 277 $(M+H)^+$ |
| Example 144 |  |  | 3.28 (Method Grad_C8_$NH_4COOH$) | 317 $(M+H)^+$ |

Example 145, racemic mixture

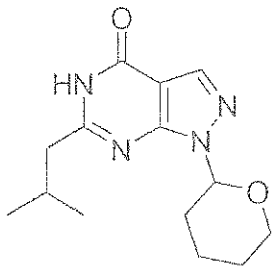
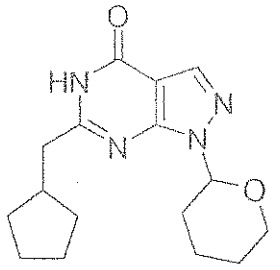
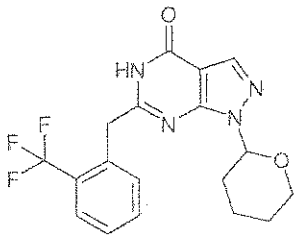


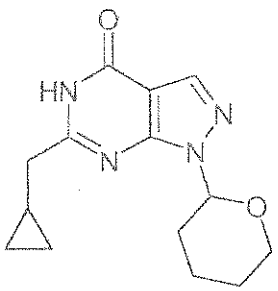
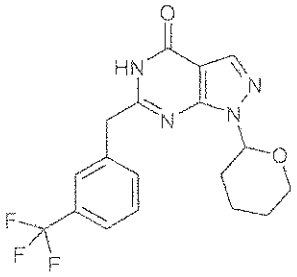
106 mg (0.47 mmol) Example 12V was mixed with 4 mL ethyl acetate and 0.5 mL dimethylformamide, 51 mg (0.61 mmol) 3.4-dihydro-2H-pyran and 88.4 mg (0.51 mmol) p-toluenesulfonic acid were added. The reaction mixture was heated to 60°C and stirred for 2h. After cooling to room temperature ethyl acetate was added and the mixture was washed with saturated sodium hydrogen carbonate and with saturated sodium chloride. The organic layer was evaporated under reduced pressure. The residue was purified by preparative HPLC-MS. 31.5 mg (21.7 %) were obtained.

MS (APCI pos): m/z = 312 $(M+H)^+$

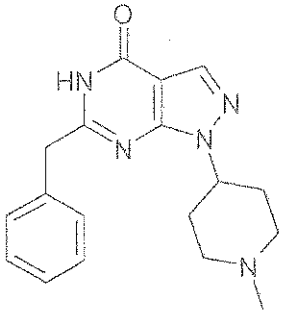
HPLC-MS (Method 2F ) $R_t$: 8.26 min

The following examples were synthesized in analogy to the preparation of Example 145, using the corresponding pyrazolopyrimidinones as starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 146<br>racem. mixture |  | Example 12W | 9.99<br>(Method 2F) | 277 $(M+H)^+$ |
| Exp. 147<br>racem. mixture |  | Example 12X | 10.98<br>(Method 2F) | 303 $(M+H)^+$ |
| Exp. 147-1<br>racem. mixture |  | Example 12Y | 10.98<br>(Method 2F) | 303 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 147-2 racem. mixture |  | Example 12AA | 9.56 (Method 2F) | 275 $(M+H)^+$ |
| Example 147-3 racem. mixture |  | Example 12Z | 11.62 (Method 2F) | 379 $(M+H)^+$ |

Example 148

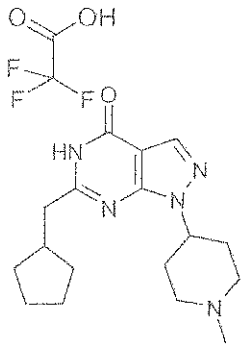
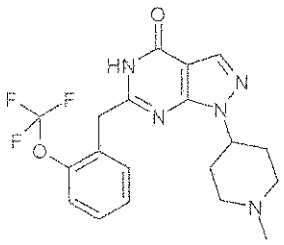


160 mg (470 mmol) of Example 12E was dissolved in 10 mL methanol and 350 mg Raney nickel was added. The reaction mixture was hydrogenated at room temperature for 6h, filtered and the solvent evaporated under reduced pressure. 100 mg (65 %) of the product were obtained.

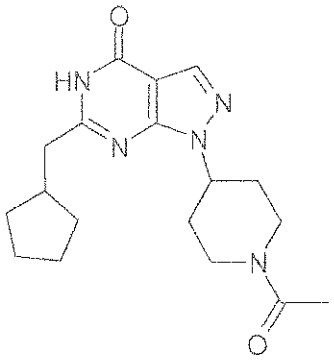
HPLC-MS (Method 1): $R_t$: 0.95 min

MS ( ESI pos ): m/z = 324 (M+H)

The following examples were synthesized in analogy to the preparation of Example 148, using the corresponding N-oxides as starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 149 |  | Example 12D | 0.95 (Method 1) | 316 $(M+H)^+$ |
| Exp. 150 |  | Example 12F | 1.11 (Method 1) | 408 $(M+H)^+$ |

Example 151



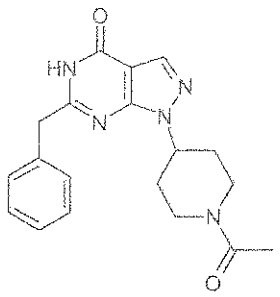
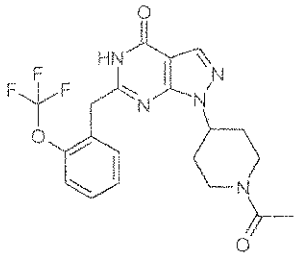
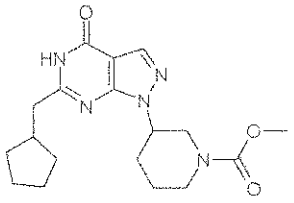
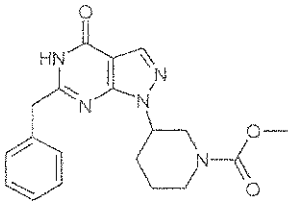
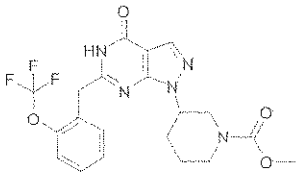
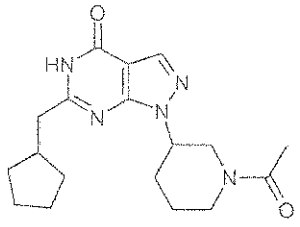
62 mg (150 mmol) of Example 13B were dissolved in 4 mL dichloromethane, 22.5 µL (300 mmol) acetyl chloride and 42 µL (300 mmol) triethylamine were added. The reaction mixture was stirred at room temperature over night. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 28 mg (55 %) of the product were obtained.

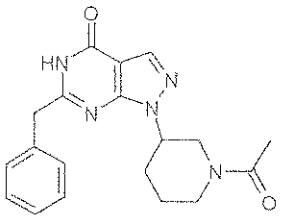
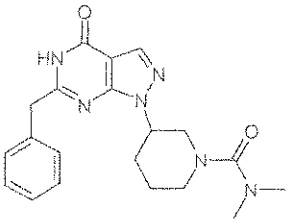
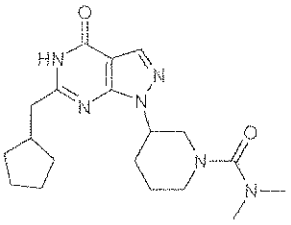
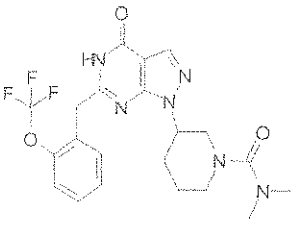
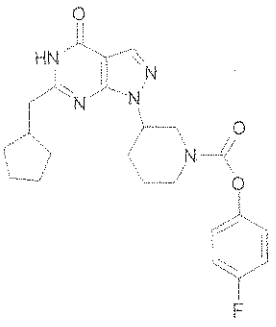
HPLC-MS (Method 1): $R_t$: 1.18 min

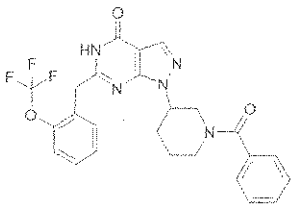
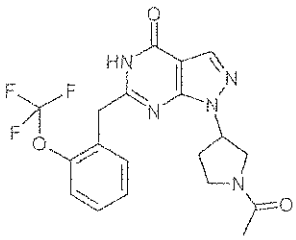
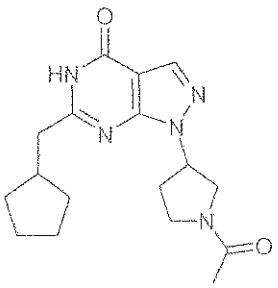
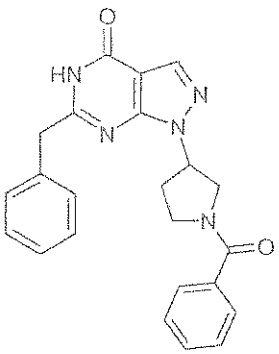
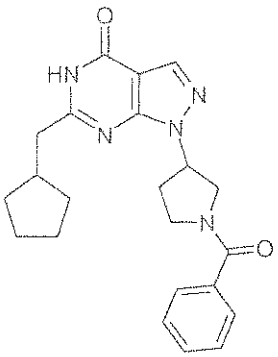
MS ( ESI pos ): m/z = 344 $(M+H)^+$

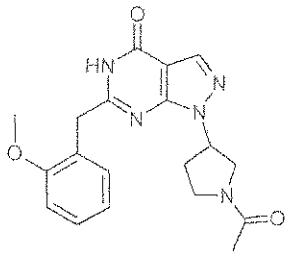
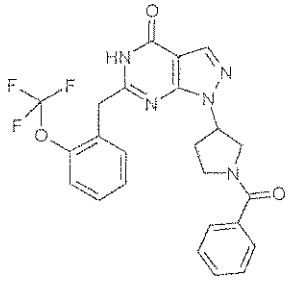
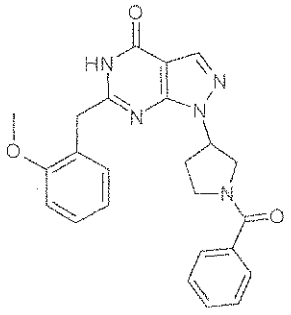
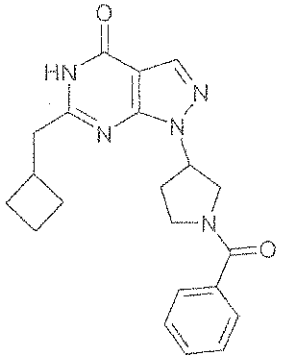
The following examples were synthesized in analogy to the preparation of Example 151, using the corresponding starting materials. It will be evident that as acylating agent not for all compounds acetylchloride has been introduced but other acylating agents like commercially available methoxychloroformate, substituted or unsubstituted aminocarbonylchloride, unsubstituted or substituted phenoxycarbonylchloride, unsubstituted or substituted benzoylchloride were used.

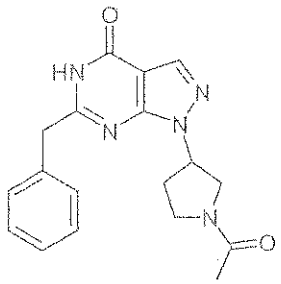
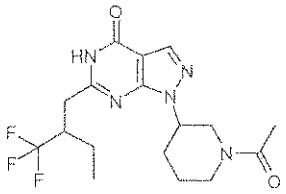
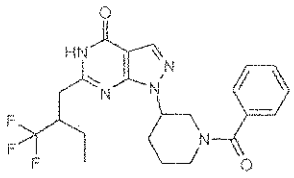
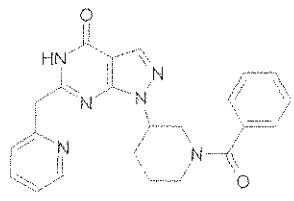
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|

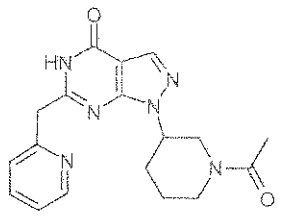
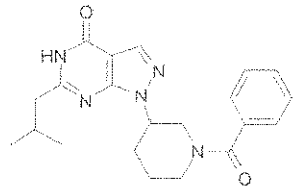
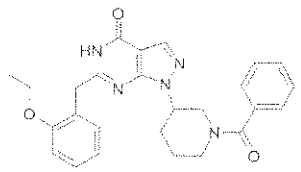
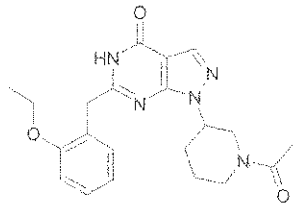
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 152 |  | Example 13K | 1.09 (Method 1) | 352 $(M+H)^+$ |
| Exp. 153 |  | Example 13L | 1.25 (Method 1) | 436 $(M+H)^+$ |
| Exp. 154 racem. mixture |  | Example 13C | 1.38 (Method 1) | 360 $(M+H)^+$ |
| Exp. 155 racem. mixture |  | Example 13D | 1.30 (Method 1) | 368 $(M+H)^+$ |
| Exp. 156 racem. mixture |  | Example 13E | 1.44 (Method 1) | 452 $(M+H)^+$ |
| Exp. 157 racem. mixture |  | Example 13C | 1.20 (Method 1) | 344 $(M+H)^+$ |

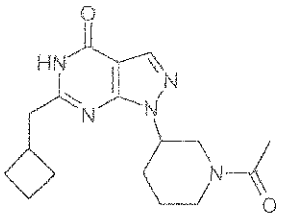
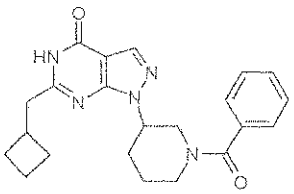
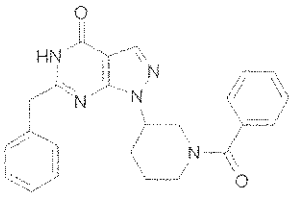
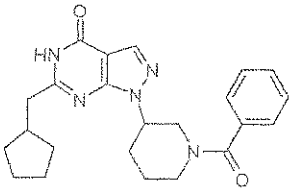
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 158 racem. mixture |  | Example 13D | 1.16 (Method 1) | 352 $(M+H)^+$ |
| Exp. 159 racem. mixture |  | Example 13D | 1.25 (Method 1) | 381 $(M+H)^+$ |
| Exp. 160 racem. mixture |  | Example 13C | 1.30 (Method 1) | 373 $(M+H)^+$ |
| Exp. 161 racem. mixture |  | Example 13E | 1.38 (Method 1) | 465 $(M+H)^+$ |
| Exp. 162 racem. mixture |  | Example 13C | 1.62 (Method 1) | 440 $(M+H)^+$ |

