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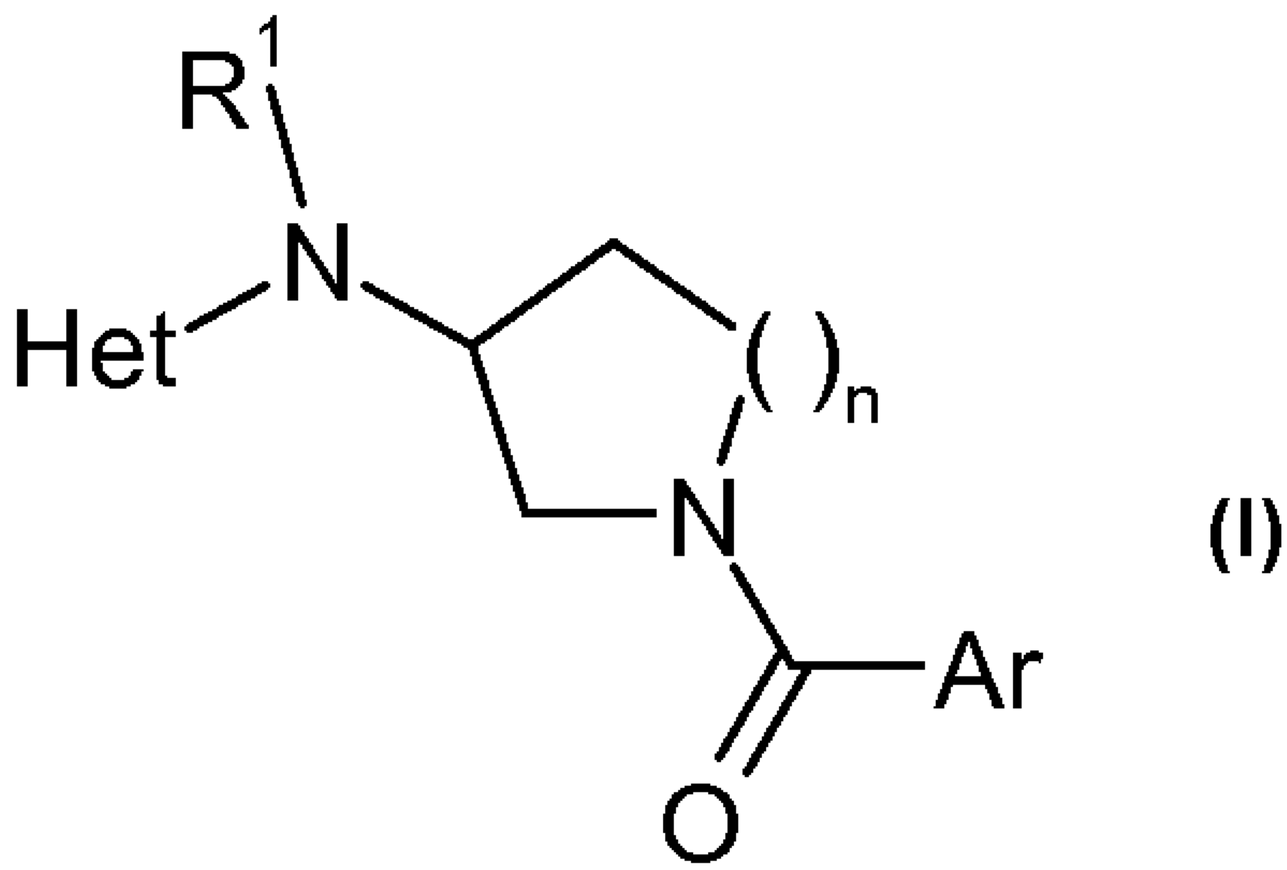
(54) Titre : DERIVES HETEROARYLES EN TANT QU'ANTAGONISTES DU RECEPTEUR A OREXINE
(54) Title: HETEROARYL DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS



(I)

(57) Abrégé/Abstract:
The present invention relates to compounds of Formula (I), wherein Ar is an unsubstituted or substituted aryl or heteroaryl group, wherein the aryl and the heteroaryl group may be substituted by one or more substituents R^2; R^2 is hydroxy, halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen, C(O)-lower alkyl, nitro, NR'R'', cyano, S-lower alkyl, SO_2-lower alkyl, cycloalkyl, heterocycloalkyl, phenyloxy, benzyloxy, phenyl, NH-phenyl or heteroaryl, wherein the phenyl and heteroaryl group is unsubstituted or substituted by one or more substituents selected from lower alkyl or halogen; R'/R'' are independently from each other hydrogen or lower alkyl; R^1 is hydrogen or lower alkyl; Het is a heteroaryl group, unsubstituted or substituted by one or more substituents selected from R^3; R^3 is hydroxy, halogen, =O, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, phenyl, lower alkoxy substituted by halogen, nitro, cyano, SO_2-lower alkyl, cycloalkyl or heterocycloalkyl; n is 1 or 2; or to pharmaceutically suitable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof. It has been found that the compounds of formula (I) are orexin receptor antagonists and the related compounds may be useful in the treatment of sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder or sleep disorders associated with neurological diseases.

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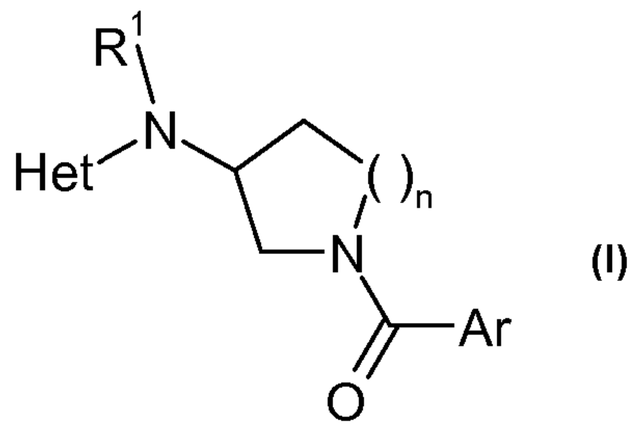
(54) Title: HETEROARYL DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS



(I)

(57) Abstract: The present invention relates to compounds of Formula (I), wherein Ar is an unsubstituted or substituted aryl or heteroaryl group, wherein the aryl and the heteroaryl group may be substituted by one or more substituents R^2; R^2 is hydroxy, halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen, C(O)-lower alkyl, nitro, NR'R", cyano, S-lower alkyl, SO_2-lower alkyl, cycloalkyl, heterocycloalkyl, phenyloxy, benzyloxy, phenyl, NH-phenyl or heteroaryl, wherein the phenyl and heteroaryl group is unsubstituted or substituted by one or more substituents selected from lower alkyl or halogen; R'/R" are independently from each other hydrogen or lower alkyl; R^1 is hydrogen or lower alkyl; Het is a heteroaryl group, unsubstituted or substituted by one or more substituents selected from R^3; R^3 is hydroxy, halogen, =O, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, phenyl, lower alkoxy substituted by halogen, nitro, cyano, SO_2-lower alkyl, cycloalkyl or heterocycloalkyl; n is 1 or 2; or to pharmaceutically suitable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof. It has been found that the compounds of formula (I) are orexin receptor antagonists and the related compounds may be useful in the treatment of sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder or sleep disorders associated with neurological diseases.

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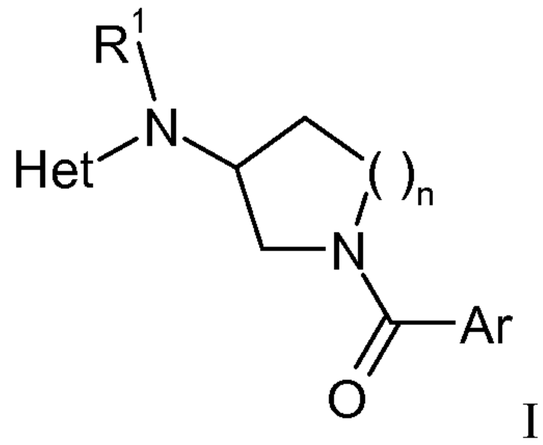
HETEROARYL DERIVATIVES AS OREXIN RECEPTOR ANTAGONISTS

The present invention relates to compounds of formula



I

wherein

Ar is an unsubstituted or substituted aryl or heteroaryl group, wherein the aryl and the heteroaryl group may be substituted by one or more substituents R^2;

R^2 is hydroxy, halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen, C(O)-lower alkyl, nitro, NR'R'', cyano, S-lower alkyl, SO_2-lower alkyl, cycloalkyl, heterocycloalkyl, phenyloxy, benzyloxy, phenyl, NH-phenyl or heteroaryl, wherein the phenyl and heteroaryl group is unsubstituted or substituted by one or more substituents selected from lower alkyl or halogen;

R'/R'' are independently from each other hydrogen or lower alkyl;

R^1 is hydrogen or lower alkyl;

Het is a heteroaryl group, unsubstituted or substituted by one or more substituents selected from R^3;

R^3 is hydroxy, halogen, =O, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, phenyl, lower alkoxy substituted by halogen, nitro, cyano, SO_2-lower alkyl, cycloalkyl or heterocycloalkyl;

n is 1 or 2;

or to pharmaceutically suitable acid addition salts, optically pure enantiomers, racemates or diastereomeric mixtures thereof.

Pop/17.10.2008

It has been found that the compounds of formula I are orexin receptor antagonists and the related compounds may be useful in the treatment of disorders, in which orexin pathways are involved like sleep disorders including sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder, restless leg syndrome, psychiatric, neurological and neurodegenerative disorders including anxiety, depression, manic depression, obsessive compulsive disorders, affective neurosis, depressive neurosis, anxiety neurosis, mood disorder, delirium, panic-attack disorder, posttraumatic stress disorders, sexual dysfunction, schizophrenia, psychosis, cognitive disorders, Alzheimer's and Parkinson's diseases, dementia, mental retardation, dyskinesias such as Huntington's disease and Tourette syndrome, addictions, craving associated with drug abuse, seizure disorders, epilepsy, metabolic diseases such as obesity, diabetes, eating disorders including anorexia and bulimia, asthma, migraine, pain, neuropathic pain, sleep disorders associated with psychiatric, neurological and neurodegenerative disorders, neuropathic pain, enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia, acute pain, burn pain, back pain, complex regional pain syndrome I and II, arthritic pain, post-stroke pain, post-operative pain, neuralgia, pain associated with HIV infection, post-chemotherapy pain, irritable bowel syndrome and other diseases related to general orexin system dysfunction.

Orexins (hypocretins), a family of hypothalamic neuropeptides, play an important role in modulating feeding behavior, energy homeostasis and the sleep-wake cycle (*Siegel, Annu. Rev. Psychol., 55, 125-148, 2004*). The orexin-A / hypocretin1 (OX-A, 33 amino acids) and orexin-B / hypocretin2 (OX-B, 28 amino acids) are derived from the same precursor by proteolytic processing of 130 amino acids prepro-orexin (*de Lecea et al., Proc Natl Acad Sci U S A, 95, 322-327, 1998; Sakurai T. et al., Cell, 92, 573-585, 1998*). The orexin levels show a diurnal variation being highest during the active cycle. Two receptor subtypes termed orexin-1 receptor (OX_1R) and orexin-2 receptor (OX_2R) have been identified. The characterization of both receptors in binding and functional assays demonstrated that OX_2R is a non-selective receptor for both OX-A and –B, whereas OX_1R is selective for OX-A, conversely OX-A is a non-selective neuropeptide and binds with similar affinities to OX_1R and OX_2R, while OX-B is selective and has a higher affinity for OX2R (*Sakurai T. et al., Cell, 92, 573-585, 1998*). Both receptors belong to the class A family of G-protein-coupled receptors (GPCRs) that couple via $G_{q/11}$ to the activation of phospholipase C leading to phosphoinositide (PI) hydrolysis and elevation of intracellular Ca^{2+} levels. However, it has been shown that OX2R could also

couple via $G_{i/o}$ to cAMP pathway (*Sakurai, Regulatory Peptides, 126, 3-10, 2005*). Northern blot analysis of adult rat tissues showed that the prepro-orexin mRNA is detected exclusively in the brain (except for a small amount in the testis) and that the OX_1R and OX_2R transcripts are also exclusively detected in the brain (*Sakurai T. et al., Cell, 92, 573-585, 1998*). Similar results were obtained using human multiple tissue Northern blot. Distribution studies in rat brain using in situ hybridization and immunohistochemistry have shown that orexin neurons are found only in the lateral hypothalamic area with their projections to the entire CNS (*Peyron et al., J Neurosci, 18, 9996-10015, 1998; Nambu et al., Brain Res., 827, 243-60, 1999*). In addition, both OX_1 and OX_2 receptors are present in brain regions important for the regulation of sleep/wakefulness.

