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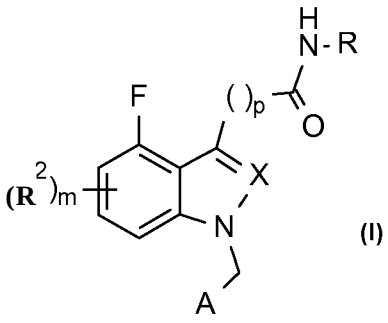
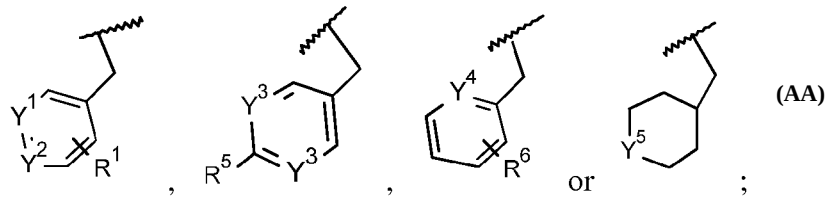
(54) Title: INDOL AND INDAZOL DERIVATIVES



(I)



(AA)

(57) Abstract: The present invention relates to indole and indazole derivatives of the following formula (I) wherein A is (AA) and the remaining variables are as defined in the specification. The compounds may be used for the treatment or prophylaxis of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

WO2015/044072 A1

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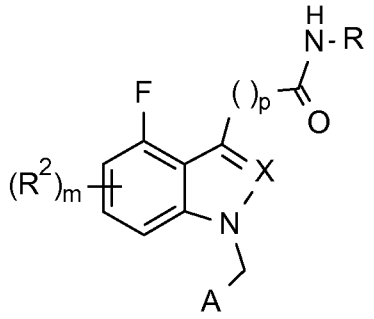
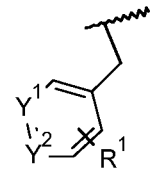
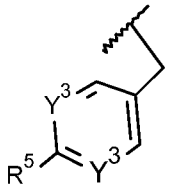
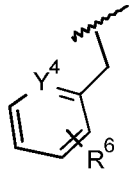
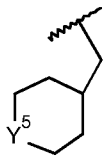
INDOL AND INDAZOL DERIVATIVES

The present invention relates to compounds of formula



I

wherein

A is  ,  ,  or  ;

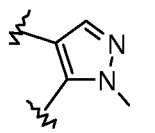
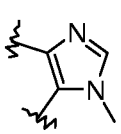
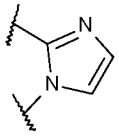
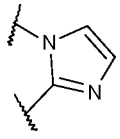
R is lower alkyl, -$(CH_2)_z$-C3_7-cycloalkyl or -$(CH_2)_z$-C4_6-heterocycloalkyl, which are optionally substituted by one to three hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2.1]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

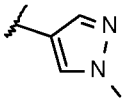
Y^3 is N;

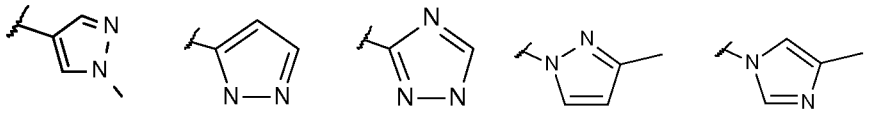
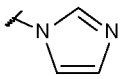
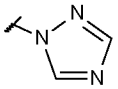
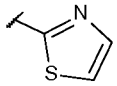
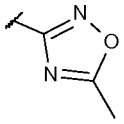
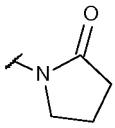
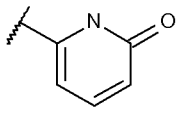
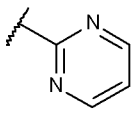
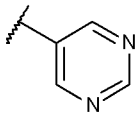
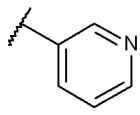
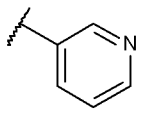
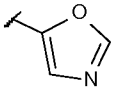
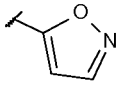
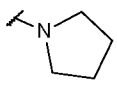
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, -C(0)NH_2, -C(0)$NHCH_3$ or -C(0)$N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of  , , , , ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , or is phenyl, -C(0)NH_2, -CH_2C(0)NH_2, -C(0)$NHCH_3$, -C(0)NH-cycloalkyl, -C(0)$N(CH_3)_2$, -NHC(0)0-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or S(0)$_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

p is 0 or 1;

m is 1, 2 or 3;

z is 0 or 1;

or to a pharmaceutically acceptable acid addition salt, to a racemic mixture or to its corresponding enantiomer and/or optical isomers thereof.

WO 2013/106795 describes a very broad scope of partially similar compounds for treating neurological and psychiatric disorders associated with muscarinic acetylcholine receptor dysfunction. The activity ($EC_{50,}$ in nM) is very low between 2400 and > 10000, and therefore these compounds are not suitable for the development of corresponding drugs.

The compounds of the present invention are muscarinic M1 receptor positive allosteric modulators (PAM) and hence are useful in the treatment of diseases, mediated by the muscarinic M1 receptor, such as Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

Acetylcholine (ACh) is a neurotransmitter which activates both nicotinic (ligand-gated ion channel) and muscarinic (metabotropic) receptors in the CNS and in the periphery.

The muscarinic receptors (mAChRs) are members of the class A G-protein-coupled receptors. To date, five distinct subtypes of mAChRs (M1-M5) have been cloned and sequenced. The muscarinic M1 receptors are predominantly distributed in the brain, with the highest expression in the cortex, thalamus, striatum and hippocampus. In clinical studies, Xanomeline, a M1/M4-preferring agonist, demonstrated robust efficacy on positive, negative and cognitive symptoms in schizophrenic patients and improved cognitive scores and reduced psychotic-like behaviors in patients with Alzheimer's disease (AD). The M1 receptor has been implicated in memory and learning processes, regulation of dopamine and NMDA receptor activity and has thus been proposed as a potential target for the treatment of AD and schizophrenia.

AD is the most common cause of dementia in later life. Pathologically AD is characterized by the deposition in the brain of amyloid in extracellular plaques and intracellular neurofibrillary tangles. The amyloid plaques are mainly composed of amyloid peptides (Abeta peptides) which originate from the β-Amyloid Precursor Protein (APP) by a series of proteolytic cleavage steps. Several forms of APP have been identified of which the most abundant are proteins of 695, 751 and 770 amino acids length. They all arise from a single gene through differential splicing. The Abeta peptides are derived from the same domain of the APP but differ at their N- and C-termini, the main species are of 40 and 42 amino-acid length by processing of the beta-amyloid precursor protein (APP) by the beta-amyloid protein cleaving enzyme. The processing leads to accumulation of Abeta in the brain.

M1 receptors are abundantly expressed postsynaptically in cortex, hippocampus and striatum which are important brain regions involved for cognition. Based on the cholinergic hypothesis i.e. degeneration of presynaptic cholinergic nerve terminals in hippocampus and

cortical regions, M1 activation should rescue the cognitive deficits which occur in AD, thus providing symptomatic treatment of this neurodegenerative disorder. Postmortem studies in AD cortical tissues have shown that M1 receptor expression are not reduced, thus providing evidence for target availability in a critical brain region. Moreover, preclinical studies have shown that M1 activation has potential as a disease-modifying therapy for AD by shifting the APP processing towards the non-amyloidogenie a-secretase pathway and by decreasing tau hyperphosphorylation. Therefore, M1 PAMs provide an approach to target both symptomatic and disease-modifying treatment of AD.

Schizophrenia is a severe, disabling, lifelong disorder that affects 1% of the population and is characterized by positive symptoms (such as hallucinations, delusions and paranoia), negative symptoms (such as social withdrawal and apathy) and cognitive impairment (for example, deficits in working memory, executive function and attention). Schizophrenia is a neurodevelopmental disorder with genetic risk factors and neuropathological changes. Aberrant activity occurs within the prefrontal - hippocampal - thalamic network in brains of schizophrenia patients. Positive symptoms of schizophrenia are suggested to be caused by dopaminergic system dysfunction, particularly increased dopamine activity within subcortical brain regions such as the striatum. Negative symptoms are thought to occur due to impaired signaling within the neurocircuitry of the ventral tegmental area and ventral striatum. Decreased NMDA receptor function in pyramidal neurons coupled with sub-optimal dopamine release in critical regions such as dorsolateral prefrontal cortex may account for some of the cognitive deficits.

M1 receptors are located in regions which are affected in schizophrenia, such as the hippocampus, cortex and striatum, in particular in the medium spiny neurons. Several reports have shown a reduction in muscarinic receptors in the prefrontal cortex and hippocampus, regions where M1 is densely expressed, in a subset of schizophrenic patients. Furthermore, preclinical studies have shown that M1 knockout mice have enhanced amphetamine-induced activity and increased striatal dopamine levels. Electrophysiology studies have revealed that activation of M1 receptors potentiates NMDA mediated hippocampal activity, modulates activity of medium spiny neurons and increases activity of medial prefrontal cortex neurons. Overall, activation of M1 receptors should modulate dysfunctional dopaminergic and glutamatergic signaling within the underlying neurocircuitry resulting in improvements in the symptoms of schizophrenia.

The clinical effects of Xanomeline and other muscarinic M1 agonist agents were however always associated with adverse effects attributed to their insufficient M1 muscarinic receptor subtype selectivity The typical observed side effects, including sweating, salivation, gastrointestinal distress and bradycardia have been attributed to the non-specific activation of peripheral M2 and M3 mAChRs. Despite a tremendous effort from a number of companies, the search for highly M1 selective agonists has failed because of the high degree of conservation between muscarinic receptor subtypes at their orthosteric acetylcholine ligand binding sites.

To circumvent the selectivity and safety issues associated with targeting the highly conserved orthosteric ACh site, an alternative approach consists of developing M1 PAMs that act at the less highly conserved allosteric binding sites.

Recently. Merck and Vanderbilt University reported M1 PAMs from different chemical classes exhibiting, as rationalized, a good level of M1 subtype selectivity. Importantly, similar to the preclinical profile of Xanomeline and other unselective M1 agonists, these M1 allosteric agents demonstrated pro-cognitive effects (in scopolamine-induced memory deficit in mice, scopolamine impaired non-human primates and in transgenic AD mice). PQCA and ML169 have been shown to promote non-amyloidogenic APP processing. Electrophysiology studies have shown that M1 PAMs potentiate carbachol-induced activity in the medial prefrontal cortex and medium spiny neurons. Moreover, unlike unselective agonists. M1 PAMs do not appear to produce side effects such as salivation at therapeutic effective doses. Additionally, they are expected to be devoid of liabilities such as receptor desensitization/intemalization following chronic dosing previously reported for orthosteric receptor agonists. In summary, the PAM approach, by activating in a truly selective manner M1 receptors, is a highly promising novel strategy to deliver both efficacious and safe therapeutic agents for the treatment of schizophrenia (positive, negative and cognitive symptoms) as well as AD (symptomatic and disease modifying).

Thus, the compounds of the invention, which are muscarinic M1 receptor positive allosteric modulators, are believed to be useful in the treatment of Alzheimer's disease and other diseases mediated by the muscarinic M1 receptor, without side effects.

Therefore, the object of the present invention was to identify compounds that are muscarinic M1 receptor positive allosteric modulators. It has been found that the compounds of formula I are active in this area and they may therefore be used for the treatment of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders

The present invention relates to compounds of formula I and to their pharmaceutically acceptable salts, to these compounds as pharmaceutically active substances, to the processes for their production, as well as to the use in the treatment or prevention of disorders, relating to muscarinic M1 receptor positive allosteric modulators, and to pharmaceutical compositions containing the compounds of formula I.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a saturated, i.e. aliphatic hydrocarbon group including a straight or branched carbon chain with 1 - 7 carbon atoms. Examples for "alkyl" are methyl, ethyl, n-propyl, isopropyl, n- butyl, i-butyl, 2-butyl, t-butyl and the like.

As used therein, the term "C3_7 -cycloalkyl" denotes a saturated carbon ring, containing from 3 to 7 carbon ring atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term "alkoxy" denotes a group -O-R' wherein R' is lower alkyl as defined above.

The term "halogen" denotes chlorine, bromine, fluorine or iodine.

The term "lower alkoxy substituted by halogen" denotes an alkyl group as defined above, wherein at least one hydrogen atoms is replaced by halogen, for example OCF_3, OCH_2F, OCH_2CF_3, $OCH_2CH_2CF_3$, $OCH_2CF_2CF_3$ and the like.

The term "C4_6 -heterocycloalkyl" denotes a non-aromatic heterocyclic ring with 4 to 6 ring atoms, containing at least one O atom, for example tetrahydropyran-4-yl, tetrahydrothiopyran, thiane 1,1-dioxide, tetrahydropyran-3-yl, oxolan-3-yl, oxetan-3-yl, oxetan-2-yl or tetrahydrofuran-2-yl.

The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable acid addition salt" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane- sulfonic acid, p-toluenesulfonic acid and the like

One embodiment of the present invention are compounds of formula I, wherein R is -$(CH_2)_z$-C4_6 -cycloalkyl, which is optionally substituted by one to three hydroxy, lower alkyl, lower alkoxy or halogen or 8endo)-7-oxabicyclo[2.2.1]heptan-2-yl; and p is 0 or 1, and the other

substituents are as described above, for example the following compounds:

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)- 1H-indazole-3-carboxamide

N-(3,3-difluorocyclobutyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-cyclobutyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4- (1-methyl- 1H-pyrazol-4-yl)benzyl)- N-((lS,2S)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2SR)-2-hydroxy-2-methylcyclohexyl)-lH-indole-3-carboxamide

N-cyclohexyl-4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2RS)-2-hydroxy-2-methylcyclohexyl)- lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)-N-((1S,2R)-2-hydroxycyclopentyl)- lH-indole-3-carboxamide

N-(2,2-difluorocyclohexyl)-4-fluoro- 1-(2-fluoro-4-(1-methyl- lH-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4,5,6,7-tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(difluoromethoxy)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(1-methyl- lH-pyrazol-4-yl)pyridin-3-

yl)methyl)- 1H-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-methoxybenzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(trifluoromethoxy)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(l -methyl- lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

l-(4-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,4-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-fluorobenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,5-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)- 1-(4-(1-methyl- 1H-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl- lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl-l-(4-(l -methyl- lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

l-benzyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)- 1-(4-(3-methyl- 1H-pyrazol- 1-yl)benzyl)- 1H-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-benzo[d]imidazol-5-yl)methyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-

indole-3-carboxamide

4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-1H-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide

4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(4-methyl-1H-imidazol-1-yl)benzyl)-1H-indole-3-carboxamide

4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-1H-indole-3-carboxamide

4,7-difluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indazole-3-carboxamide

4,7-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyridin-3-yl)methyl)-1H-indazole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide

1-(4-carbamoylbenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

1-(4-(2-amino-2-oxoethyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

1-(3-carbamoylbenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylsulfonyl)benzyl)-1H-indole-3-carboxamide

ethyl 4-((4-fluoro-3-((1S,2S)-2-hydroxycyclohexylcarbamoyl)-1H-indol-1-yl)methyl)phenylcarbamate

4-fluoro-1-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-1H-indole-3-carboxamide

4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(3-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide

1-(3-(dimethylcarbamoyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)-N-((lS,2S)-2-hydroxycyclohexyl)acetamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((l-hydroxycyclopropyl)methyl)-lH-indole-3-carboxamide

4-((4-fluoro-3-(2-((lS,2S)-2-hydroxycyclohexylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-cyclopropyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclobutyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclopentyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclohexyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclohexyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(cyclopropylmethyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(4,4-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(3,3-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(3,3-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-N-(2-fluorocyclohexyl)-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(2-fluorocyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(2-fluorocyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-phenylpyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-2-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(oxazol-5-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(isoxazol-5-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((2-phenylpyrimidin-5-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((5-phenylpyridin-2-yl)methyl)-lH-indole-3-carboxamideyl)benzyl)-1H-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((5-(thiazol-2-yl)pyridin-2-yl)methyl)-lH-indole-3-carboxamide

l-((6-(lH-imidazol-l-yl)pyridin-3-yl)methyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyriirddin-4-yl)piperidin-4-yl)methyl)-i H-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-7-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-6-ylmethyl)-lH-indole-3-carboxamide

l-(4-(cyclopropylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-lH-indole-3-carboxamide

l-(4-(lH-Pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-5-yl)benzyl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyridin-3-yl)benzyl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(pyrrolidin-l-yl)pyridin-3-yl)methyl)-lH-indole-3-carboxamide or

N-(2,2-difluorocyclohexyl)-4-fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)- lH-indole-3-carboxamide.

One further embodiment of the present invention are compounds of formula I, wherein R is $-(CH_2)_{Z}$- $_{C4\_6}$ -heterocycloalkyl, which are optionally substituted by one to three hydroxy, lower alkyl, lower alkoxy or halogen or (endo)-7-oxabicyclo[2.2.1]heptan-2-yl; p is 0 or 1; and the other substituents are as described above, for example the following compounds:

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4RS)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-N-[(3S,4R)-4-methoxyoxolan-3-yl]-l-[[4-(l-methylpyrazol-4-yl)phenyl]methyl]indole 3-carboxamide

(R)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((tetrahydrofuran-2-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-3-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-2-ylmethyl)-lH-indole-3-carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole

3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4S)-4-hydroxytetrahydro-2H pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(4-methyl-lH imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-methyl-lH-indazol 5-yl)methyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((3S,4R) or (3R,4S))-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)- lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R))-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridin-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4R) or (3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridin-3-yl)methyl)-lH-indazole-3-carboxamide

1-((6-(lH-l,2,4-triazol-l-yl)pyridin-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(thiazol-2-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(5-methyl-l,2,4-oxadiazol-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(2-oxopyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

2-[4-fluoro-l-[[2-fluoro-4-(l-methylpyrazol-4-yl)phenyl]methyl]indol-3-yl]-N-[(3R,4S)-3-hydroxyoxan-4-yl] acetamide

4,7-difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-

lH-indole-3-carboxamide

4-((4-fluoro-3-(2-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-ylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

7-cyclopropyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-(2,2-dimethyloxan-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(oxan-3-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(4-methyloxan-4-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(thian-4-yl)indole-3-carboxamide

N-(l,l-dioxothian-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(3-methyloxan-4-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(2-methyloxan-4-yl)indole-3-carboxamide

7-ethyl-4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-7-methyl-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3 -carboxamide

4-fluoro-7-methyl- 1-((1 -methyl- lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)- 1H-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy- 1H-indole-3-carboxamide

4-fluoro-7-methoxy-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

4-Fluoro- 1-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-thiopyran-4-yl)-lH-indole-3-carboxamide or

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(3-methyltetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide.

One embodiment of the invention are compounds of formula I, wherein X is N, for example the following compounds

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl) 1H-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl) 1H-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro 2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-

hydroxycyclohexyl)-lH-indazole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridin-3-yl)methyl)-lH-indazole-3-carboxamide or

4,7-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl- lH-pyrazol-4-yl)pyridin-3-yl)methyl)-1H-indazole-3-carboxamide.

One embodiment of the invention are compounds of formula I, wherein Y^1 is N, for example the following compounds

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridine 3-yl)methyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl- lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

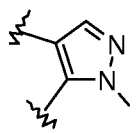
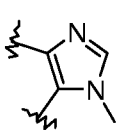
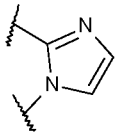
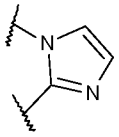
4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl- lH-pyrazol-4-yl)yridine-3-yl)methyl)-lH-indazole-3-carboxamide

l-((6-(lH-l,2,4-triazol-l-yl)yridine-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(methylcarbamoyl)yridine-3-yl)methyl)-lH-indole-3-carboxamide

One embodiment of the invention are compounds of formula I, wherein Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

for example the following compounds

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-benzo[d]yridine-5-yl)methyl) lH-indole-3-carboxamide

4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-Carboxamide

4,7-difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3 carboxamide

7-ethyl-4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH indole-3-carboxamide

4-fluoro-7-methyl- 1-((1 -methyl- lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)- 1H indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-7-ylmethyl)-lH-indole-3 carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-6-ylmethyl)-lH-indole-3 Carboxamide

4-fluoro-7-methoxy-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH indole-3-carboxamide

One embodiment of the invention are compounds of formula I, wherein the five-membered heteroaryl group for R^4 is not a pyrazole group, substituted by methyl, for example the following compounds

l-(4-carbamoylbenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-

carboxamide

4-fluoro-l-(2-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(difluoromethoxy)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-methoxybenzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(trifluoromethoxy)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(l -methyl- lH-pyrazol-4-yl)benzyl)-lH-indole 3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole 3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

l-(4-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,4-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-fluorobenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,5-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-benzyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(4-methyl-lH-yridine-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-methyl-lH-indazol-

5-yl)methyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-benzo[d]yridine-5-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-((6-(lH-l,2,4-triazol-l-yl)yridine-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

1-(4-(2-amino-2-oxoethyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

l-(3-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylsulfonyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(5-methyl-l,2,4-oxadiazol-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(2-oxopyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

ethyl 4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)phenylcarbamate

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- l-((6-(methylcarbamoyl)yridine-3-yl)methyl)- 1H-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

l-(3-(dimethylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(oxazol-5-yl)benzyl)-lH-indole-3-carboxamide

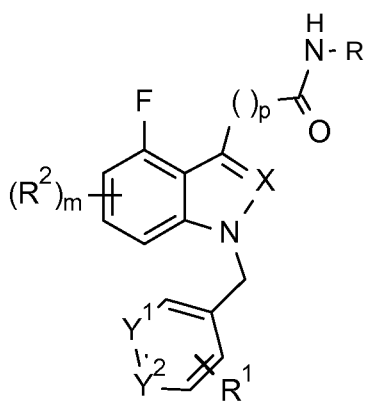
4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(isoxazol-5-yl)benzyl)-lH-indole-3-carboxamide

l-(4-(lH-Pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide or

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide.

One further embodiment of the invention are compounds of formula IA



IA,

which compounds are

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide

4,6-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4RS)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-N-[(3S,4R)-4-methoxyoxolan-3-yl]-l-[[4-(l-methylpyrazol-4-yl)phenyl]methyl]indole-3-carboxamide

N-(3,3-difluorocyclobutyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

(R)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((tetrahydrofuran-2-yl)methyl)-lH-indole-3-carboxamide

N-cyclobutyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-3-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-2-ylmethyl)-lH-indole-3-carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4- (1-methyl- 1H-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2SR)-2-hydroxy-2-methylcyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

N-cyclohexyl-4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4S)-4-hydroxytetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)- 1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2RS)-2-hydroxy-2-methylcyclohexyl)-lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)-N-((1S,2R)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

N-(2,2-difluorocyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6J-tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(difluoromethoxy)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-methoxybenzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro- l-(3-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(trifluoromethoxy)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(l -methyl- lH-pyrazol-4-yl)benzyl)-lH-indole-

3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

l-(4-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,4-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-fluorobenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,5-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

l-benzyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-1H-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-

pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-benzo[d]yridine-5-yl)methyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl- lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(3-methyl-lH-pyrazol-l-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-N-((3S,4R) or (3R,4S))-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)- lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)- l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R))-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

Fluoro-l-(4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4R) or (3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl- lH-pyrazol-4-yl)yridine-3-yl)methyl)- 1H-indazole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-((6-(lH-l,2,4-triazol-l-yl)yridine-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(thiazol-2-yl)benzyl)-lH-indole-3-carboxamide

1-(4-(2-amino-2-oxoethyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide

l-(3-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylsulfonyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(5-methyl-l,2,4-oxadiazol-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(2-oxopyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

ethyl 4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)phenylcarbamate

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(methylcarbamoyl)benzyl)-lH-indole-3-

carboxamide

1-(3-(dimethylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

2-[4-fluoro-l-[[2-fluoro-4-(l-methylpyrazol-4-yl)phenyl]methyl]indol-3-yl]-N-[(3R,4S)-3-hydroxyoxan-4-yl]acetamide

2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)-N-((lS,2S)-2-hydroxycyclohexyl)acetamide

4,7-difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-((4-fluoro-3-(2-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-ylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

4-((4-fluoro-3-(2-((lS,2S)-2-hydroxycyclohexylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((endo)-7-oxabicyclo[2.2.1]heptan-2-yl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-methyl- 1-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclopropyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclobutyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclopentyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclohexyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cycloheptyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(cyclopropylmethyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(4,4-difluorocyclohexyl)-4-fluoro- 1-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(3,3-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(2,2-dimethyloxan-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-(2,2-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-N-(2-fluorocyclohexyl)-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(oxan-3-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(4-methyloxan-4-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(thian-4-yl)indole-3-carboxamide

N-(l,l-dioxothian-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(3-methyloxan-4-yl)indole-3-carboxamide

4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(2-methyloxan-4-yl)indole-3-carboxamide

7-ethyl-4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(2-fluorocyclohexyl)-lH-indole-3-

carboxamide

N-(3,3-difluorocyclohexyl)-4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-phenylpyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl-lH-pyrazol-4-yl)benzyl)-7-methyl-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3 -carboxamide

4-fluoro-7-methyl-1-((1 -methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-2-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(oxazol-5-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(isoxazol-5-yl)benzyl)-lH-indole-3-carboxamide

l-((6-(lH-imidazol-l-yl)pyridin-3-yl)methyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-7-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-6-ylmethyl)-lH-indole-3-carboxamide

l-(4-(cyclopropylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-

indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy- 1H-indole-3-carboxamide

4-fluoro-7-methoxy-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-(lH-Pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-5-yl)benzyl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyridin-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(pyrrolidin-l-yl)pyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-Fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

4-Fluoro- 1-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3-carboxamide

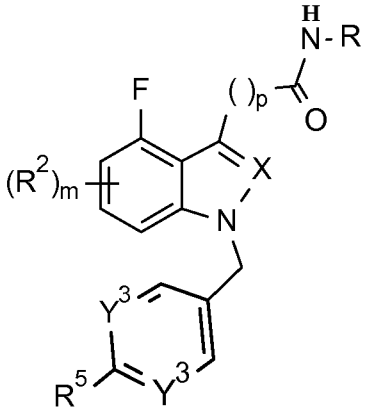
N-(2,2-difluorocyclohexyl)-4-fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)- lH-indole-3-carboxamide

N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-thiopyran-4-yl)-lH-indole-3-carboxamide or

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(3-methyltetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide.

One further embodiment of the invention are compounds of formula IB

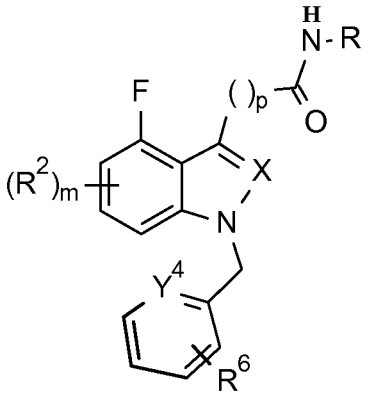


IB

which compound is

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((2-phenylpyrimidin-5-yl)methyl)-lH-indole-3-carboxamide.

One further embodiment of the invention are compounds of formula IC



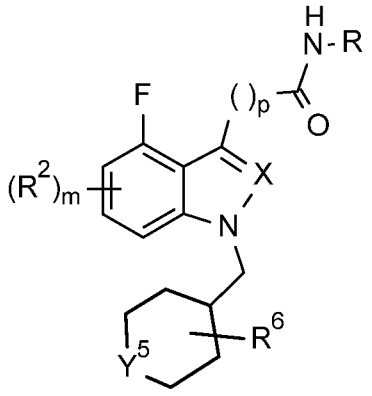
IC

which compounds are

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((2-phenylpyrimidin-5-yl)methyl)-lH-indole-3-carboxamide or

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((5-(thiazol-2-yl)pyridin-2-yl)methyl)-lH-indole-3-carboxamide.