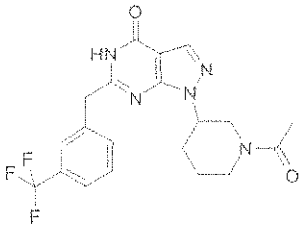
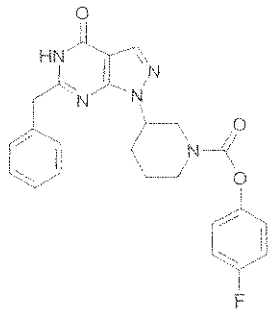
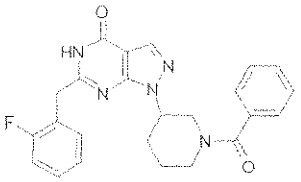
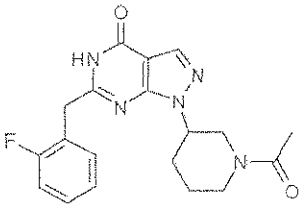
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 163 racem. mixture |  | Example 13E | 1.48 (Method 1) | 498 $(M+H)^+$ |
| Exp. 164 racem. mixture |  | Example 13G | 1.23 (Method1) | 422 $(M+H)^+$ |
| Exp. 165 racem. mixture |  | Example 13A | 1.14 (Method1) | 330 $(M+H)^+$ |
| Exp. 166 racem. mixture |  | Example 13F | 1.28 (Method1) | 400 $(M+H)^+$ |
| Exp. 167 racem. mixture |  | Example 13A | 1.36 (Method1) | 392 $(M+H)^+$ |

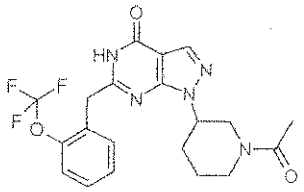
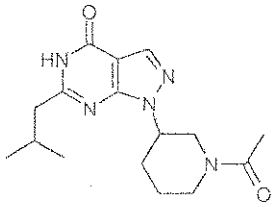
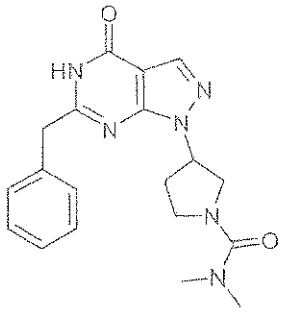
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 168 racem. mixture |  | Example 13H | 1.1 (Method 1) | 368 $(M+H)^+$ |
| Exp. 169 racem. mixture |  | Example 13G | 1.44 (Method 1) | 484 $(M+H)^+$ |
| Exp. 170 racem. mixture |  | Example 13H | 1.32 (Method 1) | 430 $(M+H)^+$ |
| Exp. 171 racem. mixture |  | Example 13I | 1.29 (Method 1) | 378 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 172 racem. mixture |  | Example 13F | 1.07 (Method 1) | 338 $(M+H)^+$ |
| Exp. 173 mixture of stereoisomers |  | Example 13M | 1.25 (Method 1) | 386 $(M+H)^+$ |
| Exp. 174 mixture of stereoisomers |  | Example 13M | 1.44 (Method 1) | 448 $(M+H)^+$ |
| Exp. 175 racem. mixture |  | Example 13N | 1.04 (Method 1) | 415 $(M+H)^+$ |

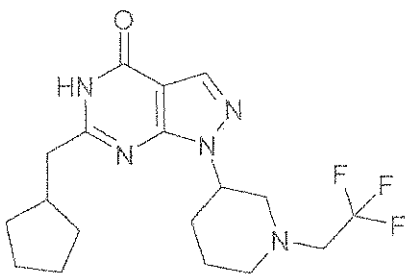
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 176<br>racem. mixture |  | Example 13N | 0.84<br>(Method 1) | 353 $(M+H)^+$ |
| Exp. 177<br>racem. mixture |  | Example 13O | 1.31<br>(Method 1) | 380 $(M+H)^+$ |
| Exp. 178<br>racem. mixture |  | Example 13P | 1.43<br>(Method 1) | 458 $(M+H)^+$ |
| Exp. 179<br>racem. mixture |  | Example 13P | 1.24<br>(Method 1) | 396 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 180<br>racem. mixture |  | Example 13Q | 1.14<br>(Method 1) | 330 $(M+H)^+$ |
| Exp. 181<br>racem. mixture |  | Example 13Q | 1.34<br>(Method 1) | 392 $(M+H)^+$ |
| Exp. 182<br>racem. mixture |  | Example 13D | 1.35<br>(Method 1) | 414 $(M+H)^+$ |
| Exp. 183<br>racem. mixture |  | Example 13C | 1.41<br>(Method 1) | 406 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 184<br>racem. mixture |  | Example 205 | 1.30<br>(Method 1) | 420 $(M+H)^+$ |
| Exp. 185<br>racem. mixture |  | Example 13D | 1.53<br>(Method 1) | 448 $(M+H)^+$ |
| Exp. 186<br>racem. mixture |  | Example 204 | 1.35<br>(Method 1) | 432 $(M+H)^+$ |
| Exp. 187<br>racem. mixture |  | Example 204 | 1.15<br>(Method 1) | 370 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 188<br>racem. mixture |  | Example 13E | 1.29<br>(Method 1) | 436 $(M+H)^+$ |
| Exp. 189<br>racem. mixture |  | Example 13O | 1.08<br>(Method 1) | 318 $(M+H)^+$ |
| Exp. 190<br>racem. mixture |  | Example 13F | 1.18<br>(Method 1) | 367 $(M+H)^+$ |

Example 191, racemic mixture

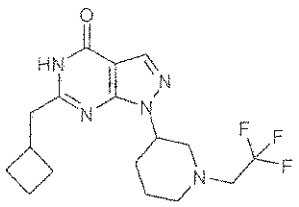
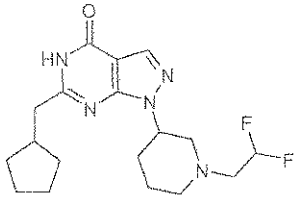


60 mg (0.2 mmol) of Example 13C were dissolved in 5 mL xylene and 57 mg (0.2 mmol) 2,2,2-trifluoroethyl-trichloromethansulfonate were added drop wise. The reaction mixture was heated to 140°C and stirred for 5h. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 24.8 mg (32 %) of the product were obtained.

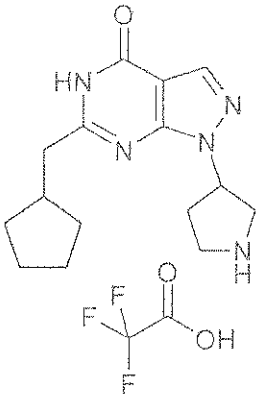
HPLC-MS (Method 1): $R_t$: 1.45 min

MS ( ESI pos ): m/z = 384 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 191, using the corresponding starting materials.

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 192<br>racem. mixture |  | Example 13Q | 1.35<br>(Method 1) | 370 $(M+H)^+$ |
| Exp. 193<br>racem. mixture |  | Example 13C | 1.07<br>(Method 1) | 366 $(M+H)^+$ |

Example 194, racemic mixture

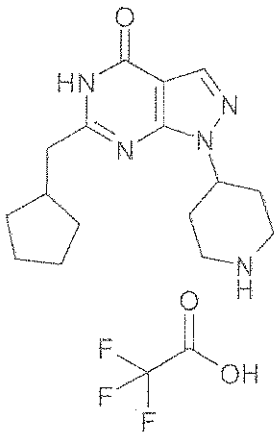


400 mg (1.35 mmol) of Example 11A were dissolved in 8 mL of absolute ethanol, 840 mg (5.4 mmol) of Example 5AC, and 220 mg (5.5 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 150°C for 30 min in a microwave oven. After cooling to room temperature, the reaction mixture was acidified with 4N hydrochloride acid. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 250 mg (46 %) of the product were obtained as a white solid.

HPLC-MS (Method 1): $R_t$: 0.93 min

MS ( ESI pos ): m/z = 288 $(M+H)^+$

Example 195



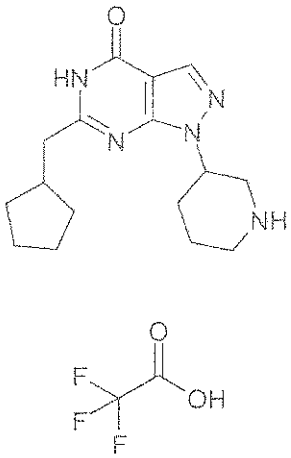
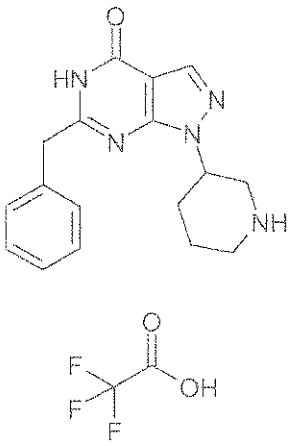
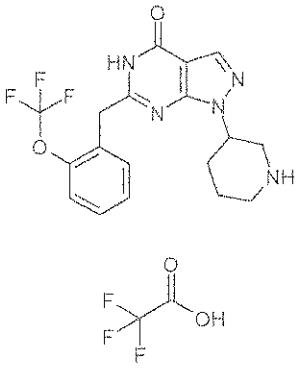
330 mg (0.82 mmol) of Example 12A were dissolved in 3 mL dichloromethane and 1 mL trifluoroacetic acid was added. The reaction mixture was stirred at room temperature over night. The solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 240 mg (70 %) of the product were obtained.

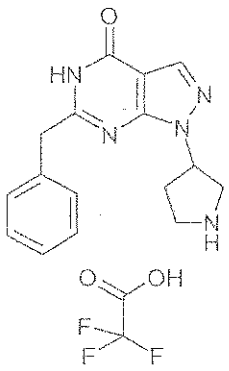
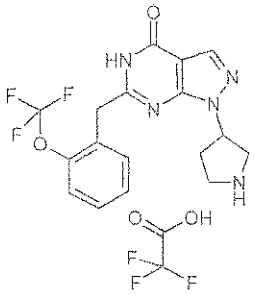
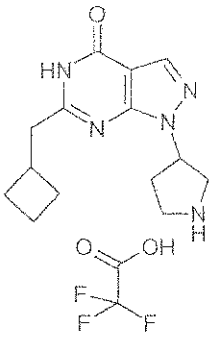
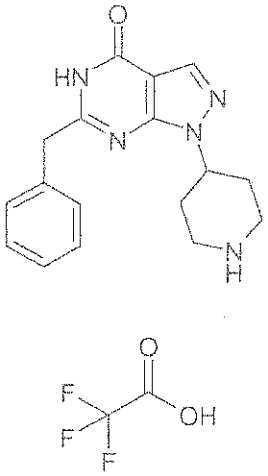
HPLC-MS (Method 1): $R_t$: 0.96 min

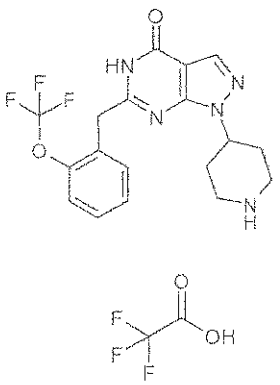
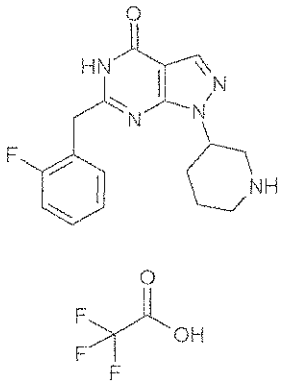
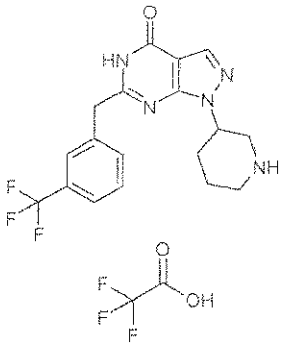
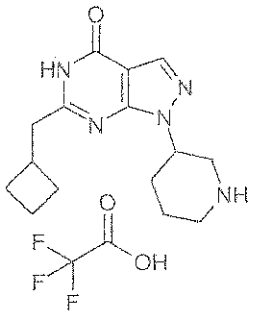
MS ( ESI pos ): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 195, using the corresponding Boc-protected amines as starting materials.

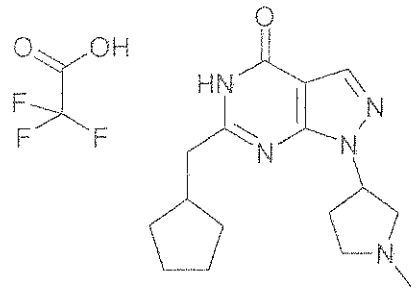
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Exp. 196<br>racem. mixture |  | Example 12L | 1.01<br>(Method 1) | 302 $(M+H)^+$ |
| Exp. 197<br>racem. mixture |  | Example 12M | 0.93<br>(Method 1) | 310 $(M+H)^+$ |
| Exp. 198<br>racem. mixture |  | Example 12N | 1.09<br>(Method 1) | 394 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 199<br>racem. mixture |  | Example 12G | 0.92<br>(Method 1) | 296 $(M+H)^+$ |
| Exp. 200<br>racem. mixture |  | Example 12H | 1.08<br>(Method 1) | 380 $(M+H)^+$ |
| Exp. 201<br>racem. mixture |  | Example 12J | 0.89<br>(Method 1) | 274 $(M+H)^+$ |
| Exp. 202 |  | Example 12B | 0.92<br>(Method1) | 310 $(M+H)^+$ |

| | | | | |
|---|---|---|---|---|
| Exp. 203 |  | Example 12C | 1.07 (Method1) | 394 $(M+H)^+$ |
| Exp. 204 racem. mixture |  | Example 12Q | 0.95 (Method 1) | 328 $(M+H)^+$ |
| Exp. 205 racem. mixture |  | Example 12R | 1.13 (Method 1) | 378 $(M+H)^+$ |
| Exp. 206 racem. mixture |  | Example 12U | 0.94 (Method 1) | 288 $(M+H)^+$ |

Example 207, racemic mixture



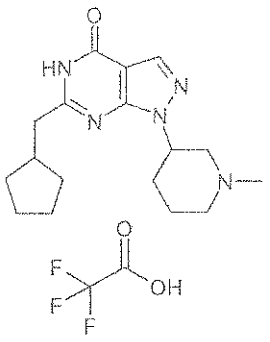
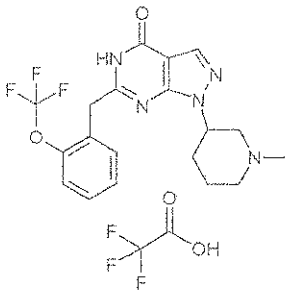
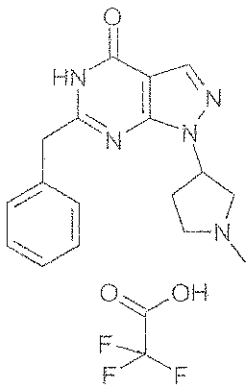
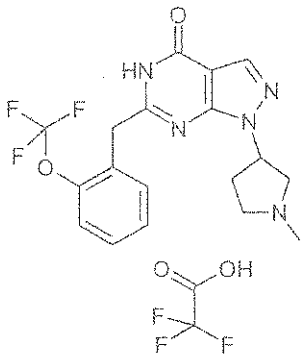
50 mg (120 mmol) of Example 13A were dissolved in 5 mL dichloromethane and 15 mg (500 mmol) of formaldehyde were added. The reaction mixture was stirred at room temperature for 1h. 15 µL (260 mmol) acetic acid and 35 mg (160 mmol) sodiumtriacetoxyborohydride were added. The reaction mixture was stirred 2h at room temperature. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile). 34 mg (65 %) of the product were obtained.