A disrupted orexin system is suggested to be the cause of narcolepsy based on following lines of evidence: (a) Prepro-orexin knockout mice possessed a phenotype with characteristics remarkably similar to narcolepsy (*Chemelli et al., Cell, 98, 437-451, 1999*), (b) a mutation (*canarc-1*), which disrupts the gene encoding OX_2R, was found to be responsible for canine narcolepsy (*Lin et al., Cell, 98, 365-376, 1999*), (c) lack of OX-A and OX-B was observed in human narcoleptic patients (*Nishino et al., Lancet, 355, 39-40, 2000; Peyron et al., Nature Medicine, 6, 991-997, 2000*), (d) it has been shown that Modafinil, an anti-narcoleptic drug with unknown mechanism of action, activates orexin neurons (*Mignot et al., Sleep, 11, 1012-1020, 1997; Chemelli et al., Cell, 98, 437-451, 1999*). The intracerebroventricular (*icv)* administration of OX-A dose-dependently increases wakefulness in rat and also reduces total REM sleep by 84% (*Piper et al., Eur. J. Neuroscience, 12, 726-730, 2000*). Taken together, these observations are consistent with a crucial role of the orexin system in the modulation of sleep/wake cycle.

Orexin plays an important role in stress and anxiety via its interaction with the corticotropin-releasing factor (CRF) system in hypothalamus (*Sakamoto et al., Regul Pept., 118, 183-91, 2004*). The *icv* injection of OX-A induces grooming (stress-response) which is blocked in part by a CRF antagonist (*Ida et al., Biochem. Biophys. Res. Comm., 270, 318-323, 2000*). OX_2R is highly expressed in adrenal medulla, whereas OX_1R is high in adrenal cortex. Both OX-A and OX-B stimulate corticosterone release in plasma and induce c-Fos in paraventricular nucleus (PVN) in the hypothalamus (*Kuru et al., Neuroreport, 11, 1977-1980, 2000*). Furthermore, orexin neurons projecting to CRF neurons express mainly the OX_2R (*Winsky-Sommerer et al., J. Neuroscience, 24, 11439-11448, 2004*). Therefore, OX2R stimulation activates the hypothalamo-pituitary-adrenal (HPA) axis. Interestingly, in this context, the orexin A-induced increases in plasma

ACTH has been reported to be attenuated by a selective antagonist to OX-2R (N-{(1S)-1-(6,7-dimethoxy-3,4-dihydro-2(1H)-isoquinolinyl)carbonyl}-2,2-dimethylpropyl)-N-{4-pyridinylmethyl}amine (*Chang et al., Neurosci Res., 21 Dec 2006*). A recent preclinical report (*Suzuki et al., Brain Research, 1044, 116-121, 2005*) has suggested an anxiogenic effect of OX-A. The *icv* injection of OX-A caused an anxiety-like behavior in mice. Effects were similar to those of corticotropin-releasing factor (CRF) that was tested at the same time for comparison. A recent study has also demonstrated the presence of functional OX1 and OX2 receptors in human adipose tissue and their roles in adipose tissue metabolism and adipogenesis (*Digby et al., J. Endocrinol., 191, 129-36, 2006*).

In summary, considering the very diverse functions played by orexin system in arousal, sleep/wakefulness, appetite regulation and their roles in anxiety and stress response, etc., one expects that the drugs (or compounds) targeting orexin system will have beneficial therapeutic effects for the treatments of diseases like sleep disorders including sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder, restless leg syndrome, psychiatric, neurological and neurodegenerative disorders including anxiety, depression, manic depression, obsessive compulsive disorders, affective neurosis, depressive neurosis, anxiety neurosis, mood disorder, delirium, panic-attack disorder, posttraumatic stress disorders, sexual dysfunction, schizophrenia, psychosis, cognitive disorders, Alzheimer's and Parkinson's diseases, dementia, mental retardation, dyskinesias such as Huntington's disease and Tourette syndrome, addictions, craving associated with drug abuse, seizure disorders, epilepsy, metabolic diseases such as obesity, diabetes, eating disorders including anorexia and bulimia, asthma, migraine, pain, neuropathic pain, sleep disorders associated with psychiatric, neurological and neurodegenerative disorders, neuropathic pain, enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia, acute pain, burn pain, back pain, complex regional pain syndrome I and II, arthritic pain, post-stroke pain, post-operative pain, neuralgia, pain associated with HIV infection, post-chemotherapy pain, irritable bowel syndrome and other diseases related to general orexin system dysfunction.

Numerous documents describe the current knowledge on orexin pathway, for example the following documents:

- Expert Opin. Ther. Patents (2006), 16(5), 631-646
- Current Opinion in Drug Discovery & Development, 2006, 9(5), 551-559

- J. Neurosci (2000), 20(20), 7760 - 7765
- Neurosci Lett, (2003), 341(3), 256-258

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 straight- or branched-chain alkyl group containing from 1-4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like. The term "alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

The term "cycloalkyl" denotes a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. Cycloalkyl groups can optionally be substituted as described below in the description and claims.

The term "heterocycloalkyl" denotes a cyclic alkyl group of three to six carbon atoms which can contain 1 or 2 atoms selected from nitrogen, oxygen or sulphur such as e.g. tetrahydrofuran, pyrrolidine or morpholine.

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

The term "aryl" means the monovalent cyclic aromatic hydrocarbon group consisting of one or more fused rings in which at least one ring is aromatic in nature. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, biphenyl, indanyl, anthraquinolyl, and the like.

The term "heteroalkyl" means a non-aromatic carbocyclic group, wherein at least one carbon atom is replaced by a heteroatom, such as N, S or O, for example pyrrolidinyl, morpholinyl, piperazinyl or piperidinyl;

"Heteroaryl" means the monovalent aromatic carbocyclic group having one or more rings incorporating one, two, or three heteroatoms within the ring (chosen from nitrogen, oxygen, or sulfur). Examples of heteroaryl radicals include, but are not limited to, imidazolyl, oxazolyl, pyrazolyl, 1,3-benzodioxol, [1,2,4]triazolyl, [1,2,4]oxadiazolyl, isoxazolyl, thiazolyl, thiophenyl, furanyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl,

pyrrolyl, quinolinyl, quinoxalinyl, quinazolinyl, isoquinolinyl, benzofuryl, benzothiophenyl, benzothiopyranyl, benzimidazolyl, benzooxazolyl, benzothiazolyl, benzopyranyl, indazolyl, indolyl, isoindolyl, naphtyridinyl, and the like.

The term "pharmaceutically acceptable acid addition salts" 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, methanesulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds are those, wherein Het is benzooxazolyl, for example the following compounds

[3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyrrol-1-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dichloro-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-methyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methylsulfanyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-difluoromethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-furan-2-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(2*H*-[1,2,4]triazol-3-yl)-phenyl]-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyridin-3-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-2-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-diethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(3'-methyl-biphenyl-2-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-4-phenyl-thiazol-5-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-3-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-furan-3-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-pyrrolidin-1-yl-phenyl)-methanone

[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(7-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(4-methyl-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone
[(R)-3-(7-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone.

A further embodiment of the invention are compounds, wherein Het is benzooxazol and Ar is an unsubstituted or R^2-substituted aryl.

A further embodiment of the invention are compounds, wherein Het is benzooxazol and Ar is an unsubstituted or R^2-substituted heteroaryl

Preferred compounds are further those, wherein Het is quinoxalinyl, for example the following compounds
(2,6-dimethoxy-phenyl)-[3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

(5-methyl-2-trifluoromethyl-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

(2-methyl-5-phenyl-thiazol-4-yl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(7-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

(R)-3-(6-tert-butyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

(R)-3-(6-fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

(R)-3-(7-chloro-6-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or

(R)-3-(6-Chloro-7-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone.

A further embodiment of the invention are compounds, wherein Het is quinoxalin and Ar is an unsubstituted or R^2-substituted aryl.

A further embodiment of the invention are compounds, wherein Het is quinoxalin and Ar is an unsubstituted or R^2-substituted heteroaryl

Preferred compounds are further those, wherein Het is benzothiazolyl, for example the following compounds

[3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(4-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(7-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(5,6-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or
(R)-3-(4-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone.

A further embodiment of the invention are compounds, wherein Het is benzothiazol and Ar is an unsubstituted or R^2-substituted aryl.

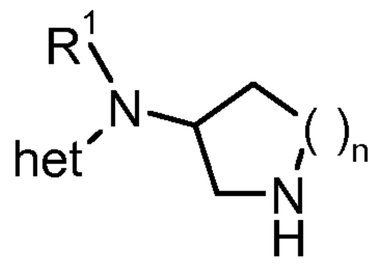
A further embodiment of the invention are compounds, wherein Het is benzothiazol and Ar is an unsubstituted or R^2-substituted heteroaryl

Preferred compounds are further those, wherein Het is pyrimidinyl, for example the following compound
(5-methyl-2-trifluoromethyl-phenyl)-[(R)-3-(2-phenyl-pyrimidin-4-ylamino)-pyrrolidin-1-yl]-methanone.

A further embodiment of the invention are compounds, wherein Het is pyrimidin and Ar is an unsubstituted or R^2-substituted aryl.

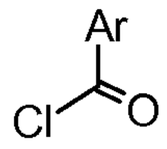
A further embodiment of the invention are compounds, wherein Het is pyrimidin and Ar is an unsubstituted or R^2-substituted heteroaryl.

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



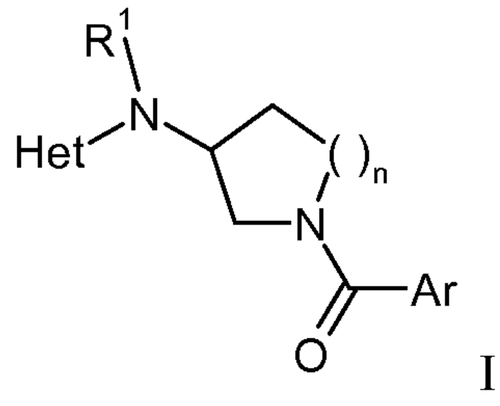
II

with an acid choride of formula



III

to the compound of formula



I

wherein the substituents are as described above, and

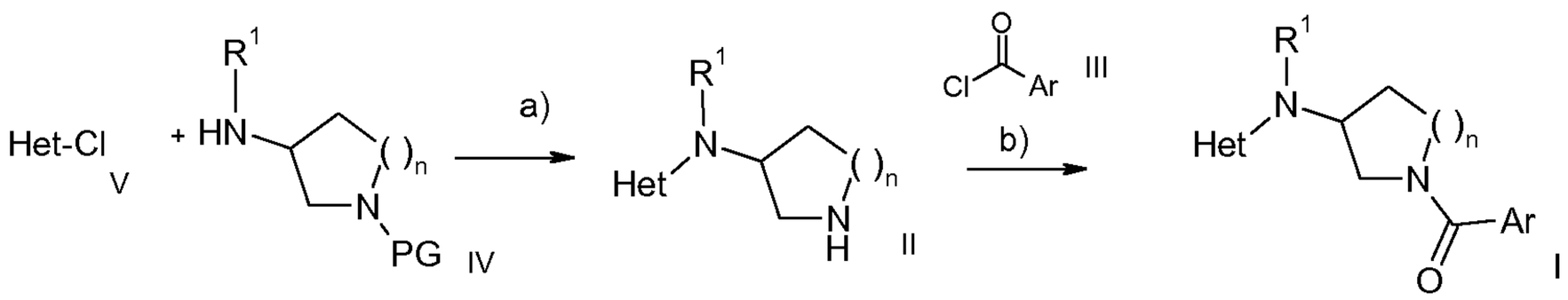
if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

General experimental procedure:

The preparation of compounds of formula **I** of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the compounds of the invention are shown in the following scheme. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

In more detail, the compounds of formula **I** can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. The reaction sequence is not limited to the one displayed in scheme 1, however, depending on the starting materials and their respective reactivity the sequence of reaction steps can be freely altered. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

Scheme 1



Step a)

Aromatic heterocyclic compounds (Het-Cl) **V** are either commercially available or can be synthesized according to procedures described in literature (for reaction conditions described in literature affecting such reactions see for example: Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999) for instance from their respective HET-OH derivatives. Protected amino piperidines or pyrrolidines (**IV**, R^1=H) are commercially available or can be synthesized according to procedures described in literature. Protected amino piperidines or pyrrolidines (**IV**, R^1=H) can conveniently be converted by reductive amination with suitable aldehydes to protected amino piperidines or pyrrolidines (**IV**, R^1=lower alkyl) which can be reacted with Het-Cl **V** in the presence or absence of a solvent and the presence or the absence of a base. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dichloromethane (DCM), dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include NEt_3, DIPEA and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield the protected intermediate (convenient PG= Boc) which can be subjected to acidic cleavage of the protecting group in the presence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dichloromethane (DCM), dioxane, tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the acid used in this stage, and any acid commonly used in this type of reaction may equally be employed here. Examples of such acid include HCl and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction

temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield amino piperidine or pyrrolidine derivatives **IV**.