One further embodiment of the invention are compounds of formula ID



ID

which compounds are

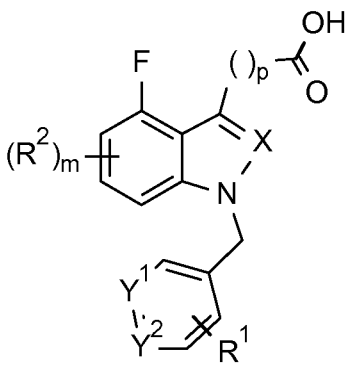
4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyrimidin-4-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide or

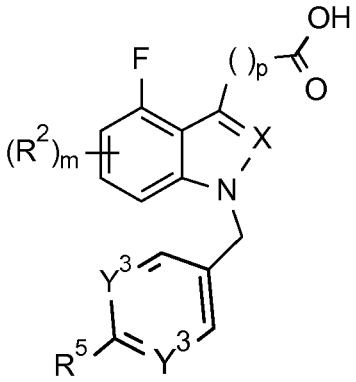
4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

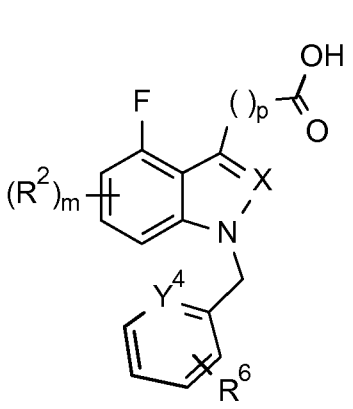
a) reacting a compound of formula



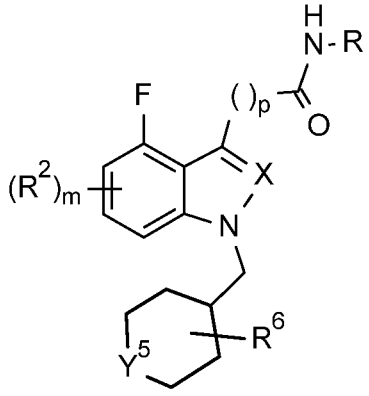
IIA,



IIB,



IIC or



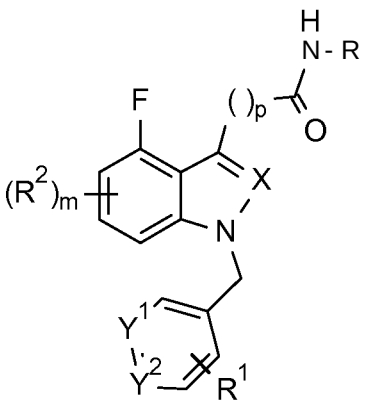
IID

with a compound of formula

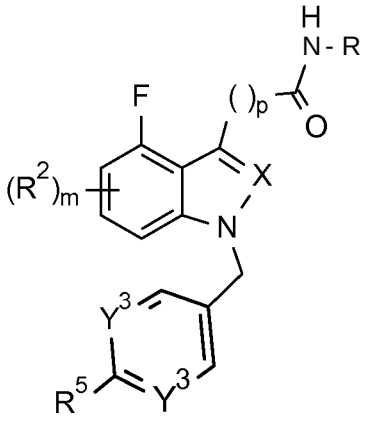
RNH_2

in the presence of an activating agent such as BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or thionyl chloride

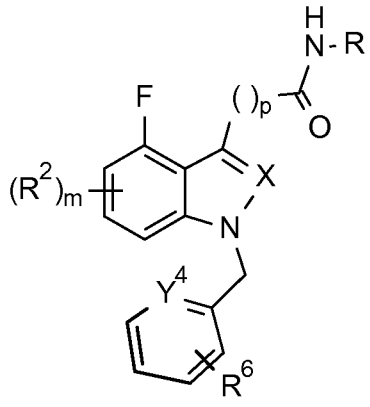
to a compound of formula



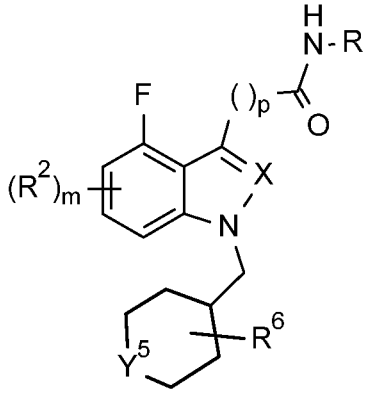
IA,



IB,



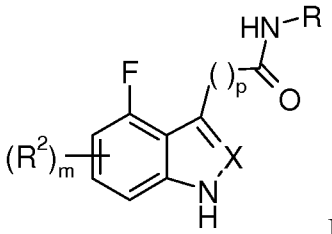
IC or



ID,

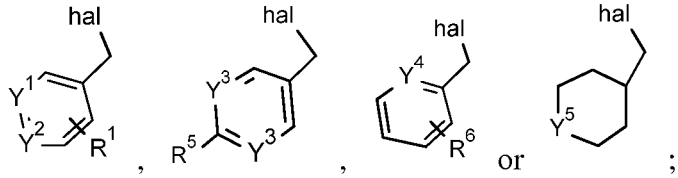
wherein the substituents are as defined above, or

b) reacting a compound of formula



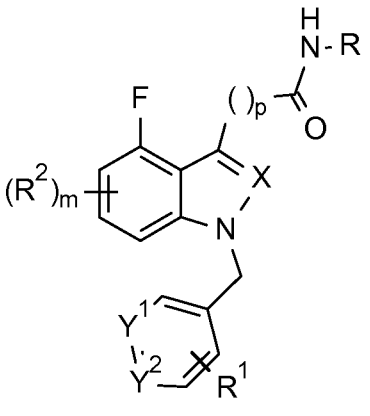
III

with a compound of formula

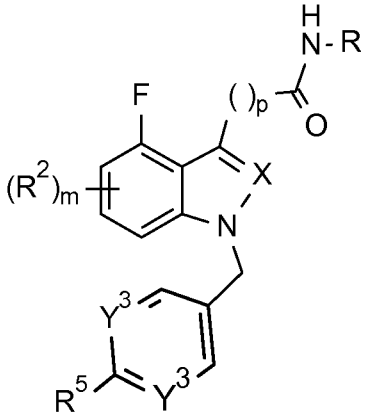


;

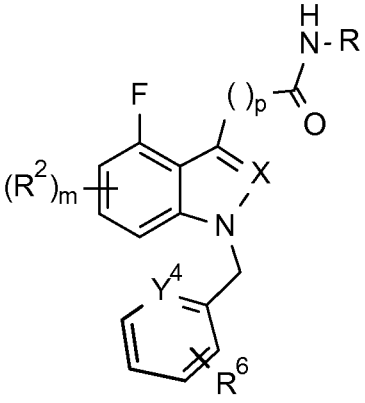
in the presence of base like cesium carbonate or sodium hydride to a compound of formula



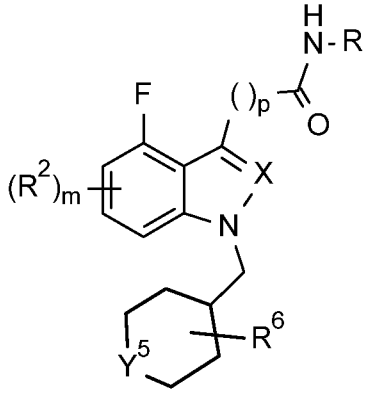
IA,



IB,



IC or

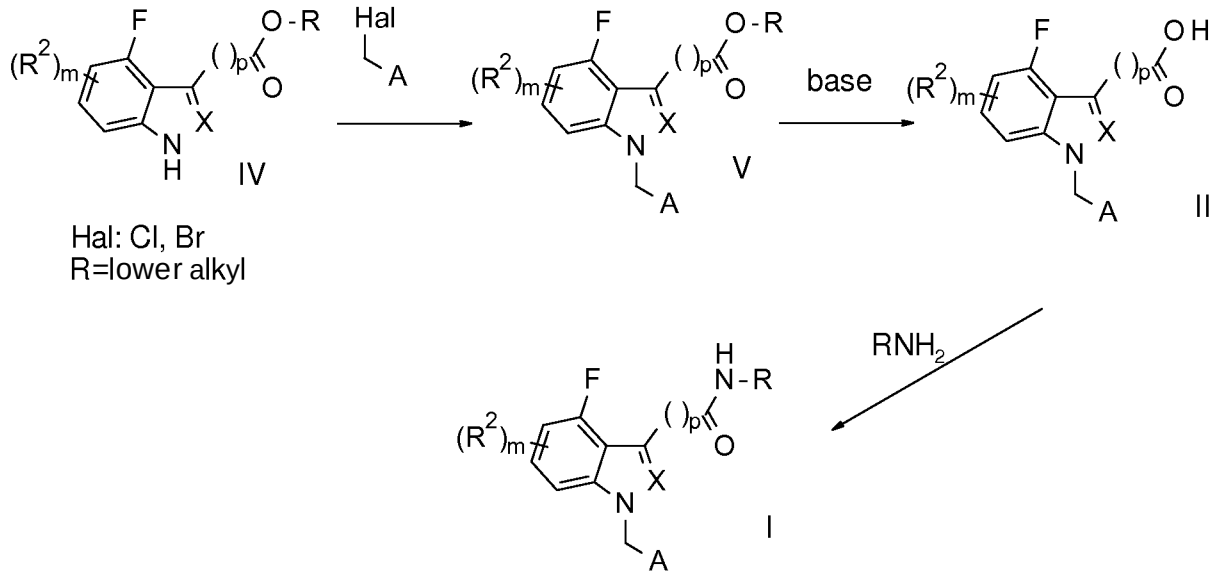


ID,

wherein Hal is halogen and the other substituents are as defined above, and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

The compounds of formula I may be prepared in accordance with process variant a) or b) and with the following schemes 1- 2. The starting material is commercially available or may be prepared in accordance with known methods.

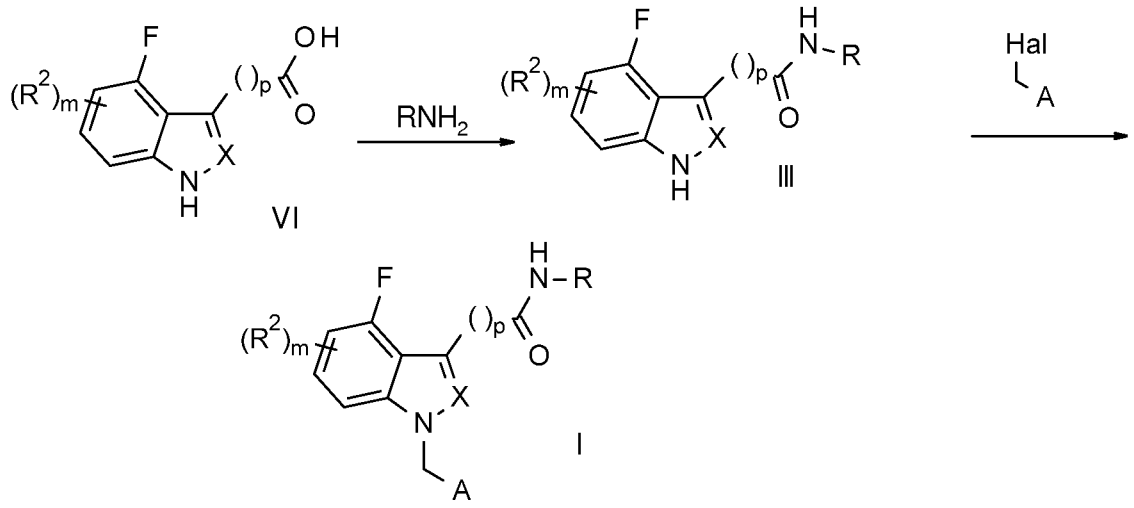
Scheme 1



The substituents are as described above.

Compounds of general formula I can be prepared by reacting ester derivatives of formula IV with an alkylating agent in the presence of a base such as sodium hydride to provide V followed by a saponification of V in the presence of a base such as lithium hydroxide and coupling of the resulting acid II with an amine RNH_2.

Scheme 2



The substituents are as described above.

Compounds of general formula I can be prepared by coupling acid derivatives of formula VI with an amine RNH_2 to provide amide III followed by reaction of III with an alkylating agent in the presence of a base such as cesium carbonate or sodium hydride.

All reactions are typically performed in a suitable solvent and under an atmosphere of argon or nitrogen.

Some substituents substituents R^1 may be derived from another precursor substituent at the end of the reaction sequence. For instance, a compound of formula I may be synthesized bearing an ester group as R^1, which is converted to a carboxamide substituent by standard procedures.

Insofar as their preparation is not described in the examples, the compounds of formula (I) as well as all intermediate products can be prepared according to analogous methods or according to the methods set forth above. Starting materials are commercially available, known in the art or can be prepared by methods known in the art or in analogy thereto.

Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination

of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the preparations and examples herein below. However, other equivalent separation or isolation procedures could, of course, also be used.

Salts of compounds of formula I

The compounds of formula I are basic and may be converted to a corresponding acid addition salt. The conversion is accomplished by treatment with at least a stoichiometric amount of an appropriate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol or methanol and the like, and the acid added in a similar solvent. The temperature is maintained between 0 °C and 50 °C. The resulting salt precipitates spontaneously or may be brought out of solution with a less polar solvent.

The acid addition salts of the basic compounds of formula I may be converted to the corresponding free bases by treatment with at least a stoichiometric equivalent of a suitable base such as sodium or potassium hydroxide, potassium carbonate, sodium bicarbonate, ammonia, and the like.

The compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. Specifically, it has been found that the compounds of the present invention have an activity as neurogenic agents.

The compounds were investigated in accordance with the test given hereinafter.

M1 PAM assay

The assay is designed to select compounds that possess modulator activity at the acetylcholine muscarinic receptor expressed in CHO cells by measuring the intracellular calcium with a Fluorometric Imaging Plate Reader System (FLIPR, Molecular Devices). The assay study the effect of several concentrations of test compounds on basal or acetylcholine- stimulated Ca^{2+} levels using FLIPR.

CHO human M1 are plated the day before the experiments at 2 x 10^5 cells/ml in PDL BioCoat 96 well black/clear plate (Becton 35 4640). The cells are grown at 37°C and 5% $C0_2$ in the following medium: F12 Nut Mix (Gibco 21765), 10% FCS heat inactivated (GIBCO 16000-044), 1 % Pen Strep (Gibco,15140) and 200 µg/ ml Geneticin (Gibco 11811). On the day of the experiment, the medium was removed and replaced by 100 ml of dye loading buffer containing Hanks Balanced Salt solution (HBSS, 14065-049, Gibco) with 20 mM HEPES (Gibco 15630-056), 2 mM Probenicid (Sigma P8761), 2mM Fluo-4AM ester (Molecular Probes F-14202), 10% Pluronic acid Molecular Probes P-3000) pH=7.4 and incubated at 37°C. After 60 minutes extracellular dye was removed and the cells were washed five times with FLIPR buffer containing HBSS (Gibco 14065-049) with 20 mM HEPES (Gibco, 15630-056), 2 mM Probenicid (Sigma P8761) pre-warmed at 37°C using and Ebml cell washer leaving 100 ml of FLIPR buffer in each well. The cell plate and the diluted compounds (1% DMSO final concentration) are placed on the platform of the FLIPR and the door closed. A signal test to check background fluorescence and basal fluorescence signal is performed. Laser intensity is adjusted if necessary. Two minutes preincubation with the diluted test compounds is provide to determine any agonist activity on the M1 receptor by comparison to 30 nM Acetylcholine control. In order to determine any modulator activity the diluted compounds were added to cells and after two minutes preincubation, the EC_2o of acetylcholine is added followed by another two minutes preincubation before the measurement of intracellular Ca^{2+} with a FLIPR (Molecular Devices).

Table with activity data

Example	hMl EC_{50}/ ratMl ECso	Example	hMl ECso/ ratMl ECso	Example	hMl ECso/ ratMl ECso
1	0.00564/ 0.06265	58	0.17359/ 10	114	0.017/ 0.015
2	0.03897/ 0.20758	59	0.00433/ 0.00435	115	0.05/ 0.028
3	0.02518/ 0.09056	60	0.10092/ 0.18255	116	0.074/ 0.32

4	0.29451/ 1.29408	61	0.34281/ 0.51525	117	0.014/ 0.029
5	0.08375/ 0.23056	62	0.43262/ 0.56325	118	0.009/ 0.029
6	0.07002/ 0.14723	63	0.01955/ 0.05425	119	0.006/ 0.012
7	0.07002/ 0.14723	64	0.0547/ 0.07993	120	0.015/ 0.032
8	0.27812/ 0.4268	65	0.03236/ 0.05995	121	0.006/ 0.017
9	0.36503/ 0.41052	66	0.21649/ 0.41204	122	0.062/ 0.154
10	0.25567/ 0.39796	67	0.08278/ 0.18328	123	0.364/ 0.68
11	0.41296/ 0.61775	68	0.26659/ 0.18163	124	0.011/ 0.024
12	0.12931/ 0.39801	69	0.34401/ -	125	0.166/ 0.623
13	0.19182/ 0.24956	70	0.10203/ 0.28411	126	0.019/ 0.051
14	0.12088/ 0.19809	71	0.00592/ 0.01202	127	0.019/ 0.026

15	0.01243/ 0.00961	72	0.0428/ 0.133	128	0.289/ 1.238
16	0.23702/ 0.3368	73	0.0658/ 0.0943	129	0.027/ 0.066
17	0.1004/ 0.1694	74	0.0548/ 0.0489	130	0.034/ 0.058
18	0.06116/ 0.18456	75	0.0401/ 0.046	131	0.036/ 0.152
19	0.22859/ 0.57922	76	0.00433/ 0.00435	132	0.003/ 0.022
20	0.20379/ 0.42486	77	0.00221/ 0.00247	133	0.048/ 0.084
21	0.06054/ 0.175	78	0.522/ 0.728	134	0.025/ 0.076
22	0.01776/ 0.06046	79	0.0168/ 0.0256	135	0.097/ 0.384
23	0.01495/ 0.02579	80	0.11/ 0.263	136	0.134/ 0.428
24	0.04629/ 0.08446	81	0.351/ -	137	0.009/ 0.034
25	0.35873/ -	82	0.435/ -	138	0.016/ 0.038

26	0.08061/ 0.20053	83	0.184/ 0.16	139	0.423/ 2.627
27	0.05596/ 0.08072	84	0.182/ 0.169	140	0.103/ 0.518
28	0.27196/ -	85	0.0429/ -	141	0.155/ 0.453
29	0.22564/ -	86	0.00691/ 0.013	142	0.075/ 0.21
30	0.01324/ 0.01411	87	0.0734/ 0.12	143	0.409/ 1.072
31	0.09063/ 0.16046	88	0.0143/ 0.0158	144	0.07/ 0.172
32	0.1047/ 0.22344	89	0.319/ -	145	0.017/ 0.036
33	0.10375/ 0.22165	90	0.341/ -	146	0.002/ 0.005
34	0.34213/ -	91	0.0249/ -	147	0.197/ 0.323
35	0.22606/ -	92	0.035/ 0.057	148	0.084/ 0.139
36	0.01546/ 0.02591	93	0.191/ 1.881	149	0.438/ 0.348

37	0.04381/ 0.03954	94	0.066/ 0.141	150	0.05/ 0.034
38	0.13074/ 0.38163	95	0.027/ 0.05	151	0.194/ 0.299
39	0.20524/ -	96	0.028/ 0.073	152	0.26/ 0.609
40	0.47648/ -	97	0.465/ 1.886	153	0.056/ 0.056
41	0.21875/ 0.45572	98	0.032 0.134	154	0.272/ 0.837
42	0.11046/ 0.20003	99	0.054/ 0.195	155	0.011/ 0.005
43	0.48838/ 0.63158	100	0.004/ 0.015	156	0.003/ 0.01
44	0.006/ 0.0098	101	0.014/ 0.042	157	0.095/ 0.117
45	0.03613/ 0.07408	102	0.029/ 0.088	158	0.023/ 0.061
46	0.0103/ 0.02216	103	0.007/ 0.032	159	0.02/ 0.047
47	0.11766/ 0.39292	104	0.165/ 0.196	160	0.196/ -

48	0.25074/ 0.52781	105	0.288/ 0.627	161	0.121/ 0.307
49	0.04448/ 0.05247	106	0.189/ 0.187	162	0.214/ 0.751
50	0.01831/ 0.01388	107	0.482/ 0.767	163	0.059/ 0.082
51	0.01228/ 0.01116	108	0.414/ 0.952	164	0.048/ 0.088
52	0.01786/ 0.027	109	0.061/ 0.079	165	0.043/ -
53	0.04414/ 0.04752	110	0.141/ 0.482	166	0.035/ -
54	0.06964/ 0.1218	111	0.127/ 0.408	167	0.047/ -
55	0.00211/ 0.00282	112	0.072/ 0.168	168	0.097/ -
56	0.13603/ 0.28466	113	0.034/ 0.077		
57	0.13923/ -				

The 168 compounds of formula (I) and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations

can be administered orally, e.g. in the form of tablets, coated tablets, dragees, hard and soft gelantine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula (I) and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragees and hard gelantine capsules. Suitable carriers for soft gelantine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelantine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula (I), but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

In addition, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

As mentioned earlier, medicaments containing a compound of formula (I) or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula (I) or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

As further mentioned earlier, the use of the compounds of formula (I) for the preparation of medicaments useful in the prevention and/or the treatment of the above recited diseases is also an object of the present invention.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Pharmaceutical compositions comprising compounds of the invention:

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1. Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granules at 50°C.
3. Pass the granules through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Capsule Formulation

Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	—
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

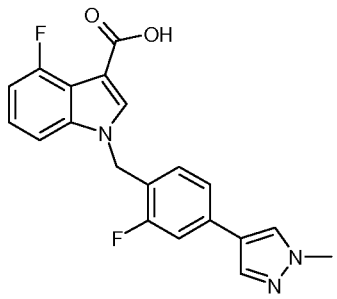
1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Experimental part

Preparation of intermediates

Example A.l

4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



Step 1 :Methyl 4-fluoro- 1-(2-fluoro-4-(1-methyl- lH-pyrazol-4-yl)benzyl)- lH-indole-3-carboxylate

A suspension of methyl 4-fluoro- lH-indole-3-carboxylate (150 mg, 777 μιηοϊ) in N,N-dimethylformamide (2 ml) was cooled in ice-bath. Sodium hydride 60% dispersion in oil (37.3 mg, 932 μιηοϊ) was added at once. The mixture was stirred at 0°C for 15 minutes. 4-(4-

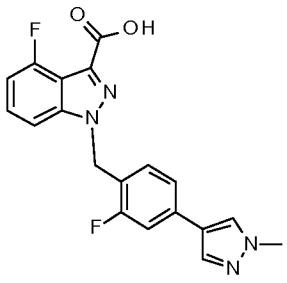
(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (example B.2) (174 mg, 777 μηοϊ) was added at once. The mixture was stirred at 0°C for 1 hour, quenched with a 20% ammonium chloride solution, diluted with water and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified with a flash column chromatography on silica (10 g) eluting with a gradient formed from n-heptane and ethyl acetate (0 to 100 %) to provide 208 mg (70 %) of the title compound as a light brown solid. MS (m/e): 382.5 $(M+H)^+$.

Step 2: 4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid

To a solution of methyl 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylate (195.9 mg, 514 μηοϊ) in THF (1.6 ml), MeOH (0.8 ml) and water (0.8 ml) was added lithium hydroxide monohydrate (64.7 mg, 1.54 mmol). The mixture was stirred at room temperature for 1 hr, then heated to 50°C for 5 hrs and finally stirred at room temperature for 2 days. The mixture was diluted with water and the solvent was evaporated in vacuo. The residue was taken up in water and HC1 2N was added dropwise to adjust the pH to 2-3. The solid was filtered and dried to provide the title compound (170 mg, 90 %) as a white solid. MS (m/e): 366.2 $(M-H)^-$.

Example A.2

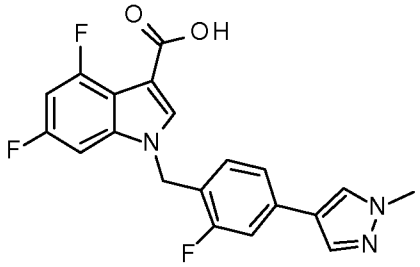
4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.l, the title compound was prepared from methyl 4-fluoro-lH-indazole-3-carboxylate (CAS 1427504-03-7) and 4-(4-(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (example B.2) White solid. MS (m/e): 369.4 $(M+H)^+$.

Example A.3

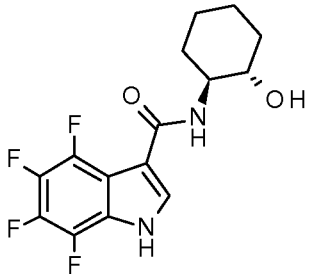
4,6-Difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.l, the title compound was prepared from ethyl 4,6-difluoro-lH-indole-3-carboxylate and 4-(4-(chloro-methyl)-3-fluorophenyl)-! -methyl- lH-pyrazole (example B.2). White solid. MS (m/e): 386.4 $(M+H)^+$.

Example A.4

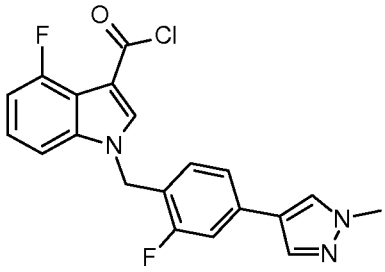
4,5,6,7-Tetrafluoro-lH-indole-3-carboxylic acid ((lS,2S)-2-hydroxy-cyclohexyl)-amide



In a 10 mL pear-shaped flask, 4,5,6,7-tetrafluoro-lH-indole-3-carboxylic acid (200 mg, 815 μηοϊ), (lS,2S)-(+)-2-aminocyclohexanol hydrochloride (136 mg, 897 μηοϊ) and (1H-benzo[d][l,2,3]triazol-l-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate(V) (469 mg, 1.1 mmol) were combined with CH_2CI_2 (4.9 ml) and triethylamine (330 mg, 452 μϊ, 3.26 mmol) to give an off-white suspension. The reaction mixture was stirred at r.t. for 2 days. The reaction mixture diluted with H_20 and extracted with CH_2C1_2. The aqueous layer extracted with EtOAc. This organic layer was dried over $MgS0_4$, filtrated and concentrated to give the title compound (390 mg, 70% pure) as an off-white solid. MS (m/e): 331.4 $(M+H)^+$.

Example A.5

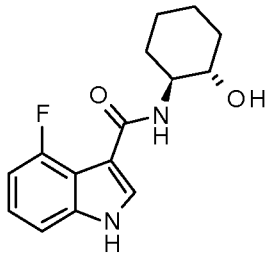
4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride



To a solution of 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (Example A.l) (200 mg, 544 μηοϊ) in dichloroethane (2 ml) under nitrogen at room temperature, was added 1 drop of N,N-dimethylformamide, followed by oxalyl chloride (212 mg, 143 μϊ, 1.63 mmol). The reaction mixture was stirred at room temperature for 3.5 hours. The mixture was evaporated to dryness to provide the title compound (222 mg, 106 %) as an off-white solid.

Example A.6

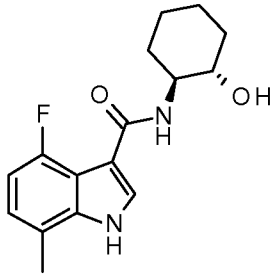
4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



To a stirred suspension of 4-fluoro-lH-indole-3-carboxylic acid (1 g, 5.58 mmol; CAS 23077-42-1) at r.t. in dichloromethane (60 ml) under an argon atmosphere were added (lS,2S)-2-aminocyclohexanol hydrochloride (931 mg, 6.14 mmol), BOP (2.96 g, 6.7 mmol) and triethylamine (2.26 g, 3.1 ml, 22.3 mmol). The resulting light brown solution was stirred at r.t. for 17 hrs. The mixture was concentrated and the residue was purified by silica gel chromatography (50 g) chromatography using a CH_2Cl_2/MeOH 9:1 gradient as eluent. The product-containing fractions were combined and concentrated to leave a viscous oil. It was triturated in CH_2Cl_2/n-heptane 3:2 (25 ml). The resulting suspension was stirred at r.t. for 1 hr. The product was collected by filtration, washed with a 1:1 mixture of CH_2Cl_2 and n-heptane, and dried to give the title compound (1.2 g, 75%) as an off-white solid. MS (m/e): 275.3 $(M-H)^-$

Example A.7

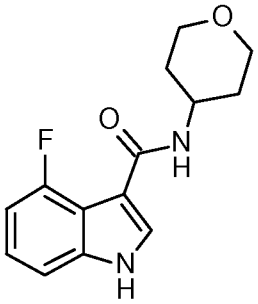
4-Fluoro-7-methyl-lH-indole-3-carboxylic acid ((lS,2S)-2-hydroxy-cyclohexyl)-amide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4-fluoro-7-methyl-lH-indole-3-carboxylic acid and (lS,2S)-(+)-2-amino-cyclohexanol hydrochloride. White solid.