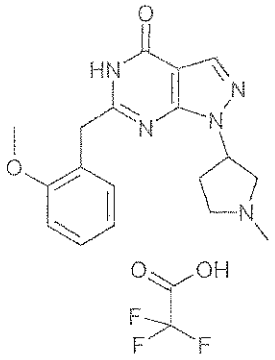
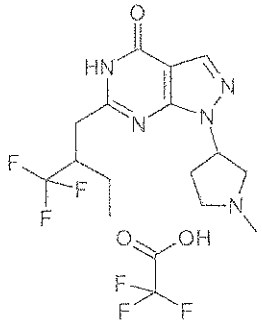
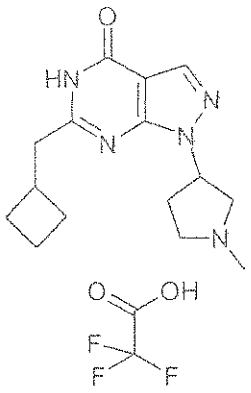
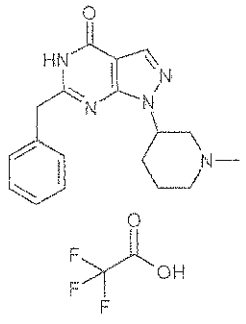
HPLC-MS (Method 1): $R_t$: 0.99 min

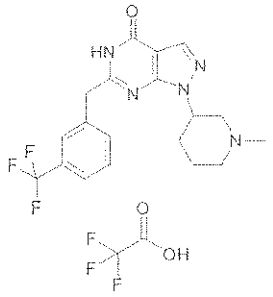
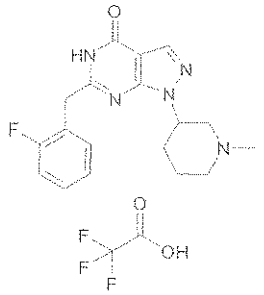
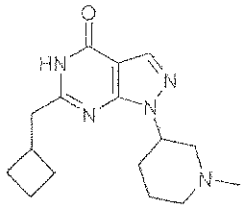
MS ( ESI pos ): m/z = 302 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of Example 207 using the corresponding amines as starting materials

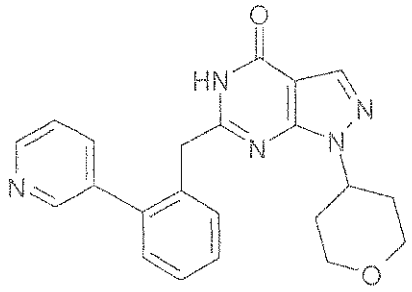
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 208<br>racem. mixture |  | Example 13C | 1.02<br>(Method 1) | 316 $(M+H)^+$ |
| Exp. 209<br>racem. mixture |  | Example 13E | 1.13<br>(Method 1) | 408 $(M+H)^+$ |
| Exp. 210<br>racem. mixture |  | Example 13F | 0.93<br>(Method 1) | 310 $(M+H)^+$ |
| Exp. 211<br>racem. mixture |  | Example 13G | 1.11<br>(Method 1) | 394 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 212 racem. mixture |  | Example 13H | 0.98 (Method 1) | 340 $(M+H)^+$ |
| Exp. 213 mixture of stereoisomers |  | Example 13J | 1.02 (Method 1) | 344 $(M+H)^+$ |
| Exp. 214 racem. mixture |  | Example 13I | 0.91 (Method 1) | 288 $(M+H)^+$ |
| Exp. 215 racem. mixture |  | Example 13D | 0.97 (Method 1) | 324 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Exp. 216 racem. mixture |  | Example 205 | 1.16 (Method 1) | 392 $(M+H)^+$ |
| Exp. 217 racem. mixture |  | Example 204 | 0.98 (Method 1) | 342 $(M+H)^+$ |
| Exp. 218 racem. mixture |  | Example 13Q | 0.95 (Method 1) | 302 $(M+H)^+$ |

Example 219



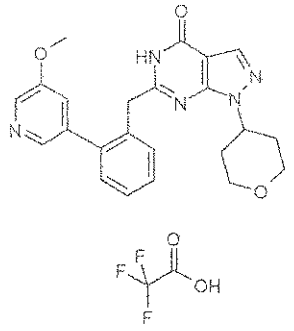
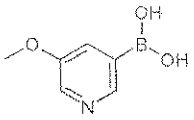
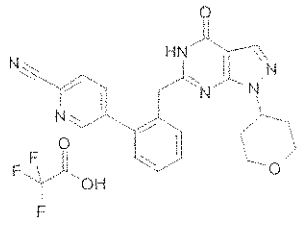
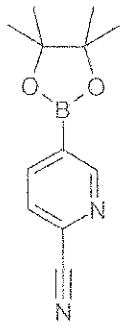
Under a argon atmosphere 100 mg (0.26 mmol) of example 5. 95 mg (0.77 mmol) pyridine-3-boronic acid, 310 µL (2.41 mmol) aqueous sodium carbonate solution (2 M), 5 mL dioxane and 20 mg (0.02 mmol) tetrakis-(triphenylphosohine)palladium(0)

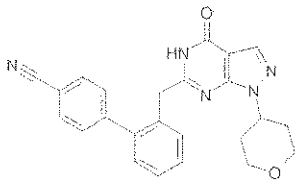
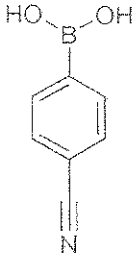
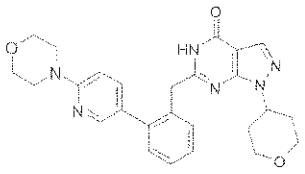
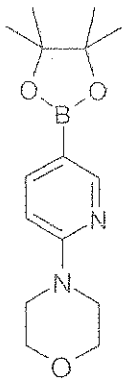
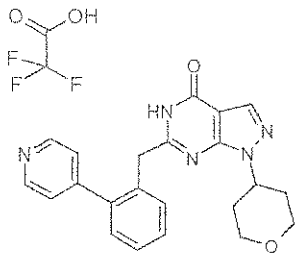
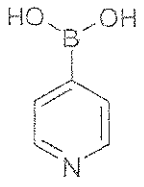
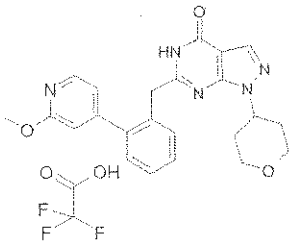
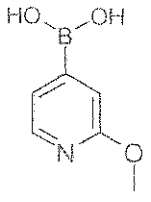
were combined. The reaction mixture was heated to 140°C for 35 min in a microwave oven. After cooling to room temperature the reaction mixture was filtered over celite. The filtrate was evaporated under reduced pressure. The residue was purified by preparative HPLC. 82 mg (83 %) of the product were obtained.

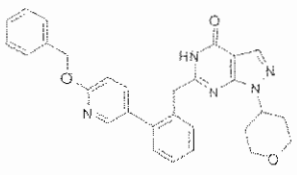
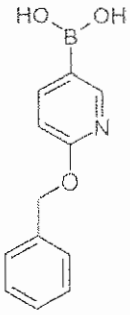
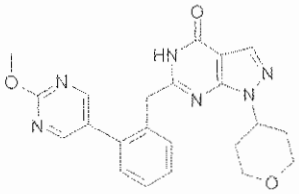
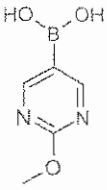
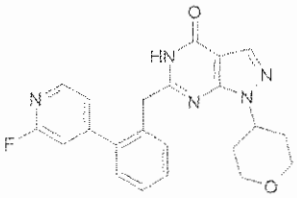
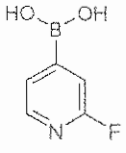
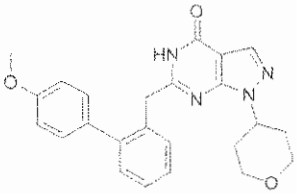
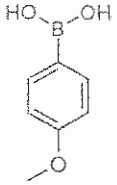
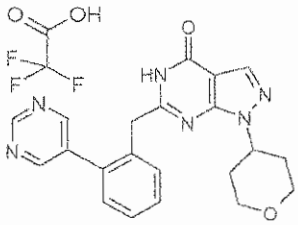
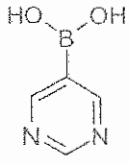
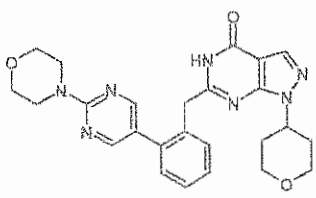
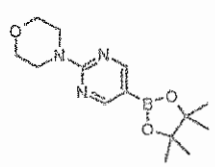
HPLC-MS (Method 1): $R_t$: 1.00 min

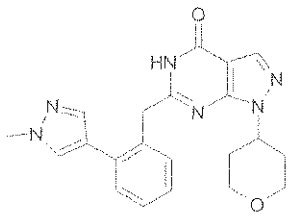
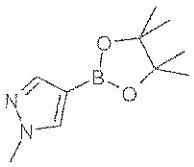
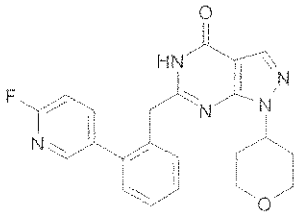
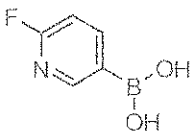
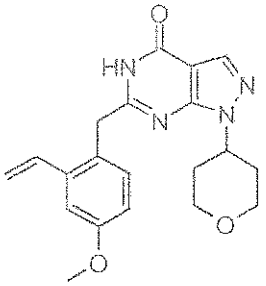
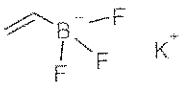
MS ( ESI pos ): m/z = 388 $(M+H)^+$

The following examples were synthesized in analogy to the preparation of example 219 using the corresponding boronic acids as starting materials.

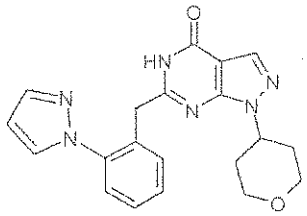
| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 220 |  |  | 1.01 (Method 1) | 418 $(M+H)^+$ |
| Example 221 |  |  | 1.24 (Method 1) | 413 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 222 |  |  | 1.34 (Method 1) | 412 $(M+H)^+$ |
| Example 223 |  |  | 1.03 (Method 1) | 473 $(M+H)^+$ |
| Example 224 |  |  | 0.96 (Method 1) | 388 $(M+H)^+$ |
| Example 225 |  |  | 1.18 (Method 1) | 418 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| Example 226 |  |  | 1.57 (Method 1) | 494 $(M+H)^+$ |
| Example 227 |  |  | 1.19 (Method 1) | 419 $(M+H)^+$ |
| Example 228 |  |  | 1.26 (Method 1) | 406 $(M+H)^+$ |
| Example 229 |  |  | 1.40 (Method 1) | 417 $(M+H)^+$ |
| Example 230 |  |  | 1.06 (Method 1) | 389 $(M+H)^+$ |
| Example 230-1 |  |  | 1.24 (Method 1) | 474 $(M+H)^+$ |

| | structure | starting material | $R_t$ [min] | MS (ESI, m/z) |
|---|---|---|---|---|
| | | | | |
| Example 230-2 |  |  | 1.16 (Method 1) | 391 $(M+H)^+$ |
| Example 230-3 |  |  | 1.25 (Method 1) | 404 $(M+H)^+$ |
| 230-4 |  |  | 1.28 (Method 1) | 367 $(M+H)^+$ |

Example 231



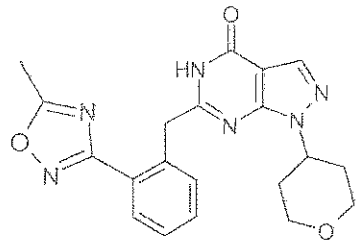
A vial was charged under inert atmosphere with Example 5 (175 mg, 0.45 mmol), pyrazole (306 mg, 4.49 mmol), copper iodide (85 mg, 0.45 mmol) and cesium

carbonate (439 mg, 1.35 mmol) were added. Dimethylformammide (5 ml), previously degassed, was then added, followed by N-N'-dimethylethylenediamine (47.87 µl; 0.45 mmol). The reaction mixture was heated to 120 °C for three hours.The suspension was then filtered over a Celite pad; Celite was washed with DMF. The volume of the organic phase was reduced under reduced pressure and, afterwards, ammonium chloride saturated solution was added, followed by ethyl acetate. The phases were separated and the organic phase was washed with brine and then dried. The crude product was purified by SPE cartridge and the product obtained was further purified by SPE Stratosphere "PL-THIOL MP" to completely remove copper salts. The solid obtained was triturated with diethyl ether. 15.5 mg of the desired compound were obtained (yield = 9.2%).

HPLC-MS (Method 1E hydro): $R_t$: 7.80 min

MS ( ESI pos ): m/z = 377 $(M+H)^+$

Example 232



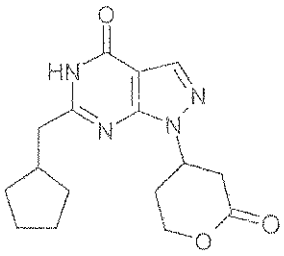
Example 53 (100 mg, 0.298 mmol) and hydroxylamine (0.073 ml, 1.19 mmol) were mixed together in absolute ethanol (4 ml) in a 50 ml flask. The reaction mixture was refluxed for 3 hours before being worked up. The solvent was then removed under reduced pressure to obtain 120 mg (content 70%, 0.228 mmol) of N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine as solid that was used as such in the next step.
N-Hydroxy-2-[4-oxo-1-(tetrahydro-pyran-4-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-ylmethyl]-benzamidine (120 mg, content 70%; 0.228 mmol) was suspended in trimethylorthoacetate (5 ml) and acetic acid was added afterwards (1 ml); the mixture was heated to 100 °C for one hour. The mixture was cooled at room

temperature and the precipitation of a solid was observed. The filtrate was evaporated under reduced pressure; the crude product was purified by flash chromatography. The product was then triturated with diethyl ether. 24 mg of the desired compound were obtained (yield 26.6%).