Step b)

Transformation of intermediate amino piperidine or pyrrolidine derivatives **II** with acids (under coupling conditions with a a coupling agent) or acid chlorides is well know in the art. For analogous examples in literature refer to Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999. However, we find it convenient to react intermediate amino piperidine or pyrrolidine derivatives **II** with acid chlorides in the presence or absence of a base and the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. Examples for suitable solvents include dichloromethane (DCM), dimethylformamide (DMF), tetrahydrofuran (THF) and the like. There is no particular restriction on the nature of the base used in this stage, and any base commonly used in this type of reaction may equally be employed here. Examples of such bases include pyridine, NEt_3, DIPEA and the like. The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the reaction with heating from ambient temperature to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 h to several days will usually suffice to yield amino piperidine or pyrrolidine derivatives **I**.

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

Intracellular Ca^{2+} mobilization assay

The Chinese Hamster Ovary (dHFr-) mutant cell line stably expressing human orexin-1 (hOX1) or human orexin-2 (hOX2) receptors were maintained in Dulbecco's Modified Eagle Medium (1X) with GlutaMax™1, 4500 mg/L D-Glucose and Sodium Pyruvate (Catalog No. 31966-021, Invitrogen, Carlsbad, CA), 5% dialyzed fetal calf serum (Catalog No. 26400-044), 100 µg/ml penicillin and 100 µg/ml streptomycin. The cells were seeded at $5x10^4$ cells/well in the poly-D-lysine treated, 96-well, black/clear-bottomed plates (Catalog No. BD356640, BD Biosciences, Palo Alto, CA). 24 h later, the cells were loaded for 1 h at 37°C with 4 µM Flou-4 acetoxymethyl ester (Catalog No. F-14202, Molecular Probes, Eugene, OR) in FLIPR buffer (1xHBSS, 20 mM HEPES, 2.5

mM Probenecid). Hanks' Balanced Salt Solution (HBSS) (10X) (catalog No. 14065-049) and HEPES (1M) (catalog No. 15630-056) were purchased from Invitrogen, Carlsbad, CA. Probenecid (250 mM) (catalog No. P8761) was from Sigma, Buchs, Switzerland. The cells were washed five times with FLIPR buffer to remove excess dye and intracellular calcium mobilization, $[Ca^{2+}]_i$ were measured using a Fluorometric Imaging Plate Reader (FLIPR-96, Molecular Devices, Menlo Park, CA) as described previously (*Malherbe et al., Mol. Pharmacol., 64, 823-832, 2003*). Orexin A (catalog No. 1455, Toris Cookson Ltd, Bristol, UK) was used as agonist. Orexin A (50 mM stock solution in DMSO) was diluted in FLIPR buffer + 0.1% BSA. The EC_{50} and EC_{80} values of orexin-A were measured daily from standard agonist concentration-response curves in CHO(dHFr-)-OX1R and –OX2R cell lines. All compounds were dissolved in 100 % DMSO. Inhibition curves were determined by addition of 11 concentrations (0.0001-10 μM) of inhibitory compounds and using EC_{80} value of orexin-A as agonist (a concentration which gave 80% of max agonist response, determined daily). The antagonists were applied 25 min (incubation at 37°C) before the application of the agonist. Responses were measured as peak increase in fluorescence minus basal, normalized to the maximal stimulatory effect induced by EC_{80} value of orexin-A or orexin- B. Inhibition curves were fitted according to the Hill equation: $y = 100/(1+(x/IC_{50})^{nH})$, where n_H = slope factor using Excel-fit 4 software (Microsoft). K_b values were calculated according to the following equation $K_b = IC_{50}/(1+[A]/EC_{50})$ where A is the concentration of agonist added which is very close to agonist EC_{80} value, and IC_{50} and EC50 values were derived from the antagonist inhibition and orexin-A or B agonist curves, respectively.

The compounds show a K_b value (μM) < 1.0 in human on orexin receptor. The preferred compounds show a K_b value < 0.5 μM as shown in the table below.

Example	**K_b (μM) OX2R (human)**	**Example**	**K_b (μM) OX2R (human)**	**Example**	**K_b (μM) OX2R (human)**
1	0.0279	84	0.0056	155	0.0304
5	0.0242	86	0.0169	157	0.0247
6	0.0104	90	0.0186	158	0.0039
7	0.0228	92	0.0029	159	0.0205

24	0.0415	93	0.0164	164	0.047
25	0.0163	94	0.0091	165	0.0185
28	0.0096	95	0.0426	166	0.009
33	0.0354	97	0.0063	167	0.001
35	0.045	100	0.01	168	0.0038
41	0.0302	102	0.0144	169	0.0021
43	0.0015	106	0.0129	170	0.0129
45	0.0031	110	0.0319	171	0.0245
47	0.0377	112	0.0344	172	0.0032
52	0.0249	113	0.0217	175	0.0187
53	0.0299	114	0.002	176	0.014
56	0.047	115	0.0068	177	0.0423
57	0.0025	116	0.0261	178	0.0244
61	0.0054	117	0.0197	181	0.028
62	0.014	118	0.039	182	0.027
63	0.0219	120	0.0188	183	0.02
65	0.0272	122	0.0193	184	0.0021
67	0.0051	123	0.0032	185	0.0075
68	0.0018	124	0.0363	189	0.028
69	0.0155	126	0.0144	192	0.0324
70	0.0024	132	0.016	200	0.0073
71	0.0097	134	0.0228	202	0.0046

72	0.0298	135	0.0394	203	0.008
73	0.0012	141	0.0138	204	0.0052
75	0.0163	148	0.0386	207	0.0046
78	0.0145	149	0.0072	212	0.0086
79	0.0173	150	0.0136	213	0.0371
82	0.0041	151	0.0355		

The compounds of formula I and the pharmaceutically acceptable salts of the compounds of formula I 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, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, 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 can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acids or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine 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 gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, glycerol, vegetable oil and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can, moreover, 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.

Medicaments containing a compound of formula I or a pharmaceutically acceptable salt thereof and a therapeutically inert carrier are also an object of the present invention,

as is a process for their production, which comprises bringing one or more compounds of formula I and/or pharmaceutically acceptable acid addition salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with one or more therapeutically inert carriers.

The most preferred indications in accordance with the present invention are those, which include sleep disorders including sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder, restless leg syndrome, psychiatric, neurological and neurodegenerative disorders including anxiety, depression, manic depression, obsessive compulsive disorders, affective neurosis, depressive neurosis, anxiety neurosis, mood disorder, delirium, panic-attack disorder, posttraumatic stress disorders, sexual dysfunction, schizophrenia, psychosis, cognitive disorders, Alzheimer's and Parkinson's diseases, dementia, mental retardation, dyskinesias such as Huntington's disease and Tourette syndrome, addictions, craving associated with drug abuse, seizure disorders, epilepsy, metabolic diseases such as obesity, diabetes, eating disorders including anorexia and bulimia, asthma, migraine, pain, neuropathic pain, sleep disorders associated with psychiatric, neurological and neurodegenerative disorders, neuropathic pain, enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia, acute pain, burn pain, back pain, complex regional pain syndrome I and II, arthritic pain, post-stroke pain, post-operative pain, neuralgia, pain associated with HIV infection, post-chemotherapy pain, irritable bowel syndrome and other diseases related to general orexin system dysfunction.

The dosage can vary within wide limits and will, of course, have to be adjusted to the individual requirements in each particular case. In the case of oral administration the dosage for adults can vary from about 0.01 mg to about 1000 mg per day of a compound of general formula I or of the corresponding amount of a pharmaceutically acceptable salt thereof. The daily dosage may be administered as single dose or in divided doses and, in addition, the upper limit can also be exceeded when this is found to be indicated.

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

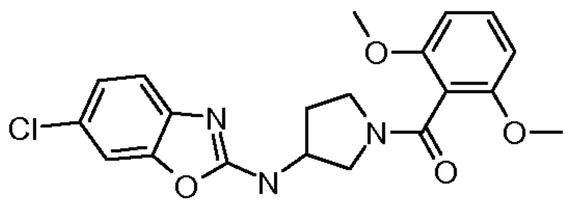
Item	Ingredients	mg/capsule			
		5 mg	25 mg	100 mg	500 mg
1.	Compound of formula I	5	25	100	500
2.	Hydrous Lactose	159	123	148	---
3.	Corn Starch	25	35	40	70
4.	Talc	10	15	10	25
5.	Magnesium Stearate	1	2	2	5
	Total	200	200	300	600

Manufacturing Procedure

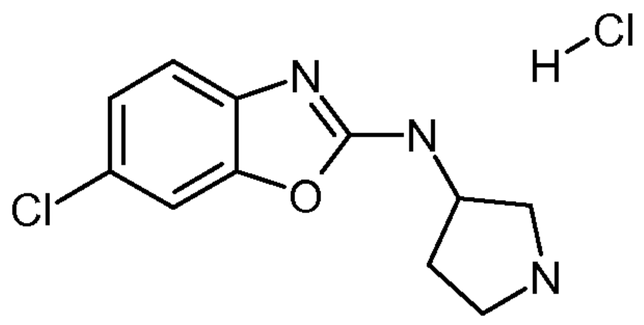
1. Mix items 1, 2 and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.

Example 1

[3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



a) step 1: (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride



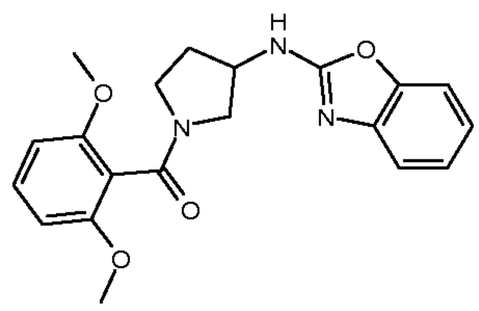
A mixture of 470 mg (2.5 mmol) 2,6-dichloro-benzooxazole (commercially available), 511 mg (2.75 mmol) 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 328 mg (3.25 mmol) NEt_3 in 8 mL DCM was stirred at room temperature over night. $KHSO_4$ aq (1N) was added and the organic layer was evaporated under reduced pressure. The residue was taken up in 10 mL HCl in dioxane (4N) and concentrated under reduced pressure to yield the crude title compound which was used without further purification in the consecutive step. (MH^+) 238.0.

b) step 2: [3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

A mixture of 110 mg (6-chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride (crude) and 120 mg (0.6 mmol) 2,6-dimethoxybenzoyl chloride in 1.6 mL pyridine was stirred at room temperature over night. The mixture was evaporated and subjected to preparative HPLC purification on reversed phase eluting with a gradient formed from acetonitrile, water and NEt_3. The combined product containing fractions were evaporated to yield 1.6 mg of the title compound. (MH^+) 402.2.

Example 2

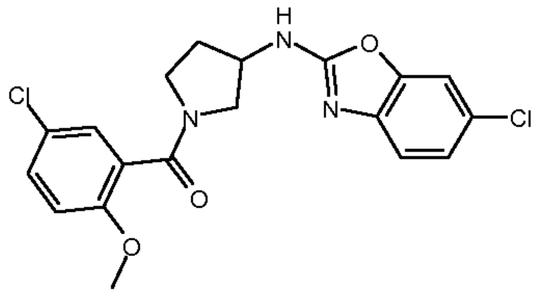
[3-(Benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2-chloro-benzooxazole (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 368.2

Example 3

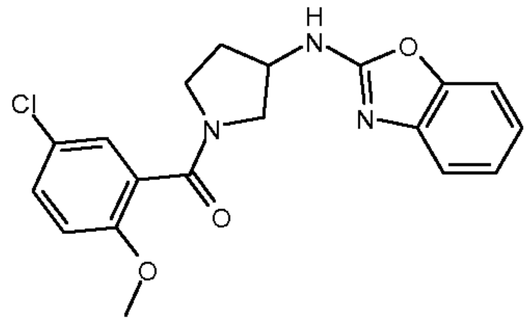
[3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-chloro-2-methoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzooxazole (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 5-chloro-2-methoxy-benzoyl chloride (commercially available). (MH^+) 406.1

Example 4

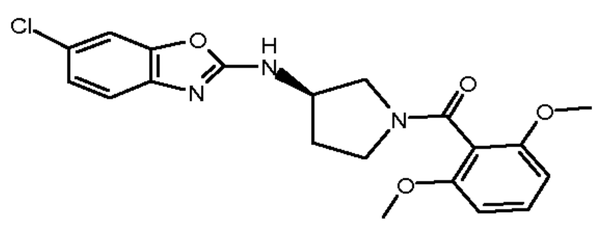
[3-(Benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-chloro-2-methoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2-chloro-benzooxazole (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 5-chloro-2-methoxy-benzoyl chloride (commercially available). (MH^+) 372.2.