Example A.8

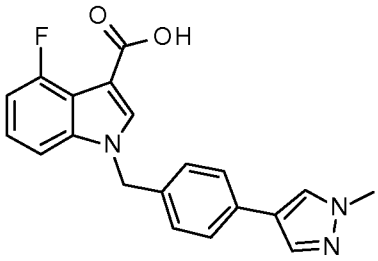
4-Fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4-fluoro-lH-indole-3-carboxylic acid (CAS 23077-42-1) and tetrahydro-2H-pyran-4-amine. White solid. MS (m/e): 263.2 $(M+H)^+$.

Example A.9

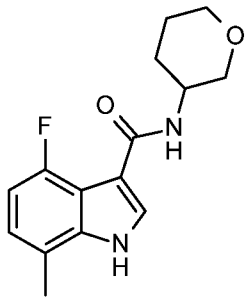
4-Fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.l, the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5). Off-white solid. MS (m/e): 350.6 $(M+H)^+$.

Example A.10

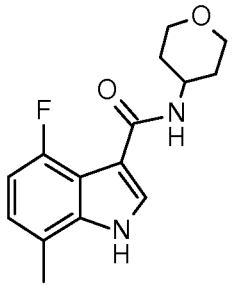
4-Fluoro-7-methyl-lH-indole-3-carboxylic acid (tetrahydro-pyran-3-yl)-amide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4-fluoro-7-methyl-lH-indole-3-carboxylic acid and tetrahydro-pyran-3-ylamine. Light yellow solid.

Example A.ll

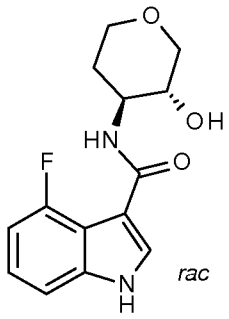
4-Fluoro-7-methyl-lH-indole-3-carboxylic acid (tetrahydro-pyran-4-yl)-amide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4-fluoro-7-methyl-lH-indole-3-carboxylic acid and tetrahydro-pyran-4-ylamine. White foam. MS (m/e): 277.2 $(M+H)^+$.

Example A.12

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



Step 1 : 4-Fluoro-N-((3RS,4SR)-3-hvdroxytetrahvdro-2H-pyran-4-yl)-lH-indole-3-carboxamide

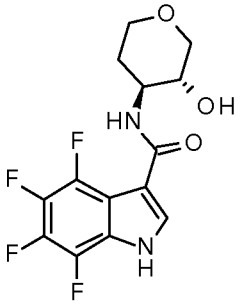
In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and (3RS,4SR)-4-aminotetrahydro-2H-pyran-3-ol (CAS 215940-92-4). Light yellow solid. MS (m/e): 279.4 $(M+H)^+$.

Step 2: 4-Fluoro-N-((3R,4S) or (3S,4R)-3-hvdroxytetrahvdro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (310 mg, 1.1 mmol) was separated on a Reprosil Chiral NR column to provide 136 mg (44%) of the title compound as an off-white solid (+ enantiomer). MS (m/e): 279.4 $(M+H)^+$.

Example A.13

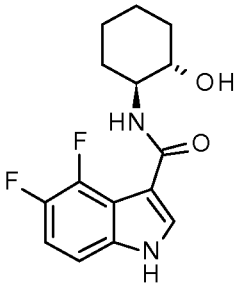
4,5,6,7-Tetrafluoro-lH-indole-3-carboxylic acid ((3RS,4SR)-3-hydroxy-tetrahydro-pyran-4-yl)-amide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4,5,6,7-tetrafluoro-lH-indole-3-carboxylic acid and (3RS,4SR)-4-amino-tetrahydro-2H-pyran-3-ol (CAS 215940-92-4). White solid.

Example A.14

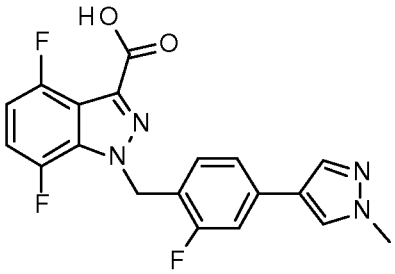
4,5-Difluoro-lH-indole-3-carboxylic acid ((lS,2S)-2-hydroxy-cyclohexyl)-amide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4,5-difluoro-lH-indole-3-carboxylic acid and (lS,2S)-(+)-2-aminocyclohexanol hydrochloride. Light brown solid.

Example A.15

4,7-Difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylic acid



Step 1: 4,7-Difluoro-lH-indazole-3-carboxylic acid

A solution of 4,7-difluoroindoline-2,3-dione (2.0 g, 10.9 mmol) in IN NaOH (11.8 ml) was stirred at 50°C for 30 mins. The solution was allowed to cool to r,t. and maintained for lhr. The reaction mixture was cooled to 0°C and treated with a pre-cooled (0°C) solution of sodium nitrite (754 mg in 2.8 ml H_20). This solution was added to a stirred solution of H_2S0_4 (1.2 ml in 22 ml H_20) at 0°C and the reaction mixture was maintained at that temperature for 30 min. A cold (0°C) solution of $SnCl_2$ (5.9 g, 26.2 mmol) in concentrated HCl (4.2 ml) was slowly added to the reaction mixture within 10 min; and the reaction mixture was maintained for 60 min. The reaction mixture was extracted with 15% MeOH/CH_2Cl_2. Evaporation of the solvent provided the title compound as a brown sticky solid (600 mg, 55%) which was used in the next step without purification.

Step 2: Methyl 4,7-difluoro-lH-indazole-3-carboxylate

A solution of 4,7-difluoro-lH-indazole-3-carboxylic acid (4.5 g, 22.7 mmol) in MeOH (45 ml) was treated with H_2S0_4 (0.41 ml) and stirred at 50°C over night. After completion of the reaction, the reaction mixture was concentrated. The crude product was purified by silica gel chromatography using 15% EtOAc in hexane as eluent to provide the title compound as an off-white solid (500 mg, 10%).

Step 3: Methyl 4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylate

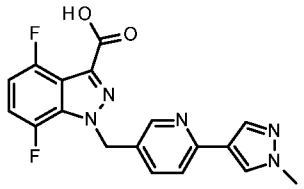
To a stirred solution of methyl 4,7-difluoro-lH-indazole-3-carboxylate (250 mg, 1.2 mmol) at 0°C in DMF (3.00 ml) under an argon atmosphere was added sodium hydride 60% dispersion in mineral oil (47.1 mg, 1.2 mmol) in one portion. After stirring for 15 min at 0°C, 4-(4-(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (example B.2; 265 mg, 1.2 mmol) was added in one portion. The ice bath was removed, and stirring at r.t. was continued for 17 hrs. The reaction mixture was taken up in H_20 (10 ml) and sat. aq. NaCl (10 ml) and extracted with EtOAc. The aqueous phase was back-extracted with EtOAc (10 ml). The combined organics were washed with water (20 ml) and brine (20 ml), dried over $MgS0_4$, filtered and concentrated. The crude product was purified by silica gel chromatography using a EtOAc/heptane gradient as eluent providing the title compound (251 mg, 53 mg) as yellow solid, along with its regioisomer (103 mg, 22 mg) methyl 4,7-difluoro-2-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-2H-indazole-3-carboxylate. MS (m/e): 401.1 $(M+H)^+$.

Step 4: 4,7-Difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylic acid

To a stirred solution of methyl 4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylate (246mg, 614 μηοϊ) at r.t. in THF (2 ml) and methanol (1 ml) under an argon atmosphere were added water (1.7 ml) and 1 N NaOH (1.23 ml, 1.23 mmol). Stirring at r.t. was continued for 17 hrs. The mixture (clear orange solution) was treated with 1 N HCl (1.2 ml). The light yellow suspension was stirred at r.t. for 1 hr. The solid was collected by filtration, washed with H_20 and dried to provide the title compound (221 mg, 93%) as light yellow solid. MS (m/e): 385.1 $(M-H)^-$.

Example A.16

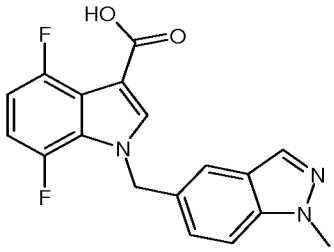
4,7-Difluoro-l-[[6-(l-methylpyrazol-4-yl)pyridine-3-yl]methyl]indazole-3-carboxylic acid



The title compound was prepared in analogy to the procedures described in example A.15, using 5-(chloromethyl)-2-(l-methyl-lH-pyrazol-4-yl)pyridine (example B.l) as alkylating agent in the 3rd step. Off-white solid. MS (m/e): 368.2

Example A.17

4,7-Difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxylic acid



Step 1: Methyl 4,7-difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxylate

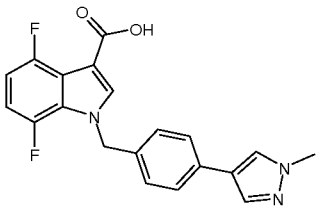
The title compound was obtained in analogy to the procedure described in example 26, reacting methyl 4,7-difluoro-lH-indole-3-carboxylate and 5-(bromomethyl)-l-methyl-lH-indazole hydrobromide. White solid. MS (m/e): 356.5 $(M+H)^+$.

Step 2: 4,7-Difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxylic acid

The title compound was obtained in analogy to the procedure described in example A.l, step 2. White solid. MS (m/e): 342.5 $(M+H)^+$.

Example A.18

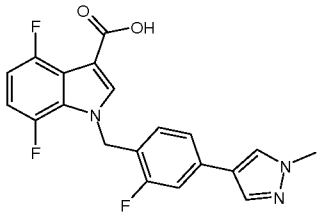
4,7-Difluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 4,7-difluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5). White solid. MS (m/e): 368.5 $(M+H)^+$.

Example A.19

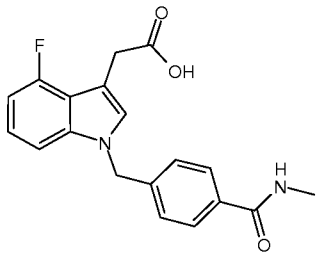
4,7-Difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 4,7-difluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)-3-fluorophenyl)- 1-methyl- lH-pyrazole (example B.2). White solid. MS (m/e): 386.5 $(M+H)^+$.

Example A.20

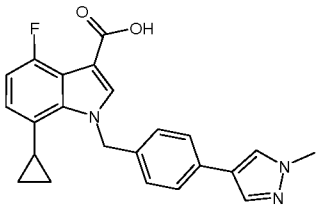
2-(4-Fluoro-l-(4-(methylcarbamoyl)benzyl)-lH-indol-3-yl)acetic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from ethyl 2-(4-fluoro-lH-indol-3-yl)acetate (CAS 919295-78-6) and 4-(chloromethyl)-N-methylbenzamide (example B.6). Brown solid. MS (m/e): 341.2 $(M+H)^+$.

Example A.21

7-Cyclopropyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



Step 1: l-(7-Bromo-4-fluoro- lH-indol-3-yl)-2,2,2-trifluoro-ethanone

To a solution of 7-bromo-4-fluoro-lH-indole (23 g, 107.4 mmol) in DMF (220 ml) under nitrogen at room temperature was added trifluoro acetic anhydride (29.8 ml, 214.95 mmol). The reaction mixture was stirred at 40°C for 8 hours, cooled to room temperature, diluted with water (250 ml) and extracted with ethyl acetate (2x500 ml). The combined organic layers were washed with brine (250 ml), aqueous sodium carbonate solution (200 ml) and dried over sodium sulfate, filtered and concentrated. The residue was purified with flash column chromatography on silica eluting with 15% ethyl acetate in hexane to provide 20 g (60 %) of the title compound as an off-white solid. LC-MS (ESI): 310 (M).

Step 2: 7-Bromo-4-fluoro-lH-indole-3-carboxylic acid

To a solution of l-(7-bromo-4-fluoro-lH-indol-3-yl)-2,2,2-trifluoro-ethanone (5 g, 16.12 mmol) in methanol (60 ml) and water (60 ml) under nitrogen at room temperature was added NaOH (9.6 g, 241.93 mmol). The mixture was stirred at 140°C for 16 hours, cooled to room temperature and concentrated. The residue was diluted with water (150 ml) and washed with ethyl acetate (100 ml). The aqueous layer was treated with 50% aqueous HC1 until pH~4 and extracted with ethyl acetate (2x 200 ml). The combined organics were washed with brine (100 ml) and aqueous sodium carbonate solution (100 ml), dried over sodium sulfate, filtered and concentrated to provide the title compound as a off white-solid (2.3 g, 55 %). LC-MS (ESI): 256 $(M-H)^-$.

Step 3: Methyl 7-bromo-4-fluoro-lH-indole-3-carboxylate

HC1 gas was bubbled through a solution of 7-bromo-4-fluoro-lH-indole-3-carboxylic acid (11.2 g, 43.4 mmol) in methanol (200 ml) at room temperature for 30 min. The reaction mixture was then stirred at 60°C for 16 hours and concentrated. The residue was diluted with water (200 ml)

and extracted with ethyl acetate (2x 500 ml). The combined organics were washed with brine (250 ml) and aqueous sodium carbonate solution (250 ml), dried over sodium sulfate, filtered and concentrated. The residue was purified with flash column chromatography on silica eluting with 20% ethyl acetate in hexane to provide the title compound as a brown solid (7.1 g, 60 %). LC-MS (ESI): 271 $(M-H)^-$.

Step 4: Methyl 7-cyclopropyl-4-fluoro-lH-indole-3-carboxylate

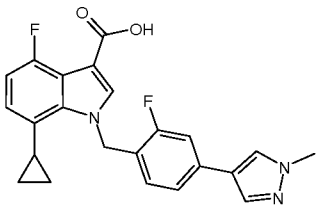
To a solution of 7-bromo-4-fluoro-lH-indole-3-carboxylic acid methyl ester (4.5 g, 16.5 mmol) in toluene (200 ml) were added cyclopropyl boronic acid (2.8 g, 33.08 mmol), tricyclohexylphosphine (0.232 g, 0.827 mmol), and K_3PO_4 (7.01 g, 33.08 mmol). The reaction mixture was purged with argon for 20 min. $Pd(OAc)_2$ (0.371 g, 1.65 mmol) was added and the mixture was purged with argon for another 10 min. The reaction mixture was then heated to 100°C and stirred at this temperature for 16 hours in a sealed tube. The mixture was cooled to room temperature and filtered through a celite pad which was washed with EtOAc (100 ml). Water (200 ml) was added to the filtrate. The aqueous layer was extracted with EtOAc (3x 200 ml). The combined organics were washed with water (100 ml) and brine (100 ml), dried over Na_2S0_4 and concentrated. The residue was purified with flash column chromatography on silica eluting with 20% ethyl acetate in hexane to provide the title compound as a grey solid (2.3 g, 60 %). LC-MS (ESI): 234 $(M+H)^+$.

Step 5: 7-Cyclopropyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid

In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 7-cyclopropyl-4-fluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5). Off-white solid. MS (m/e): 388.3 $(M-H)^-$.

Example A.22

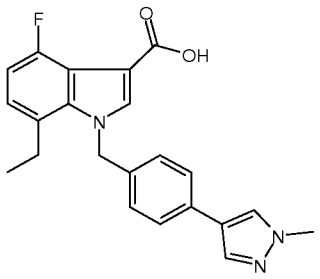
7-Cyclopropyl-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.21, the title compound was prepared from methyl 7-cyclopropyl-4-fluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (example B.2). Off-white solid. MS (m/e): 406.2 $(M-H)^-$.

Example A.23

7-Ethyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid



Step 1: Methyl 4-fluoro-7-vinyl-lH-indole-3-carboxylate

To a solution of methyl 7-bromo-4-fluoro-lH-indole-3-carboxylate (example A.21, step 3) (1.0 g, 3.68 mmol) and 4,4,5,5-tetramethyl-2-vinyl-[l,3,2]dioxaborolane (1.13 g, 7.35 mmol) at room temperature in 1,4-dioxane (30 ml) and water (3 ml) was added CS_2CO_3 (2.39 g, 7.35 mmol) and the mixture was purged with argon for 10 min. [l,l'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) dichloromethane adduct (0.08 g, 0.37 mmol) was added and the reaction mixture was purged with argon for another 10 min. The reaction mixture was then heated to 80°C and stirred at this temperature for 16 hours under argon. The reaction mixture was cooled to room temperature, filtered through a celite pad which was washed with EtOAc (50 ml). The filtrate was diluted with water (100 ml) and extracted with EtOAc (2x100 ml). The combined organics were washed with water (50 ml) and brine (50 ml), dried over Na_2S0_4 and concentrated. The residue was purified with flash column chromatography on silica eluting with

20% ethyl acetate in hexane to provide the title compound as a white solid (500 mg, 62 %). LC-MS (ESI): 220 $(M+H)^+$.

Step 2: Methyl 7-ethyl-4-fluoro-lH-indole-3-carboxylate

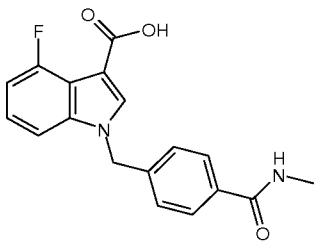
A mixture of methyl 4-fluoro-7-vinyl-lH-indole-3-carboxylate (500 mg, 2.28 mmol) and 10% palladium on activated charcoal (4 mg, 0.039 mmol) in methanol (10 ml) was stirred for 4 hours at room temperature under hydrogen atmosphere (balloon pressure). The palladium catalyst was filtered off and the filtrate was concentrated. The residue was purified with flash column chromatography on silica eluting with 20% ethyl acetate in hexane to provide the title compound as an off- white solid (450 mg, 89 %). LC-MS (ESI):220 $(M-H)^-$.

Step 3: 7-Ethyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid

In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 7-ethyl-4-fluoro-lH-indole-3-carboxylate and 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5). White solid. MS (m/e): 378.2 $(M+H)^+$.

Example A.24

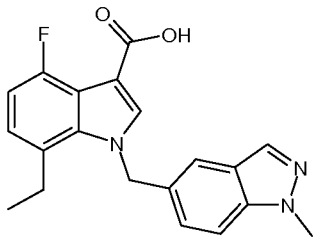
4-Fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and 4-(chloromethyl)-N-methylbenzamide (example B.6). Off-white solid. LC-MS (ESI): 327.0 $(M+H)^+$.

Example A.25

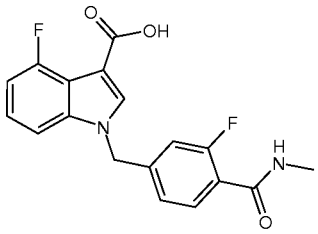
7-Ethyl-4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 7-ethyl-4-fluoro-lH-indole-3-carboxylate and 5-(bromomethyl)-l-methyl-lH-indazole hydrobromide. White solid. MS (m/e): 355.2 $(M+H)^+$.

Example A.26

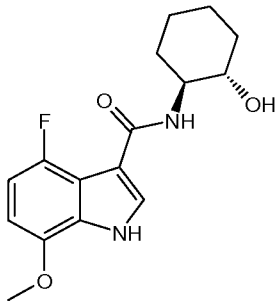
4-Fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxylic acid



In analogy to the procedures described for the synthesis of example A.17, the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and 4-(chloromethyl)-2-fluoro-N-methylbenzamide (example B.7). Off-white solid. MS (m/e): 345.1 $(M+H)^+$.

Example A.27

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-lH-indole-3-carboxamide

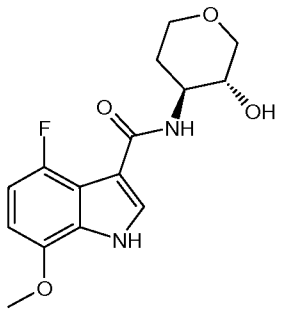


To a stirred solution of (lS,2S)-2-aminocyclohexanol hydrochloride (CAS 13374-30-6) (111 mg, 734 μηοΐ) at room temperature in dichloromethane (5 ml) under an argon atmosphere were

added 4-fluoro-7-methoxy-lH-indole-3-carboxylic acid (150 mg, 667 μηοϊ), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (354 mg, 800 μηοϊ) and triethylamine (270 mg, 370 μϊ, 2.67 mmol). Stirring at r.t. was continued for 17 hours. The reaction mixture was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 10%) to provide the title compound as an off-white solid (162 mg, 79 %). MS (m/e): 305.2 $(M-H)^-$.

Example A.28

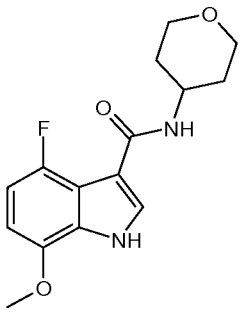
4-Fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.27, the title compound was prepared from 4-fluoro-7-methoxy-lH-indole-3-carboxylic acid and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.l). Off-white solid. MS (m/e): 307.1 $(M-H)^-$.

Example A.29

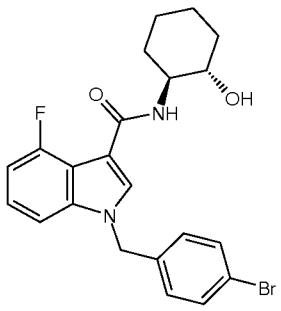
4-Fluoro-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.27, the title compound was prepared from 4-fluoro-7-methoxy-lH-indole-3-carboxylic acid and 4-aminotetrahydropyran. Off-white solid. MS (m/e): 291.2 $(M-H)^-$.

Example A.30

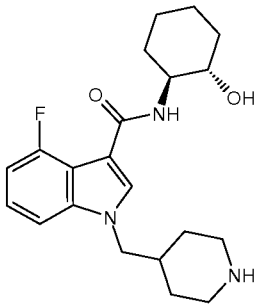
l-(4-Bromobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.17, step 1, the title compound was prepared from 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and l-bromo-4-(bromomethyl)benzene. White solid. MS (m/e): 445.3 $(M+H)^+$.

Example A.31

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(piperidin-4-ylmethyl)-lH-indole-3-carboxamide



Step 1: tert-Butyl 4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yPmethyPpiperidine- 1-carboxylate

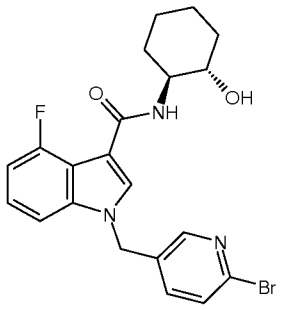
In analogy to the procedure described for the synthesis of example A.17, step 1, the title compound was prepared from 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and 4-methanesulfonyloxymethylpiperidine-l-carboxylic acid tert-butyl ester (CAS 161975-39-9). White solid. MS (m/e): 474.4 $(M+H)^+$.

Step 2: 4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(piperidin-4-ylmethyl)-lH-indole-3-carboxamide

To a solution of tert-butyl 4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)piperidine-l-carboxylate (200 mg, 422 μmol) at 0°C in dioxane (5 ml) under an argon atmosphere was added HCl 4M solution in dioxane (528 μï, 2.11 mmol). The mixture was stirred at room temperature for 5 hours. The reaction mixture was cooled again to 0°C and HCl 4M solution in dioxane (528 μï, 2.11 mmol) was added and the mixture was stirred at room temperature for another 17 hours. The mixture was concentrated. The residue was dissolved in CH_2Cl_2/MeOH (95:5) and washed with aqueous saturated Na_2C0_3 solution. The organic layer was dried over $MgS0_4$, filtered and concentrated to provide the title compound as a light yellow solid (149 mg, 89%). MS (m/e): 374.3 $(M+H)^+$.

Example A.32

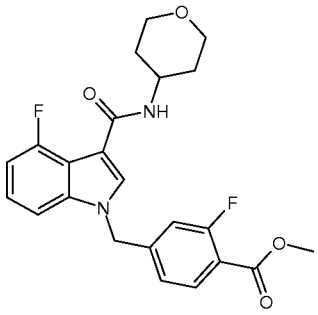
l-((6-Bromopyridin-3-yl)methyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.17, step 1, the title compound was prepared from 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and 2-bromo-5-pyridylmethyl chloride. White solid. MS(m/e): 448.2 $(M+H)^+$.

Example A.33

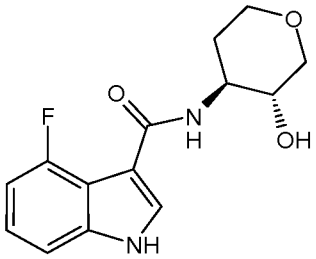
Methyl 2-fluoro-4-((4-fluoro-3-(tetrahydro-2H-pyran-4-ylcarbamoyl)-lH-indol-l-yl)methyl)benzoate



In analogy to the procedure described for the synthesis of example A.17, step 1, the title compound was prepared from 4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.8) and methyl 4-(bromomethyl)-2-fluorobenzoate. White solid. MS (m/e): 429.3 $(M+H)^+$.

Example A.34

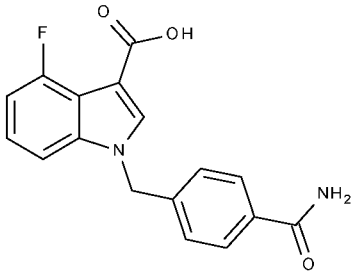
4-Fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.27, the title compound was prepared from 4-fluoro-indole-3-carboxylic acid (CAS 23077-42-1) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.l). Light-yellow solid. MS (m/e): 279.1 $(M+H)^+$.

Example A.35

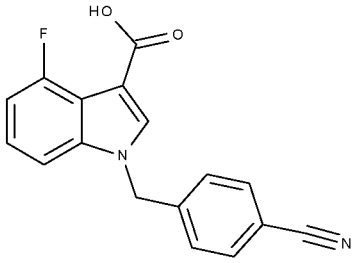
l-(4-Carbamoyl-benzyl)-4-fluoro-lH-indole-3-carboxylic acid



In analogy to the procedure described for the synthesis of example A.l (step: 1 and 2), the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and 4-chloromethyl-benzonitrile. MS (m/e): 313.4 $(M+H)^+$.

Example A.36

l-(4-Cyanobenzyl)-4-fluoro-lH-indole-3-carboxylic acid



Stepl: Methyl l-(4-cyanobenzyl)-4-fluoro-lH-indole-3-carboxylate

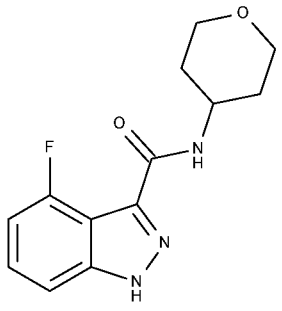
In analogy to the procedure described for the synthesis of example A.l (step 1), the title compound was prepared from methyl 4-fluoro-lH-indole-3-carboxylate and 4-chloromethyl-benzonitrile.

Step 2: l-(4-Cyanobenzyl)-4-fluoro-lH-indole-3-carboxylic acid

In a sealed tube, methyl l-(4-cyanobenzyl)-4-fluoro-lH-indole-3-carboxylate (187 mg, 607 μηοϊ) and lithium iodide (812 mg, 6.1 mmol) were combined with pyridine (8.7 ml). The reaction mixture was stirred at 135°C for 19 hrs, then treated with water and HC1 2N. The precipitate was filtered, washed with water and dried to provide 85 mg (48%) of the title compound as an off white solid. MS (m/e): 295.4 $(M+H)^+$.

Example A.37

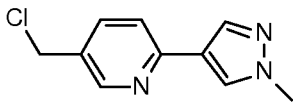
4-Fluoro-N-tetrahydropyran-4-yl-lH-indazole-3-carboxamide



In analogy to the procedure described for the synthesis of example A.6, the title compound was prepared from 4-fluoro-lH-indazole-3-carboxylic acid and tetrahydro-pyran-4-ylamine. MS (m/e): 264.4 $(M+H)^+$.