HPLC/MS (Method 1E hydro)

MS ( ESI pos ): m/z = 393 $(M+H)^+$

Example 233



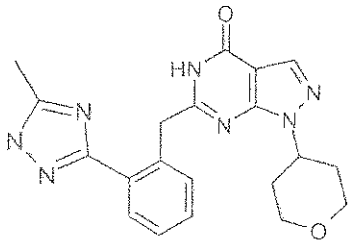
Example 12X (250 mg, 1.14 mmol) was dissolved in 20 ml of hot methanol. Alumina (neutral) was added and the solvent was then removed to give a white powder which was transferred into a 2 ml Wheaton vial; 5,6-Dihydro-2H-pyran-2-oxo was added followed by DMFe (1ml) and the vial was closed tightly. The suspension was heated to 80°C with orbital shaking during 4 days. The reaction was then filtered and the alumina was washed with methanol, ethyl acetate and dicholoromethane; the organic solutions were combined and solvents removed under reduced pressure. The crude product was purified by flash chromatography.

Eluent: (gradient starting with n-hexane/ethyl acetate 9/1 to ethyl acetate (100%) followed by ethyl acetate/methanol 99/1 to 94/6). 70 mg of the desired compound were obtained as solid (19.3 %).

HPLC-MS (Method 2F): $R_t$: 9.06 min

MS ( ESI pos ): m/z = 317 $(M+H)^+$

Example 234

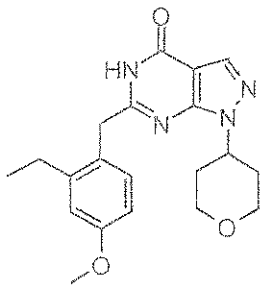


Example 53 (160 mg, content 80% ,0.38 mmol) and hydrazine hydrate (0.186 ml, 3.81 mmol) were mixed together in absolute ethanol (4 ml) in a 25 ml flask. The reaction mixture was refluxed for 6 hours before being worked up. The solvent was removed under reduced pressure to obtain 200 mg (content 70%, 0.38 mmol) of the desired material used as such in the next step. The material (200mg, 70% content, 0.38 mmol) was suspended in trimethylorthoacetate (6 ml). Acetic acid is added (0.6 ml) and the solution was heated to 80°C for 30 minutes. Trimethylortoacetate and acetic acid were removed under reduced pressure and the crude product was partitioned between water and dichloromethane. The organic phase is dried and the crude product purified by flash chromatography. (gradient: starting with dichloromethane/methanol 98/2 and finishing with dichloromethane/methanol 90/10). The product was further purified by trituration with diethyl ether. 8 mg of the desired compound were obtained (4%).

HPLC-MS (Method 1E hydro): $R_t$: 6.82 min

MS ( ESI pos ): m/z = 392 $(M+H)^+$

Example 235

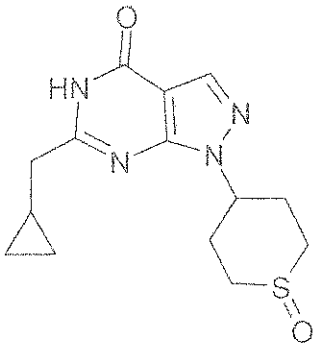


22 mg (0.06 mmol) of example 230-4 in 3 ml methanol were hydrogenated over Pd/C (10 %) under atmospheric pressure. The catalyst was removed. The solvent was evaporated and the residue chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 15.7 mg (71 %) of the product.

HPLC-MS (Method 1): $R_t$: 1.35 min

MS ( ESI pos ): m/z = 369 $(M+H)^+$

Example 236

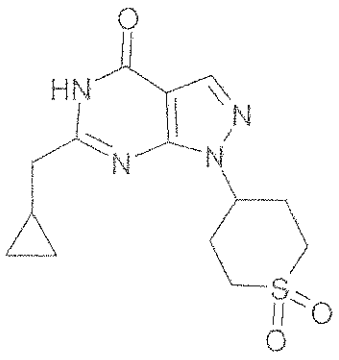


100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 30 µL (0.35 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 h and acetonitrile/water was added. The mixture was chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 50.3 mg (65 %) of the product.

HPLC-MS (Method 1): $R_t$: 0.88 min

MS ( ESI pos ): m/z = 307 $(M+H)^+$

Example 237



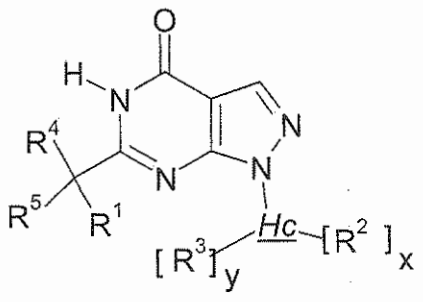
100 mg (73 %, 0.251 mmol) of example 40-5 were dissolved in 2 ml acetic acid and 200 µL (2.33 mmol) hydrogen peroxide solution in water (35 %) were added. The mixture was stirred for 3 days and acetonitrile/water was added. The mixture was chromatographed by HPLC (eluent A: water + 0.13 % TFA, eluent B: acetonitrile) to yield 21.5 mg (27 %) of the product.

HPLC-MS (Method 1): $R_t$: 0.93 min

MS ( ESI pos ): m/z = 323 $(M+H)^+$

## Claims

1. A compound according to general formula I,



(I)

wherein

***Hc*** is selected from the group of tetrahydropyranyl, tetrahydrofuranyl, piperidinyl, pyrrolidinyl;

$\mathbf{R^1}$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently of one another selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, and $CF_3$- ;

$\mathbf{R^2}$ independently of any other $\mathbf{R^2}$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $\mathbf{R^2}$ shall be independently of any other $\mathbf{R^2}$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2$N-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl;

**x** is 0, 1, 2, 3 or 4;

**y** is 0 or 1;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein

***Hc*** is selected from the group of 3- or 4-piperidinyl and 3- pyrrolidinyl;

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, and $CF_3$-;

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

and in cases $R^2$ is attached to a nitrogen which is a ring member of ***Hc***, this $R^2$ shall be independently of any other $R^2$: H-, $C_{1-6}$-alkyl-CO-, $C_{1-6}$-alkyl-O-CO-, $C_{1-6}$-alkyl-, phenyl-CO-, phenyl-O-CO-, $(C_{1-6}\text{-alkyl})_2N$-CO-,

where the above-mentioned members may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl;

**x** is 0, 1, 2, 3 or 4;

**y** is 0, or 1;

and pharmaceutically acceptable salts thereof.

3. A compound according to claim 1, wherein

***Hc*** is selected from the group of 3- or 4-tetrahydropyranyl and 3-tetrahydrofuranyl.

$R^1$ being selected from the group of

phenyl, 2-, 3- and 4-pyridyl-, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ethyl, 1- and 2-propyl, 1- and 2-butyl-, 1-, 2- and 3-pentyl-, tetrahydrofuranyl and tetrahydropyranyl,

where these groups may optionally be substituted by one or more substituents independently selected from the group consisting of fluorine, chlorine, bromine, iodine, oxo, NC-, $C_{1-6}$-alkyl-O-, $C_{1-6}$-alkyl-, $CF_3O$-, $CF_3$-;

$R^2$ independently of any other $R^2$ being selected from the group of H- and $C_{1-6}$-alkyl-,

where the above-mentioned $C_{1-6}$-alkyl-group(s) may optionally be substituted independently of one another by one or more fluorine substituents;

$R^3$ being selected from the group of

H-, hydroxy and $C_{1-6}$-alkyl-O-, whereby $C_{1-6}$-alkyl-O- may optionally be substituted by one or more fluorine, chlorine, bromine and HO-;

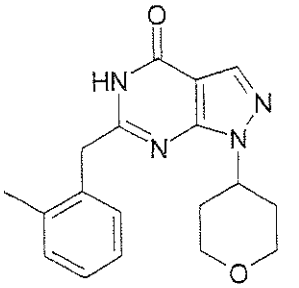
$R^4$ and $R^5$ independently of one another being selected from the group of H-, fluorine, and methyl;

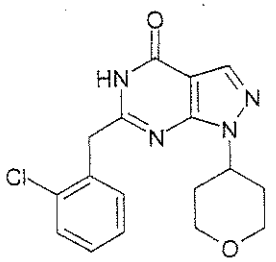
**x** is 0, 1, 2, 3 or 4;

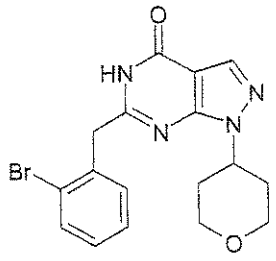
**y** is 0, or 1;

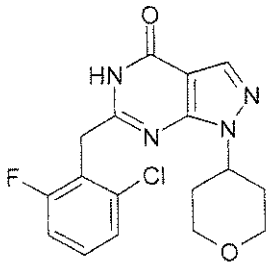
and pharmaceutically acceptable salts thereof.

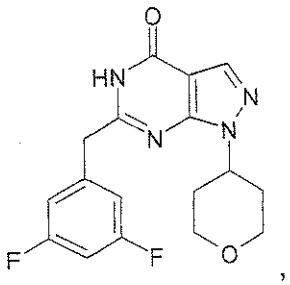
4. The compound according to claim 1 selected from the group consisting of


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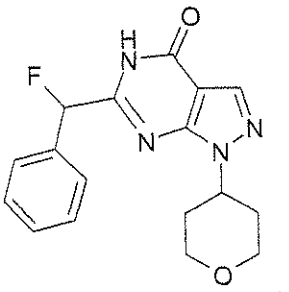

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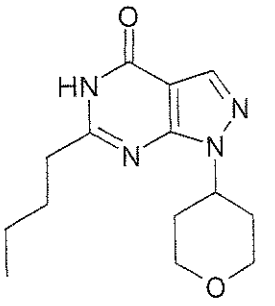

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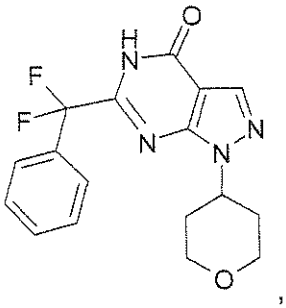
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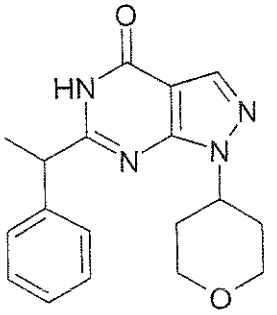
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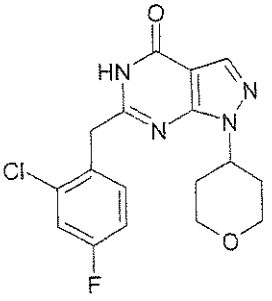
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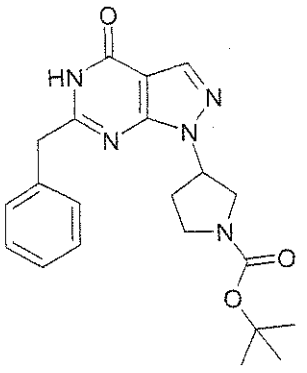
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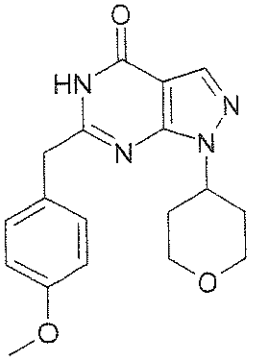
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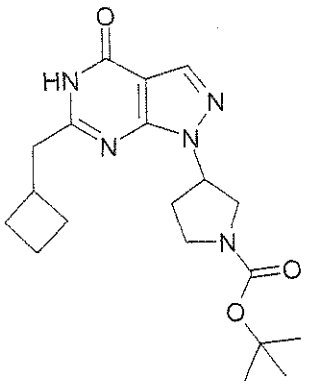
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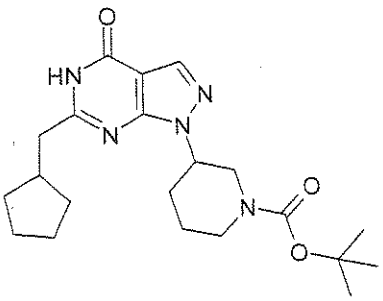
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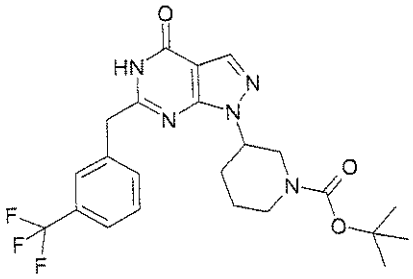
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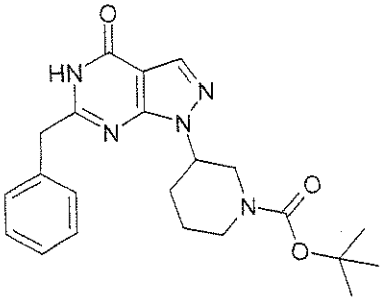
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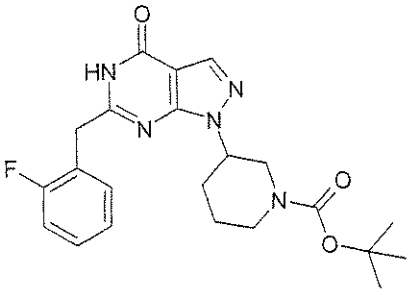
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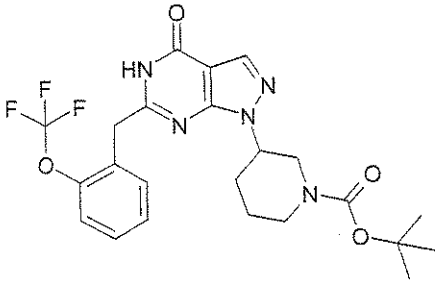
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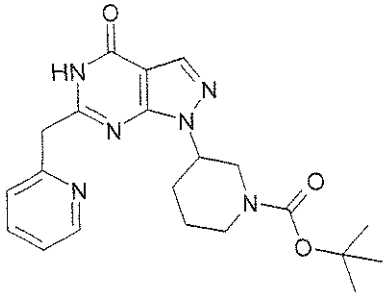
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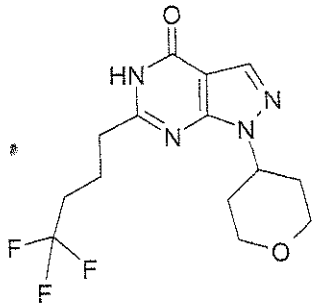
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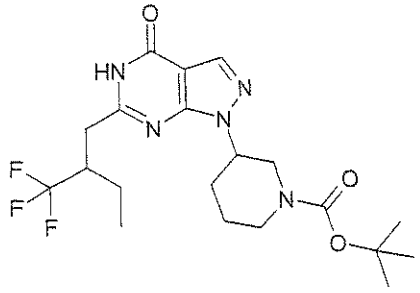
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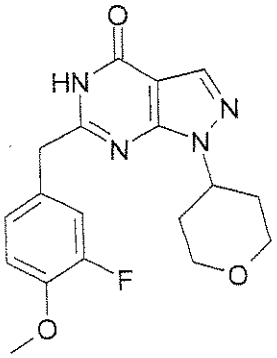
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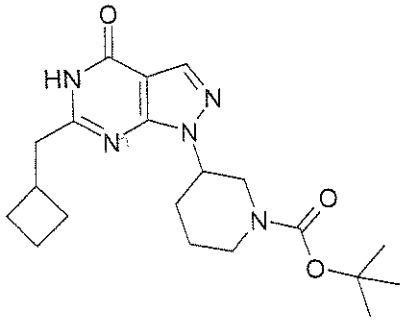