Example 5

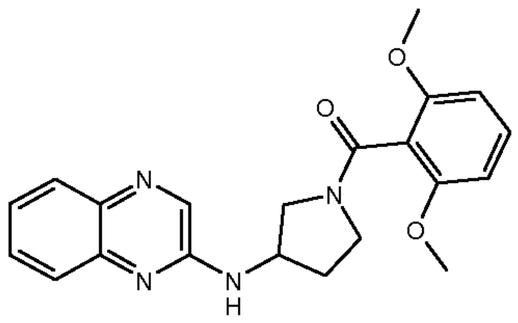
[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzooxazole (commercially available), 3-(R)-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 402.2.

Example 6

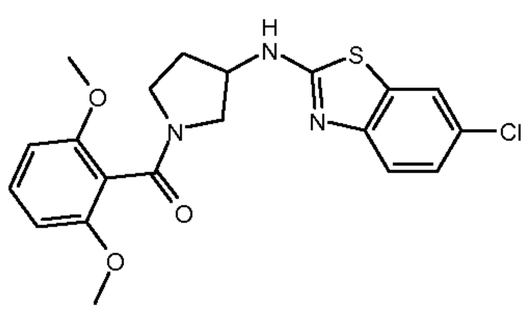
(2,6-Dimethoxy-phenyl)-[3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2-chloro-quinoxaline (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) (coupling at elevated temperature) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 379.2.

Example 7

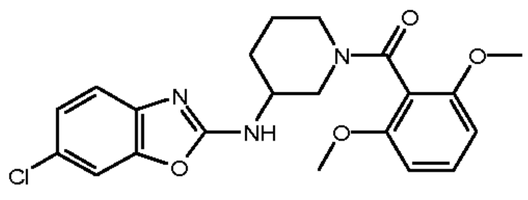
[3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzothiazole (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 418.2.

Example 8

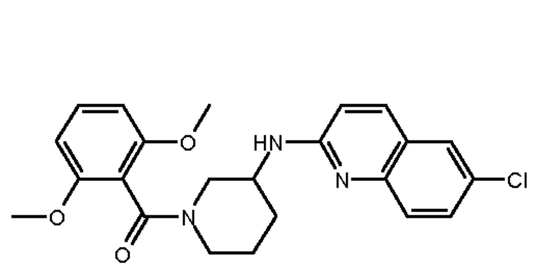
[3-(6-Chloro-benzooxazol-2-ylamino)-piperidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzooxazole (commercially available), 3-amino-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 416.2.

Example 9

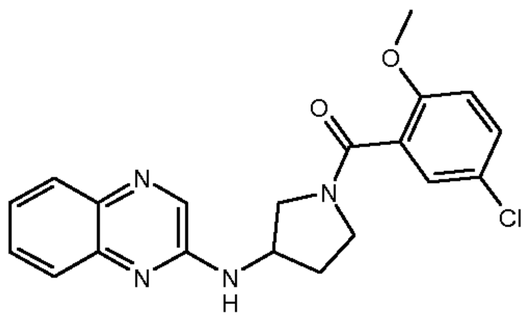
[3-(6-Chloro-quinolin-2-ylamino)-piperidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-quinoline (commercially available), 3-amino-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available). (MH^+) 426.2.

Example 10

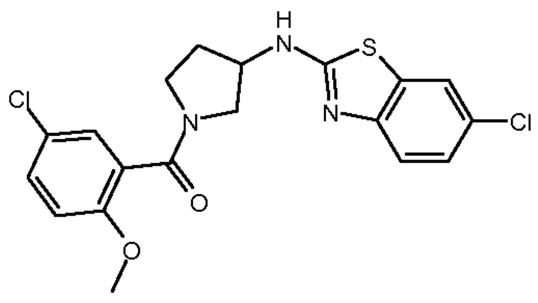
(5-Chloro-2-methoxy-phenyl)-[3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2-chloro-quinoxaline (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 5-chloro-2-methoxy-benzoyl chloride (commercially available). (MH^+) 383.2.

Example 11

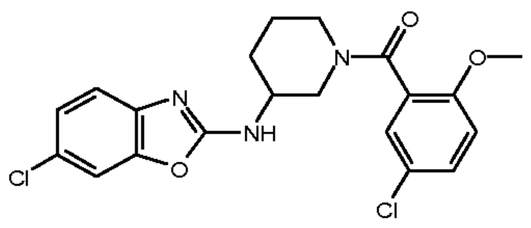
[3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-chloro-2-methoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzothiazole (commercially available), 3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 5-chloro-2-methoxy-benzoyl chloride (commercially available). (MH^+) 422.1.

Example 12

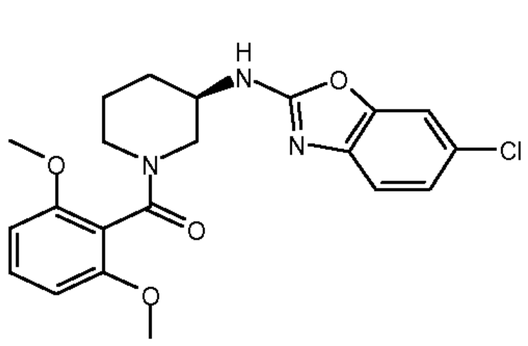
[3-(6-Chloro-benzooxazol-2-ylamino)-piperidin-1-yl]-(5-chloro-2-methoxy-phenyl)-methanone



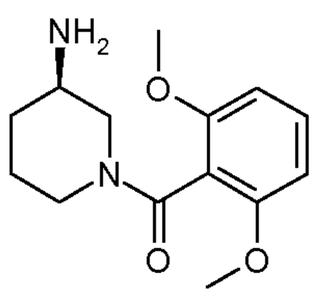
In analogy to the procedure described for the synthesis of [3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1) the title compound was prepared from 2,6-dichloro-benzooxazole (commercially available), 3-amino-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and 5-chloro-2-methoxy-benzoyl chloride (commercially available). (MH^+) 420.1.

Example 13

[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-piperidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



a) step 1: ((R)-3-Amino-piperidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone



A mixture of 0.143 g (0.786 mmol) 2,6-dimethoxybenzoic acid (commercially available), 0.15 g (0.749 mmol) (R)-piperidin-3-yl-carbamic acid tert-butyl ester (commercially available), 0.264 g (0.824 mmol) TBTU and 0.145 g (1.123 mmol) DIPEA in 9.2 mL DMF was stirred at room temperature over night. DMF was evaporated and the residue was purified by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid. The product containing fractions were evaporated and the residue was treated with 4N HCl in dioxane and stirred at 50 °C over night. The mixture was evaporated to dryness and treated with $NaHCO_3$ aq. and DCM. The organic

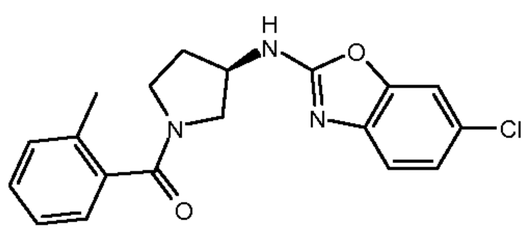
layer was separated, dried with $MgSO_4$ and evaporated to yield 22 mg (11 %) of the title compound as colourless oil. (MH^+) 265.1.

b) step 2:

A mixture of 22 mg (0.083 mmol) ((R)-3-Amino-piperidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone, 15.6 mg (0.083 mmol) 2,6-dichlorobenzoxazole and 12.6 mg (0.125 mmol) NEt_3 in 3 mL DCM was stirred at room temperature over night. The mixture was evaporated to dryness and the residue was purified by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid. The product containing fractions were evaporated to yield 12 mg (35 %) of the title compound as colourless oil. (MH^+) 416.2.

Example 14

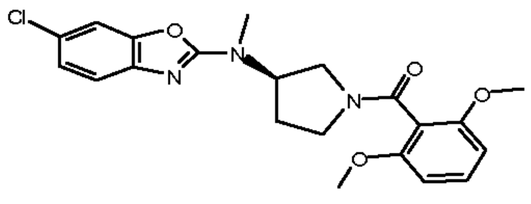
[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-*o*-tolyl-methanone



A mixture of 32.9 mg (0.12 mmol) (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride, 19.6 mg (0.144 mmol) 2-methyl-benzoic acid, 53.9 mg (0.168 mmol) TBTU and 77.5 mg (0.6 mmol) DIPEA in 2 mL DMF was stirred at room temperature for 16 h. The mixture was concentrated, taken up in methanol and formic acid and subjected to purification by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid. The product containing fractions were evaporated to yield 26.2 mg (61 %) of the title compound. (MH^+) 356.1.

Example 15

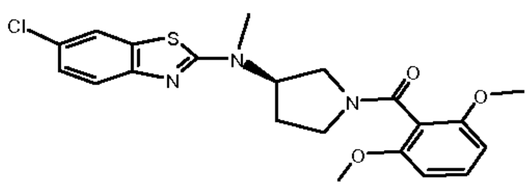
{(R)-3-[(6-Chloro-benzooxazol-2-yl)-methyl-amino]-pyrrolidin-1-yl}-(2,6-dimethoxy-phenyl)-methanone



A mixture of 20 mg (0.05 mmol) [3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 1), 353 mg (2.48 mmol) methyliodid and 10 mg (0.075 mmol) K_2CO_3 in 0.5 mL DMF was stirred at 75 °C. The mixture was concentrated, water and methanol was added and the mixture was subjected to purification by preparative HPLC on reversed phase eluting with a gradient formed from acetonitrile, water and formic acid. The product containing fractions were evaporated to yield 9.6 mg (461 %) of the title compound as light yellow solid. (MH^+) 418.1.

Example 16

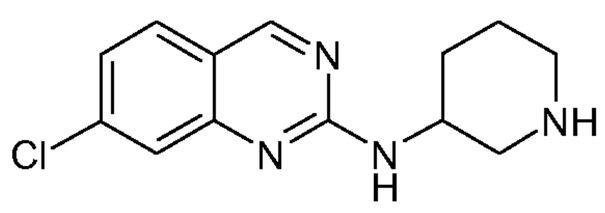
{(R)-3-[(6-Chloro-benzothiazol-2-yl)-methyl-amino]-pyrrolidin-1-yl}-(2,6-dimethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of {(R)-3-[(6-Chloro-benzooxazol-2-yl)-methyl-amino]-pyrrolidin-1-yl}-(2,6-dimethoxy-phenyl)-methanone (example 15) the title compound was prepared from [3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone (example 7) and methyliodide. (MH^+) 432.1.

Intermediate 1

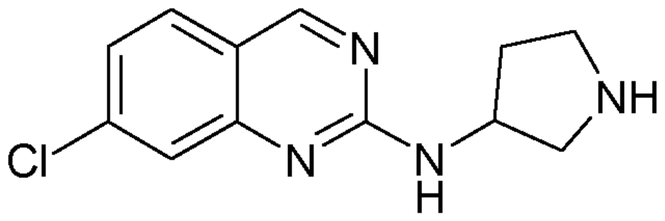
(7-Chloro-quinazolin-2-yl)-piperidin-3-yl-amine



In analogy to the procedure described for the synthesis of (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride (example 1, step 1) the title compound was prepared from 2,7-dichloro-quinazoline (Synthesis 1978, 5, 379-82) and 3-Amino-piperidine-1-carboxylic acid tert-butyl ester (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 263.1.

Intermediate 2

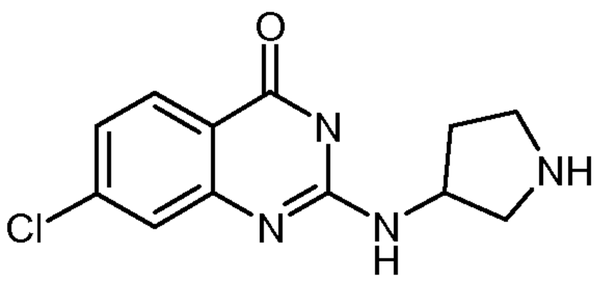
(7-Chloro-quinazolin-2-yl)-pyrrolidin-3-yl-amine



In analogy to the procedure described for the synthesis of (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride (example 1, step 1) the title compound was prepared from 2,7-dichloro-quinazoline (Synthesis 1978, 5, 379-82) and 3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 249.1.