Example B.l

5-(Chloromethyl)-2-(l-methyl-lH-pyrazol-4-yl)pyridine



Step 1: (6-(l-Methyl-lH-pyrazol-4-yl)pyridine-3-yl)methanol

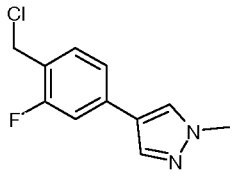
To a solution of (6-chloropyridin-3-yl)methanol (1 g, 6.8 mmol) in dioxane (20 ml) under nitrogen at room temperature was added l-methyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-lH-pyrazole (2.16 g, 10.2 mmol) followed by [l,l'-bis(diphenylphosphino)ferrocene] dichloropalladium(II) dichloromethane adduct (276 mg, 341 μηοϊ). A solution of sodium carbonate (2.17 g, 20.5 mmol) in water (16 ml) was added to the mixture. The reaction mixture was stirred at 80°C for 1 hour and cooled to room temperature. Ethyl acetate (20 ml) and water (10 ml) were added. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate and concentrated. The crude brown solid was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 100%) to provide 1 g (77%) of the title compound as a grey solid. MS (m/e): 190.2 $(M+H)^+$.

Step 2: 5-(Chloromethyl)-2-(l-methyl-lH-pyrazol-4-yl)pyridine

To a 0°C solution of (6-(l-methyl-lH-pyrazol-4-yl)pyridine-3-yl)methanol (1 g, 5.3 mmol) in dichloromethane (30 ml) was added a solution of thionyl chloride (1.27 g, 775 μϊ, 10.6 mmol) in dichloromethane (5 ml). The reaction mixture was stirred at room temperature for 3 hours and quenched with a saturated solution of sodium hydrogen carbonate (30 ml). The aqueous layer was extracted with dichloromethane. The combined organic layers were dried over sodium sulfate and evaporated. The crude material was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate (0 to 20%) to provide 930 mg (85%) of the title compound as a light grey solid. MS (m/e): 208.2 $(M+H)^{+\cdot}$

Example B.2

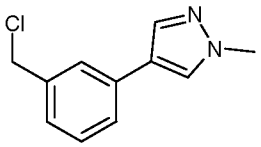
4-(4-(Chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole



In analogy to the procedures described for the synthesis of example B.l, the title compound was prepared from 4-bromo-2-fluorophenyl)-methanol. MS (m/e): 225.4 $(M+H)^+$.

Example B.3

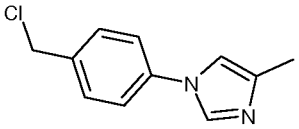
4-(3-(Chloromethyl)phenyl)-l-methyl-lH-pyrazole



In analogy to the procedure described for the synthesis of example B.l, the title compound was prepared from 3-bromophenyl-methanol. MS (m/e): 207.4 $(M+H)^+$.

Example B.4

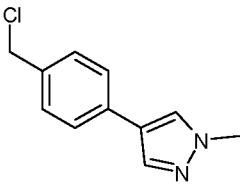
l-(4-Chloromethyl-phenyl)-4-methyl-lH-imidazole



In analogy to the procedure described for the synthesis of example B.l (step 2), the title compound was prepared from (4-(4-methyl-lH-imidazol-l-yl)phenyl)methanol. MS (m/e): 207.3 $(M+H)^+$.

Example B.5

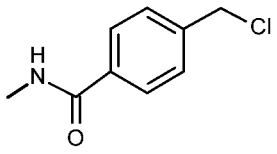
4-(4-(Chloromethyl)phenyl)-l-methyl-lH-pyrazole



In analogy to the procedure described for the synthesis of example B.l, the title compound was prepared from 4-bromophenyl-methanol. MS (m/e): 207.4 $(M+H)^+$.

Example B.6

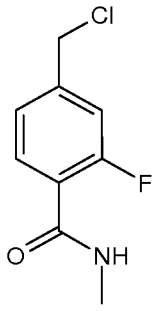
4-(Chloromethyl)-N-methylbenzamide



To a stirred, cooled solution of 4-(chloromethyl)benzoyl chloride (1.6 g, 8.49 mmol) at 0°C in dichloromethane (15 ml) under an argon atmosphere were added methylamine hydrochloride (521 mg, 7.72 mmol). A solution of triethylamine (3.12 g, 4.28 ml, 30.9 mmol) in dichloromethane (15 ml) was added dropwise. Stirring at 0°C was continued for 44 hrs. The mixture was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 10 %) to provide 10 mg (y: 0.6%) of the title compound as a white solid. MS (m/e): 184.2 $(M+H)^+$.

Example B.7

4-(Chloromethyl)-2-fluoro-N-methylbenzamide



Step 1: 2-Fluoro-4-formyl-N-methylbenzamide

To a stirred suspension of 2-fluoro-4-formylbenzoic acid (1 g, 5.95 mmol) at r.t. in dichloromethane (3 ml) under an argon atmosphere was added dropwise thionyl chloride (849 mg, 521 µï, 7.14 mmol). DMF (0.25 ml) was then added dropwise. The mixture was then refluxed for 2 hours. The mixture was cooled to room temperature and it was added dropwise to stirred, cooled (0°C) methylamine 40% solution in water (1.66 g, 1.85 ml, 21.4 mmol) for 15 min. When the addition was complete, stirring at 0°C was continued for 1 hour. The mixture was concentrated and the residue was purified with flash column chromatography on silica

eluting with a gradient formed from dichloromethane and methanol (0 to 10 %) to provide the title compound as an off-white solid (330 mg, 36 %). MS (m/e): 182.1 $(M+H)^+$.

Step 2: 2-Fluoro-4-(hydroxymethyl)-N-methylbenzamide

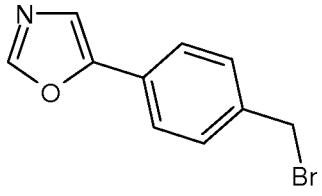
To a stirred, cooled (0°C) solution of 2-fluoro-4-formyl-N-methylbenzamide (320 mg, 1.77 mmol) in dichloromethane (8 ml) and methanol (2 ml) under an argon atmosphere was added portionwise sodium borohydride (134 mg, 3.53 mmol). The cooling bath was removed and stirring at room temperature was continued for 6 hours. The mixture was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 10 %) to provide the title compound as an off-white solid (288 mg, 89 %). MS (m/e): 184.1 $(M+H)^+$.

Step 3: 4-(Chloromethyl)-2-fluoro-N-methylbenzamide

To a stirred, cooled (0°C) suspension of 2-fluoro-4-(hydroxymethyl)-N-methylbenzamide (275 mg, 1.5 mmol) in dichloromethane (10 ml) under an argon atmosphere was added dropwise a solution of thionyl chloride (357 mg, 219 µï, 3.00 mmol) in dichloromethane (2 ml). The cooling bath was removed and stirring at room temperature was continued for 6 hours.
The mixture was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 10 %) to provide the title compound as a white solid (255 mg, 84 %). MS (m/e): $(M+H)^+$.

Example B.8

5-(4-Bromomethyl-phenyl)-oxazole

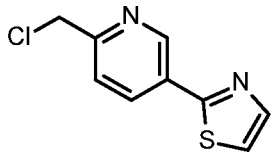


To a stirred solution of 5-(4-methylphenyl)-l,3-oxazole (2 g) at room temperature in tetrachloromethane (60 ml) were added NBS (2.9 g) and dibenzoylperoxide (150 mg). The mixture was stirred at 77°C under a 150 watt lamp for 6 hours and then cooled to room temperature. The insoluble material was filtered off. The filtrate was washed with water and aqueous $NaHC0_3$ solution, dried ($MgS0_4$), filtered and concentrated. The residue was purified

with flash column chromatography on silica eluting with 50 % heptane in diisopropylether to provide the title compound (1.35 g, 45 %). MS (m/e): 237 (M).

Example B.9

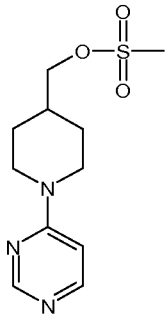
2-(4-(Chloromethyl)phenyl)thiazole



To a solution at 0° of (5-(thiazol-2-yl)pyridin-2-yl)methanol (65 mg, 338 μηοϊ) in dichloromethane (5 ml) was added under an argon atmosphere sulfurous dichloride (80.5 mg, 49.1 μϊ, 676 μηοϊ). The mixture was stirred at r.t for 3 h. The solvent was evaporated. The residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound (40 mg, 56%) as light yellow solid. MS (m/e): 211.1 $(M+H)^+$.

Example B.10

(l-(Pyrimidin-4-yl)piperidin-4-yl)methyl methanesulfonate



Step 1: Ethyl l-(pyrimidin-4-yl)piperidine-4-carboxylate

A mixture of 4-bromopyrimidine hydrochloride (200 mg, 1.02 mmol), cesium carbonate (333 mg, 1.02 mmol) and ethyl piperidine-4-carboxylate (161 mg, 158 μϊ, 1.02 mmol) in 1,4-dioxane (5 ml) under an argon atmosphere was stirred at 100° for 17 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0

to 5 %) to provide the title compound as a light yellow viscous oil (153 mg, 63 %). MS (m/e): 236.3 $(M+H)^+$.

Step 2: (l-(Pyrimidin-4-yl)piperidin-4-yl)methanol

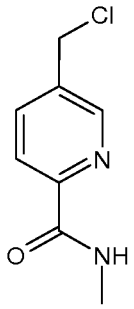
To a solution of ethyl l-(pyrimidin-4-yl)piperidine-4-carboxylate (150 mg, 638 μηοϊ) in methanol (5 ml) and dichloromethane (5 ml) at 0°C under argon was added sodium borohydride (145 mg, 3.83 mmol) in one portion. The cooling bath was removed and the mixture was stirred at room temperature for 4 hours. The mixture was cooled again to 0°C and sodium borohydride (145 mg, 3.83 mmol) was added in one portion. The mixture was stirred at room temperature for 17 hr and concentrated. The residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound as a white solid (80 mg, 65 %). MS (m/e): 194.2 $(M+H)^+$.

Step 3: (l-(Pyrimidin-4-yl)piperidin-4-yl)methyl methanesulfonate

To a stirred solution of (l-(pyrimidin-4-yl)piperidin-4-yl)methanol (80 mg, 414 μηοϊ) and triethylamine (83.8 mg, 115 μϊ, 828 μηοϊ) in dichloromethane (2 ml) at 0°C under argon was added dropwise a solution of methanesulfonyl chloride (94.8 mg, 64.3 μϊ, 828 μηοϊ) in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 3 hours. Sodium bicarbonate (34.8 mg, 414 μηοϊ) was added and the mixture was stirred for 5 min and filtered. The filtrate was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound as a yellow viscous oil (34.5 mg, 31 %). MS (m/e): 272.2 $(M+H)^+$.

Example B.ll

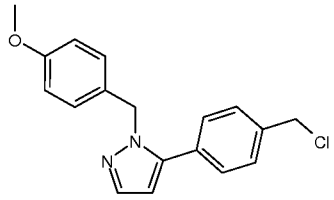
5-(Chloromethyl)-N-methylpicolinamide



In analogy to the procedures described for the synthesis of example B.10, step 2 and example B.9, the title compound was prepared from methyl 6-(methylcarbamoyl)nicotinate (CAS 173371-36-3). Off-white solid. MS (m/e): 185.1 $(M+H)^+$.

Example B.12

5-(4-(Chloromethyl)phenyl)-l-(4-methoxybenzyl)-lH-pyrazole



Step 1: 5-Iodo-l-(4-methoxybenzyl)-lH-pyrazole

To a solution of 5-iodo-lH-pyrazole (0.2 g, 1.03 mmol) in dimethyl acetamide (3 ml) at 0°C under argon was added sodium hydride 60% dispersion in mineral oil (41.2 mg, 1.03 mmol) in one portion. After stirring at 0°C for 15 min, l-(bromomethyl)-4-methoxybenzene (207 mg, 1.03 mmol) was added in one portion. The cooling bath was removed and the mixture was stirred at room temperature for 17 hours. The mixture was diluted with ethyl acetate, and washed with water. The aqueous phase was back extracted with ethyl acetate. The combined organics were washed with water, dried over $MgS0_4$, filtered and evaporated. The residue was purified with flash column chromatography on silica eluting with a gradient formed from heptane and ethyl acetate (0 to 50 %) to provide the title compound as a colorless viscous oil (270 mg, 83 %). MS (m/e): 315.1 $(M+H)^+$.

Step 2: (4-(l-(4-Methoxybenzyl)-lH-pyrazol-5-yl)phenyl)methanol

A mixture of 5-iodo-l-(4-methoxybenzyl)-lH-pyrazole (0.27 g, 860 μηοϊ) and 4-(hydroxymethyl)phenylboronic acid (170 mg, 1.12 mmol) at room temperature in 1,2-dimethoxyethane (6 ml) and 2M aqueous Na_2C0_3 solution (1.43 ml, 2.86 mmol) was purged with argon in an ultrasonic bath for 5 min. Then triphenylphosphine (45.1 mg, 172 μηοϊ) and palladium(II) acetate (19.3 mg, 86.0 μηοϊ) were added and the mixture was stirred at 85°C under argon for 17 hr. The mixture was cooled to room temperature, poured onto water and extracted with ethyl acetate. The organic layer was washed with water, dried with $MgS0_4$, filtered and evaporated. The residue was purified with flash column chromatography on silica eluting with a

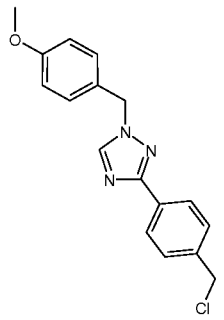
gradient formed from heptane and ethyl acetate (0 to 50 %) to provide the title compound as a colorless viscous oil (160 mg, 63 %). MS (m/e): 295.2 $(M+H)^+$.

Step 3: 5-(4-(Chloromethyl)phenyl)-l-(4-methoxybenzyl)-lH-pyrazole

In analogy to the procedures described for the synthesis of example B.9, the title compound was prepared from (4-(l-(4-methoxybenzyl)-lH-pyrazol-5-yl)phenyl)methanol. Off-white solid. MS (m/e): 313.2 $(M+H)^+$.

Example B.13

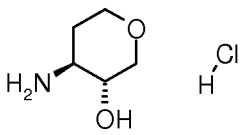
3-(4-(Chloromethyl)phenyl)-l-(4-methoxybenzyl)-lH-l,2,4-triazole



In analogy to the procedures described for the synthesis of example B.13, the title compound was prepared from 5-bromo-lH-l,2,4-triazole.White solid. MS (m/e): 314.2 $(M+H)^+$.

Example C.l

(3R,4S)-4-Aminotetrahydropyran-3-ol hydrochloride



Step 1: Methanesulfonic acid tetrahvdro-pyran-4-yl ester

To a solution of tetrahydro-2H-pyran-4-ol (25 g, 245 mmol) and triethyl amine (40.1 ml, 294 mmol) in CH_2CI_2 (500 ml) at 0°C was added dropwise methanesulfonylchloride (20.7 ml, 269 mmol) over a period of 40 min, keeping the temperature between 0° - 4°C. The reaction mixture was then allowed to stir at 0°C for lhr. The cooling bath was removed and the mixture was stirred for another 90 mins at 25°C. The mixture was washed with water (2 x 125ml), dried over anhydrous Na_2S0_4, filtered and concentrated under vacuum to get methanesulfonic acid tetrahydro-pyran-4-yl ester (38 g, 86%; crude) as a liquid that was used in the next step without any further purification.

Step 2: 3, 6-Dihydro-2H-pyran

A mixture of tetrahydro-2H-pyran-4-yl methanesulfonate (20 g, 111 mmol) and DBU (18.8 ml, 125.6 mmol) was distilled under normal atmospheric pressure. The fraction at 90° - 96°C was 6-dihydro-2H-pyran (6 g, 64%) as a colourless liquid.

Step 3: (1SR, 6RS)-3 J-Dioxa-bicycloK.l.Olheptane

To a solution of 3,6-dihydro-2H-pyran (6 g, 71.4 mmol,) in CH_2CI_2 (300 ml) was added 3-chloroperbenzoic acid (25 g, 107.1 mmol) portionwise at 25°C, and stirred at that temperature for 21 hrs. The resultant white suspension was diluted with water (250 ml) and then with aqueous solution of Na_2S0_3. The mixture was stirred at 25°C for 10 min, then basified by addition of saturated aqueous solution of $NaHC0_3$. The organic layer was separated, and the aqueous layer was re-extracted with CH_2CI_2. The combined organic layers were washed with saturated aqueous solution of $NaHC0_3$ (100 ml), and brine (80 ml), dried over anhydrous $Na_2SC"4$, filtered and concentrated in vacuo to afford the title compound (5 g, 70%; crude) as a yellow liquid.

Step 4: (3SR,4RS)-4-Azidotetrahydropyran-3-ol

To a solution of (lSR,6RS)-3,7-dioxabicyclo[4.1.0]heptane (5 g, 49.9 mmol) in MeOH (50ml) were added sodium azide (24.3 g, 374.6 mmol), ammonium chloride (20 g, 374.6 mmol) and water (5 ml), and the resultant mixture was stirred at 25°C for 19 hrs, and then at 70°C for 2 hrs. The mixture was cooled 0°C, and the precipitated solid was filtered and washed with methanol. The filtrate was concentrated in vacuo. Resultant residue was taken in ethyl acetate, and filtered. Removal of the filtrate in vacuo yielded the title compound (5 g, 70%; crude) as a yellow liquid.

Step 5: (3SR,4RS)-4-Aminotetrahvdropyran-3-ol

To a solution of (3SR,4RS)-4-azidotetrahydropyran-3-ol (5g, 35 mmol) in ethyl acetate (50 ml), was added $Pd(OH)_2$ on charcoal (1.25 g, 1.4 mmol). The mixture was purged with argon, and then allowed to stir under a balloon pressure of hydrogen for 21 hrs at 25°C. Removal of the catalyst by filtration followed by evaporation of the filtrate in vacuo afforded the title compound (4 g, crude).

Step 6: (3S, 4R)-3-Hvdroxy-tetrahvdro-pyran-4-yl)-carbamic acid benzyl ester and ((3R, 4S)-3-hvdroxy-tetrahydro-pyran-4-yl)-carbamic acid benzyl ester

To a solution of (3SR,4RS)-4-aminotetrahydropyran-3-ol (10 g, 85.4 mmol) and Et_3N (23.6 ml, 170.9 mmol) in CH_2CI_2 (100 ml) was added benzyl chloroformate (9.8 ml, 59.9 mmol) dropwise

at 0°C. After completion of addition, the mixture was stirred at 25°C for 2 hrs. The mixture was washed with water (60 ml). The aqueous layer was re-extracted with CH_2CI_2. The combined organic layers were dried over anhydrous Na_2S0_4, filtered and concentrated in vacuo to get the mixture the two regioisomeric pairs of enantiomers (16 g). This crude product was purified by silica gel chromatography using 45% EtOAc in hexane as eluent to get the pair of enantiomers with the desired regioisomery as white solid (4.5 g, 21%). This enantiomeric mixture was subject to chiral separation by SFC to afford (3S,4R)-3-hydroxy-tetrahydro-pyran-4-yl)-carbamic acid benzyl ester (1.7 g, 8%) and ((3R,4S)-3-hydroxy-tetrahydro-pyran-4-yl)-carbamic acid benzyl ester (1.7 g, 8 %) both as a white solid.

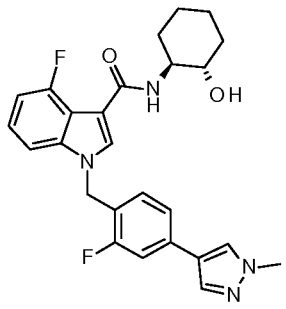
Step 7: (3R,4S)-4-Amino-tetrahydro-pyran-3-ol hydrochloride

To a solution of ((3R,4S)-3-hydroxy-tetrahydro-pyran-4-yl)-carbamic acid benzyl ester (1.1 g, 4.4 mmol) in MeOH (50 ml) was added 10% palladium on charcoal (140 mg, 0.13 mmol), and stirred the reaction mixture under hydrogen atmosphere for lhr. The catalyst was filtered off. The filtrate was acidified with 1.25 M HCl in MeOH and concentrated in vacuo to get (3R,4S)-4-amino-tetrahydro-pyran-3-ol hydrochloride as an off white solid (500 mg, 97%).

Description of examples

Example 1

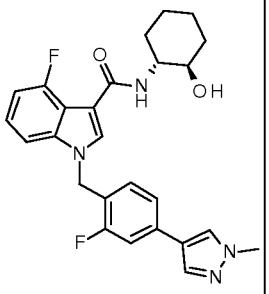
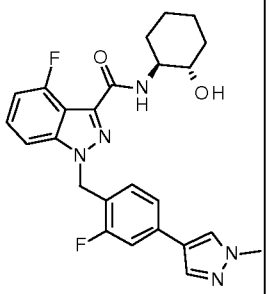
4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

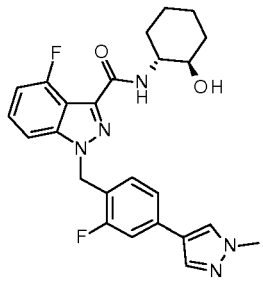
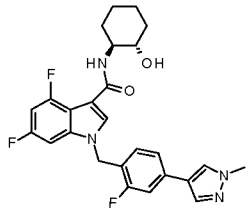
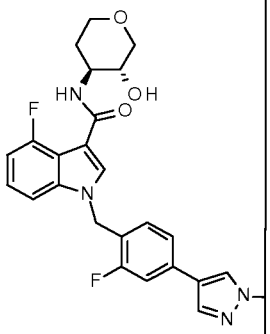
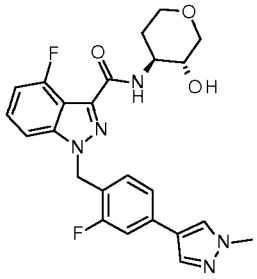


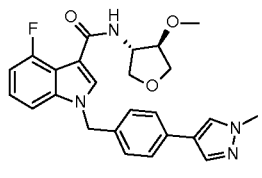
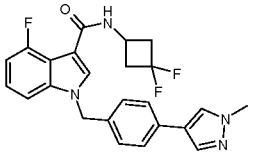
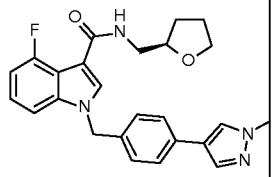
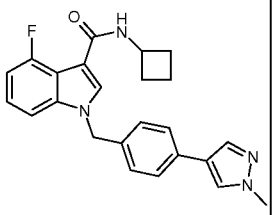
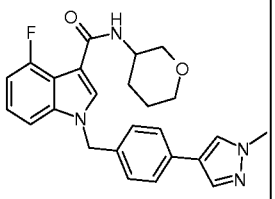
To a suspension of 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.l) (30 mg, 81.7 μιηοΐ) in N,N-dimethylformamide (1 ml) was added triethylamine (41.3 mg, 56.8 μΐ, 408 μιηοΐ). The mixture was stirred at room temperature for 15 minutes. (Benzotriazol-l-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (47.0 mg, 106 μιηοΐ) was added. The suspension was stirred at room temperature for 1 hour. (lS,2S)-2-Aminocyclohexanol hydrochloride (12.4 mg, 81.7 μιηοΐ) was added. The mixture was

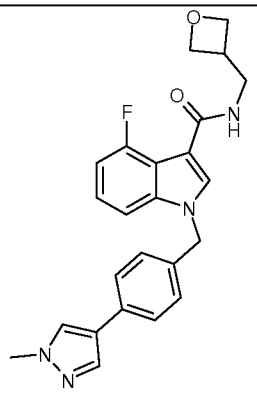
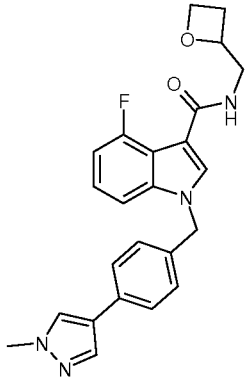
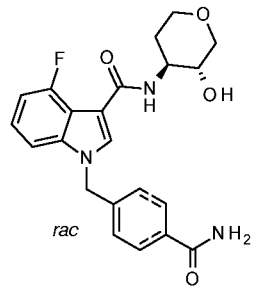
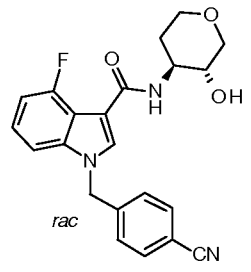
stirred at room temperature for 16 hours. The solvent was removed in vacuo. The residue was taken in water. The aqueous layer was extracted with ethyl acetate. The combined extracts were dried over sodium sulfate, filtered and concentrated in vacuo. The crude oil was purified with flash column chromatography on silica eluting with a gradient formed from heptane and ethyl acetate (0 to 100%) to provide 10 mg (25%) of the title compound as a light yellow solid. MS (m/e): 465.5 $(M+H)^+$.

In analogy to example 1, examples 2 to 16 of the following table were prepared by coupling an acid derivative with an amine.

Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
2		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1R,2R)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.1) and (1R,2R)-2-aminocyclohexanol hydrochloride	465.5
3		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indazole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indazole-3-carboxylic acid (example A.2) and (1S,2S)-2-aminocyclohexanol hydrochloride	466.5

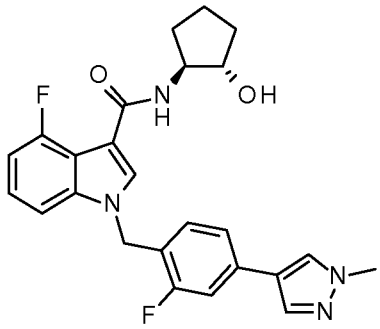
4		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1R,2R)-2-hydroxycyclohexyl)-1H-indazole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indazole-3-carboxylic acid (example A.2) and (1R,2R)-2-aminocyclohexanol hydrochloride	466.5
5		4,6-difluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4,6-difluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.3) and (1S,2S)-2-aminocyclohexanol hydrochloride	483.6
6		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((3RS,4RS)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.1) and (3RS,4SR)-4-aminotetrahydro-2H-pyran-3-ol (CAS: 215940-92-4)	467.5
7		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indazole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indazole-3-carboxylic acid (example A.2) and (3RS,4SR)-4-aminotetrahydro-2H-pyran-3-ol (CAS: 215940-92-4)	468.5

8		4-fluoro-N-[(3S,4R)-4-methoxyoxolan-3-yl]-1-[[4-(1-methylpyrazol-4-yl)phenyl]methyl]indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and (3S,4R)-4-methoxy-tetrahydro-furan-3-ylamine	419.5
9		N-(3,3-difluorocyclobutyl)-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and 3,3-difluoro-cyclobutylamine	439.6
10		(R)-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((tetrahydrofuran-2-yl)methyl)-1H-indole-3-carboxamide	(R)4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and [-1-(tetrahydrofuran-2-yl)]-methylamine	433.7
11		N-cyclobutyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and cyclobutylamine	403.6
12		4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-1H-indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and tetrahydro-pyran-3-ylamine	433.7

13		4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(oxetan-3-ylmethyl)-1H-indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and oxetan-3-yl-methylamine	419.6
14		4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(oxetan-2-ylmethyl)-1H-indole-3-carboxamide	4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.9) and oxetan-2-yl-methylamine	419.6
15		1-(4-carbamoylbenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	1-(4-carbamoyl-benzyl)-4-fluoro-1H-indole-3-carboxylic acid (example A.35) and (3RS,4SR)-4-aminotetrahydro-2H-pyran-3-ol (CAS: 215940-92-4)	412.5
16		1-(4-cyanobenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	1-(4-cyanobenzyl)-4-fluoro-1H-indole-3-carboxylic acid (example A.36) and (3RS,4SR)-4-aminotetrahydro-2H-pyran-3-ol (CAS: 215940-92-4)	394.6

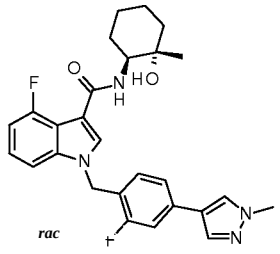
Example 17

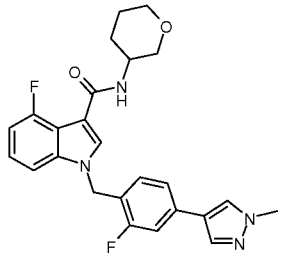
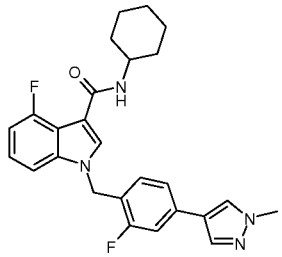
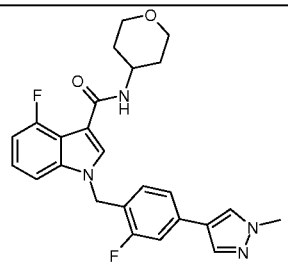
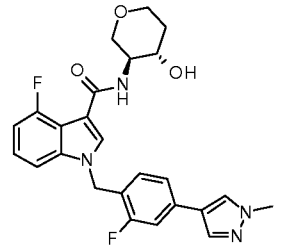
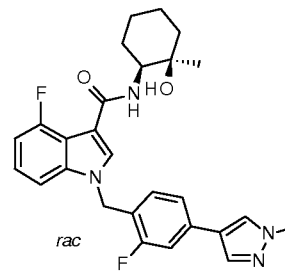
4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

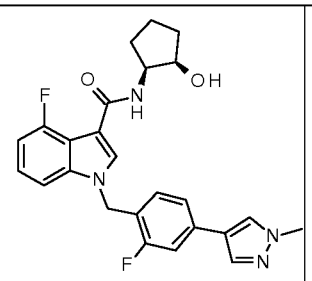
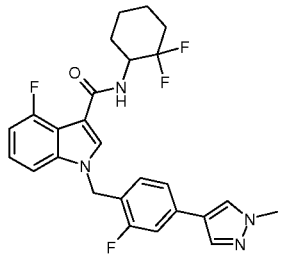


To a solution of 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride (example A.5) (30 mg, 77.8 μηοϊ) and triethylamine (31.5 mg, 43.3 μϊ, 311 μηοϊ) in dichloromethane (1.2 ml) was added (lS,2S)-2-aminocyclopentanol hydrochloride (12.3 mg, 85.5 μηοϊ). The mixture was stirred at room temperature overnight. The solvent was removed in vacuo. Water was added. The resulting precipitate was filtrated, washed with diethyl ether and dried to provide 26 mg (74%) of the title compound as an off-white solid. MS (m/e): 451.4 $(M+H)^+$.