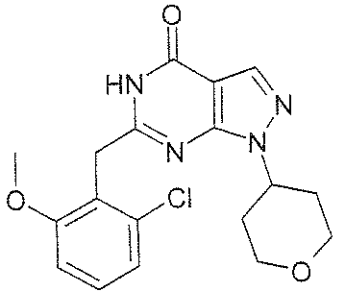
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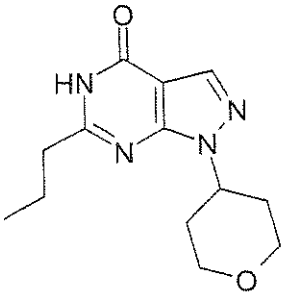


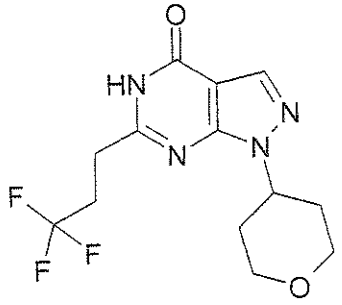
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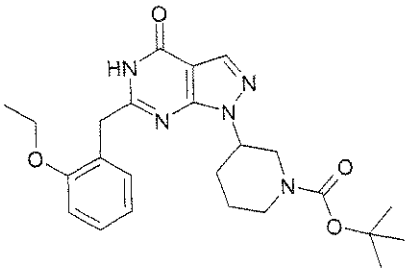


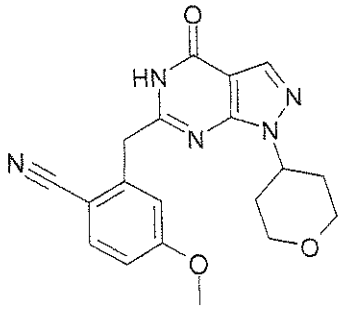


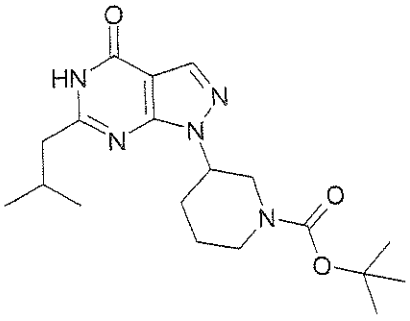


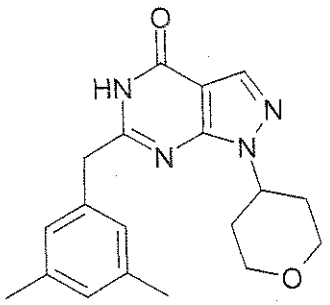


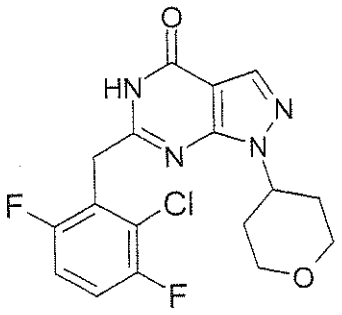


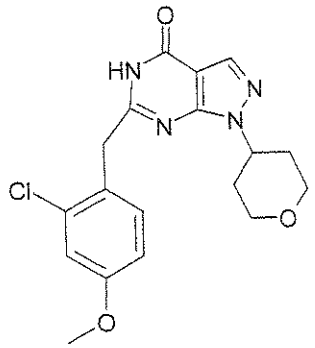


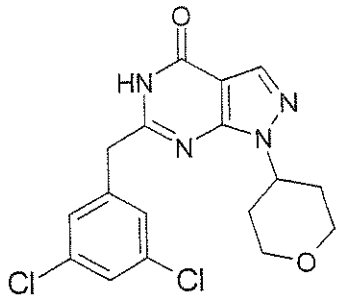


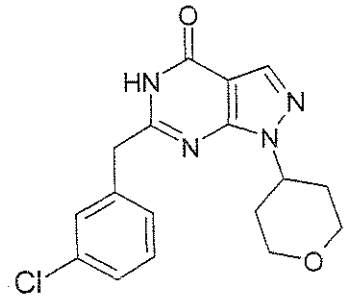


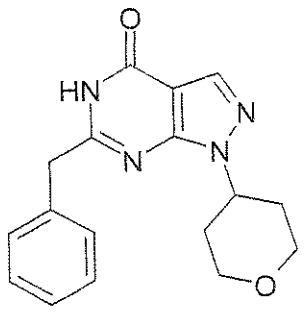


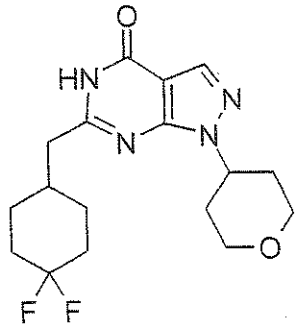


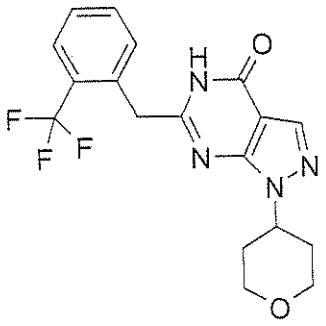




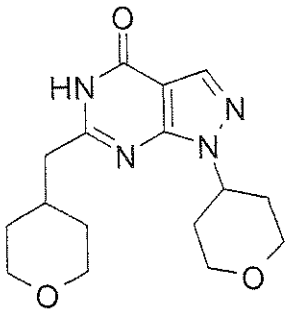




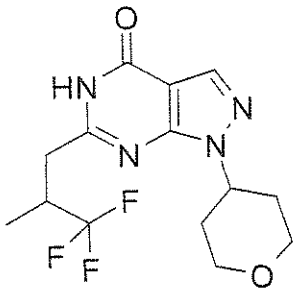




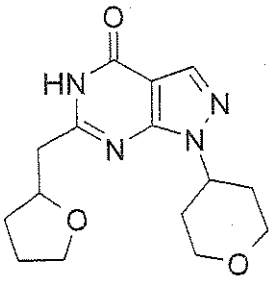
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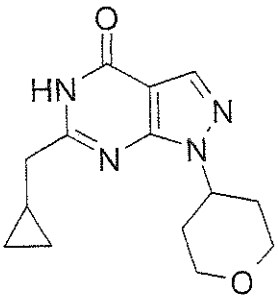
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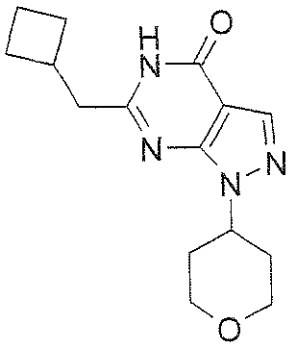
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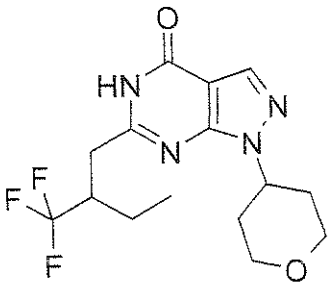
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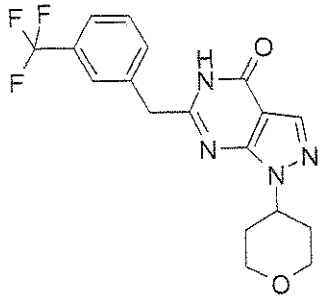
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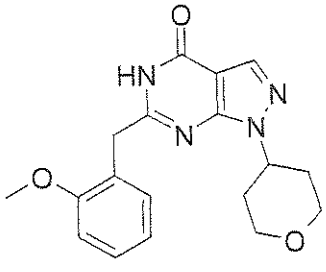
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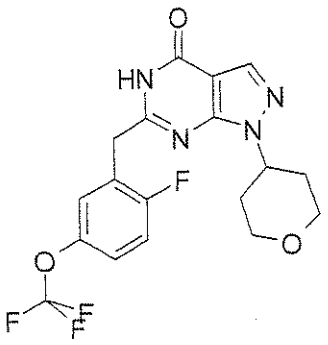
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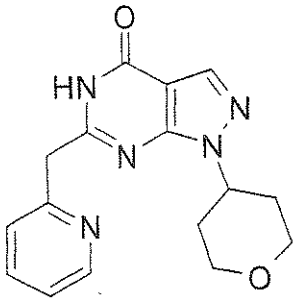


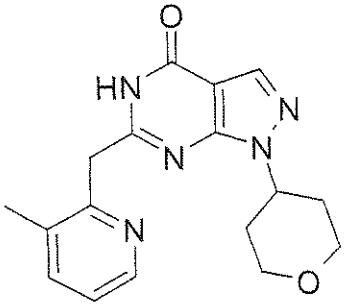
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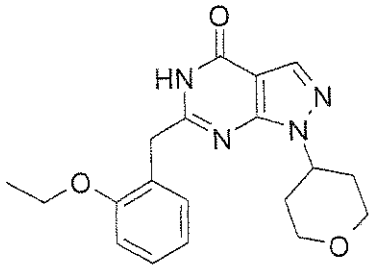


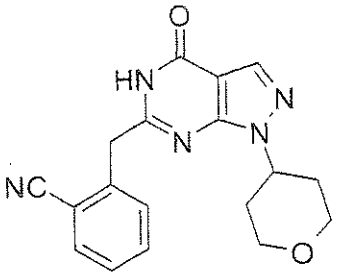
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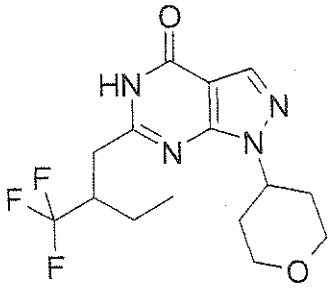


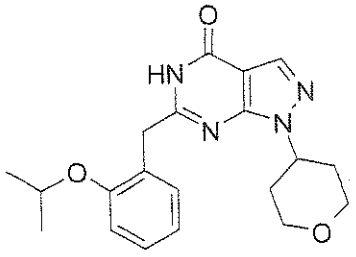


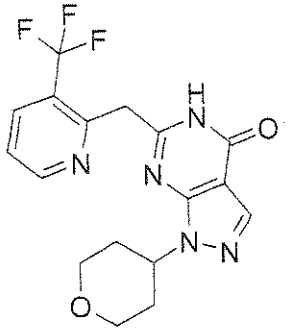


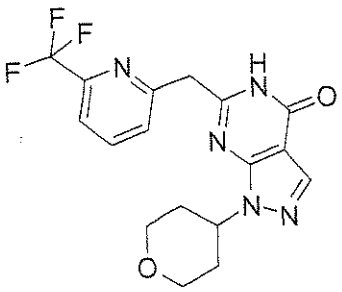


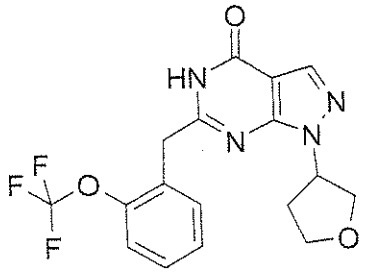


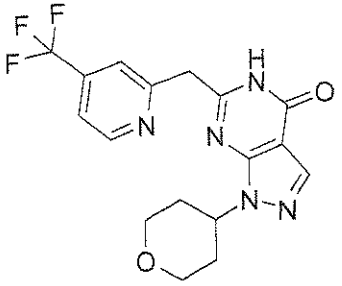


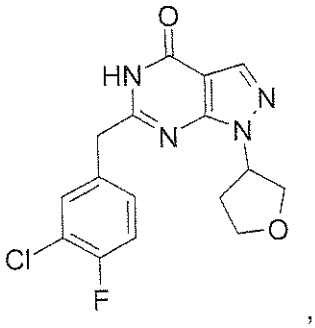


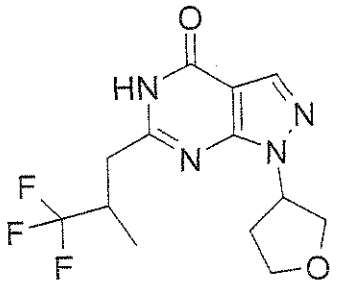


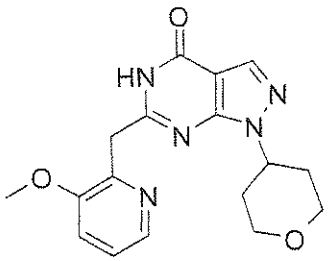


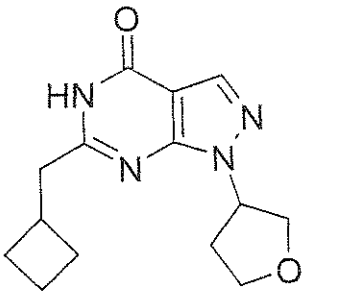


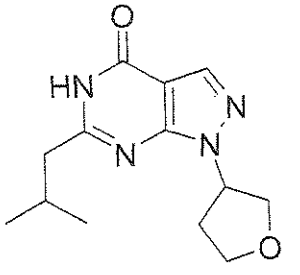


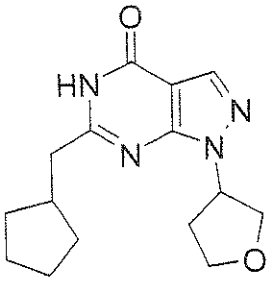


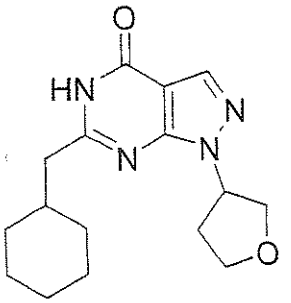




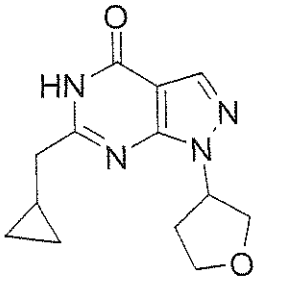




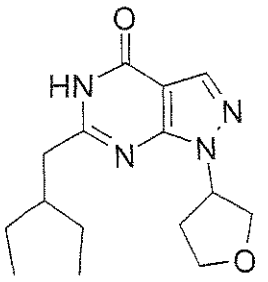




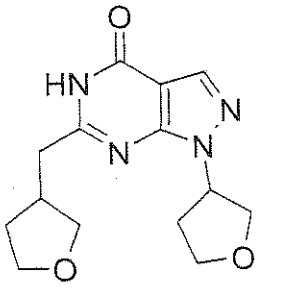
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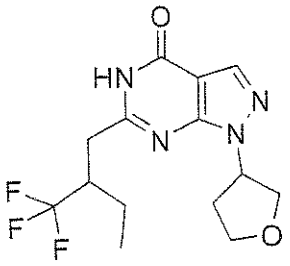
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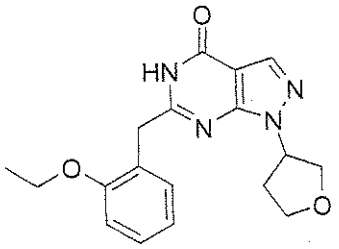
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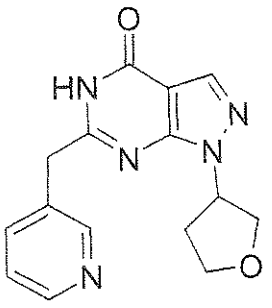
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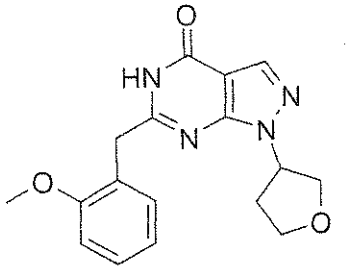
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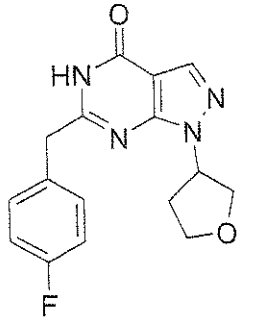
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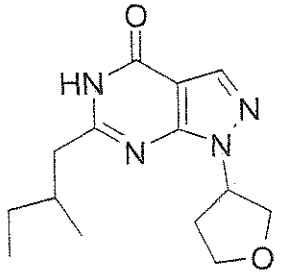
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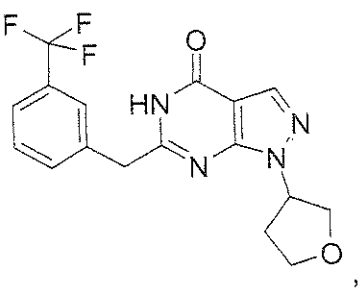