Intermediate 3

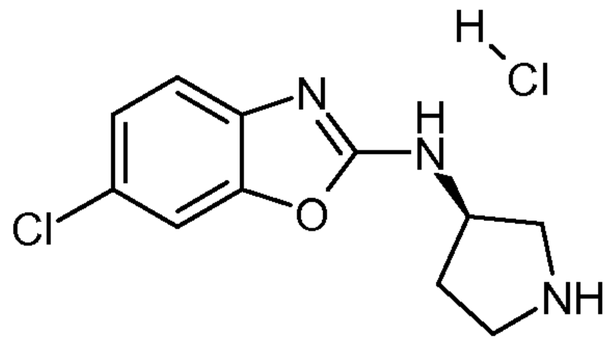
7-Chloro-2-(pyrrolidin-3-ylamino)-3H-quinazolin-4-one



In analogy to the procedure described for the synthesis of (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride (example 1, step 1) the title compound was prepared from 2,7-Dichloro-4(3H)-quinazolinone (Bioorganic & Medicinal Chemistry 2003, 11, 2439-2444) and 3-Amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 265.1

Intermediate 4

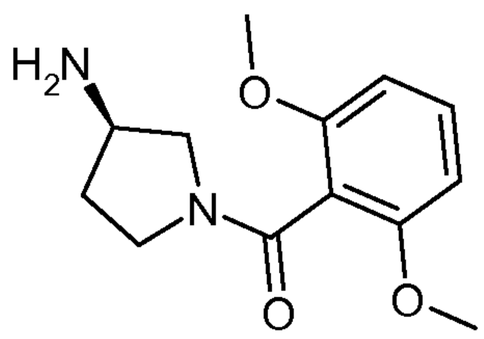
(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride



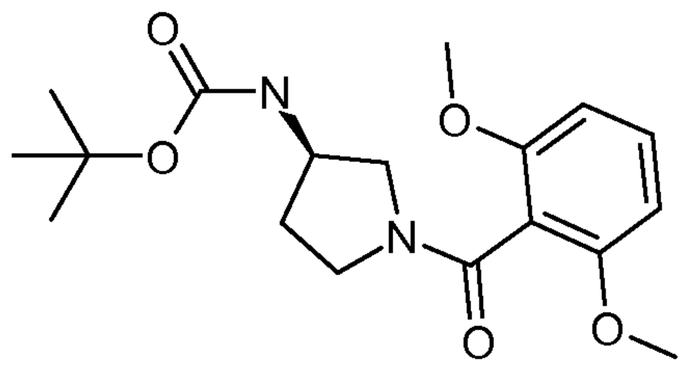
In analogy to the procedure described for the synthesis of (6-Chloro-benzooxazol-2-yl)-pyrrolidin-3-yl-amine; hydrochloride (example 1, step 1) the title compound was prepared from 2,6-dichloro-benzoxazole (commercially available) and R-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 238.0.

Intermediate 5

((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone



a) step 1: [(R)-1-(2,6-Dimethoxy-benzoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester



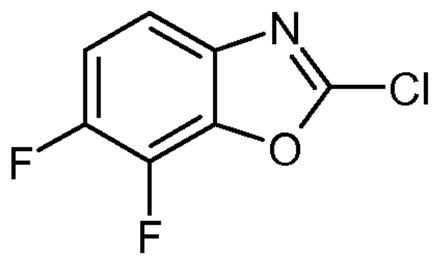
A mixture of 2.94 g (15.8 mmol) (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2,6-dimethoxybenzoyl chloride (commercially available) and 2.08 g (2.05 mmol) NEt_3 in 15 mL DCM was stirred at room temperature over night. The mixture was absorbed on isolute SPE and purified by column chromatography on silica eluting with a gradient formed from heptane and ethyl acetate to yield 3.78 g (68 %) of the title compound as white foam. (MH^+) 351.2

b) step 2:

A mixture of 3.78 g (10.8 mmol) [(R)-1-(2,6-Dimethoxy-benzoyl)-pyrrolidin-3-yl]-carbamic acid tert-butyl ester and 13.5 mL 4N HCl in dioxane was stirred at room temperature for 1 h. The mixture was concentrated, $NaHCO_3$ aq. sat. was added and extracted with DCM. The combined organic layers were evaporated to yield 2.6 g of the title compound which was used without further purification. (MH^+) 251.1

Intermediate 6

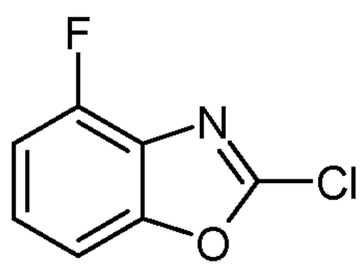
2-Chloro-6,7-difluoro-benzooxazole



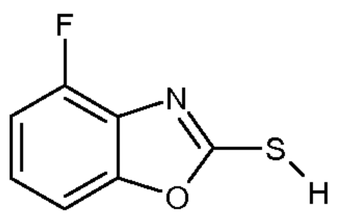
Commercially available

Intermediate 7

2-Chloro-4-fluoro-benzooxazole



a) step 1: 4-Fluoro-benzooxazole-2-thiol



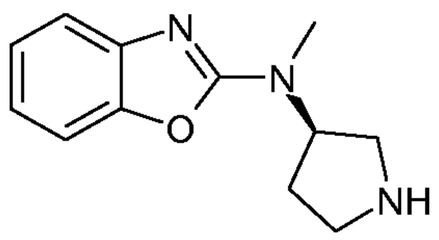
A mixture of 1 g (7.867 mmol) 2-amino-3-fluorophenol and 1.42 g (8.654 mmol) potassium ethylxanthogenate in 28 mL methanol was heated in a 70 °C oil bath for 3 h. The solvent was removed in vacuo. The residue was dissolved in 50 mL water. The aqueous layer was acidified with HCl 2N. The solid was filtered, washed with water and dried to provide 568 mg (42.7 %) of the title compound as a light grey solid. MS(m/e): 168.0 ($M-H^+$).

b) step 2: 2-Chloro-4-fluoro-benzooxazole

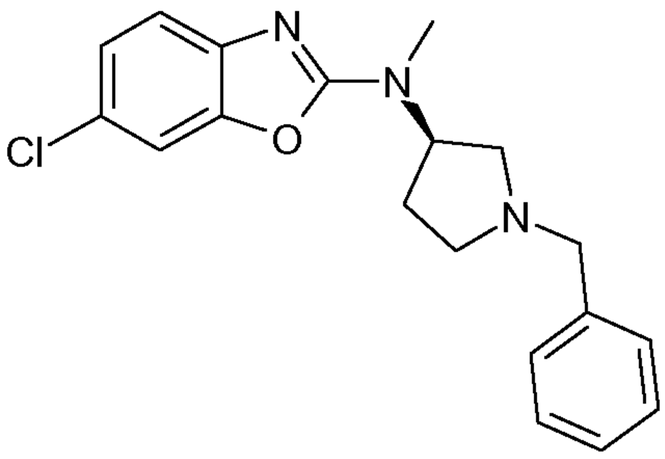
To a solution of 560 mg (3.31 mmol) 4-fluoro-benzooxazole-2-thiol in 3.6 mL (49.65 mmol) thionyl chloride was added dropwise 60.3 L N,N-dimethylformamide dry at room temperature. The mixture was stirred at room temperature for 2.5 h. The solvent was removed in vacuo. The crude compound was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 434 mg (76.4 %) of the title compound as a white solid. MS(m/e): 171 ($M+H^+$).

Intermediate 8

Benzooxazol-2-yl-methyl-(R)-pyrrolidin-3-yl-amine



a) step 1: ((R)-1-Benzyl-pyrrolidin-3-yl)-(6-chloro-benzooxazol-2-yl)-methyl-amine



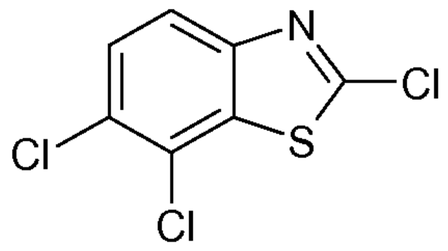
A mixture of 0.5 g (2.6 mmol) 2,6-dichloro benzoxazole, 0.68 g (3.58 mmol) ((R)-1-benzyl-pyrrolidin-3-yl)-methyl-amine and 0.4 g (4 mmol) NEt_3 in 12 mL DCM was stirred over night at room temperature. DCM was added and the mixture was washed with $NaHCO_3$ aq., dried with $MgSO_4$ and evaporated to dryness to yield the title compound as yellow oil which was used in the consecutive step without further purification. (MH^+) 342.1

b) step 2:

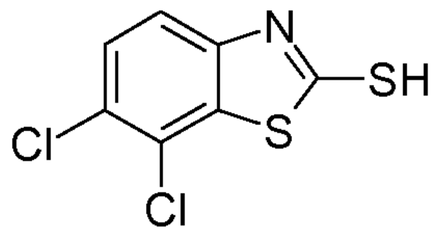
A solution of 0.99 g ((R)-1-Benzyl-pyrrolidin-3-yl)-(6-chloro-benzooxazol-2-yl)-methyl-amine in 5 mL ethanol and 0.4 mL acetic acid was hydrogenated over Pd/C 10% to yield after filtration and evaporation the title compound as yellow oil which was used in the consecutive step without further purification. (MH^+) 218.0

Intermediate 9

2,6,7-Trichloro-benzothiazole



a) step 1: 6,7-dichloro-benzothiazole-2-thiol



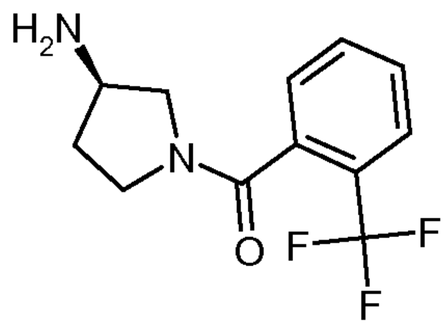
A mixture of 1.5 g (8.33 mmol) 3.4-dichloro-2-fluoroaniline and 1.64 g (10.00 mmol) potassium ethylxanthogenate in 8mL dry N,N-dimethylformamide was heated in a 95 °C oil bath for 5 h. The reaction mixture was cooled to room temperature and diluted with water (25 mL). The mixture was acidified with aqueous HCl 2N. The precipitate was collected by filtration, washed with water and dried to provide 1.8 g (92 %) of the title compound as a white solid. MS(m/e): 233.8 ($M-H^+$).

b) step 2: 2,6,7-Trichloro-benzothiazole

To a suspension of 300 mg (1.270 mmol) 6,7-dichloro-benzothiazole-2-thiol in 1.4 mL (19.05 mmol) thionyl chloride was added dropwise 32.3 L N,N-dimethylformamide dry at room temperature. The mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo. The residue was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 127 mg (41.9 %) of the title compound as a yellow solid. MS(m/e): 239 ($M+H^+$).

Intermediate 10

((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone

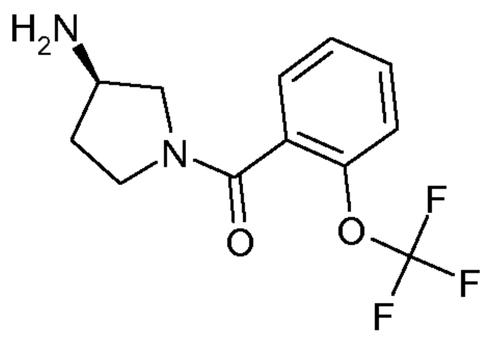


A mixture of 0.363 g (1.95 mmol) (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 0.38 g (2 mmol) 2-trifluoromethyl-benzoic acid (commercially available), 0.69 g (2.15 mmol) TBTU and 0.378 g (2.92 mmol) DIPEA in 8 mL DMF was stirred at room temperature for 16 h. $KHSO_4$ aq. was added and the mixture was extracted with ethyl acetate. The combined organic layers were evaporated

and the residue was treated with 4.87 mL 4N HCl in dioxane and stirred for 16 h at room temperature. The mixture was concentrated and methanol and water was added and the mixture was passed over a basic solid phase extraction cartridge eluting with methanol. The title compound was obtained after evaporation and used without further purification in the consecutive step. (MH^+) 259.1.

Intermediate 11

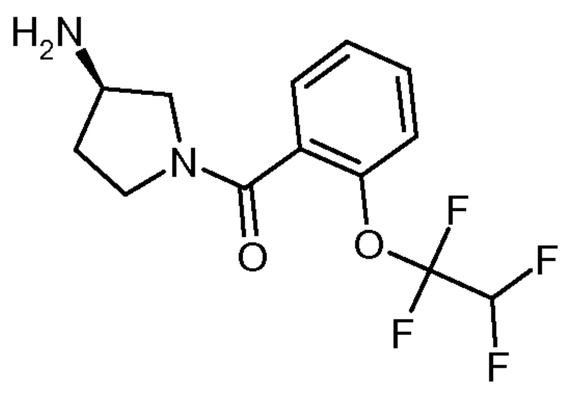
((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-trifluoromethoxy-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 275.1.

Intermediate 12

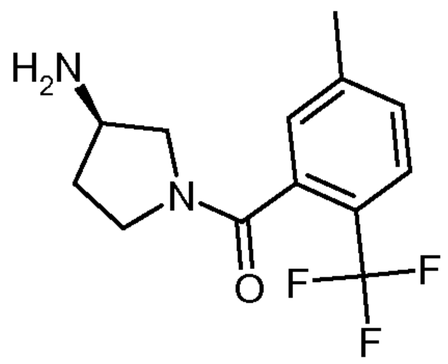
((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-(1,1,2,2-Tetrafluoro-ethoxy)-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 307.1.