In analogy to Example 17, compounds 18 to 25 of the following table were prepared from 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride (example A.5) and an amine derivative:

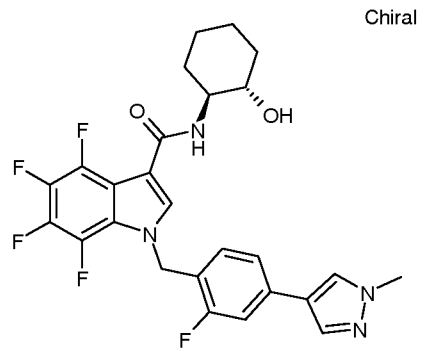
Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
18		4-fluoro-l-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((lSR,2SR)-2-hydroxy-2-methylcyclohexyl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride (example A.5) and (lSR,2SR)-2-amino-1-methylcyclohexanol hydrochloride	479.5

19		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carbonyl chloride (example A.5) and tetrahydro-2H-pyran-3-amine hydrochloride	451.4
20		N-cyclohexyl-4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carbonyl chloride (example A.5) and cyclohexanamine	449.5
21		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carbonyl chloride (example A.5) and tetrahydro-2H-pyran-4-amine	451.4
22		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((3S,4S)-4-hydroxytetrahydro-2H-pyran-3-yl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carbonyl chloride (example A.5) and (3S,4S)-3-aminotetrahydro-2H-pyran-4-ol	467.5
23		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1SR,2RS)-2-hydroxy-2-methylcyclohexyl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carbonyl chloride (example A.5) and (1RS,2SR)-2-amino-1-methylcyclohexanol hydrochloride	479.4

24		4-fluoro-l-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((lS,2R)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride (example A.5) and (lS,2R)-2-aminocyclopentanol hydrochloride	451.4
25		N-(2,2-difluorocyclohexyl)-4-fluoro-l-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carbonyl chloride (example A.5) and 2,2-difluorocyclohexanamine hydrochloride	485.4

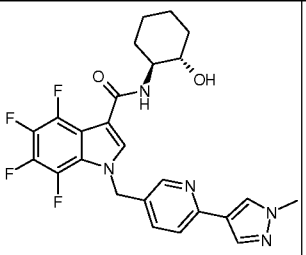
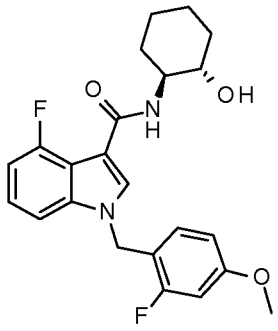
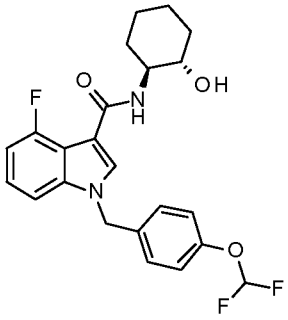
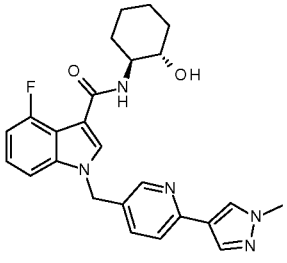
Example 26

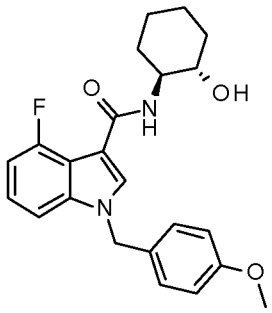
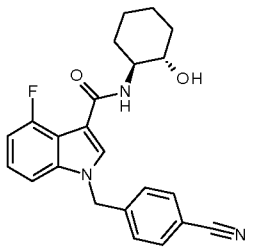
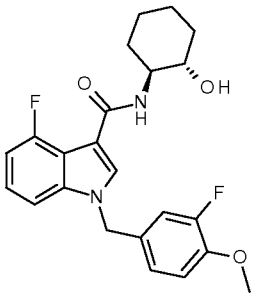
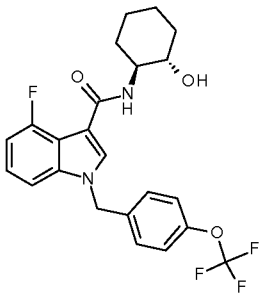
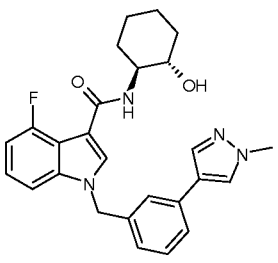
4,5,6,7-Tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

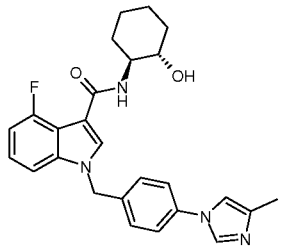
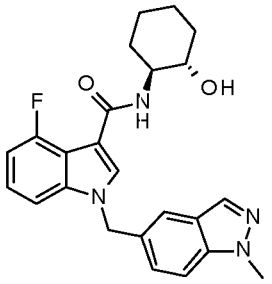
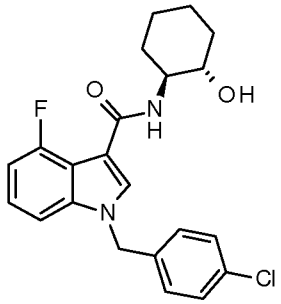
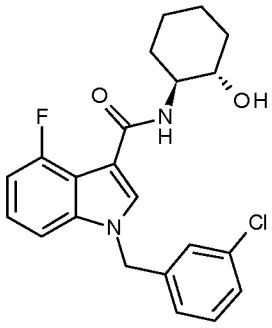


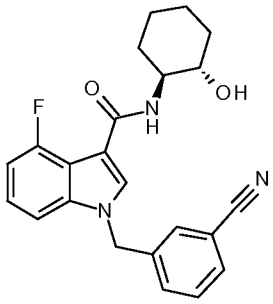
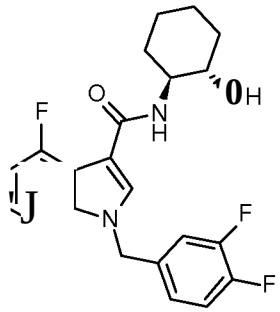
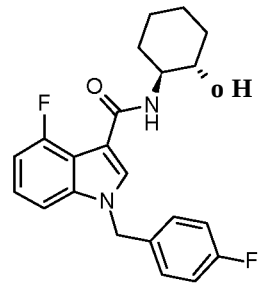
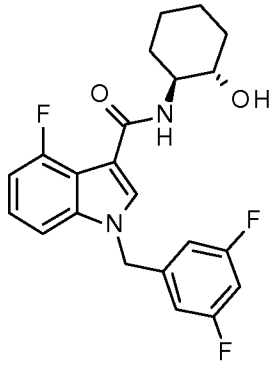
In a microwave tube, 4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (50 mg, 104 μηοϊ; example A.4), 4-(4-(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (34 mg, 151 μηοϊ; example B.2) and cesium carbonate (98.7 mg, 303 μηοϊ) were combined with N,N-dimethylaceamide (633 μϊ) to give a colorless suspension. The reaction mixture was stirred at r.t. for 2 days, then was taken up in H_20 and extracted with EtOAc. The organic layers were washed H_20 and then with saturated NaCl solution, dried over MgS04 and concentrated in vacuo. The crude material was purified by silica gel chromatography using a CH_2Cl_2/MeOH gradient as eluent to provide the title compound (39 mg, 72%) as colorless solid. MS (m/e): 519.4 $(M+H)^+$

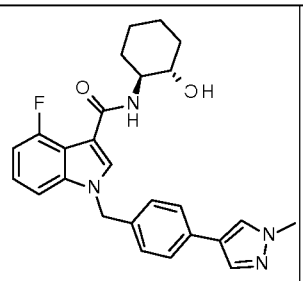
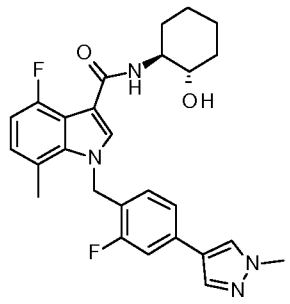
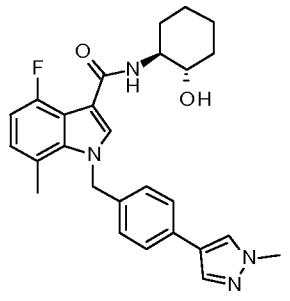
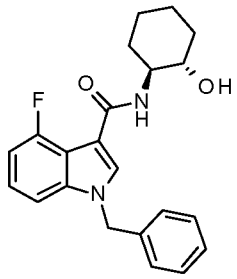
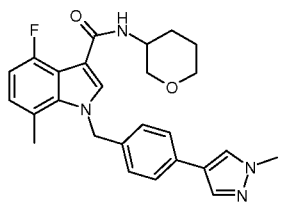
In analogy to Example 26, compounds 27 to 61 of the following table were prepared by reaction of the indicated amides with an alkylating agent.

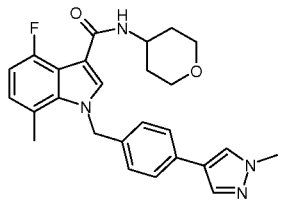
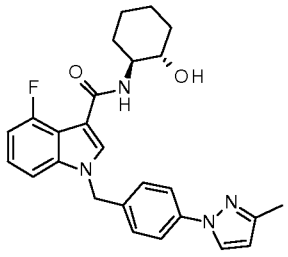
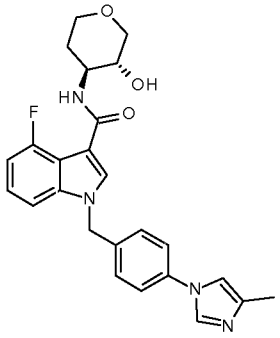
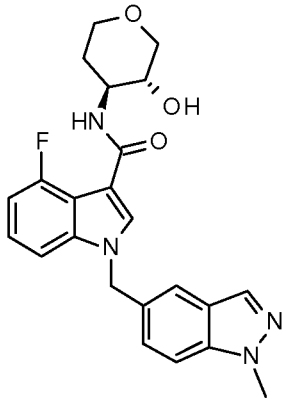
Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
27		4,5,6,7-tetrafluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)methyl)-1H-indole-3-carboxamide	4,5,6,7-tetrafluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.4) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.1)	502.4
28		4-fluoro-1-(2-fluoro-4-methoxybenzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(chloromethyl)-2-fluoro-4-methoxybenzene	415.5
29		1-(4-(difluoromethoxy)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(bromomethyl)-4-(difluoromethoxy)benzene	433.4
30		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.1)	448.5

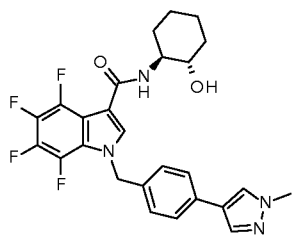
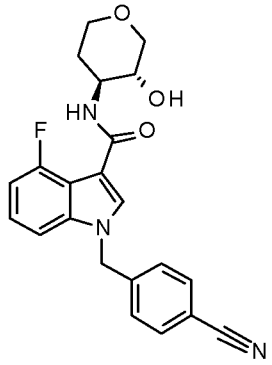
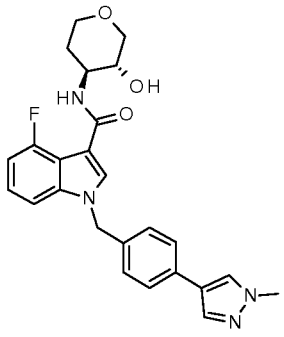
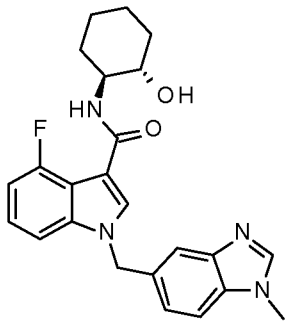
31		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-methoxybenzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(bromomethyl)-4-methoxybenzene	397.5
32		1-(4-cyanobenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(chloromethyl)benzonitrile	392.5
33		4-fluoro-1-(3-fluoro-4-methoxybenzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(bromomethyl)-2-fluoro-1-methoxybenzene	415.5
43		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(trifluoromethoxy)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(bromomethyl)-4-(trifluoromethoxy)benzene	451.4
35		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(3-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(3-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.3)	447.5

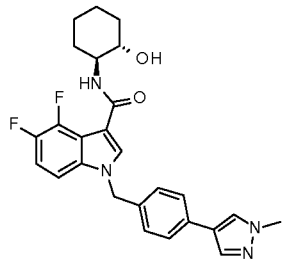
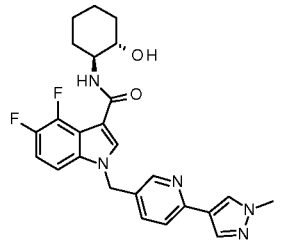
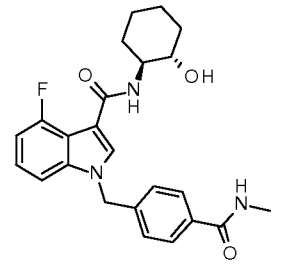
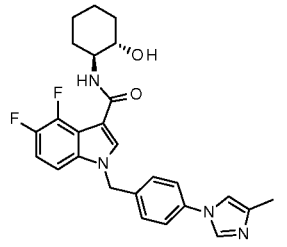
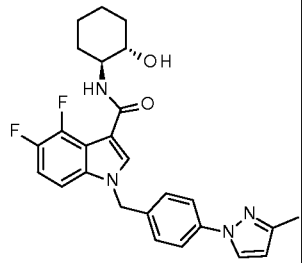
36		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(4-methyl-1H-imidazol-1-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(4-chloromethyl-phenyl)-4-methyl-1H-imidazole (example B.4)	447.5
37		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((1-methyl-1H-indazol-5-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(bromomethyl)-1-methyl-1H-indazole hydrobromide	421.5
38		1-(4-chlorobenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-chloro-4-(chloromethyl)benzene	401.4
39		1-(3-chlorobenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-chloro-3-(chloromethyl)benzene	401.4

40		l-(3-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide (example A.6) and 3-(bromomethyl)benzonitrile	392.5
41		l-(3,4-difhiorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide (example A.6) and 4-(chloromethyl)- 1,2-difluorobenzene	403.4
42		4-fluoro-l-(4-fluorobenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide (example A.6) and 1-(chloromethyl)-4-fluorobenzene	385.5
43		l-(3,5-difhiorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide (example A.6) and 1-(chloromethyl) -3,5-difluorobenzene	403.5

44		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	447.5
45		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-7-methyl-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.7) and 4-(4-(chloromethyl)-3-fluorophenyl)-1-methyl-1H-pyrazole (example B.2)	479.6
46		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-7-methyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.7) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	461.7
47		1-benzyl-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and (bromomethyl)benzene	367.5
48		4-fluoro-7-methyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid (tetrahydro-pyran-3-yl)-amide (example A.10) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	447.5

49		4-fluoro-7-methyl-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid (tetrahydro-pyran-4-yl)-amide (example A.11) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	447.7
50		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(4-chloromethyl-phenyl)-3-methyl-1H-pyrazole	447.4
51		4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(4-methyl-1H-imidazol-1-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.12) and 1-(4-chloromethyl-phenyl)-4-methyl-1H-imidazole (example B.4)	449.4
52		4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-((1-methyl-1H-indazol-5-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.12) and 5-(bromomethyl)-1-methyl-1H-indazole hydrobromide	441.2

53		4,5,6,7-tetrafluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4,5,6,7-tetrafluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.4) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	501.6
54		1-(4-cyanobenzyl)-4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S)or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.12) and 4-(chloromethyl)benzonitrile	394.5
55		4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.12) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	449.4
56		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((1-methyl-1H-benzo[d]yridine-5-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(chloromethyl)-1-methyl-1H-benzo[d]imidazole	421.5

57		4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4,5-difluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.14) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	465.5
58		4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)pyridine-3-yl)methyl)-1H-indole-3-carboxamide	4,5-difluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.14) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.1)	466.7
59		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(chloromethyl)-N-methylbenzamide (example B.6)	424.7
60		4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(4-methyl-1H-imidazol-1-yl)benzyl)-1H-indole-3-carboxamide	4,5-difluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.14) and 1-(4-chloromethyl-phenyl)-4-methyl-1H-imidazole (example B.4)	465.5
61		4,5-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-1H-indole-3-carboxamide	4,5-Difluoro-1H-indole-3-carboxylic acid ((1S,2S)-2-hydroxy-cyclohexyl)-amide (example A.14) and 1-(4-chloromethyl-phenyl)-4-methyl-1H-imidazole (example B.4) and 1-(4-(chloromethyl)phenyl)-3-methyl-1H-pyrazole	465.5

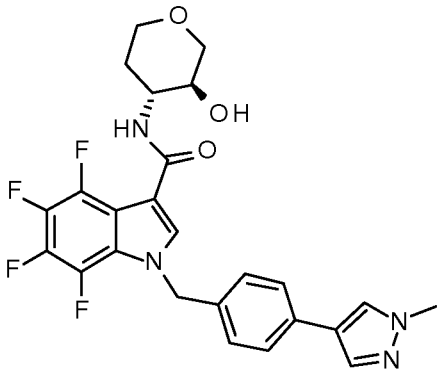
Example 62

4,5,6,7-Tetrafluoro-N-((3S,4R) or (3R,4S))-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

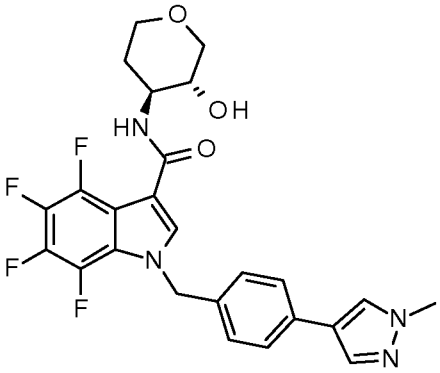
and

Example 63

4,5,6,7-Tetrafluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide



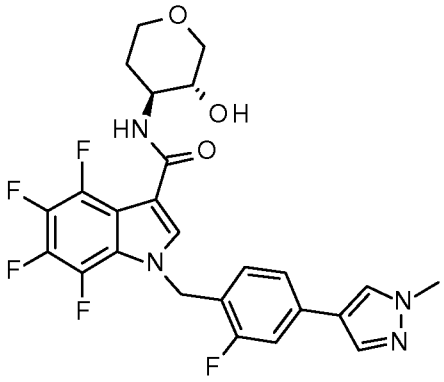
and



In analogy to the procedure described for the synthesis of example 26, the title compounds were prepared from 4,5,6,7-tetrafluoro-lH-indole-3-carboxylic acid ((3RS,4SR)-3-hydroxy-tetrahydro-pyran-4-yl)-amide (example A.13) and 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5) followed by chiral separation on a Reprosil chiral NR column. Example 62: (-) enantiomer, MS (m/e): 503.4 $(M+H)^+$ and example 63: (+) enantiomer, MS (m/e): 503.4 $(M+H)^+$.

Example 64

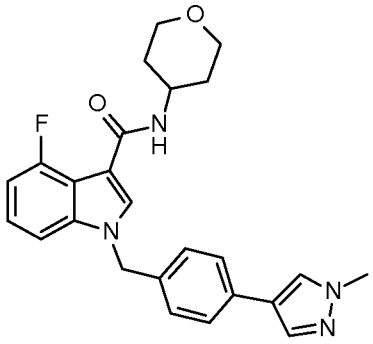
4,5,6,7-Tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R))-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example 26, the title compound was prepared from the chiral version of 4,5,6,7-tetrafluoro-lH-indole-3-carboxylic acid ((3RS,4SR)-3-hydroxy-tetrahydro-pyran-4-yl)-amide (example A.13) and 4-(4-(chloromethyl)-3-fluorophenyl)- 1-methyl- lH-pyrazole (example B.2) followed by purification with separation chromatography with a gradient formed from methylene chloride and methanol (0-5%) to provide 53 mg (44%) of the title compound as a white solid. MS (m/e): 519.5 $(M+H)^+$.

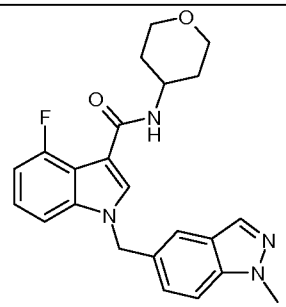
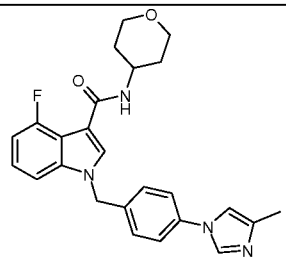
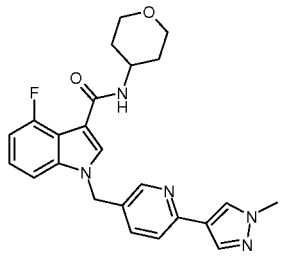
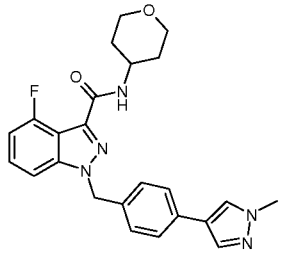
Example 65

Fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



To a suspension of 4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.8) (50 mg, 191 μηοϊ) in N,N-dimethylformamide (500 μΐ) under nitrogen at 0°C was added sodium hydride 60% dispersion in oil (9.15 mg, 229 μηοϊ). The mixture was stirred at 0°C for 15 minutes. After this time, 4-(4-(chloromethyl)phenyl)-l-methyl-lH-pyrazole (example B.5) (39.4 mg, 191 μηοϊ) was added at once. The mixture was stirred under ice-bath cooling for 5 hours, quenched with a 20% ammonium chloride solution and diluted with water. The crude material was purified with flash column chromatography on amine eluting with a gradient formed from n-heptane and ethyl acetate (0 to 80%) to provide 60 mg (73 %) of the title compound as a white solid. MS (m/e): 433.5 $(M+H)^+$.

In analogy to Example 65, compounds 66 to 69 of the following table were prepared by reaction of the indicated amides with an alkylating agent.

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
66		4-fluoro-1-((1-methyl-1H-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.8) and 5-(bromomethyl)-1-methyl-1H-indazole hydrobromide	407.5
67		4-fluoro-1-(4-(4-methyl-1H-imidazol-1-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.8) and 1-(4-chloromethyl-phenyl)-4-methyl-1H-imidazole (example B.4)	433.5
68		4-fluoro-1-((6-(1-methyl-1H-pyrazol-4-yl)yridine-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.8) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.l)	434.4
69		4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indazole-3-carboxamide	4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indazole-3-carboxamide (example A.37) and 4-(4-(chloromethyl)phenyl)-1-methyl-1H-pyrazole (example B.5)	434.5

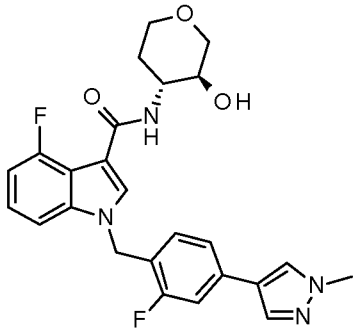
Example 70

4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4R) or (3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

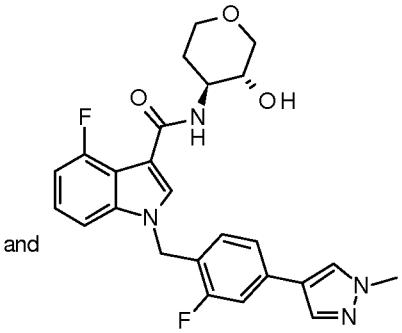
and

Example 71

4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

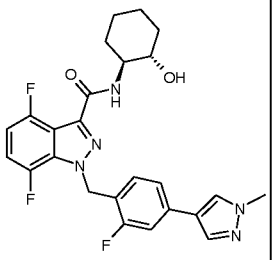


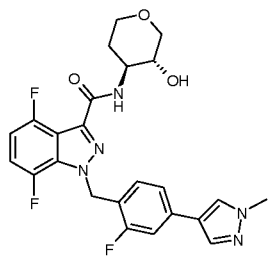
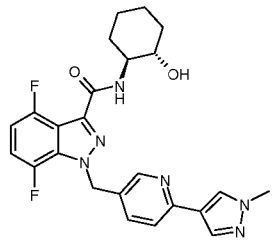
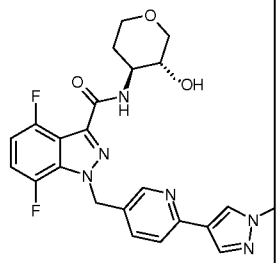
and



4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example 6) (220 mg) was separated on a Reprosil Chiral NR column to provide 94 mg (43%) of the title compound (example 81, (-) enantiomer) as an off-white solid, MS (m/e): 467.3 $(M+H)^+$ and 91 mg (41%) of the compound (example 82, (+) enantiomer) as an off-white solid. MS (m/e): 467.4 $(M+H)^+$.

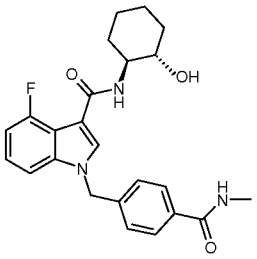
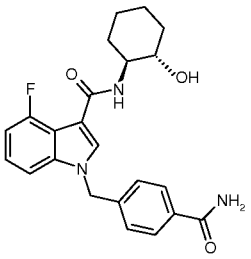
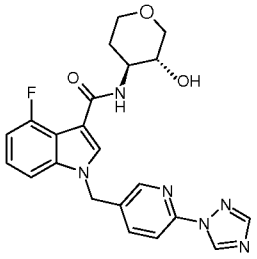
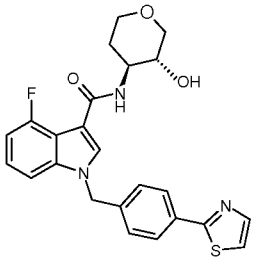
In analogy to example 1, examples 72 to 75 of the following table were prepared by coupling an acid derivative with an amine.