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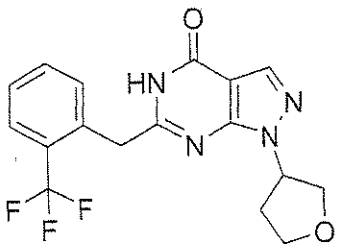


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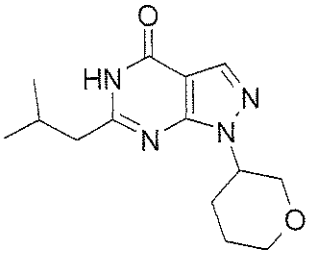




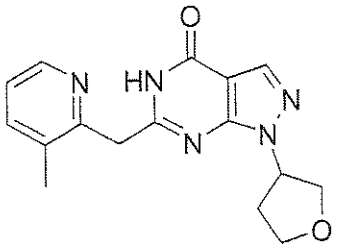
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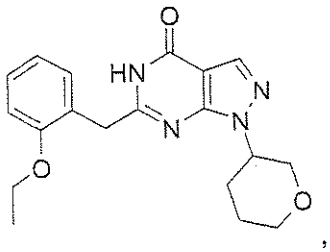
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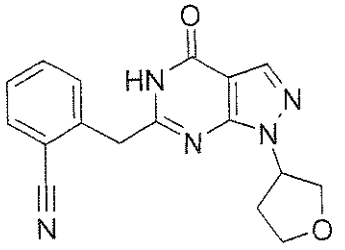
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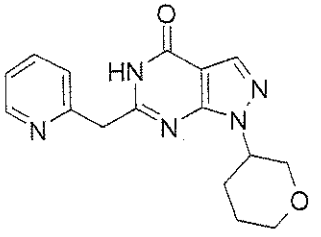
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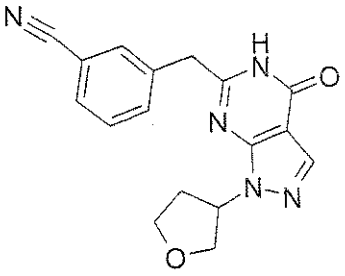
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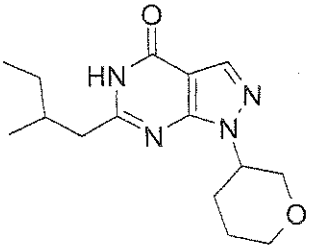
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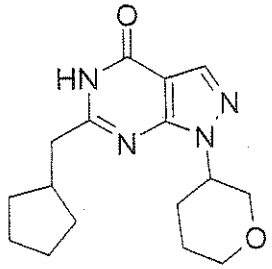
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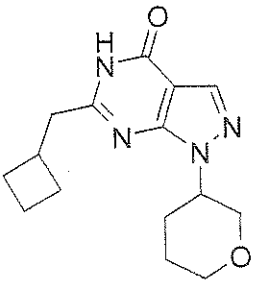
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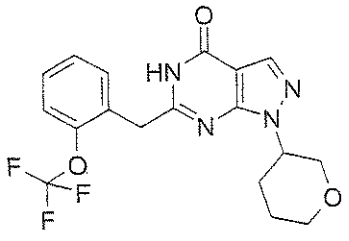
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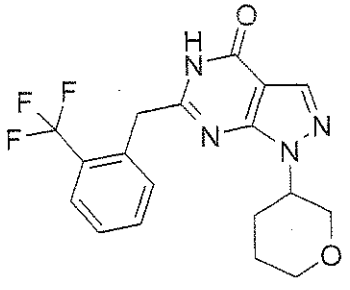
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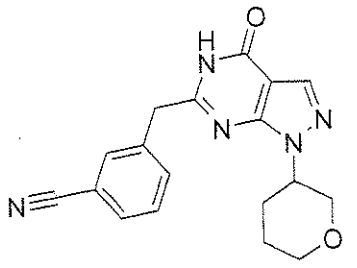
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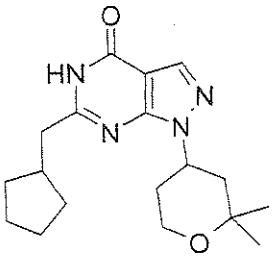
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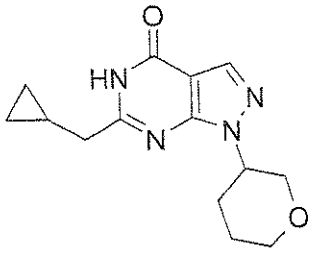
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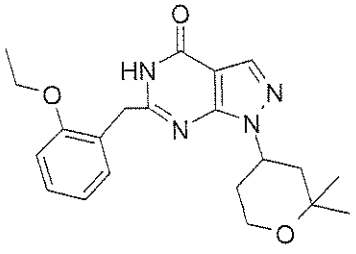
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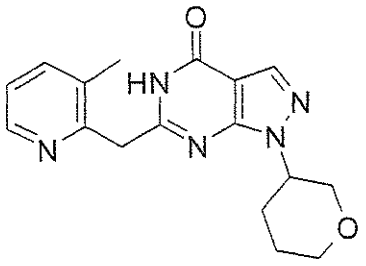
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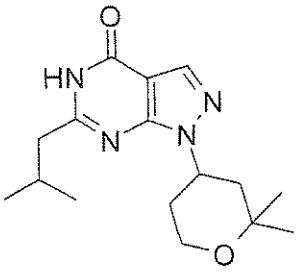
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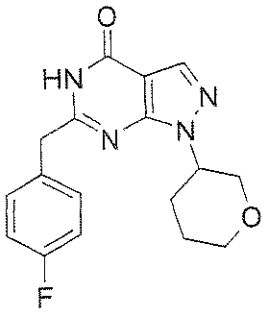
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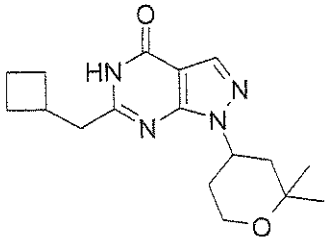
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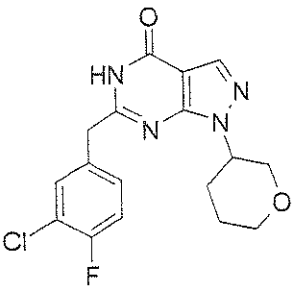
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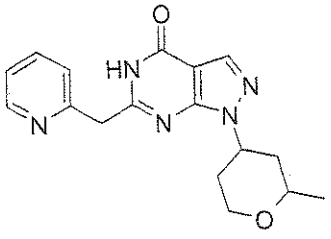
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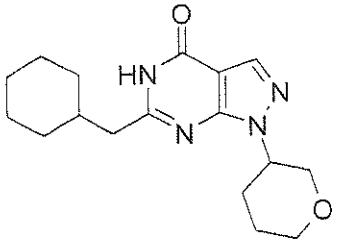
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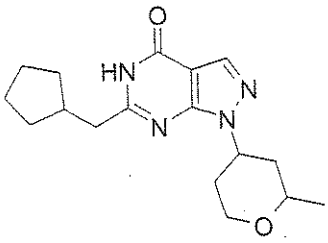
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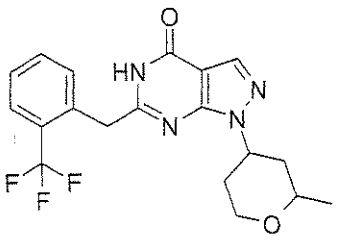
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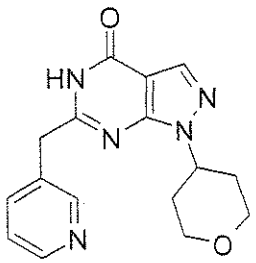


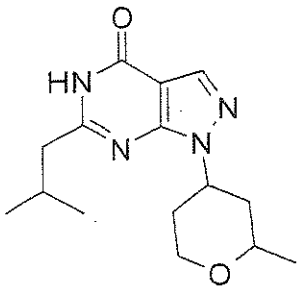
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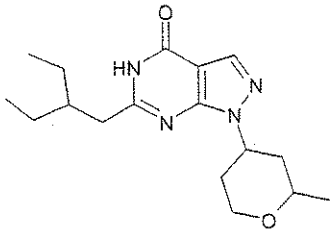


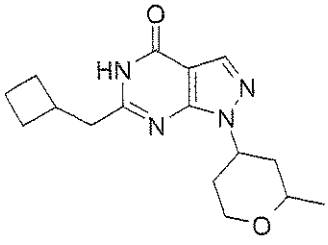
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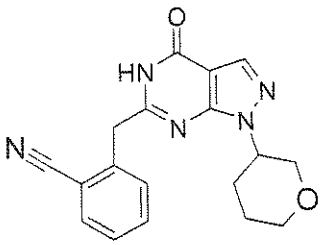