Intermediate 13

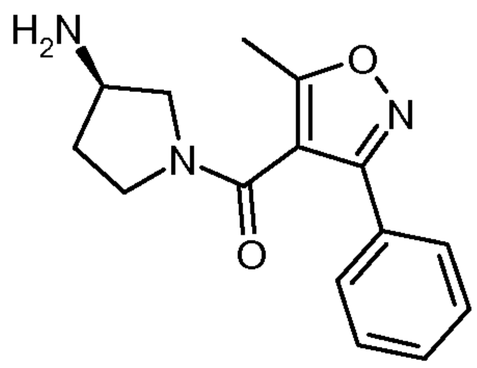
((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 5-Methyl-2-trifluoromethyl-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 273.1.

Intermediate 14

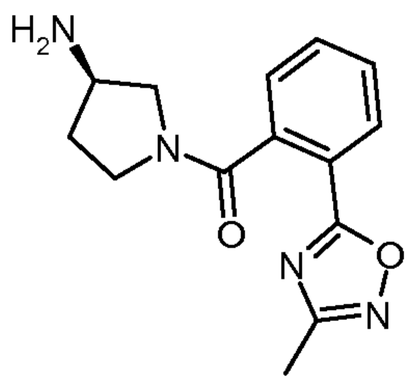
((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 272.1.

Intermediate 15

((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

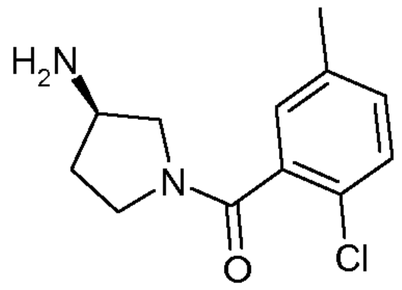


In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared

from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 273.1.

Intermediate 16

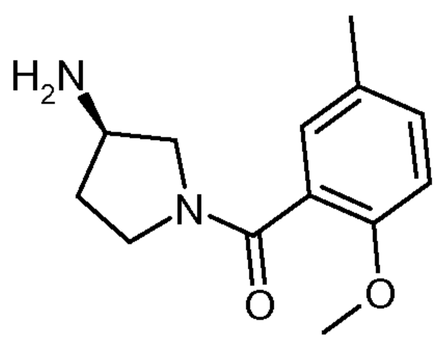
((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-Chloro-5-methyl-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 239.0

Intermediate 17

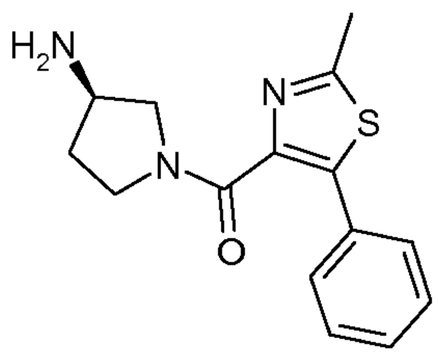
((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-Methoxy-5-methyl-benzoic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions.

Intermediate 18

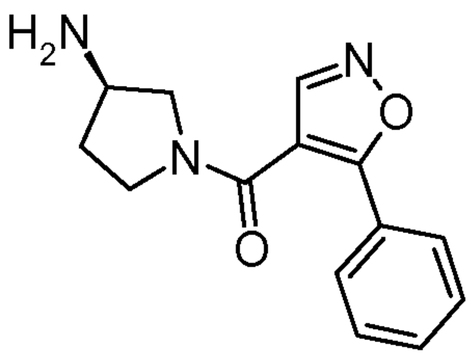
((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone



In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 2-Methyl-5-phenyl-thiazole-4-carboxylic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 288.1.

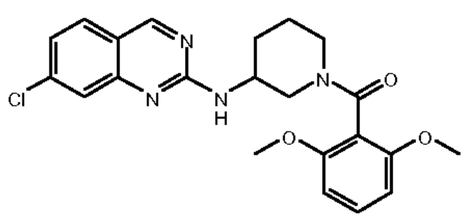
Intermediate 19

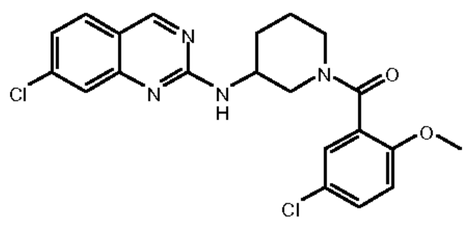
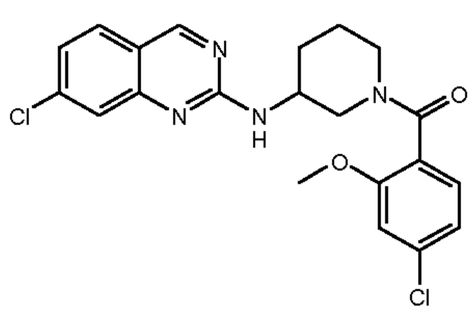
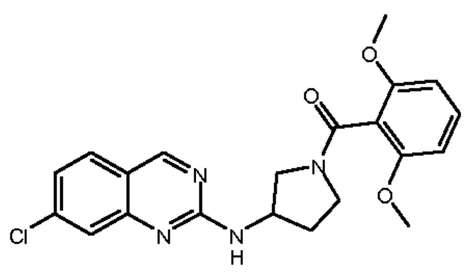
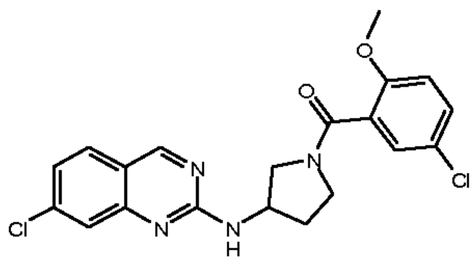
((R)-3-Amino-pyrrolidin-1-yl)-(5-phenyl-isoxazol-4-yl)-methanone

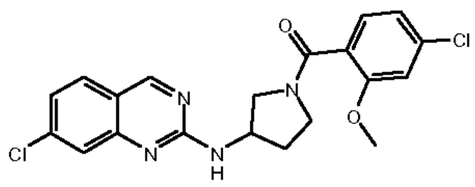
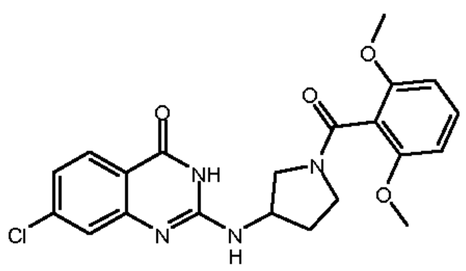
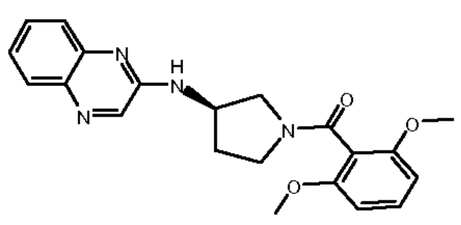


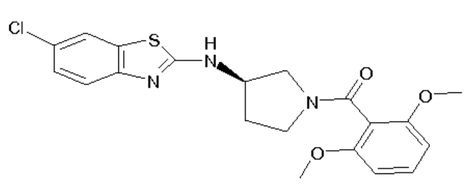
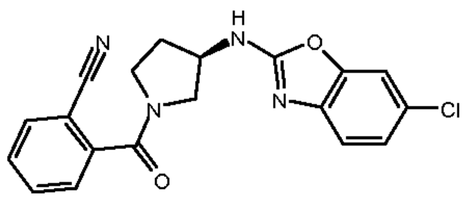
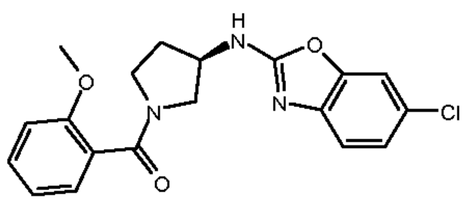
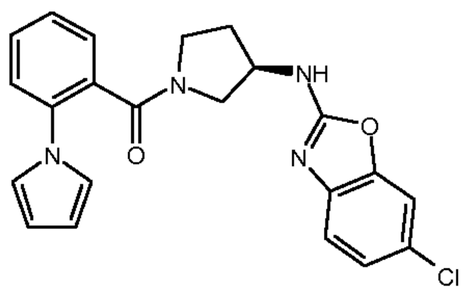
In analogy to the procedure described for the synthesis of ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10) the title compound was prepared from (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester (commercially available), 5-phenyl-4-isoxazolecarboxylic acid (commercially available) and subsequent cleavage of the tert-butyl oxy carbonyl protecting group under acidic conditions. (MH^+) 258.3.

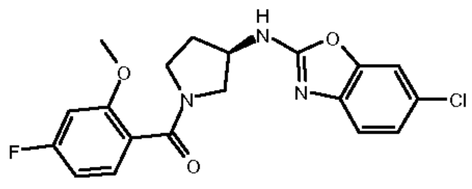
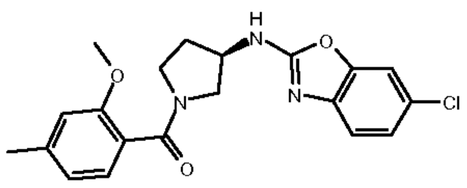
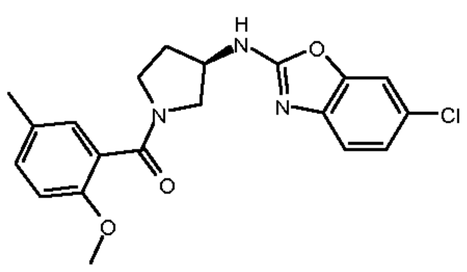
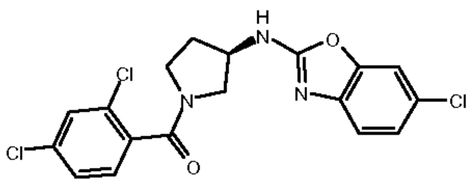
In analogy to the procedures described for examples 1, 13 and 14 further compounds have been synthesized from the starting materials listed in table 1. Table 1 comprises examples 17- 199.

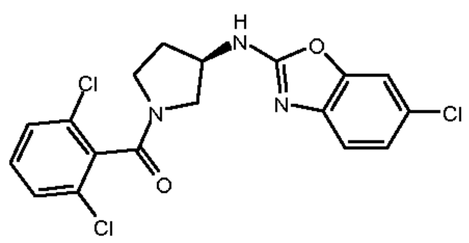
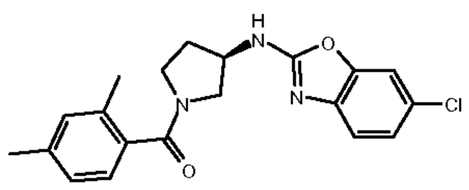
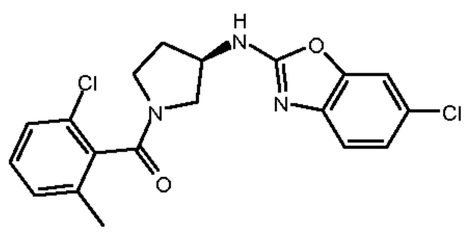
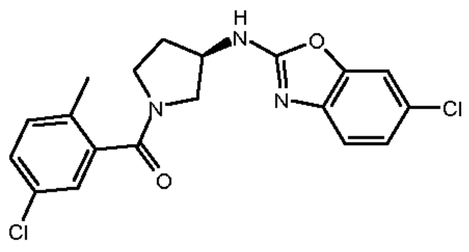
No.	structure	MW	name	starting materials	MW found (MH+)
17		426.9	[3-(7-Chloro-quinazolin-2-ylamino)-piperidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	(7-Chloro-quinazolin-2-yl)-piperidin-3-yl-amine (intermediate 1) and 2,6-Dimethoxy-benzoyl chloride (commercially available)	427.3