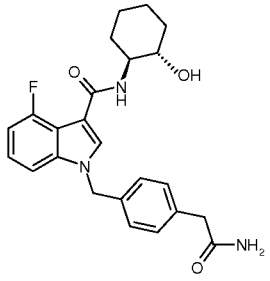
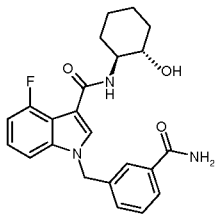
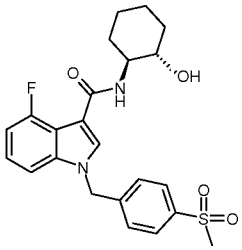
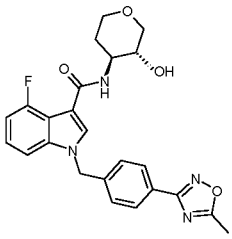
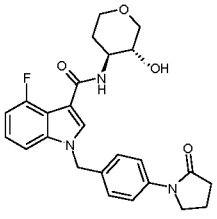
Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
72		4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide	4,7-difluoro-l-(2-fluoro-4-(1-methyl-lH-pyrazol-4-yl)benzyl)-lH-indazole-3-carboxylic acid (example A.15) and (lS,2S)-2-aminocyclohexanol hydrochloride	484.2

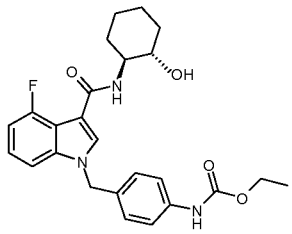
73		4,7-difluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indazole-3-carboxamide	4,7-difluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indazole-3-carboxylic acid (example A.15) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.1)	486.1
74		4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-((6-(1-methyl-1H-pyrazol-4-yl)yridine-3-yl)methyl)-1H-indazole-3-carboxamide	4,7-difluoro-1-[[6-(1-methylpyrazol-4-yl)yridine-3-yl]methyl]indazole-3-carboxylic acid (A.16) and (1S,2S)-2-aminocyclohexanol hydrochloride	469.3
75		4,7-difluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(1-methyl-1H-pyrazol-4-yl)yridine-3-yl)methyl)-1H-indazole-3-carboxamide	4,7-difluoro-1-[[6-(1-methylpyrazol-4-yl)yridine-3-yl]methyl]indazole-3-carboxylic acid (A.16) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.l)	467.3

In analogy to Example 26, compounds 76 to 85 following table were prepared by reaction of the indicated amides with an alkylating agent.

5

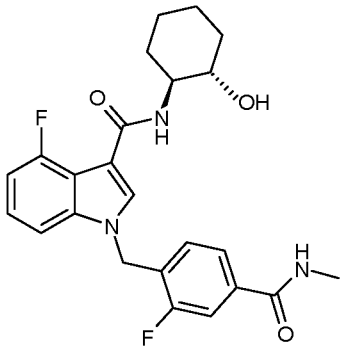
Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
76		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(chloromethyl)-N-methylbenzamide (CAS 220875-88-7)	424.7
77		1-(4-carbamoylbenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-(chloromethyl)benzamide (CAS 84545-14-2)	410.3
78		1-((6-(1H-1,2,4-triazol-1-yl)yridine-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (A.12) and 5-(chloromethyl)-2-(1H-1,2,4-triazol-1-yl)pyridine (CAS 1250524-50-5)	437.3
79		4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(thiazol-2-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (A.12) and 2-(4-(chloromethyl)phenyl)thiazole (CAS 906352-61-2)	452.3

80		1-(4-(2-amino-2-oxoethyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 2-(4-(bromomethyl)phenyl)acetamide (CAS 847486-99-1)	424.3
81		1-(3-carbamoylbenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 3-(chloromethyl)benzamide (CAS 135654-16-9)	410.3
82		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(methylsulfonyl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 1-(bromomethyl)-4-(methylsulfonyl)benzene (CAS 53606-06-7)	445.2
83		4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(5-methyl-1,2,4-oxadiazol-3-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (A.12) and 3-(4-(chloromethyl)phenyl)-5-methyl-1,2,4-oxadiazole (CAS 449209-35-2)	451.3
84		4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(2-oxopyrrolidin-1-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (A.12) and 1-(4-(chloromethyl)phenyl)pyrrolidin-2-one (CAS 36152-29-1)	452.3

85		ethyl 4-((4-fluoro-3-((1S,2S)-2-hydroxycyclohexylcarbamoyl)-1H-indol-1-yl)methyl)phenylcarbamate	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and (4-chloromethyl-phenyl)-carbamic acid ethyl ester (CAS 873372-18-0)	452.4

Example 86

Preparation of 4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



Step 1: Methyl 3-fluoro-4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)benzoate

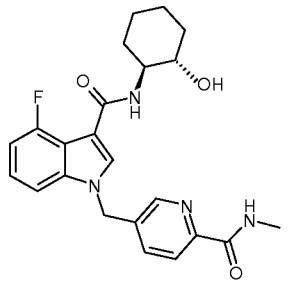
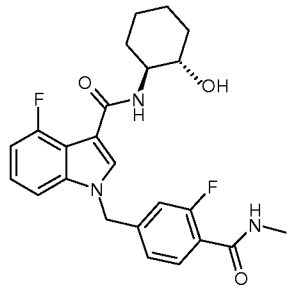
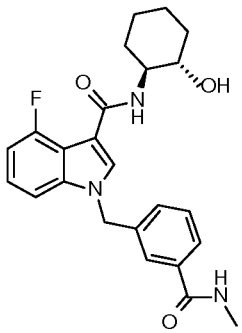
The title compound was obtained in analogy to the procedure described in example 26, reacting 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and 4-bromomethyl-3-fluoro-benzoic acid methyl ester (CAS 128577-47-9). Off-white solid. MS (m/e): 443.5 $(M+H)^+$.

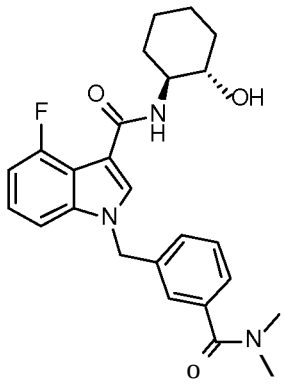
Step 2: 4-Fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

To a stirred suspension of methylamine hydrochloride (22.9 mg, 339 μιηοϊ) at r.t. in dioxane (3 ml) under an argon atmosphere was added trimethylaluminum 2M solution in toluene (170 μϊ, 339 μιηοϊ) in one portion. After stirring for 2 hrs at r.t., methyl 3-fluoro-4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)benzoate (50 mg, 113 μιηοϊ) was added in one portion. The reaction mixture was heated to 100°C and stirring at that temperature was

continued overnight. The orange slurry was cooled to r.t. and treated with 0.5 ml of water. Then, $MgSO_4$ was added. After stirring for 15 min at r.t., the mixture was filtered and the cake was washed with methanol. The filtrate was concentrated. The crude product was purified by silica gel chromatography using a CH_2Cl_2/MeOH gradient as eluent to provide the title compound (18 mg, 36 %) as white solid. MS (m/e): 442.2 $(M+H)^+$.

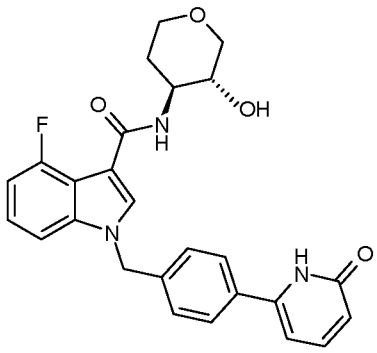
In analogy to Example 86, compounds 87 to 90 of the following table were prepared by reaction of the indicated amides with an alkylating agent, followed by conversion of the ester with methyl- or dimethylamine hydrochloride in the presence of trimethylaluminium.

Expl. No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
87		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-chloromethyl-pyridine-2-carboxylic acid ethyl ester (CAS 39977-48-5), then methylamine hydrochloride	425.3
88		4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and methyl 4-(bromomethyl)-2-fluorobenzoate (CAS 85070-57-1), then methylamine hydrochloride	442.3
89		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(3-(methylcarbamoyl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and methyl 3-(bromomethyl)benzoate (CAS 1129-28-8), then methylamine hydrochloride	424.3

90		l-(3-(dimethylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)- 1H-indole-3-carboxamide (example A.6) and methyl 3-(bromomethyl)benzoate (CAS 1129-28-8), then dimethylamine hydrochloride	438.3

Example 91

Preparation of 4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



Step 1: l-(4-Bromobenzyl)-4-fluoro-N-((3R,4S)-3-hvdroxytetrahvdro-2H-pyran-4-yl)-lH-indole-3-carboxamide

The title compound was obtained in analogy to the procedures described in example 26, reacting 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.12) and 1-bromo-4-(chloromethyl)benzene. White solid. MS (m/e): 447.1 $(M+H)^+$.

Step 2: 4-fluoro-N-((3R,4S)-3-hvdroxytetrahydro-2H-pyran-4-yl)- l-(4-(6-methoxypyridin-2-yl)benzyl)-lH-indole-3-carboxamide

To a solution of l-(4-bromobenzyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (128 mg, 286 μηοϊ) and 6-methoxypyridin-2-ylboronic acid (65.7 mg, 429 μηοϊ) in 1,2-dimethoxyethane (2 ml) under an argon atmosphere was added cesium carbonate (186 mg, 572 μηοϊ), water (0.2 ml) and tetrakis(triphenylphosphine)palladium(0) (9.9 mg, 8.6 μηοϊ). The reaction mixture was stirred at 90° overnight, cooled to r.t and concentrated.

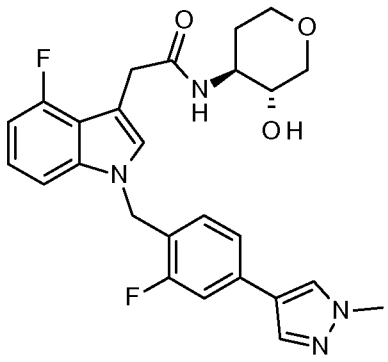
The crude product was purified by silica gel chromatography using a CH_2Cl_2/MeOH gradient as eluent to provide the title compound (92 mg, 68%) as a white solid. MS (m/e): 476.3 $(M+H)^+$.

Step 3: 4-Fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hvdroxycvclohexyl)-lH-indole-3-carboxamide

To a solution of 4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(6-methoxy-pyridin-2-yl)benzyl)-lH-indole-3-carboxamide (50 mg, 105 μηοϊ) in acetonitrile (0.6 ml) at r.t under an argon atmosphere was added sodium iodide (23 mg, 155 μηοϊ) and trimethylchlorosilane (17 mg, 20.2 μϊ, 158 μηοϊ). To this mixture was added dropwise a solution of acetonitrile (0.1 ml)/water (52 μϊ). The mixture was stirred at 60° for 7 hrs. After cooling to r.t. the mixture was poured on 10% aqueous Na_2S20_3 solution and extracted with CH_2C1_2. The organic phase was washed with water, dried over $MgS0_4$, filtered and concentrated. The crude product was purified by silica gel chromatography using a CH_2Cl_2/MeOH gradient as eluent to provide the title compound (15 mg, 28%) as a white solid. MS (m/e): 462.3 $(M+H)^+$.

Example 92

2-[4-Fluoro-l-[[2-fluoro-4-(l-methylpyrazol-4-yl)phenyl]methyl]indol-3-yl]-N-[(3R,4S)-3-hydroxyoxan-4-yl]acetamide



Step 1: Ethyl 2-(4-fluoro-lH-indol-3-yl)acetate

To a stirred mixture of 4-fluoro-lH-indole (1 g, 7.4 mmol) and ethyl 2-diazoacetate (1.06 g, 973 μϊ, 9.25 mmol) in dichloromethane (50 ml) was added at r.t. and under an argon atmosphere copper(II)trifluoromethanesulfonate (134 mg, 370 μηοϊ) (exothermic). The mixture was stirred at r.t overnight, then diluted with CH_2C1_2, washed with water, dried over $MgS0_4$, filtered and evaporated. The crude product was purified by silica gel chromatography using a heptane/EtOAc gradient as eluent to obtain the title compound as a mixture with the isomeric

ethyl 2-(4-fluoroindol-l-yl)acetate (815 mg) which was used in the next step without further purification. MS (m/e): 222.2 $(M+H)^+$.

Step 2: Ethyl 2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)acetate

To a stirred solution of ethyl 2-(4-fluoro-lH-indol-3-yl)acetate (0.8 g, 2.17 mmol) in N,N-dimethylacetamide (10 ml) was added at r.t. and under an argon atmosphere 4-(4-(chloromethyl)-3-fluorophenyl)-l-methyl-lH-pyrazole (487 mg, 2.17 mmol) and cesium carbonate (707 mg, 2.2 mmol). The mixture was stirred at r.t overnight, then diluted with EtOAc and washed with water. The aqueous layer was back extracted with EtOAc. The combined organics were washed with water, dried over MgS04, filtered and evaporated. The crude product was purified by silica gel chromatography using a heptane/EtOAc gradient as eluent to obtain the title compound (548 mg, 62%) as a colorless viscous oil. MS (m/e): 410.3 $(M+H)^+$.

Step 3: 2-(4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)acetic acid

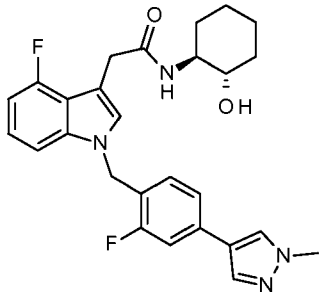
To a suspension of ethyl 2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)acetate (0.54 g, 1.32 mmol) in MeOH (1.5 ml) and THF (1.5 ml) was added at r.t. and under an argon atmosphere potassium hydroxide solution 1 M in water (2.64 ml, 2.64 mmol). The mixture was stirred at 75° for 4 hrs, then cooled to r.t.. 2M HC1 in water (2.64 ml, 5.3 mmol) was added under stirring at 0°. The mixture was stirred at r.t for 30 min. The precipitate was filtered, washed with water, collected and dried to provide the title compound (475 mg, 94%) as an off-white solid. MS (m/e): 382.3 $(M+H)^+$.

Step 4: 2-r4-Fluoro- l-rr2-fluoro-4-(l-methylpyrazol-4-yl)phenyllmethyllindol-3-yll-N-r(3R,4S)-3-hydroxyoxan-4-yll acetamide

To a solution of 2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)acetic acid (50 mg, 131 μιηοϊ) in DMF (1 ml) was added at r.t. and under an argon atmosphere (3R,4S)-4-aminotetrahydro-2H-pyran-3-ol hydrochloride (20.1 mg, 131 μιηοϊ), DIEA (50.8 mg, 68.7 μϊ, 393 μιηοϊ) and HATU (59.8 mg, 157 μιηοϊ). The yellow solution was stirred at r.t overnight. The mixture was poured on water and extracted with EtOAc. The organic layer was washed with water, dried with $MgS0_4$, filtered and evaporated. The crude product was purified by silica gel chromatography using a CH_2Cl_2/MeOH gradient as eluent to obtain the title compound (30 mg, 48%) as a white solid. MS (m/e): 481.3 $(M+H)^+$.

Example 93

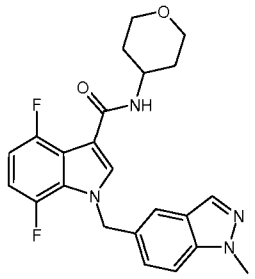
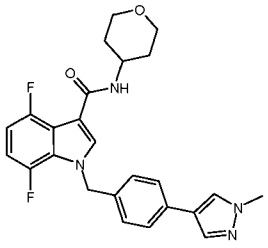
Preparation of 2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)-N-((lS,2S)-2-hydroxycyclohexyl)acetamide

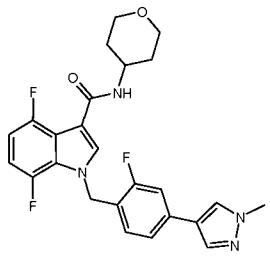
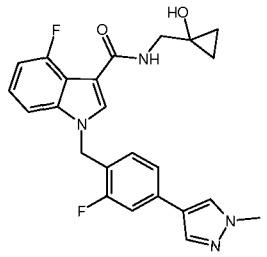
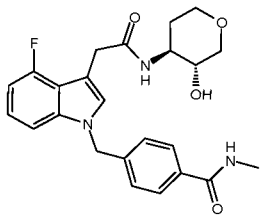
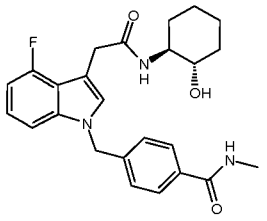


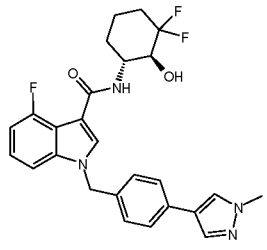
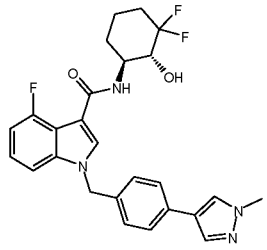
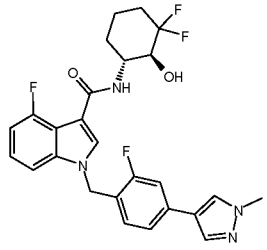
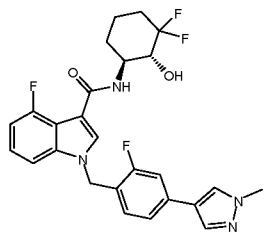
The title compound was obtained in analogy to the procedures described in example 92. Off-white solid. MS (m/e): 479.3 $(M+H)^+$.

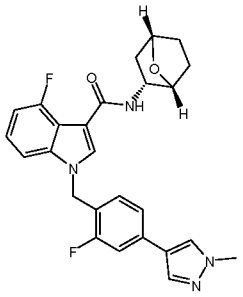
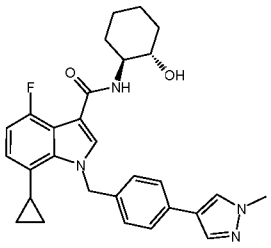
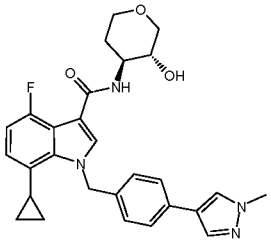
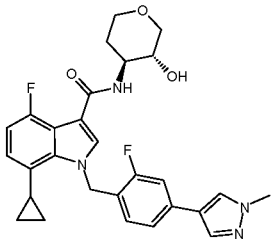
Examples 94 to 131

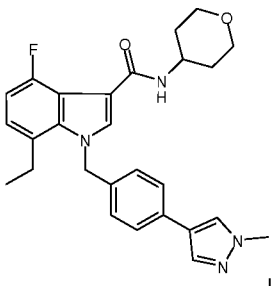
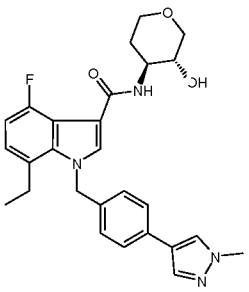
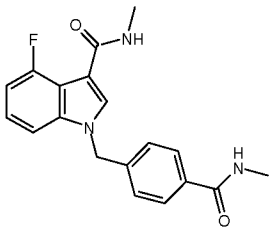
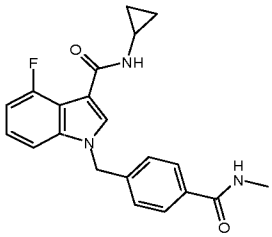
In analogy to example 1, examples 94 to 131 of the following table were prepared by coupling an acid derivative with an amine.

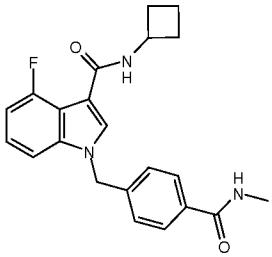
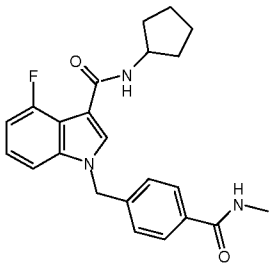
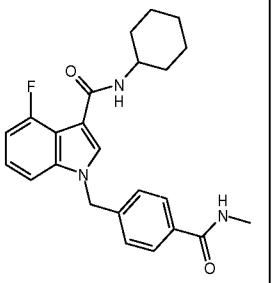
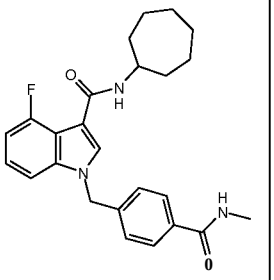
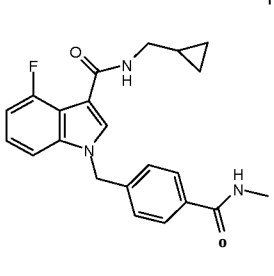
Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
94		4,7-difluoro-1-((1-methyl-1H-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4,7-difluoro-1-((1-methyl-1H-indazol-5-yl)methyl)-1H-indole-3-carboxylic acid (example A.17) and tetrahydro-pyran-4-yl-amine	425.3
95		4,7-difluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4,7-difluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.18) and tetrahydro-pyran-4-yl-amine	451.3

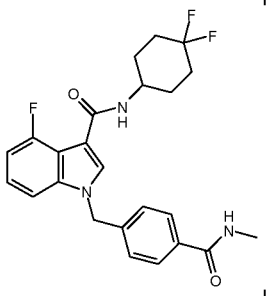
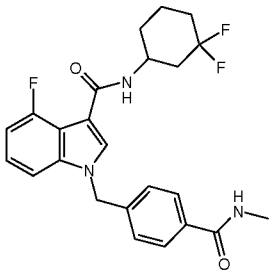
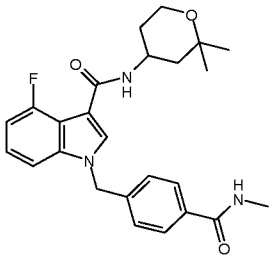
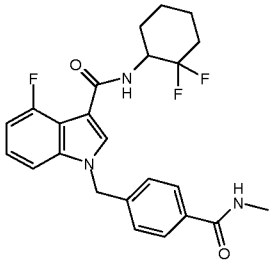
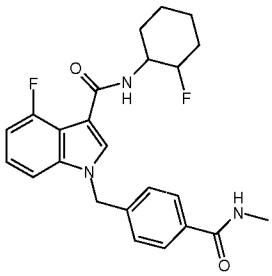
96		4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide	4,7-difluoro-l-(2-fluoro-4-(1-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.19) and tetrahydro-pyran-4-yl-amine	469.3
97		4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((l-hydroxycyclopropyI)methyl)-1H-indole-3-carboxamide	4-fluoro- l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.l) and 1-(aminomethyl)cyclopropanol	437.3
98		4-((4-fluoro-3-(2-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-ylamino)-2-oxoethyl)-lH-indol- 1-yl)methyl)-N-methylbenzamide	2-(4-fluoro-l-(4-(methylcarbamoyl)benzyl)-lH-indol-3-yl)acetic acid (example A.20) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.l)	440.3
99		4-((4-fluoro-3-(2-((lS,2S)-2-hydroxycyclohexylamino)-2-oxoethyl)-lH-indol- 1-yl)methyl)-N-methylbenzamide	2-(4-fluoro-l-(4-(methylcarbamoyl)benzyl)-lH-indol-3-yl)acetic acid (example A.20) and (3R,4S)-4-aminotetrahydro-2H-pyran-3-ol hydrogen chloride	438.4

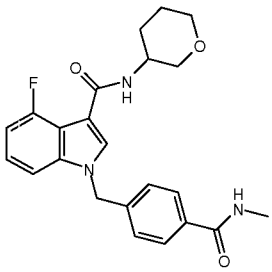
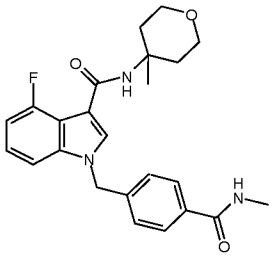
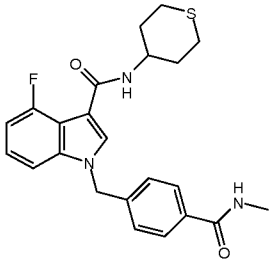
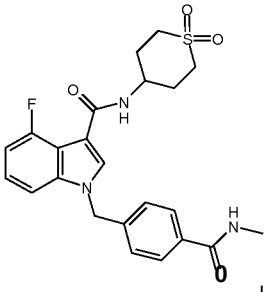
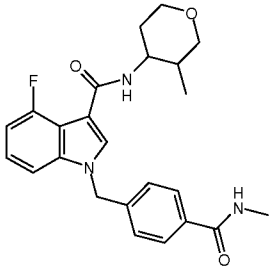
100		N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide	4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.9) and (lS,6R)-6-amino-2,2-difluorocyclohexanol (CAS 1109284-40-3)	483.3
101		N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide	(R)4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.9) and (lR,6S)-6-amino-2,2-difluorocyclohexanol	483.3
102		N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide	4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.l) and (lS,6R)-6-amino-2,2-difluorocyclohexanol (CAS 1109284-40-3)	501.3
103		N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxylic acid (example A.l) and (lR,6S)-6-amino-2,2-difluorocyclohexanol	501.3

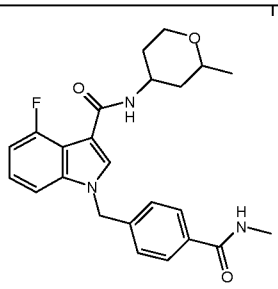
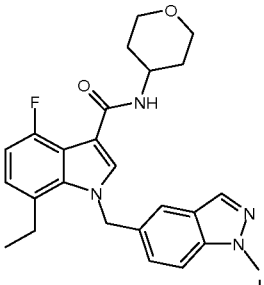
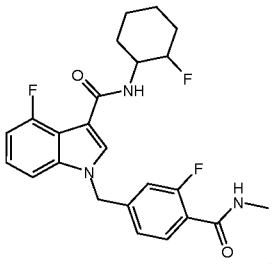
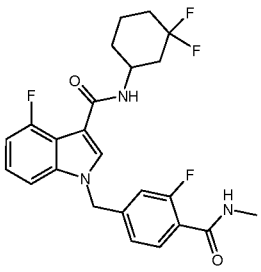
104		N-((endo)-7-oxabicyclo[2.2.1]heptan-2-yl)-4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.1) and (endo)-7-oxabicyclo[2.2.1]heptan-2-amine dihydrochloride	463.2
105		7-cyclopropyl-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	7-cyclopropyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.21) and (3R,4S)-4-aminotetrahydro-2H-pyran-3-ol hydrogen chloride	487.3
106		7-cyclopropyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	7-cyclopropyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.21) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.1)	489.3
107		7-cyclopropyl-4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	7-cyclopropyl-4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.22) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.1)	507.3

108		7-ethyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	7-ethyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.23) and tetrahydro-pyran-4-yl-amine	461.3
109		7-ethyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	7-ethyl-4-fluoro-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxylic acid (example A.23) and (3R,4S)-4-aminotetrahydropyran-3-ol hydrochloride (example C.1)	477.3
110		4-fluoro-N-methyl-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and methylamine hydrochloride	340
111		N-cyclopropyl-4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and cyclopropylamine	365.6

112		N-cyclobutyl-4-fluoro-l-[[4-(methylcarbamoyl) phenyl] methyl] indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and cyclobutylamine	380
113		N-cyclopentyl-4-fluoro-l-[[4-(methylcarbamoyl) phenyl] methyl] indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and cyclopentylamine	394
114		N-cyclohexyl-4-fluoro-l-[[4-(methylcarbamoyl) phenyl] methyl] indole-3-carboxamide	**4-fluoro-l**-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and cyclohexylamine	408
115		N-cycloheptyl-4-fluoro-l-[[4-(methylcarbamoyl) phenyl] methyl] indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and cycloheptylamine	422
116		N-(cyclopropylmethyl)-4-fluoro-l-[[4-(methylcarbamoyl) phenyl] methyl] indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and (cyclopropylmethyl) amine	380