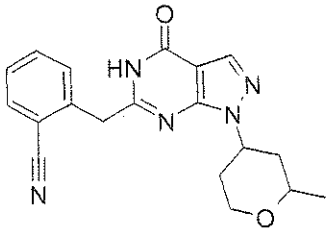


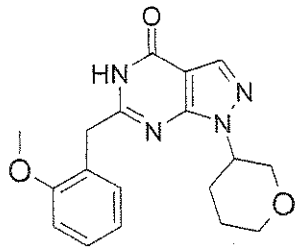


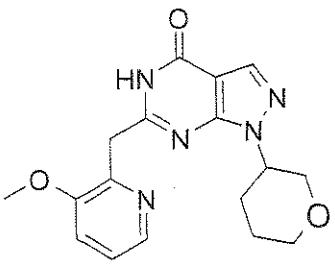


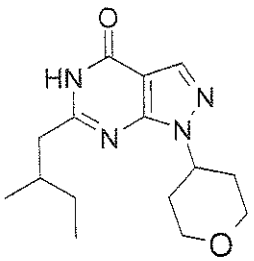


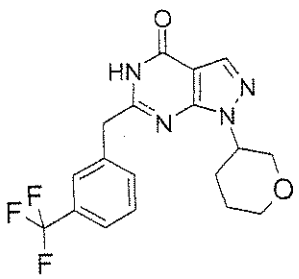




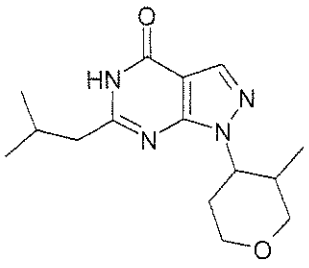




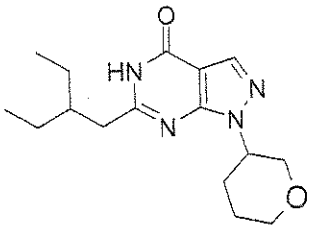




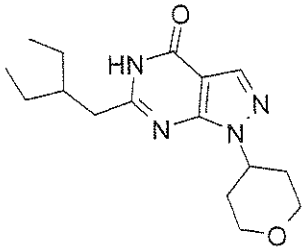
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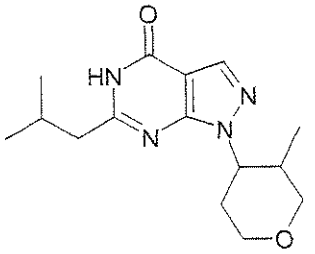
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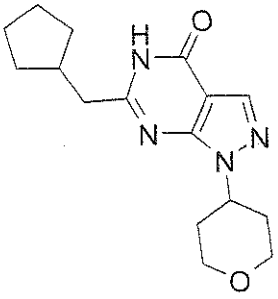
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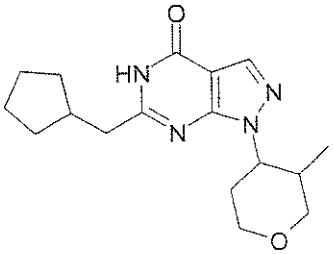
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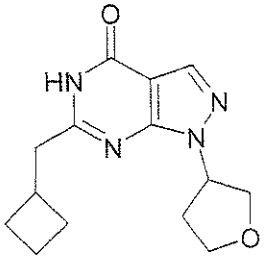
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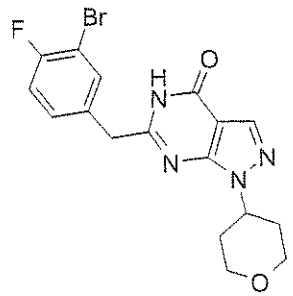
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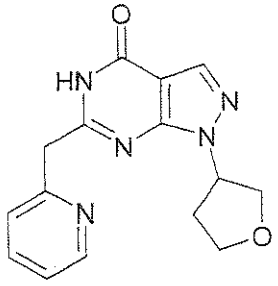
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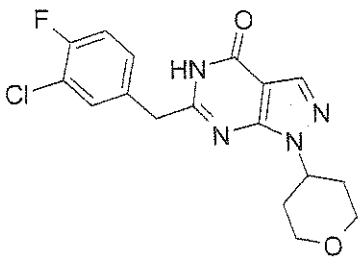
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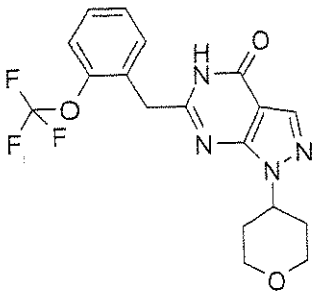
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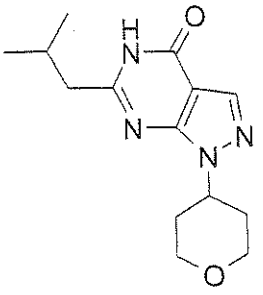
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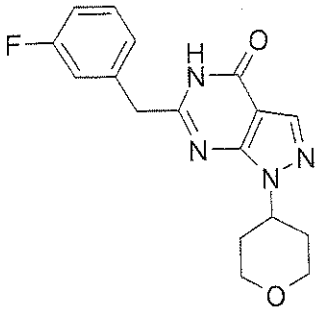
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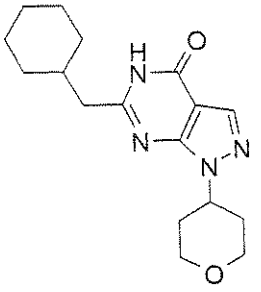
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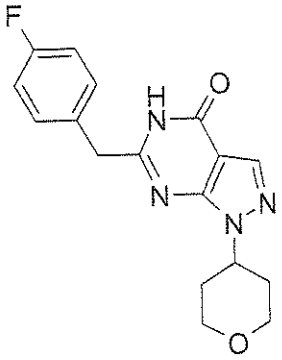
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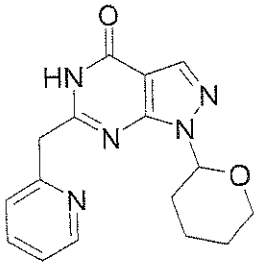
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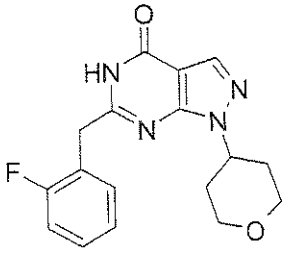
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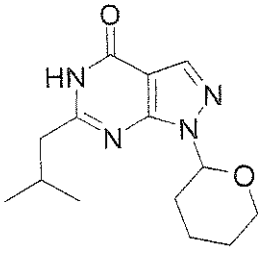
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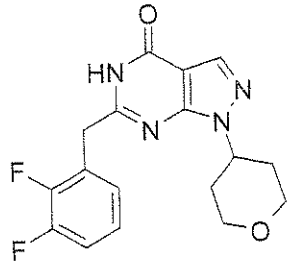
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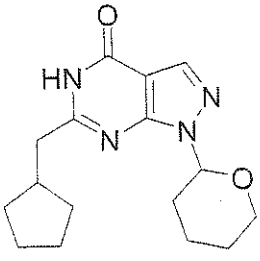
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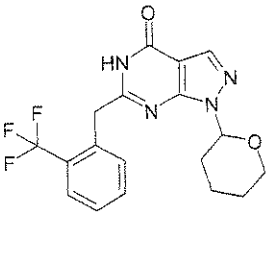
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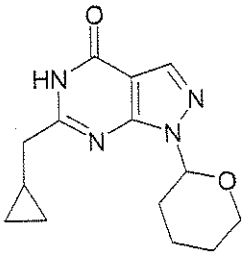
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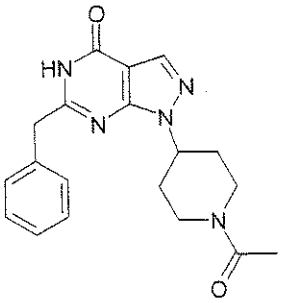
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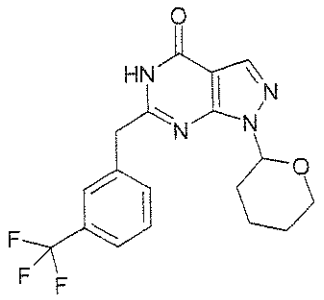
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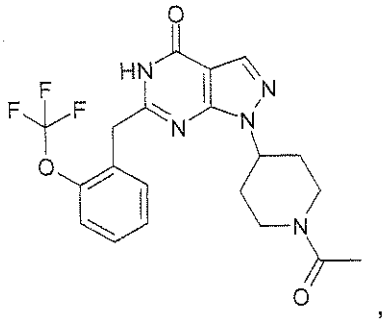
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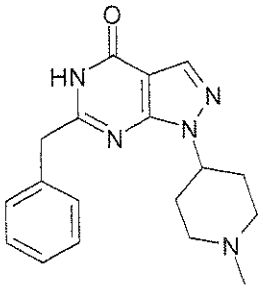
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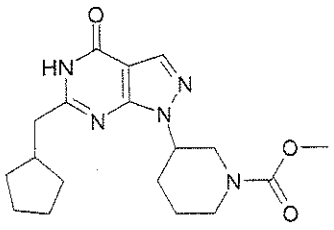
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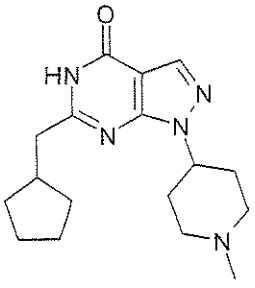
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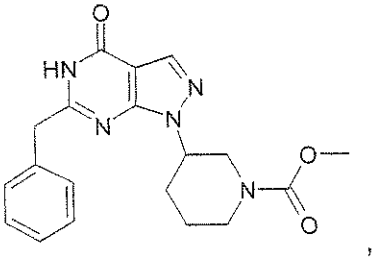
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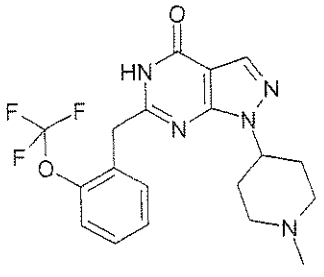
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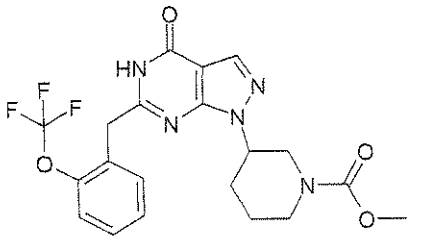
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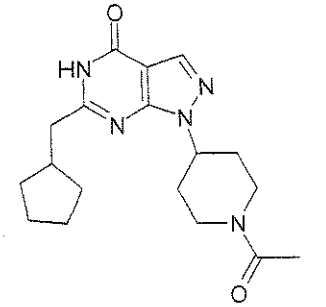
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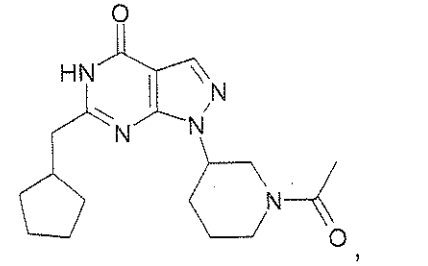
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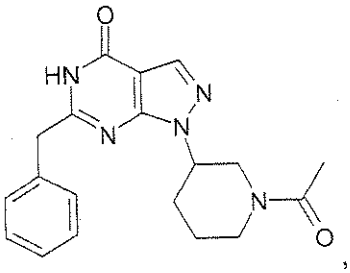
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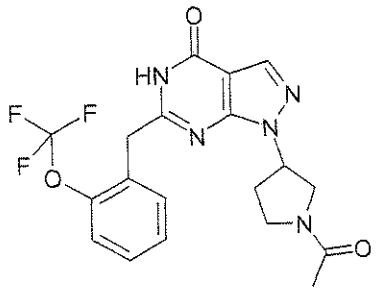


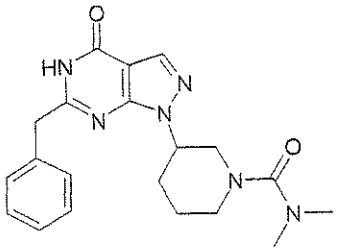
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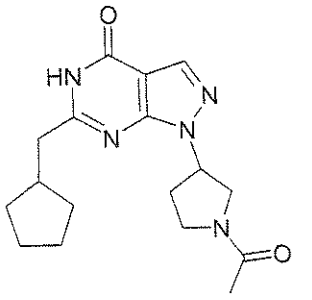


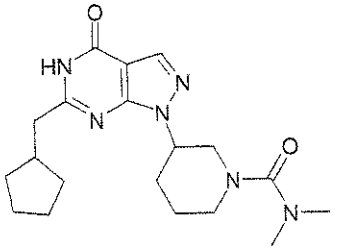
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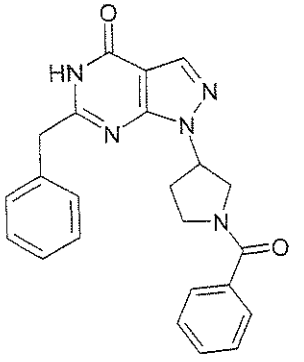