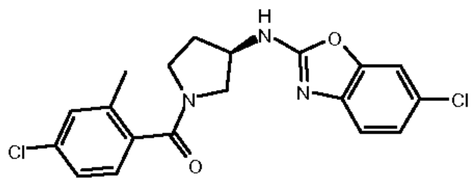
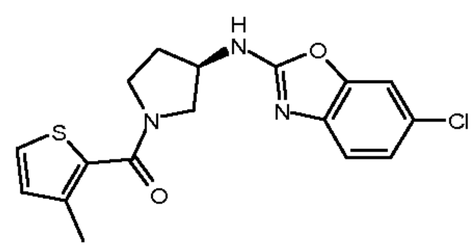
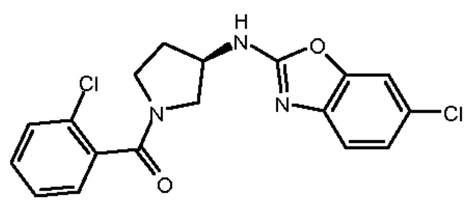
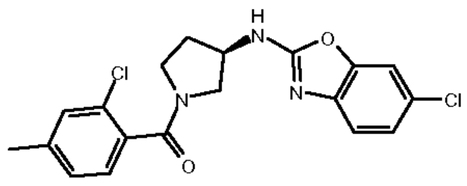
No.	structure	MW	name	starting materials	MW found (MH+)
18		431.3	(5-Chloro-2-methoxy-phenyl)-[3-(7-chloro-quinazolin-2-ylamino)-piperidin-1-yl]-methanone	(7-Chloro-quinazolin-2-yl)-piperidin-3-yl-amine (intermediate 1) and 5-Chloro-2-methoxy-benzoyl chloride (commercially available)	431.1
19		431.3	(4-Chloro-2-methoxy-phenyl)-[3-(7-chloro-quinazolin-2-ylamino)-piperidin-1-yl]-methanone	(7-Chloro-quinazolin-2-yl)-piperidin-3-yl-amine (intermediate 1) and 4-Chloro-2-methoxy-benzoic acid (commercially available)	431.1
20		412.9	[3-(7-Chloro-quinazolin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	(7-Chloro-quinazolin-2-yl)-pyrrolidin-3-yl-amine (intermediate 2) and 2,6-Dimethoxy-benzoyl chloride (commercially available)	413.3
21		417.3	(5-Chloro-2-methoxy-phenyl)-[3-(7-chloro-quinazolin-2-ylamino)-pyrrolidin-1-yl]-methanone	(7-Chloro-quinazolin-2-yl)-pyrrolidin-3-yl-amine (intermediate 2) and 5-Chloro-2-methoxy-benzoyl chloride (commercially available)	417.4

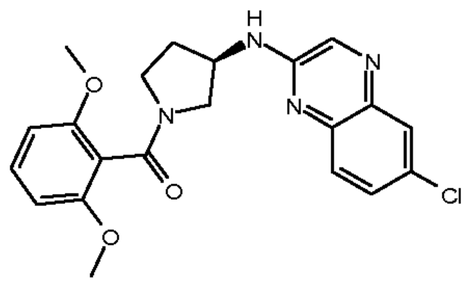
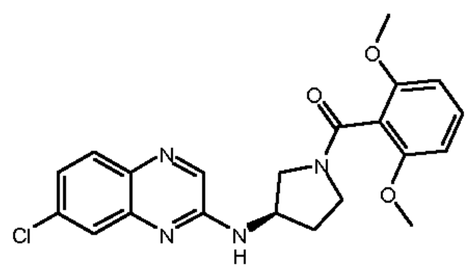
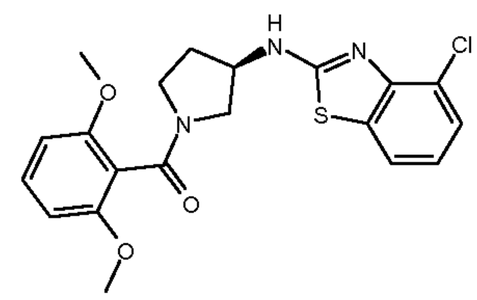
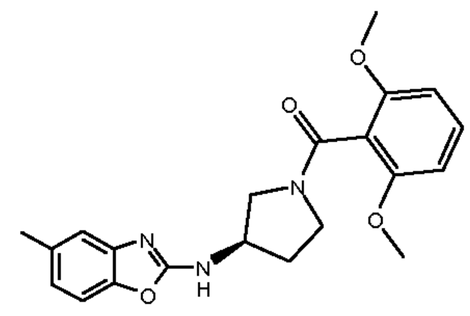
No.	structure	MW	name	starting materials	MW found (MH+)
22		417.3	(4-Chloro-2-methoxy-phenyl)-[3-(7-chloro-quinazolin-2-ylamino)-pyrrolidin-1-yl]-methanone	(7-Chloro-quinazolin-2-yl)-pyrrolidin-3-yl-amine (intermediate 2) and 4-Chloro-2-methoxy-benzoic acid (commercially available)	417.4
23		428.9	7-Chloro-2-[1-(2,6-dimethoxy-benzoyl)-pyrrolidin-3-ylamino]-3*H*-quinazolin-4-one	7-Chloro-2-(pyrrolidin-3-ylamino)-3H-quinazolin-4-one (intermediate 3) and 2,6-Dimethoxy-benzoyl chloride (commercially available)	429.4
24		378.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-chloro-quinoxaline (commercially available), 3-(R)-amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) (coupling at elevated temperature) and 2,6-dimethoxybenzoyl chloride (commercially available)	379.2

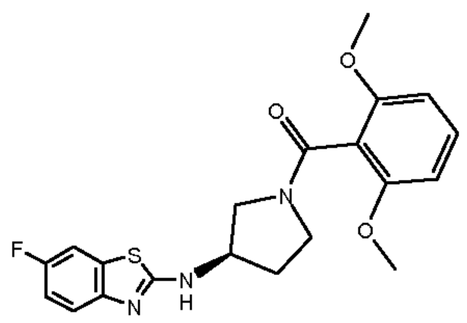
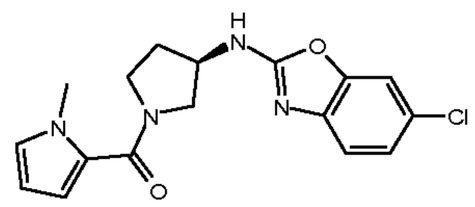
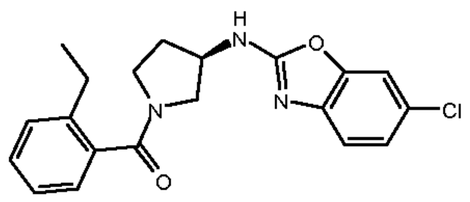
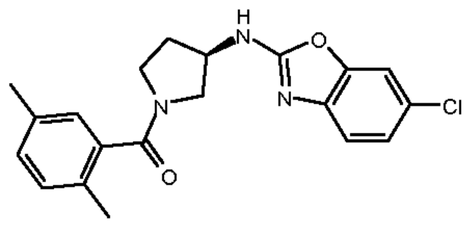
No.	structure	MW	name	starting materials	MW found (MH+)
25		417.9	[(R)-3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2,6-dichloro-benzothiazole (commercially available), 3-(R) -amino-pyrrolidine-1-carboxylic acid tert-butyl ester (commercially available) and 2,6-dimethoxybenzoyl chloride (commercially available).	418.1
26		366.8	2-[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidine-1-carbonyl]-benzonitrile	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride and 2-Cyano-benzoic acid (commercially available)	367.1
27		371.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methoxy-benzoic acid (commercially available)	372.1
28		406.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyrrol-1-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Pyrrol-1-yl-benzoic acid (commercially available)	407.1

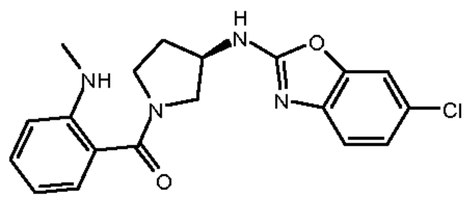
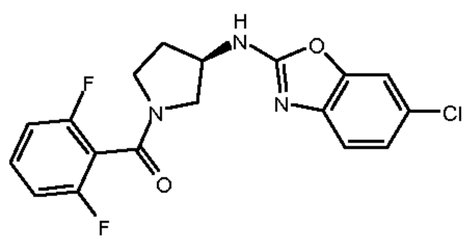
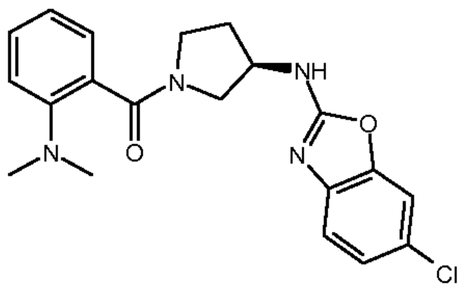
No.	structure	MW	name	starting materials	MW found (MH+)
29		389.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(4-fluoro-2-methoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 4-Fluoro-2-methoxy-benzoic acid (commercially available)	390.1
30		385.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-4-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methoxy-4-methyl-benzoic acid (commercially available)	386.1
31		385.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methoxy-5-methyl-benzoic acid (commercially available)	386.1
32		410.7	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,4-dichloro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,4-Dichloro-benzoic acid (commercially available)	410

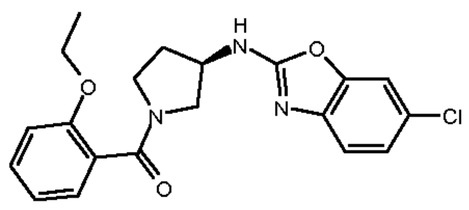
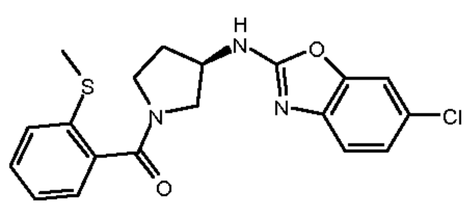
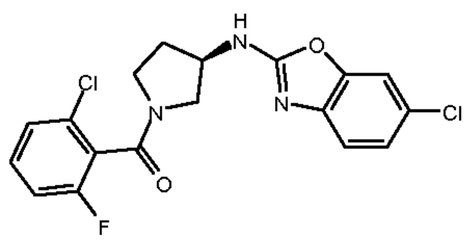
No.	structure	MW	name	starting materials	MW found (MH+)
33		410.7	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dichloro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,6-Dichloro-benzoic acid (commercially available)	410
34		369.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,4-dimethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,4-Dimethyl-benzoic acid (commercially available)	370.1
35		390.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Chloro-6-methyl-benzoic acid (commercially available)	390.1
36		390.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-chloro-2-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Chloro-2-methyl-benzoic acid (commercially available)	390.1

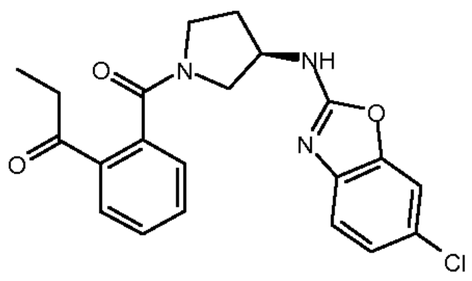
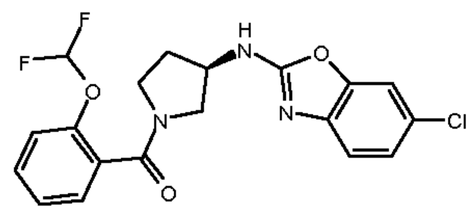
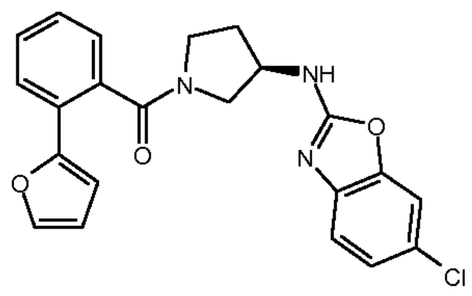
No.	structure	MW	name	starting materials	MW found (MH+)
37		390.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(4-chloro-2-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 4-Chloro-2-methyl-benzoic acid (commercially available)	390.1
38		361.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(3-methyl-thiophen-2-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 3-Methyl-thiophene-2-carboxylic acid (commercially available)	362.1
39		376.2	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Chloro-benzoic acid (commercially available)	376
40		390.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-4-methyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Chloro-4-methyl-benzoic acid (commercially available)	390.1

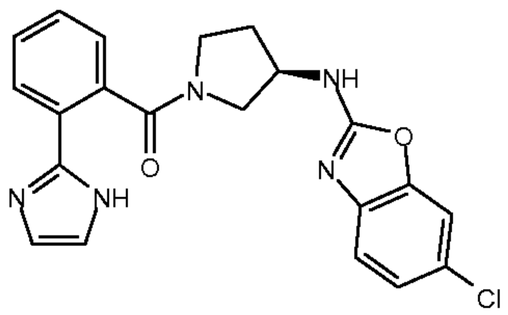
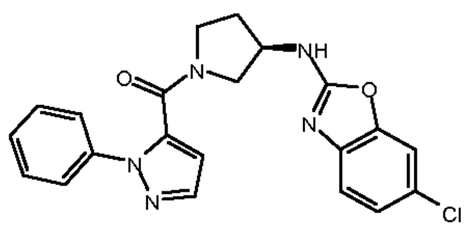
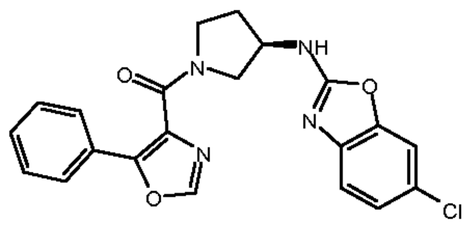
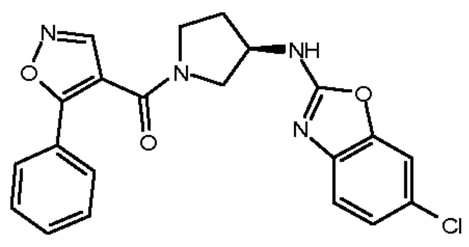
No.	structure	MW	name	starting materials	MW found (MH+)
41		412.9	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5) and 2,6-Dichloro-quinoxaline (commercially available)	413.1
42		412.9	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5) and 2,7-Dichloro-quinoxaline (commercially available)	413.1
43		417.9	[(R)-3-(4-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5) and 2,4-dichloro-benzothiazole (commercially available)	418.1
44		381.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(5-methyl-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5) and 2-chloro-5-methyl-1,3-benzoxazole (commercially available)	382.2