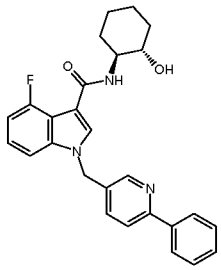
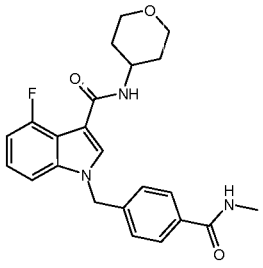
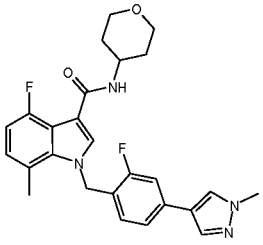
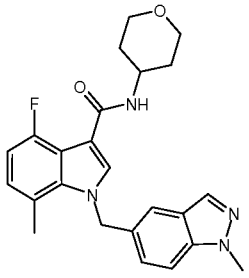
117		N-(4,4-difluorocyclohexyl)-4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 4,4-difluorocyclohexan-1-amine	444
118		N-(3,3-difluorocyclohexyl)-4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 3,3-difluorocyclohexan-1-amine hydrochloride	444
119		N-(2,2-dimethyloxan-4-yl)-4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 2,2-dimethyloxan-4-amine	438
120		N-(2,2-difluorocyclohexyl)-4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 2,2-difluorocyclohexan-1-amine	444
121		4-fluoro-N-(2-fluorocyclohexyl)-1-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 2-fluorocyclohexan-1-amine	426

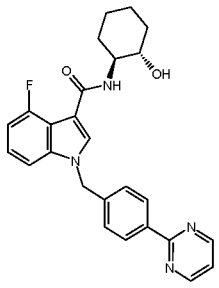
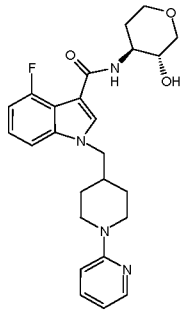
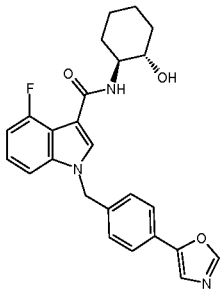
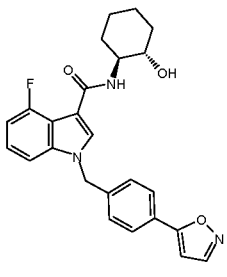
122		4-fluoro-l-[[4-(methylcarbamoyl) phenyl]methyl]-N-(oxan-3-yl)indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and oxan-3-amine	410
123		4-fluoro-l-[[4-(methylcarbamoyl) phenyl]methyl]-N-(4-methyloxan-4-yl)indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 4-methyloxan-4-amine	424
124		4-fluoro-l-[[4-(methylcarbamoyl) phenyl]methyl]-N-(thian-4-yl)indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and thian-4-amine	426
125		N-(l,l-dioxothian-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl) phenyl]methyl]indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 4-aminotetrahydrothiopyrandioxide	458
126		4-fluoro-l-[[4-(methylcarbamoyl) phenyl]methyl]-N-(3-methyloxan-4-yl)indole-3-carboxamide	4-fluoro-l-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 3-methyloxan-4-amine	424

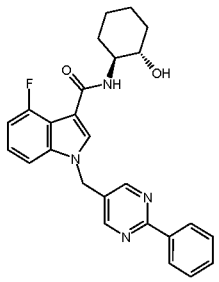
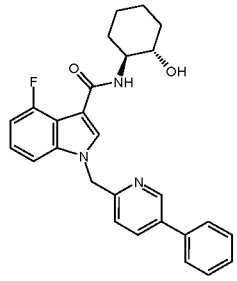
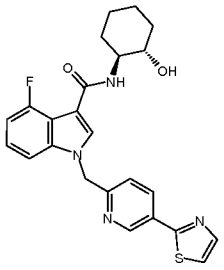
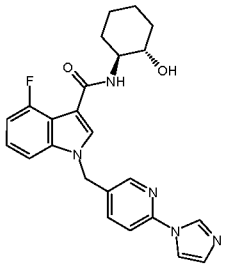
127		4-fluoro-1-[[4-(methylcarbamoyl) phenyl]methyl]-N-(2-methyloxan-4-yl)indole-3-carboxamide	4-fluoro-1-{[4-(methylcarbamoyl) phenyl] methyl}-1H-indole-3-carboxylic acid (example A.24) and 2-methyloxan-4-amine	424
128		7-ethyl-4-fluoro-1-((1-methyl-1H-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	7-ethyl-4-fluoro-1-((1-methyl-1H-indazol-5-yl)methyl)-1H-indole-3-carboxylic acid (example A.25) and tetrahydro-pyran-4-yl-amine	435.4
129		4-fluoro-1-(3-fluoro-4-(methylcarbamoyl) benzyl)-N-(2-fluorocyclohexyl)-1H-indole-3-carboxamide	4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxylic acid (example A.26) and 2-fluorocyclohexan-1-amine	444.3
130		N-(3,3-difluorocyclohexyl)-4-fluoro-1-(3-fluoro-4-(methylcarbamoyl) benzyl)-1H-indole-3-carboxamide	4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxylic acid (example A.26) and 3,3-difluorocyclohexan-1-amine hydrochloride	462.3

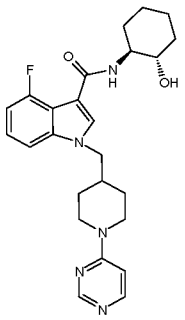
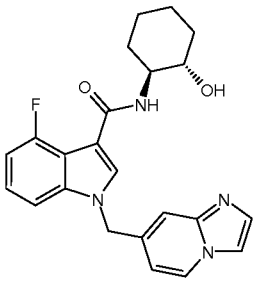
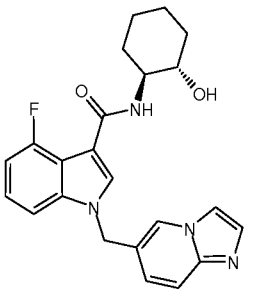
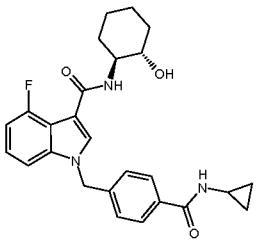
Examples 131 to 154

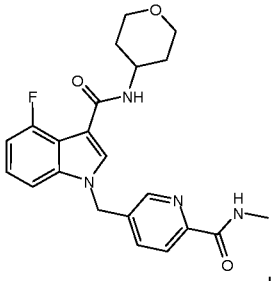
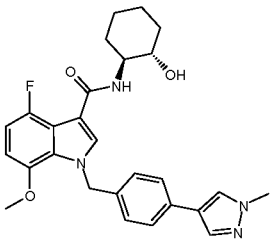
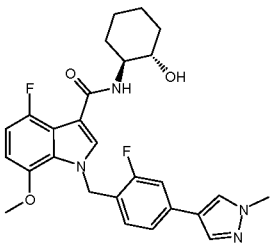
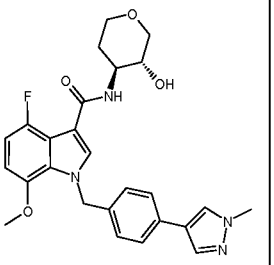
In analogy to example 26, examples 131 to 154 of the following table were prepared by reaction of the indicated amides with an alkylating agent.

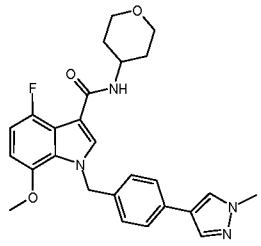
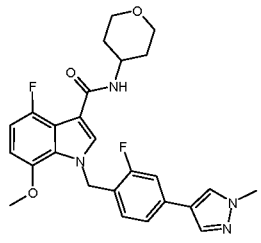
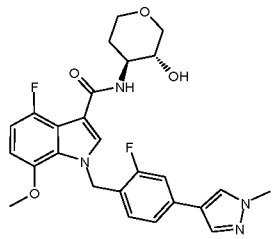
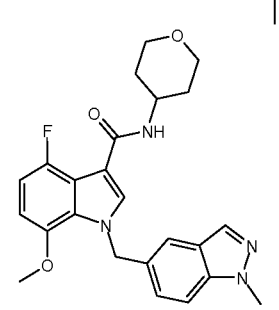
Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
131		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-phenylpyridin-3-yl)methyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 2-chloromethyl-5-phenylpyridine (CAS 146775-28-2)	444.4
132		4-fluoro-1-(4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-Fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.8) and 4-(chloromethyl)-N-methylbenzamide (example B.6)	410.3
133		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-7-methyl-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid (tetrahydro-pyran-3-yl)-amide (example A.11) and 4-(4-(Chloromethyl)-3-fluorophenyl)-1-methyl-1H-pyrazole (example B.2)	465.3
134		4-fluoro-7-methyl-1-((1-methyl-1H-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-7-methyl-1H-indole-3-carboxylic acid (tetrahydro-pyran-3-yl)-amide (example A.11) and 5-(bromomethyl)-1-methyl-1H-indazole hydrobromide	421.3

135		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(pyrimidin-2-yl)benzyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 2-[4-(chloromethyl)phenyl] pyrimidine	445.3
136		4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1-((1-(pyridin-2-yl)piperidin-4-yl)methyl)-1H-indole-3-carboxamide	4-Fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.34) and [1-(2-pyridyl)-4-piperidyl]methyl methanesulfonate (CAS 199117-81-2)	453.3
137		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(oxazol-5-yl)benzyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(4-bromomethyl-phenyl)-oxazole (example B.8)	434.3
138		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(isoxazol-5-yl)benzyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(4-bromomethyl-phenyl)-isoxazole (CAS 169547-50-6)	434.3

139		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((2-phenylpyrimidin-5-yl)methyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(chloromethyl)-2-phenyl-pyrimidine	445.3
140		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((5-phenylpyridin-2-yl)methyl)-1H-indole-3-carboxamideyl)benzyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 2-chloromethyl-5-phenylpyridine (CAS 146775-28-2)	444.3
141		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((5-(thiazol-2-yl)pyridin-2-yl)methyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 2-(4-(chloromethyl)phenyl) thiazole (example B.9)	451.3
142		1-((6-(1H-imidazol-1-yl)pyridin-3-yl)methyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 5-(chloromethyl)-2-(1H-imidazol-1-yl)pyridine	434.2

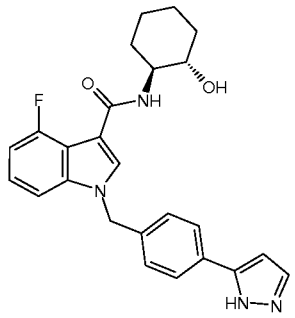
143		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((1-(pyrimidin-4-yl)piperidin-4-yl)methyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and (1-(pyrimidin-4-yl)piperidin-4-yl)methyl methanesulfonate (example B.10)	452.4
144		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(imidazo[1,2-a]pyridin-7-ylmethyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 7-(chloromethyl)imidazo[1,2-a]pyridine	407.3
145		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(imidazo[1,2-a]pyridin-6-ylmethyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 6-(chloromethyl)imidazo[1,2-a]pyridine hydrochloride	407.3
146		1-(4-(cyclopropylcarbamoyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide	4-Fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.6) and 4-chloromethyl-N-cyclopropyl-benzamide (CAS 873371-67-6)	450.2

147		4-fluoro-1-((6-(methylcarbamoyl) pyridin-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide (example A.8) and 5-(chloromethyl)-N-methylpicolinamide (example B.11)	411.2
148		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-7-methoxy-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-7-methoxy-1H-indole-3-carboxamide (example A.27) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.1)	477.3
149		4-fluoro-1-(2-fluoro-4-(1-methyl-1H-pyrazol-4-yl)benzyl)-N-((1S,2S)-2-hydroxycyclohexyl)-7-methoxy-1H-indole-3-carboxamide	4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-7-methoxy-1H-indole-3-carboxamide (example A.27) and 4-(4-(chloromethyl)-3-fluorophenyl)-1-methyl-1H-pyrazole (example B.2)	495.2
150		4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide	4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-1H-indole-3-carboxamide (example A.28) and 5-(chloromethyl)-2-(1-methyl-1H-pyrazol-4-yl)pyridine (example B.1)	479.2

151		4-fluoro-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide	4-fluoro-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.29) and 5-(chloromethyl)-2-(1-methyl-lH-pyrazol-4-yl)pyridine (example B.l)	463.2
152		4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide	4-fluoro-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.29) and 4-(4-(chloromethyl)-3-fluorophenyl)-1-methyl-1H-pyrazole (example B.2)	481.2
153		4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-lH-indole-3-carboxamide	4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-1H-indole-3-carboxamide (example A.28) and 4-(4-(chloromethyl)-3-fluorophenyl)-1-methyl-1H-pyrazole (example B.2)	497.2
154		4-fluoro-7-methoxy-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide	4-fluoro-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.29) and 5-(bromomethyl)-1-methyl-lH-indazole hydrobromide	437.2

Example 155

l-(4-(lH-Pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide



Step 1: 4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-(4-methoxybenzyl)-lH-pyrazol-5-yl)benzyl)-lH-indole-3-carboxamide

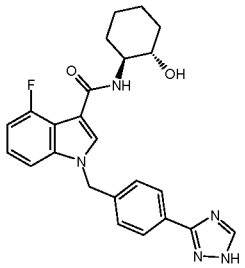
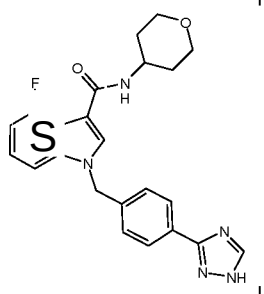
In analogy to the procedure described for the synthesis of example 26, the title compound was prepared from 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and 5-(4-(chloromethyl)phenyl)-l-(4-methoxybenzyl)-lH-pyrazole (example B.12). White solid. MS (m/e): 553.5 $(M+H)^+$.

Step 2: l-(4-(lH-pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

A mixture of 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-(4-methoxybenzyl)-lH-pyrazol-5-yl)benzyl)-lH-indole-3-carboxamide (95 mg, 172 μmol) and 10 % palladium on activated charcoal (91.5 mg, 86.0 μηοΐ) at room temperature in EtOH (3 ml) and acetic acid (3.00 ml) was stirred under a hydrogen atmosphere (balloon pressure) for 17 hours. The catalyst was filtered and rinsed with EtOH. The filtrate was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound as a white solid (11.9 mg, 16 %). MS (m/e): 433.3 $(M+H)^+$.

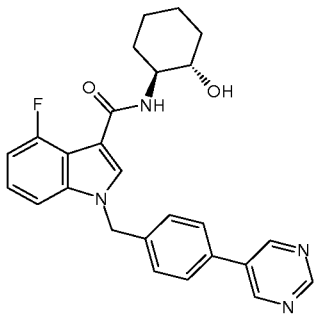
Examples 156 and 157

In analogy to the procedures described for the synthesis of example 155, examples 156 and 157 of the following table were prepared by the reaction of the indicated amides with an alkylating agent, followed by hydrogenation.

Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
156		l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide	4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.6) and 3-(4-(chloromethyl)phenyl)_1.(4. methoxybenzyl)- 1H-1,2,4-triazole (example B.13)	433.5
157		l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide	4-Fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.8) and 3-(4-(chloromethyl)phenyl) .1.(4. methoxybenzyl)- 1H-1,2,4-triazole (example B.13)	420.3

Example 158

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-5-yl)benzyl)-lH-indole-3-carboxamide

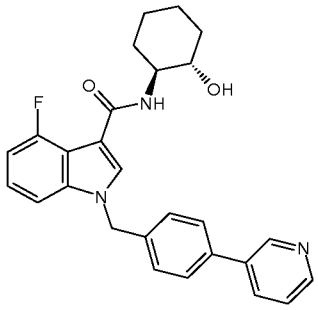


To a solution of l-(4-bromobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.30) (0.1 g, 225 μηοϊ) and pyrimidin-5-ylboronic acid (41.7 mg, 337

μηοϊ) in 1,2-dimethoxyethane (2 ml) under argon was added cesium carbonate (146 mg, 449 μηοϊ), water (0.2 ml) and tetrakis(triphenylphosphine)palladium(0) (7.78 mg, 6.74 μηοϊ). The mixture was stirred at 90°C for 17 hours, cooled to room temperature and filtered. The cake was rinsed with dchloromethane. The filtrate was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound as a white solid (48.3 mg, 43 %). MS (m/e): 445.3 $(M+H)^+$.

Example 159

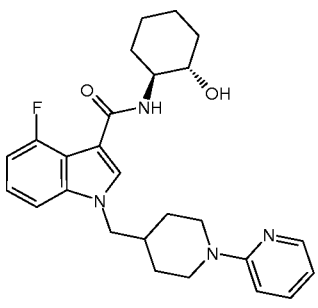
4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyridin-3-yl)benzyl)-lH-indole-3-carboxamide



In analogy to the procedure described for the synthesis of example 158, the title compound was prepared by the reaction of l-(4-bromobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide (example A.30) and pyridin-3-ylboronic acid. Off-white solid. MS (m/e): 444.3 $(M+H)^+$.

Example 160

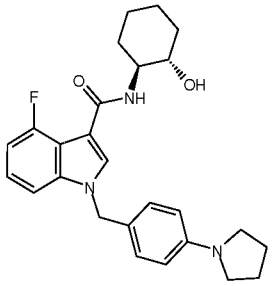
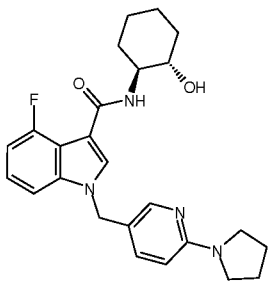
4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide



To a stirred mixture of 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(piperidin-4-ylmethyl)-lH-indole-3-carboxamide (example A.31) (150 mg, 402 μηοϊ), 2-bromopyridine (63.5 mg, 38.5 μϊ, 402 μmol), potassium carbonate (99.9 mg, 723 μηο) and water (15.2 mg, 15.2 μϊ, 843 μηοϊ) in xylene (9 ml) at room temperature under argon were added palladium(II) acetate (3.61 mg, 16.1 μηοϊ) and 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (11.6 mg, 20.1 μηοϊ). The reaction mixture was degassed and back-filled with argon (3 times). The mixture was then heated to 140°C for 17 hours, cooled to room temperature, diluted with dichloromethane, stirred at room temperature for 5 min and filtered. The filtrate was concentrated and the residue was purified with flash column chromatography on silica eluting with a gradient formed from dichloromethane and methanol (0 to 5 %) to provide the title compound as an off-white solid (27 mg, 15 %). MS (m/e): 451.3 $(M+H)^+$.

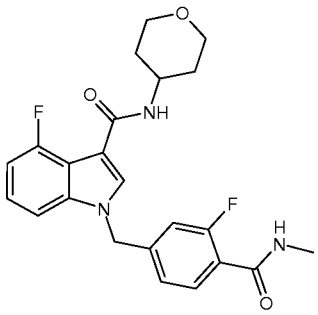
Example 161 and 162

In analogy to the procedure described for the synthesis of example 160, examples 161 and 162 of the following table were prepared.

Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
161		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(pyrrolidin-1-yl)benzyl)-1H-indole-3-carboxamide	1-(4-bromobenzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.30) and pyrrolidine	436.4
162		4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-((6-(pyrrolidin-1-yl)pyridin-3-yl)methyl)-1H-indole-3-carboxamide	1-((6-bromopyridin-3-yl)methyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide (example A.32) and pyrrolidine	437.4

Example 163

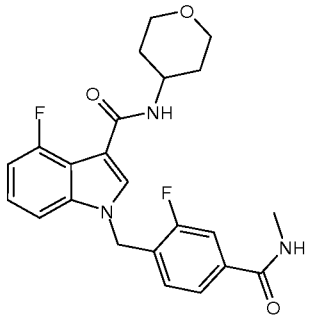
4-Fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



The title compound was obtained in analogy to the procedure described in example 86, reacting methyl 2-fluoro-4-((4-fluoro-3-(tetrahydro-2H-pyran-4-ylcarbamoyl)-lH-indol-l-yl)methyl)benzoate (example A.33) and methylamine hydrochloride. White solid. MS (m/e): 423.3 $(M+H)^+$.

Example 164

4-Fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide



Step 1: methyl 3-fluoro-4-((4-fluoro-3-(tetrahydro-2H-pyran-4-ylcarbamoyl)-lH-indol-l-yPmethyPbenzoate

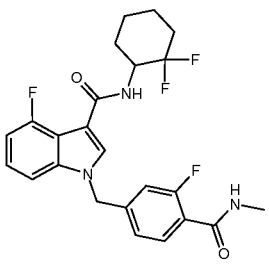
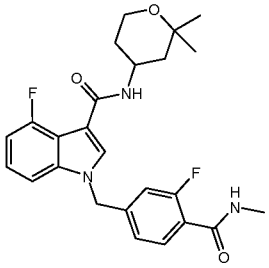
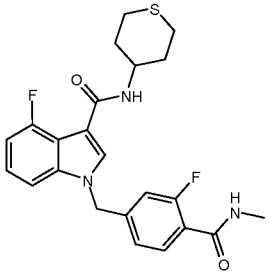
The title compound was obtained in analogy to the procedure described in example 26, reacting 4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide (example A.8) and methyl 4-(bromomethyl)-3-fluorobenzoate (CAS 128577-47-9). Off-white solid. MS (m/e): 429.3 $(M+H)^+$.

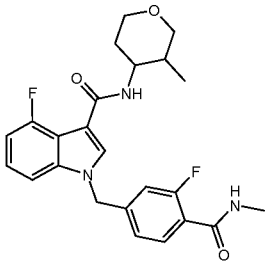
Step 2: 4-Fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

The title compound was obtained in analogy to the procedure described in example 86, reacting methyl 3-fluoro-4-((4-fluoro-3-(tetrahydro-2H-pyran-4-ylcarbamoyl)-lH-indol-l-yl)methyl)benzoate and methylamine hydrochloride. White solid. MS (m/e): 428.3 $(M+H)^+$.

Examples 165 to 168

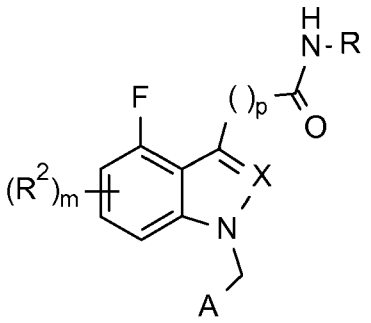
In analogy to example 1, examples 165 to 168 of the following table were prepared by coupling an acid derivative with an amine.

Example No.	Structure	Systematic Name	Starting materials	MW found (MH^+)
165		N-(2,2-difluorocyclohexyl)-4-fluoro-l-(3-fluoro-4-(methylcarbamoyl) benzyl)- lH-indole-3-carboxamide	4-Fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxylic acid (example A.26) and 2,2-difluorocyclohexan- 1-amine	462.2
166		N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-4-fluoro- 1-(3-fluoro-4-(methylcarbamoyl) benzyl)- lH-indole-3-carboxamide	4-Fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxylic acid (example A.26) and 2,2-dimethyloxan-4-amine	456.2
167		4-fluoro-l-(3-fluoro-4-(methylcarbamoyl) benzyl)-N-(tetrahydro-2H-thiopyran-4-yl)-lH-indole-3-carboxamide	4-Fluoro- 1-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxylic acid (example A.26) and thian-4-amine	444.2

168		4-fluoro-1-(3-fluoro-4-(methylcarbamoyl) benzyl)-N-(3-methyltetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide	4-Fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-1H-indole-3-carboxylic acid (example A.26) and 3-methyloxan-4-amine	442.3

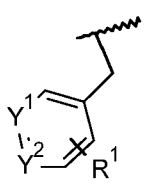
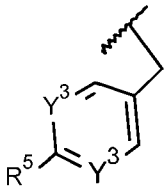
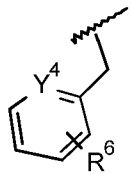
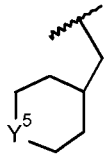
Claims

1. A compound of formula I



I

wherein

A is  ,  ,  or  ;

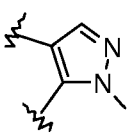
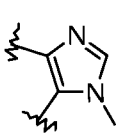
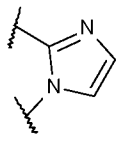
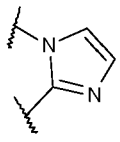
R is lower alkyl, -$(CH_2)_z$-C_{3-7}-cycloalkyl or -$(CH_2)_z$- C_{4-6}-heterocycloalkyl, which are optionally substituted by one to tree hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2.1]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

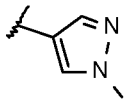
Y^3 is N;

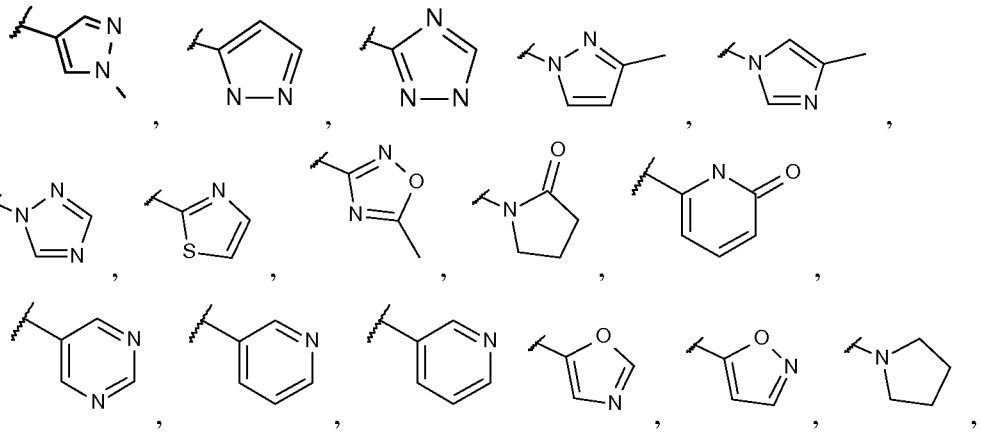
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, -C(0)NH_2, -C(0)$NHCH_3$ or -C(0)$N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of  , or is phenyl, -C(0)NH_2, -CH_2C(0)NH_2, -C(0)$NHCH_3$, -C(0)NH-cycloalkyl, -C(0)$N(CH_3)_2$, -NHC(0)0-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or S(0)$_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

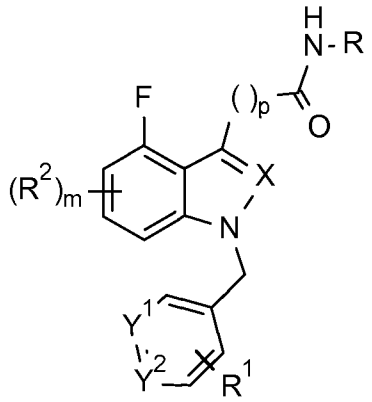
p is 0 or 1;

m is 1, 2 or 3;

z is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

2. Compounds of formula IA according to claim 1



IA

wherein

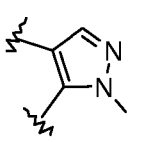
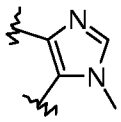
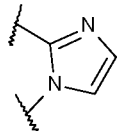
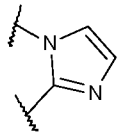
R is lower alkyl, -$(CH_2)_z$-C_{3-7}-cycloalkyl or -$(CH_2)_z$- C_{4-6}-heterocycloalkyl, which are optionally substituted by one to three hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2. l]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or $Y^1$and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

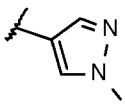
Y^3 is N;

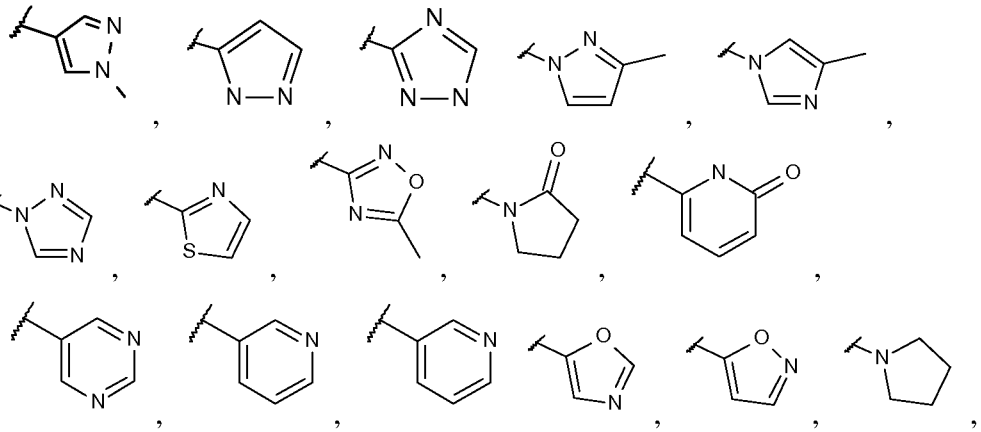
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, -C(0)NH_2, -C(0)$NHCH_3$ or -C(0)$N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of  , or is phenyl, $-C(0)NH_2$, $-CH_2C(0)NH_2$, $-C(0)NHCH_3$, -C(0)NH-cycloalkyl, $-C(0)N(CH_3)_2$, -NHC(0)0-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or $S(0)_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

p is 0 or 1;

m is 1, 2 or 3;

z is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

3. A compound of formula IA according to claim 2, which compounds are

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide 4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lR,2R)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide