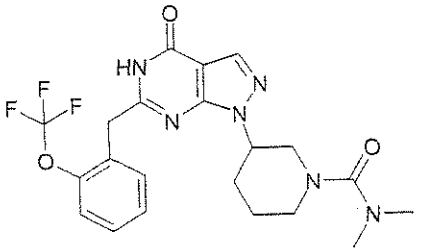


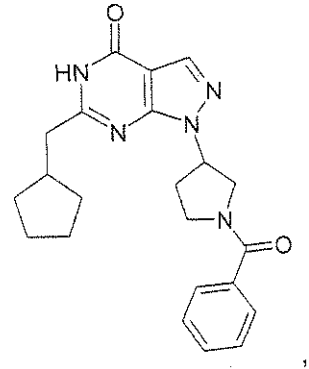


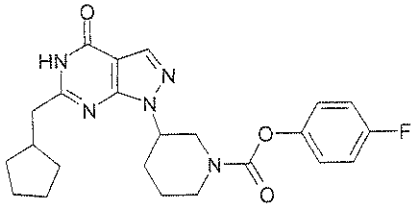




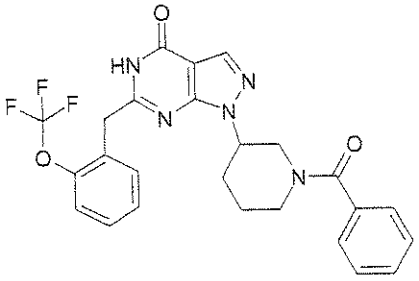


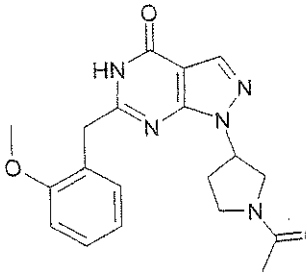


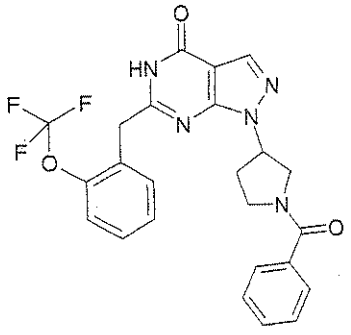


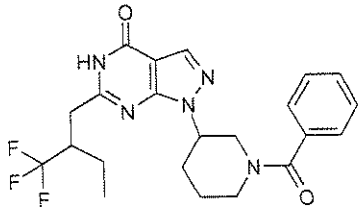


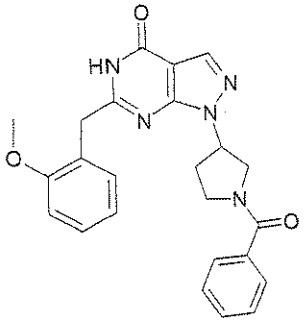


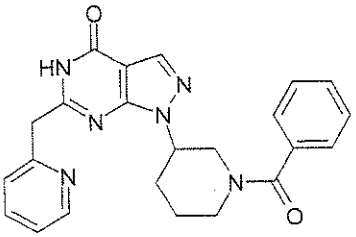


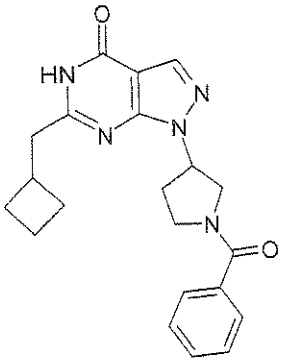


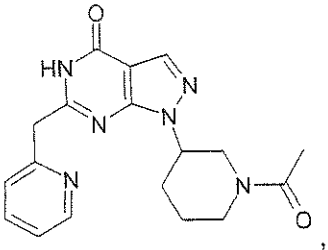


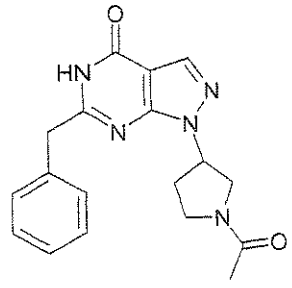


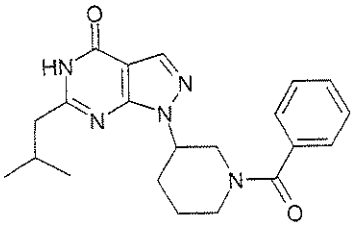


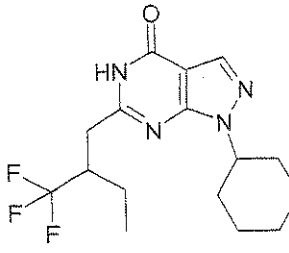


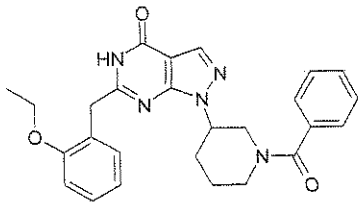




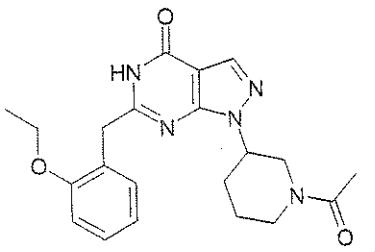


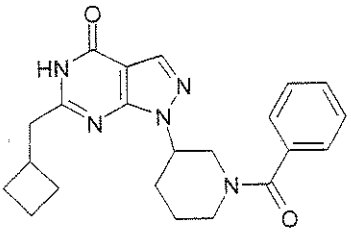




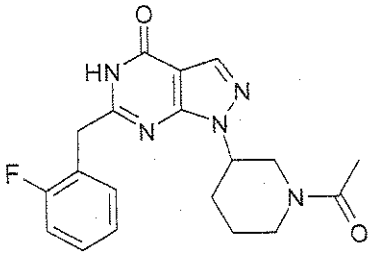




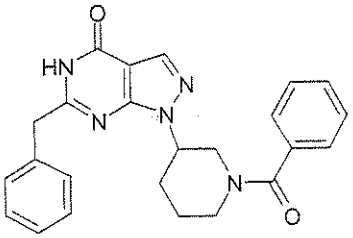




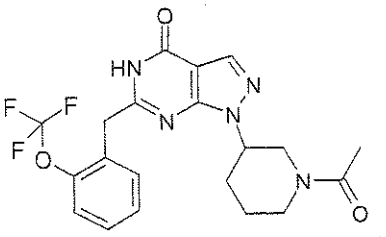
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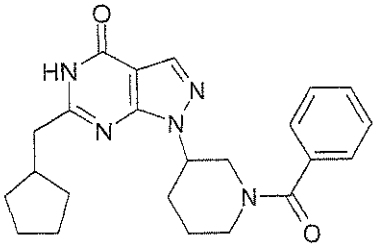
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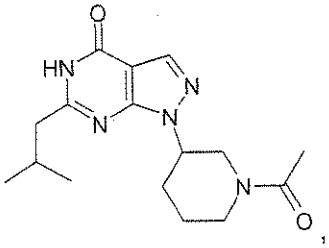
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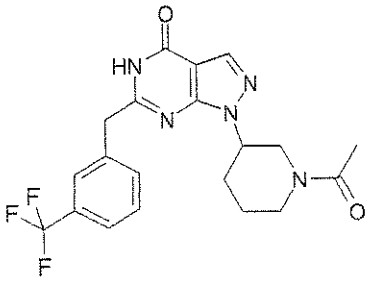
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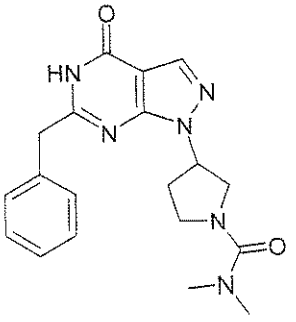
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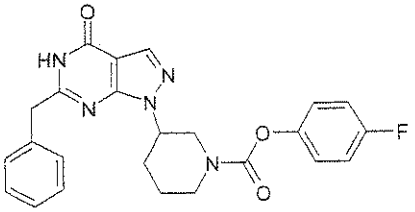
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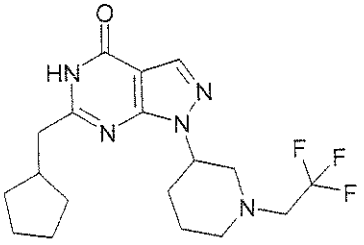
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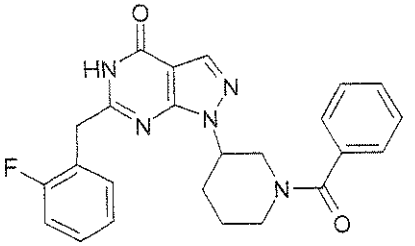
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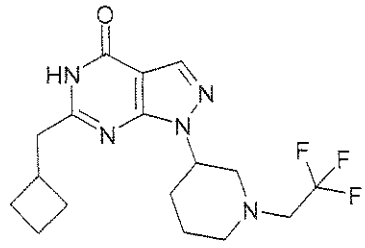
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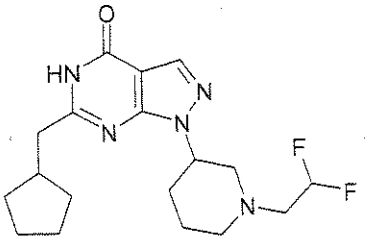
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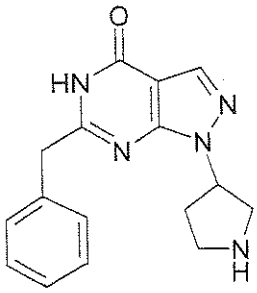


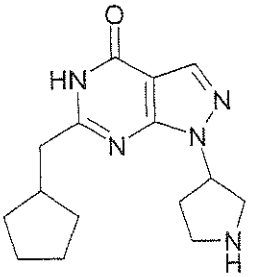
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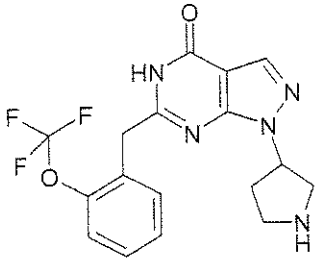


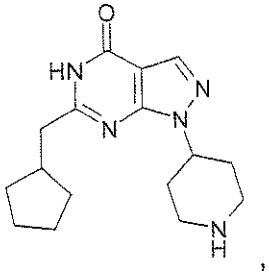
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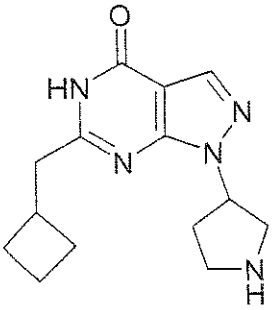


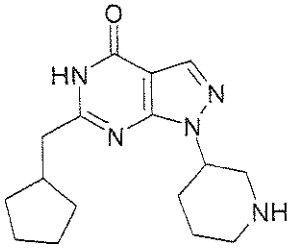


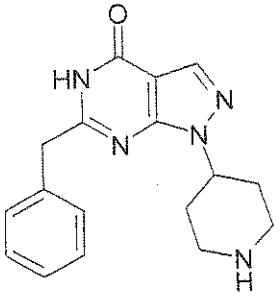


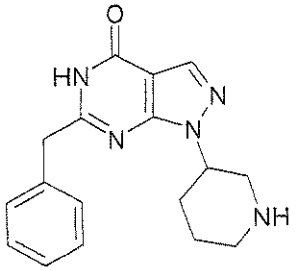


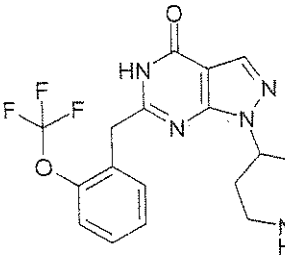


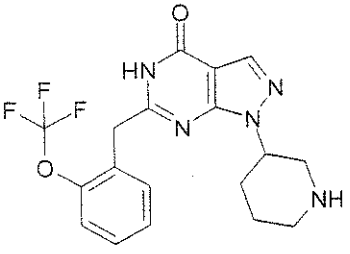




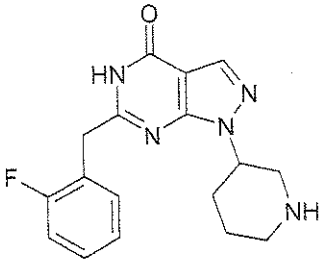


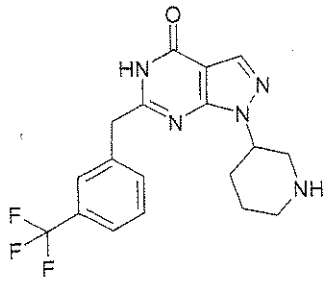


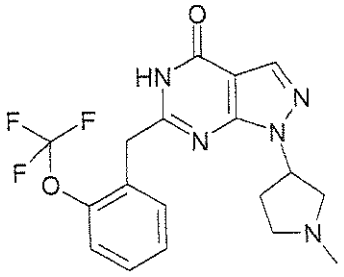


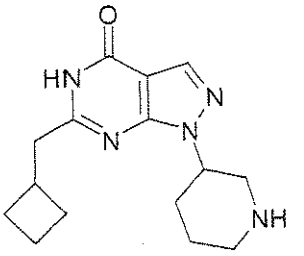


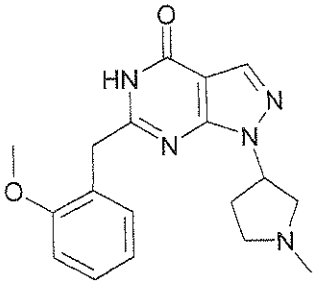


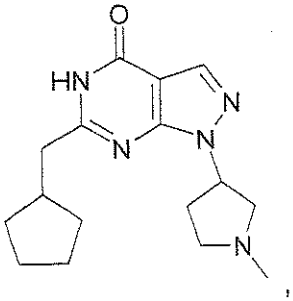


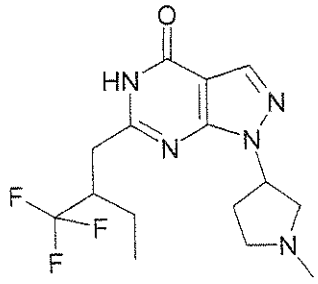


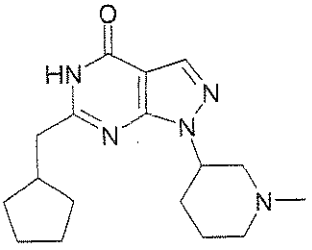


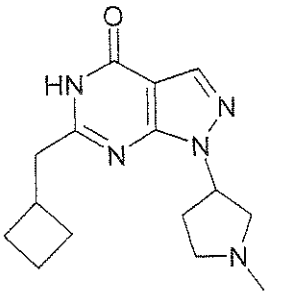


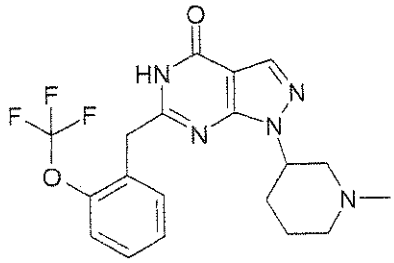


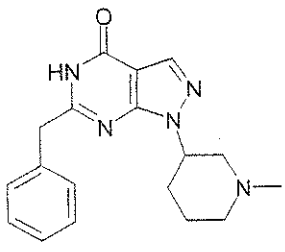






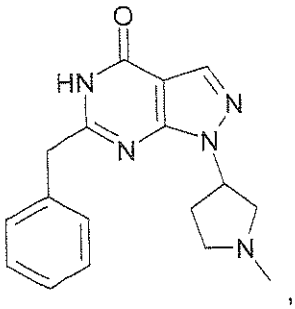


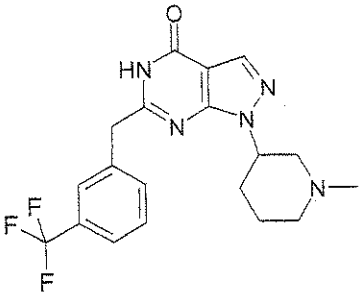


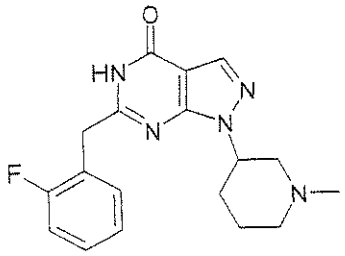




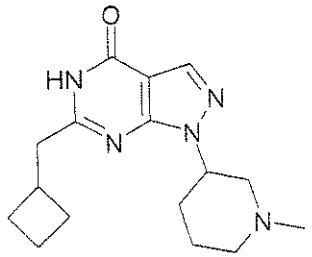






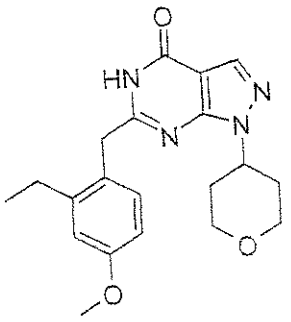

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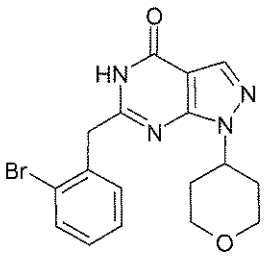
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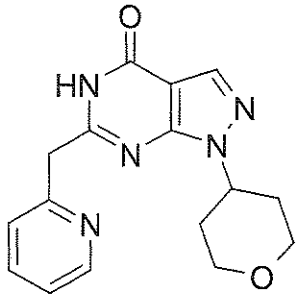
and the stereoisomeres of each thereof or tautomeres of each thereof or solvates of each thereof or pharmaceutically acceptable salts of each thereof.

5. The compound according to any of claims 1, 3 and 4, in which the compound is



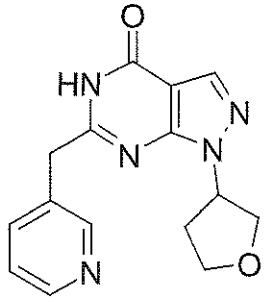

or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

6. The compound according to any of claims 1, 3 and 4, in which the compound is



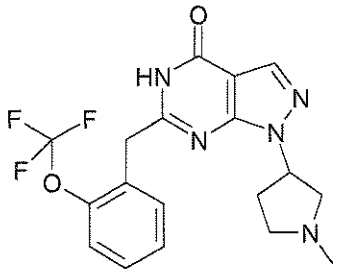

or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

7. The compound according to any of claims 1, 3 and 4, in which the compound is



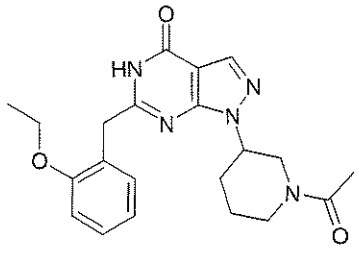
or the stereoisomeres thereof or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

8. The compound according to any of claims 1, 2 and 4, in which the compound is



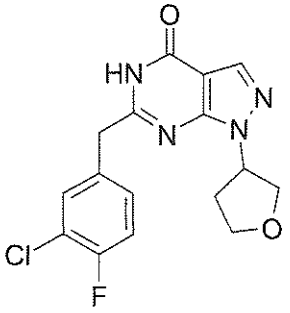
or the stereoisomeres thereof or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

9. The compound according to any of claims 1, 2 and 4, in which the compound is



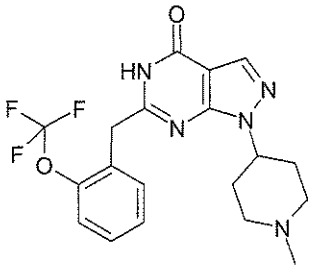
or the stereoisomeres thereof or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

10. The compound according to any of claims 1, 3 and 4, in which the compound is



or the stereoisomeres thereof or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

11. The compound according to any of claims 1, 2 and 4, in which the compound is



or tautomeres thereof or solvates thereof or pharmaceutically acceptable salts thereof.

12. The compound according to any of claims 1 to 11 for use as a medicament.

13. The compound according to any of claims 1 to 11 for use in the treatment of a disease that is accessible by the inhibition of PDE9.

14. The compound according to any of claims 1 to 11 for use in the treatment, amelioration or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory.

15. The compound according to claim 14, for use in the treatment, amelioration or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal

lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, schizophrenia with dementia or Korsakoff's psychosis.

16. The compound according to any of claims 14 or 15 for use in the treatment of Alzheimer's disease.

17. The compound according to any of claims 14 or 15 for use in the treatment of cognitive impairment which is due to Alzheimer's disease.

18. Pharmaceutical composition comprising a compound according to any of claims 1 to 11 and a pharmaceutical carrier.

19. Combination of a compound according to any of claims 1 to 11 with another active agent for the treatment of Alzheimer's disease.