4,6-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-

hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4RS)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)- lH-indazole-3-carboxamide

4-fluoro-N-[(3S,4R)-4-methoxyoxolan-3-yl]-l-[[4-(l-methylpyrazol-4-yl)phenyl]methyl]indole-3-carboxamide

N-(3,3-difluorocyclobutyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

(R)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((tetrahydrofuran-2-yl)methyl)-lH-indole-3-carboxamide

N-cyclobutyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-3-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(oxetan-2-ylmethyl)-lH-indole-3-carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3RS,4SR)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4- (1-methyl- 1H-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2SR)-2-hydroxy-2-methylcyclohexyl)-lH-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

N-cyclohexyl-4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4S)-4-hydroxytetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-

indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lSR,2RS)-2-hydroxy-2-methylcyclohexyl)-lH-indole-3-carboxamide

4-fluoro- 1-(2-fluoro-4-(1-methyl- 1H-pyrazol-4-yl)benzyl)-N-((1S,2R)-2-hydroxycyclopentyl)-lH-indole-3-carboxamide

N-(2,2-difluorocyclohexyl)-4-fluoro- 1-(2-fluoro-4-(1-methyl- lH-pyrazol-4-yl)benzyl)- 1H-indole-3-carboxamide

4,5,6,7-tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro- l-(2-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(difluoromethoxy)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(1-methyl- lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-methoxybenzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro- l-(3-fluoro-4-methoxybenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(trifluoromethoxy)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(l -methyl- lH-pyrazol-4-yl)benzyl)- lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

l-(4-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-chlorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3-cyanobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,4-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(4-fluorobenzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(3,5-difluorobenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(1-methyl-1H-pyrazol-4-yl)benzyl)-1H-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

l-benzyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-3-yl)-lH-indole-3-carboxamide

4-fluoro-7-methyl-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1-(4-(3-methyl-1H-pyrazol-1-yl)benzyl)-1H-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-methyl-lH-indazol-5-yl)methyl)-lH-indole-3-carboxamide

4,5,6,7-tetrafluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

l-(4-cyanobenzyl)-4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-methyl-lH-benzo[d]yridine-5-yl)methyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l-methyl-lH-pyrazol-4-yl)pyridine-3-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-lH-indole-3-carboxamide

4,5-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(3-methyl-lH-pyrazol-l-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-N-((3S,4R) or (3R,4S))-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4,5,6,7-Tetrafluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R))-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

Fluoro-l-(4-(l -methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(4-methyl-lH-imidazol-l-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3S,4R) or (3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S) or (3S,4R)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indazole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((6-(l-methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-lH-indazole-3-carboxamide

4,7-difluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(l -methyl-lH-pyrazol-4-yl)yridine-3-yl)methyl)-lH-indazole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylcarbamoyl)benzyl)-lH-indole-3-

carboxamide

l-(4-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-((6-(lH-l,2,4-triazol-l-yl)yridine-3-yl)methyl)-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(thiazol-2-yl)benzyl)-lH-indole-3-carboxamide

1-(4-(2-amino-2-oxoethyl)benzyl)-4-fluoro-N-((1S,2S)-2-hydroxycyclohexyl)-1H-indole-3-carboxamide

l-(3-carbamoylbenzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(methylsulfonyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(5-methyl-l,2,4-oxadiazol-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(2-oxopyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

ethyl 4-((4-fluoro-3-((lS,2S)-2-hydroxycyclohexylcarbamoyl)-lH-indol-l-yl)methyl)phenylcarbamate

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-1H-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(3-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

1-(3-(dimethylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

2-[4-fluoro-l-[[2-fluoro-4-(l-methylpyrazol-4-yl)phenyl]methyl]indol-3-yl]-N-[(3R,4S)-3-hydroxyoxan-4-yl]acetamide

2-(4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indol-3-yl)-N-((lS,2S)-2-hydroxycyclohexyl)acetamide

4,7-difluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4,7-difluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-((4-fluoro-3-(2-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-ylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

4-((4-fluoro-3-(2-((lS,2S)-2-hydroxycyclohexylamino)-2-oxoethyl)-lH-indol-l-yl)methyl)-N-methylbenzamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lR,2S)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

N-((lS,2R)-3,3-difluoro-2-hydroxycyclohexyl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)- lH-indole-3-carboxamide

N-((endo)-7-oxabicyclo[2.2.1]heptan-2-yl)-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

7-cyclopropyl-4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

7-ethyl-4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-methyl- 1-[[4- (methylcarbamoyl)phenyl]methyl]indole-3-carboxamide

N-cyclopropyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-cyclobutyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-cyclopentyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-cyclohexyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-cycloheptyl-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-(cyclopropylmethyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-(4,4-difluorocyclohexyl)-4-fluoro- 1-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-(3,3-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-(2,2-dimethyloxan-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
N-(2,2-difluorocyclohexyl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
4-fluoro-N-(2-fluorocyclohexyl)-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(oxan-3-yl)indole-3-carboxamide
4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(4-methyloxan-4-yl)indole-3-carboxamide
4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(thian-4-yl)indole-3-carboxamide
N-(l,l-dioxothian-4-yl)-4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]indole-3-carboxamide
4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(3-methyloxan-4-yl)indole-3-carboxamide
4-fluoro-l-[[4-(methylcarbamoyl)phenyl]methyl]-N-(2-methyloxan-4-yl)indole-3-carboxamide
7-ethyl-4-fluoro-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide
4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(2-fluorocyclohexyl)-lH-indole-3-carboxamide
N-(3,3-difluorocyclohexyl)-4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide
4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-phenylpyridin-3-yl)methyl)-lH-indole-3-carboxamide
4-fluoro-l-(4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide
4-fluoro-l-(2-fluoro-4-(l -methyl- lH-pyrazol-4-yl)benzyl)-7-methyl-N-(tetrahydro-2H-pyran-4-yl)- lH-indole-3 -carboxamide

4-fluoro-7-methyl-1-((1-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-1H-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-2-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(oxazol-5-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(isoxazol-5-yl)benzyl)-lH-indole-3-carboxamide

l-((6-(lH-imidazol-l-yl)pyridin-3-yl)methyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-7-ylmethyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(imidazo[l,2-a]pyridin-6-ylmethyl)-lH-indole-3-carboxamide

l-(4-(cyclopropylcarbamoyl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

4-fluoro-l-((6-(methylcarbamoyl)pyridin-3-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((lS,2S)-2-hydroxycyclohexyl)-7-methoxy-1H-indole-3-carboxamide

4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-7-methoxy-l-(4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-7-methoxy-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-fluoro-l-(2-fluoro-4-(l-methyl-lH-pyrazol-4-yl)benzyl)-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-7-methoxy-1H-indole-3-carboxamide

4-fluoro-7-methoxy-l-((l-methyl-lH-indazol-5-yl)methyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

l-(4-(lH-Pyrazol-5-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-lH-indole-3-carboxamide

l-(4-(lH-l,2,4-triazol-3-yl)benzyl)-4-fluoro-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrimidin-5-yl)benzyl)-lH-indole-3-carboxamide

4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyridin-3-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-(4-(pyrrolidin-l-yl)benzyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((6-(pyrrolidin-l-yl)pyridin-3-yl)methyl)-lH-indole-3-carboxamide

4-Fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

4-Fluoro-1-(2-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide

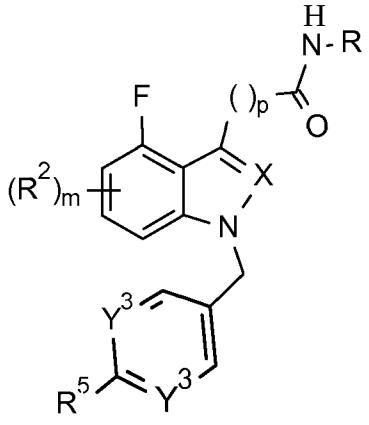
N-(2,2-difluorocyclohexyl)-4-fluoro-1-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

N-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-lH-indole-3-carboxamide

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(tetrahydro-2H-thiopyran-4-yl)-lH-indole-3-carboxamide or

4-fluoro-l-(3-fluoro-4-(methylcarbamoyl)benzyl)-N-(3-methyltetrahydro-2H-pyran-4-yl)-lH-indole-3-carboxamide.

4. A compound of formula IB according to claim 1,



IB

wherein

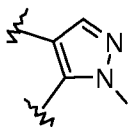
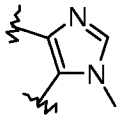
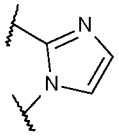
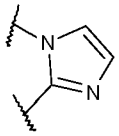
R is lower alkyl, -$(CH_2)_z$-C_{3-7}-cycloalkyl or -$(CH_2)_z$- C_{4-6}-heterocycloalkyl, which are optionally substituted by one to tree hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2.1]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

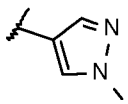
Y^3 is N;

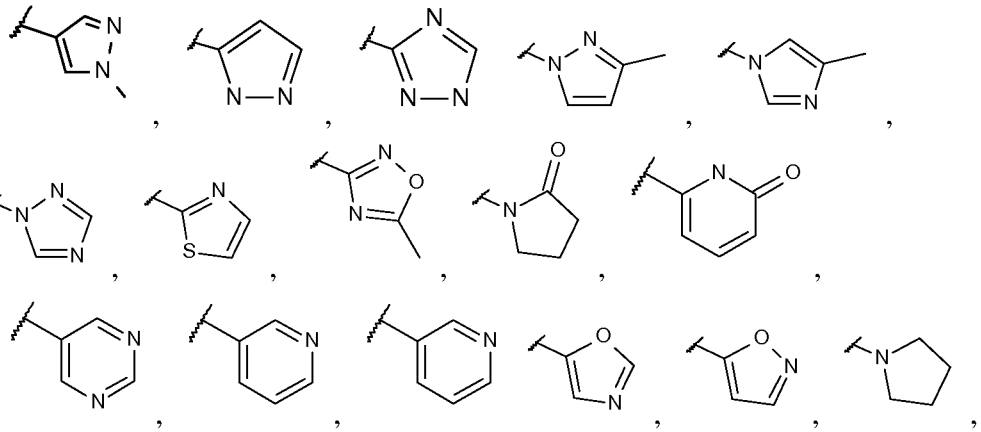
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, -C(0)NH_2, -C(0)$NHCH_3$ or -C(0)$N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of 

or is phenyl, -C(0)NH_2, -CH_2C(0)NH_2, -C(0)NHCH_3, -C(0)NH-cycloalkyl, -C(0)N$(CH_3)_2$, -NHC(0)0-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or S(0)$_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

p is 0 or 1;

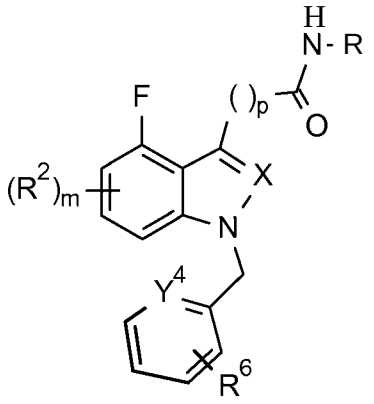
m is 1, 2 or 3;

z is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

5. A compound of formula IB according to claim 4, which compound is 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((2-phenylpyrimidin-5-yl)methyl)-lH-indole-3-carboxamide.

6. A compound of formula IC according to claim 1



IC

wherein

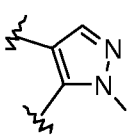
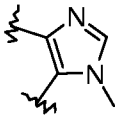
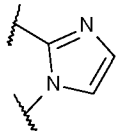
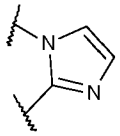
R is lower alkyl, -$(CH_2)_z$-C_{3-7}-cycloalkyl or -$(CH_2)_z$- C_{4-6}-heterocycloalkyl, which are optionally substituted by one to tree hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2.1]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

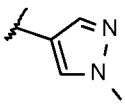
Y^3 is N;

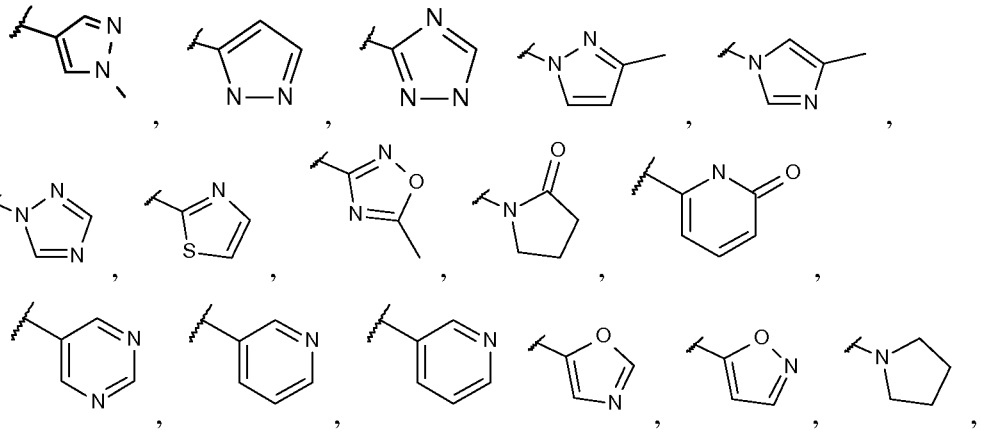
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, -$C(0)NH_2$, -$C(0)NHCH_3$ or -$C(0)N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of  , or is phenyl, $-C(0)NH_2$, $-CH_2C(0)NH_2$, $-C(0)NHCH_3$, -C(0)NH-cycloalkyl, $-C(0)N(CH_3)_2$, $-NHC(0)0$-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or $S(0)_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

p is 0 or 1;

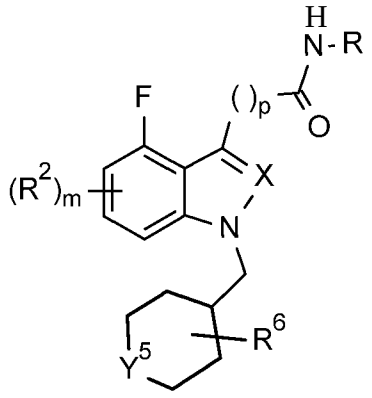
m is 1, 2 or 3;

z is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

7. A compound of formula IC according to claim 6, which compounds are 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((2-phenylpyrimidin-5-yl)methyl)-lH-indole-3-carboxamide or 4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((5-(thiazol-2-yl)pyridin-2-yl)methyl)-lH-indole-3-carboxamide.

8. A compound of formula ID according to claim 1



ID

wherein

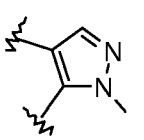
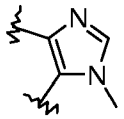
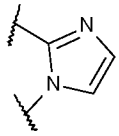
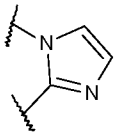
R is lower alkyl, -$(CH_2)_z$-C_{3-7}-cycloalkyl or -$(CH_2)_z$-C_{4-6}-heterocycloalkyl, which are optionally substituted by one to tree hydroxy, lower alkyl, lower alkoxy or halogen, or is (endo)-7-oxabicyclo[2.2.1]heptan-2-yl;

X is CH or N;

Y^1 is CR^3 or N;

Y^2 is CR^4; or

or Y^1 and Y^2 may form together with the carbon atoms to which they are attach

 ,  ;  or  ;

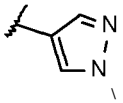
Y^3 is N;

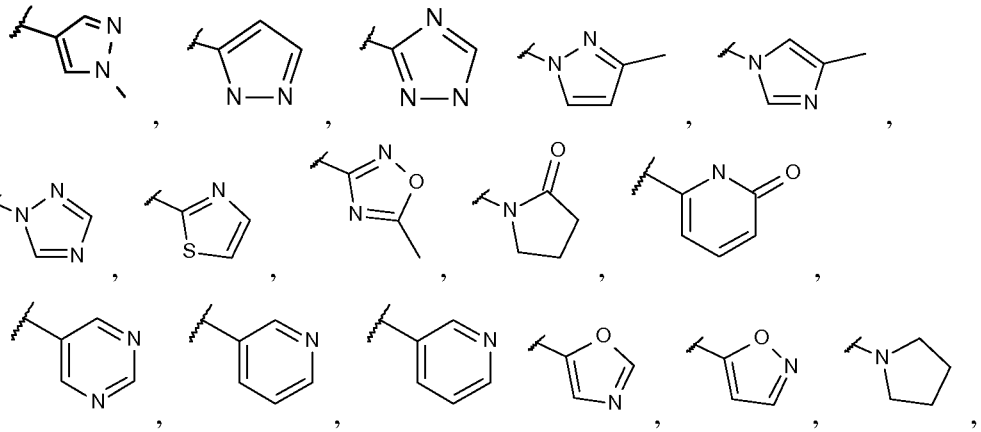
Y^4 is N;

Y^5 is NR^7;

R^1 is hydrogen or halogen;

R^2 is hydrogen, halogen, cycloalkyl, lower alkyl or lower alkoxy;

R^3 is hydrogen, halogen,  , CN, $-C(0)NH_2$, $-C(0)NHCH_3$ or $-C(0)N(CH_3)_2$;

R^4 is hydrogen, a 5 or 6 membered heteroaryl or heterocyclyl group, selected from the group consisting of  , or is phenyl, $-C(0)NH_2$, $-CH_2C(0)NH_2$, $-C(0)NHCH_3$, -C(0)NH-cycloalkyl, $-C(0)N(CH_3)_2$, -NHC(0)0-lower alkyl, CN, lower alkoxy, lower alkoxy substituted by halogen, halogen or $S(0)_2CH_3$;

R^5 is phenyl;

R^6 is phenyl or thiazol-2-yl;

R^7 is pyridin-2-yl or pyrimidin-4-yl;

p is 0 or 1;

m is 1, 2 or 3;

z is 0 or 1;

or a pharmaceutically acceptable acid addition salt, a racemic mixture or its corresponding enantiomer and/or optical isomers thereof.

9. A compound of formula ID according to claim 8, which compounds are

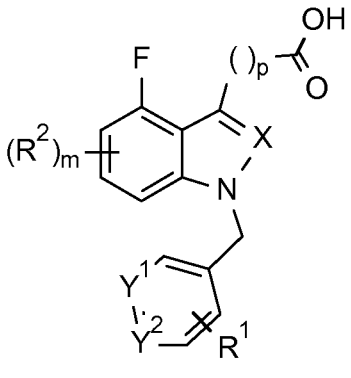
4-fluoro-N-((3R,4S)-3-hydroxytetrahydro-2H-pyran-4-yl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide

4-fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyrimidin-4-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide or

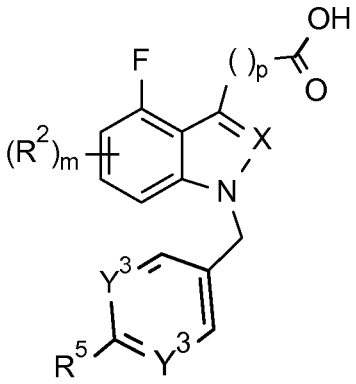
4-Fluoro-N-((lS,2S)-2-hydroxycyclohexyl)-l-((l-(pyridin-2-yl)piperidin-4-yl)methyl)-lH-indole-3-carboxamide.

10. A process for the manufacture of a compound of formula I as defined in any one of claims 1 to 9, which process comprises

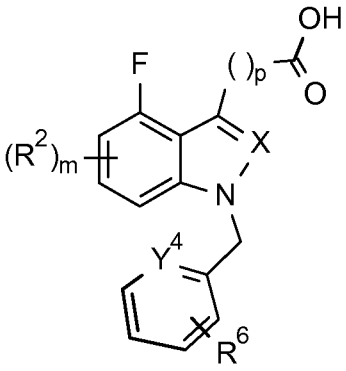
a) reacting a compound of formula



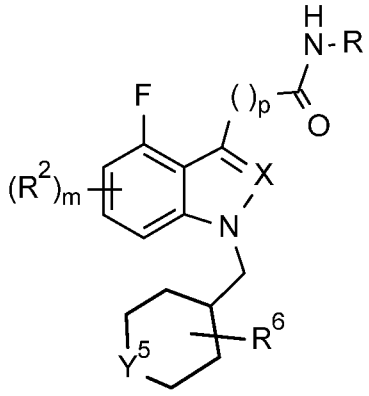
IIA,



IIB,



IIC or



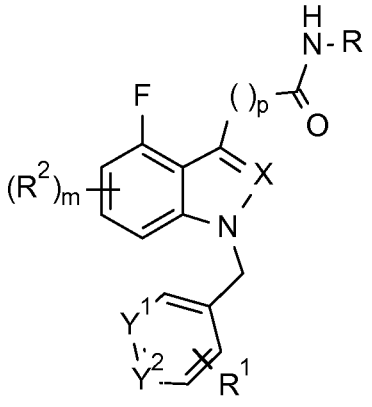
IID

with a compound of formula

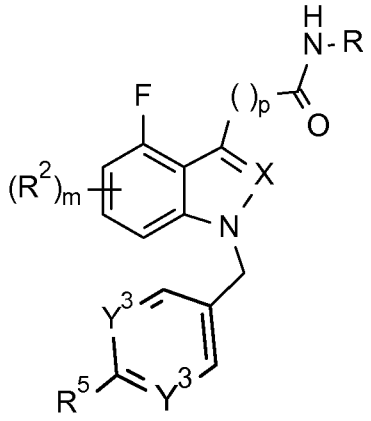
RNH_2

in the presence of an activating agent such as BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate or thionyl chloride

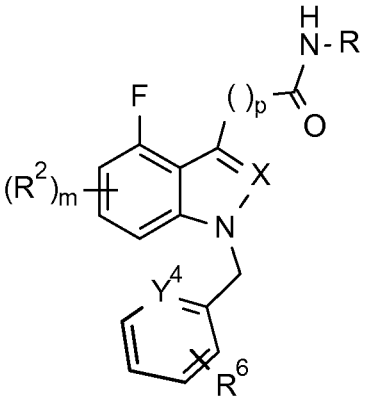
to a compound of formulas



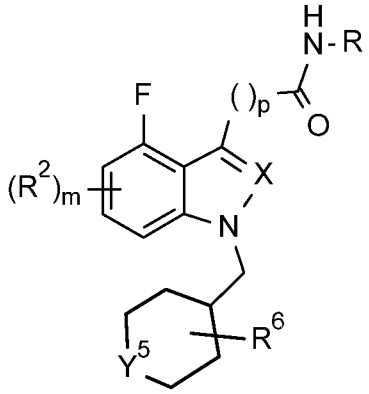
IA,



IB,



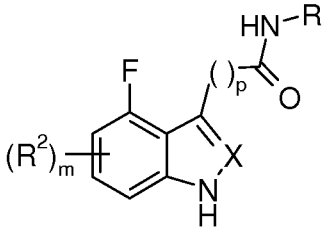
IC or



ID,

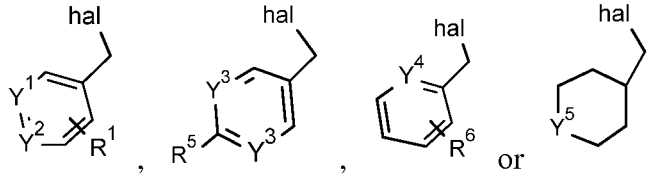
wherein the substituents are as defined in claim 1, or

b) reacting a compound of formula

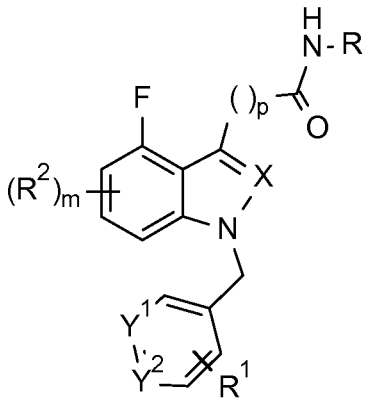


III

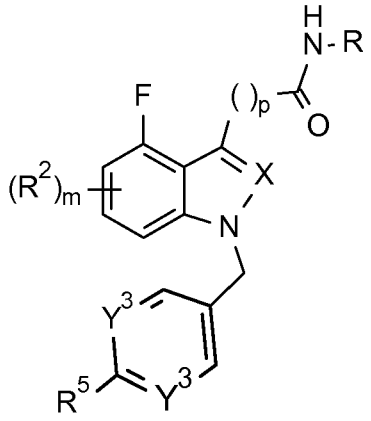
with a compound of formulas



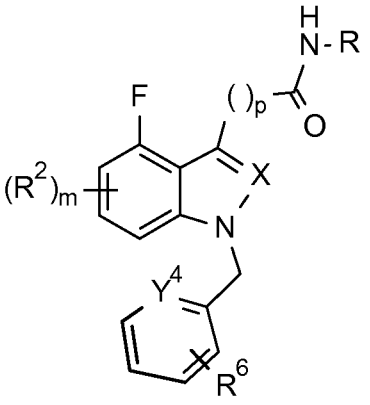
; in the presence of base like cesium carbonate or sodium hydride to a compound of formulas



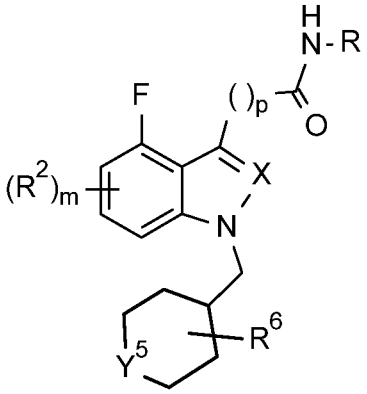
IA,



IB,



IC or



ID,

wherein Hal is halogen and the other substituents are as defined in claim 1, and, if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

11. A compound according to any one of claims 1 to 9, when manufactures by a process according to claim 10.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutical acceptable carrier and/or adjuvant.

13. Pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutical acceptable carrier and/or adjuvant for use in the treatment of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

14. Compounds according to any one of claims 1 to 9 for use as therapeutic active substances.

15. Compounds according to any one of claims 1 to 9 for use as therapeutic active substances in the treatment of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

16. The use of a compound according to any one of claims 1 to 9 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

17. A method for the treatment or prophylaxis of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders, .which method comprises administering an effective amount of a compound as defined in any one of claim 1 to 9.

18. The use of a compound according to any one of claims 1 to 9 for the treatment or prophylaxis of Alzheimer's disease, cognitive impairment, schizophrenia, pain or sleep disorders.

19. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/070092

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 10
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/070092

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/42 C07D403/10 C07D405/12 C07D405/14 C07D413/14
C07D417/14 C07D471/04 A61K31/404 A61K31/416 A61P25/28
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/106795 A1 (UNIV VANDERBILT [US]) 18 July 2013 (2013-07-18)	1-18
Y	Abstract; claims; examples, e.g. compounds B8, B9, B28.	1-18

Y	WO 2011/084368 A1 (MERCK SHARP & DOHME [US]; KUDUK SCOTT D [US]; SCHLEGEL KELLY-ANN [US];) 14 July 2011 (2011-07-14) Abstract; claims; examples.	1-18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" documentwhich may throw doubts on priority claim(s) orwhich is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2014	27/11/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/070092

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013106795 A1	18-07-2013	US 2014206676 A1	24-07-2014
		WO 2013106795 A1	18-07-2013
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		TW 201130824 A	16-09-2011
		US 2012252808 A1	04-10-2012
		WO 2011084368 A1	14-07-2011

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 19

Claim 19 is unclear to such an extend (Article 6 PCT) that the claim has not been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.