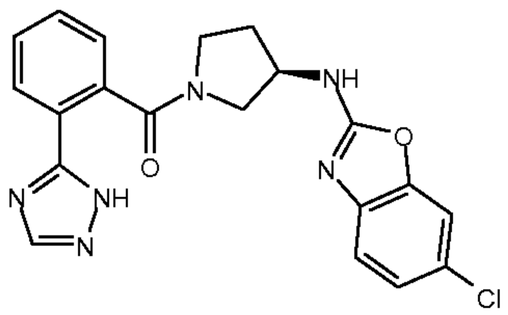
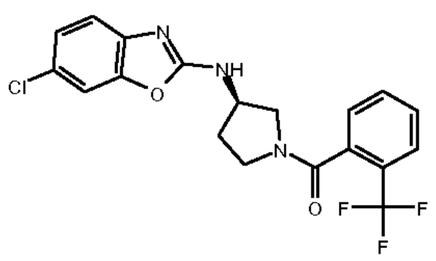
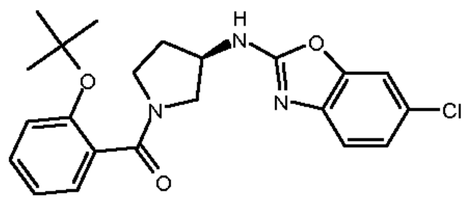
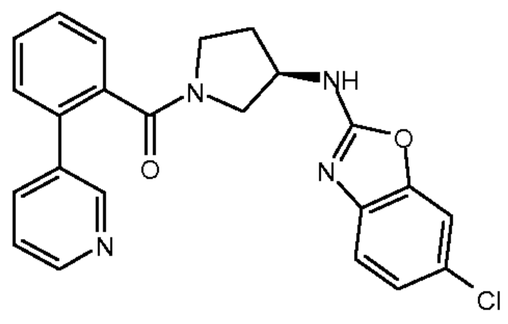
No.	structure	MW	name	starting materials	MW found (MH+)
45		401.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5) and 2-Chloro-5-fluorobenzothiazole (commercially available)	402.1
46		344.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(1-methyl-1*H*-pyrrol-2-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 1-Methyl-1H-pyrrole-2-carboxylic acid (commercially available)	345.1
47		369.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Ethyl-benzoic acid (commercially available)	370.1
48		369.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,5-dimethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,5-Dimethyl-benzoic acid (commercially available)	370.1

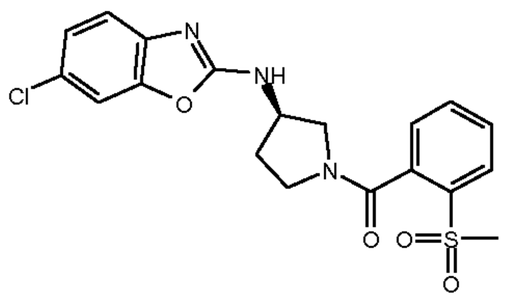
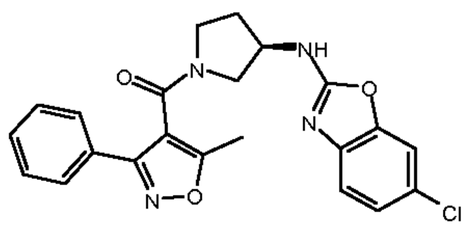
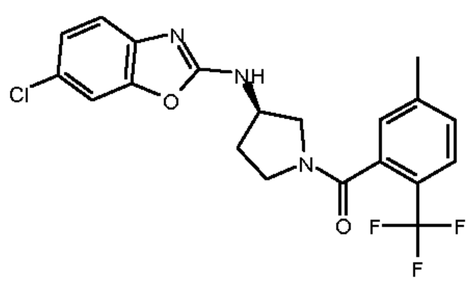
No.	structure	MW	name	starting materials	MW found (MH+)
49		370.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methylamino-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methylamino-benzoic acid (commercially available)	371.1
50		377.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-difluoro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,6-Difluoro-benzoic acid (commercially available)	378.1
51		384.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-dimethylamino-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Dimethylamino-benzoic acid (commercially available)	385.1

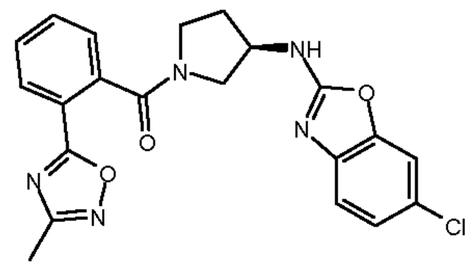
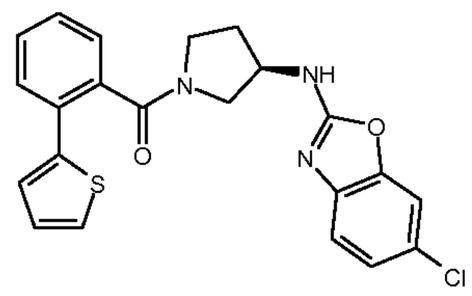
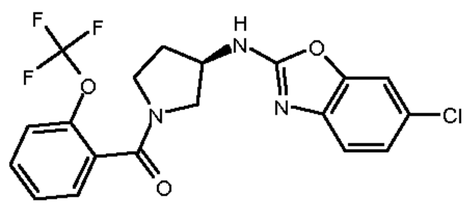
No.	structure	MW	name	starting materials	MW found (MH+)
52		385.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Ethoxy-benzoic acid (commercially available)	386.1
53		387.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methylsulfanyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methylsulfanyl-benzoic acid (commercially available)	388.1
54		394.2	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-fluoro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Chloro-6-fluoro-benzoic acid (commercially available)	394

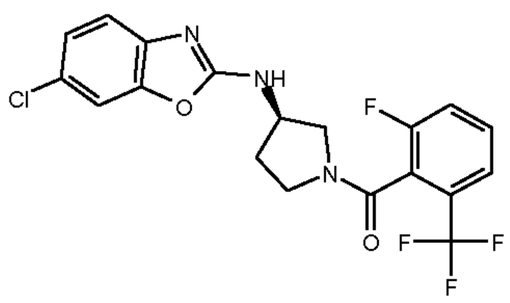
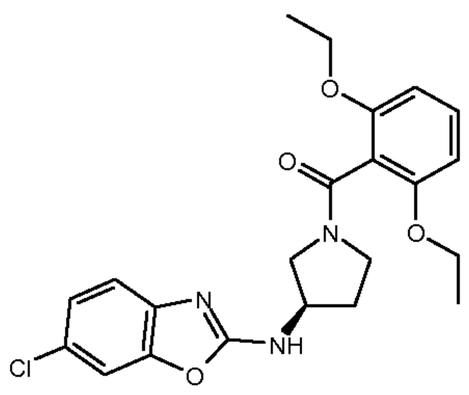
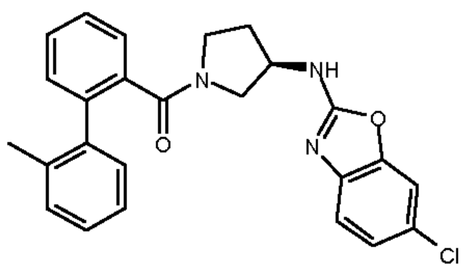
No.	structure	MW	name	starting materials	MW found (MH+)
55		397.9	1-{2-[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidine-1-carbonyl]-phenyl}-propan-1-one	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Propionyl-benzoic acid (commercially available)	398.1
56		407.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-difluoromethoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Difluoromethoxy-benzoic acid (commercially available)	408.1
57		407.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-furan-2-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Furan-2-yl-benzoic acid (commercially available)	408.1

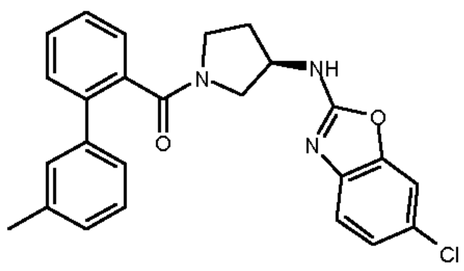
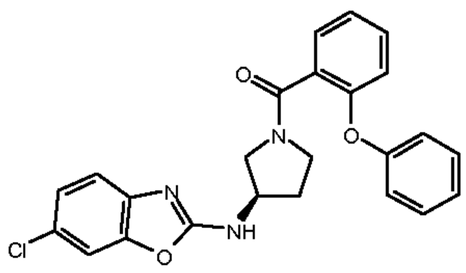
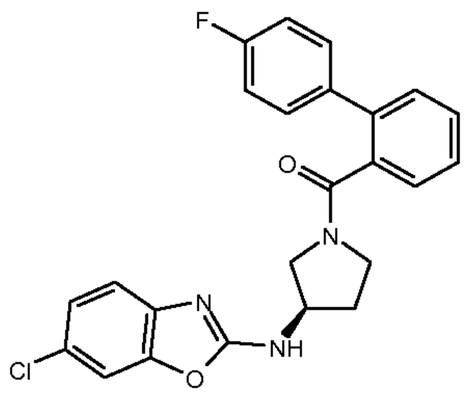
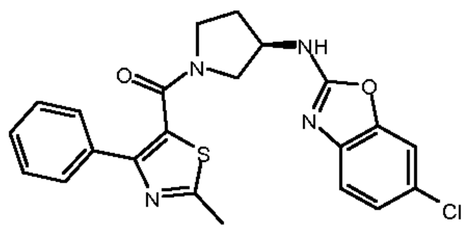
No.	structure	MW	name	starting materials	MW found (MH+)
58		407.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1*H*-imidazol-2-yl)-phenyl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-(1H-Imidazol-2-yl)-benzoic acid (commercially available)	408.1
59		407.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-phenyl-2*H*-pyrazol-3-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Phenyl-2H-pyrazole-3-carboxylic acid (commercially available)	408.1
60		408.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-oxazol-4-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Phenyl-oxazole-4-carboxylic acid (commercially available)	409.1
61		408.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Phenyl-isoxazole-4-carboxylic acid (commercially available)	409.1

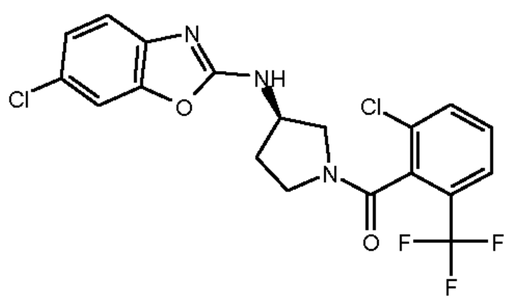
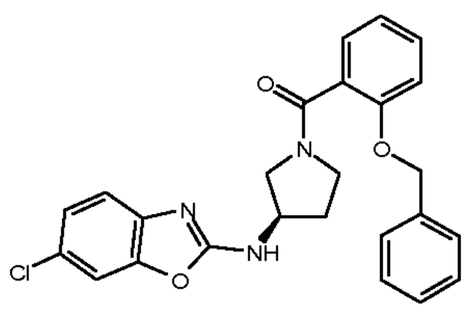
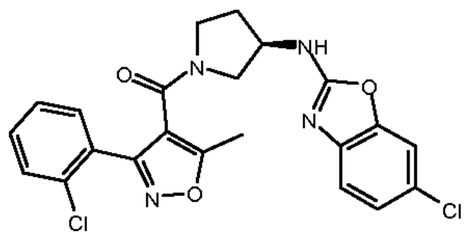
No.	structure	MW	name	starting materials	MW found (MH+)
62		408.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(2*H*-[1,2,4]triazol-3-yl)-phenyl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-(2H-[1,2,4]Triazol-3-yl)-benzoic acid (commercially available)	409.1
63		409.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Trifluoromethyl-benzoic acid (commercially available)	410.1
64		413.9	(2-*tert*-Butoxy-phenyl)-[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-tert-Butoxy-benzoic acid (commercially available)	414.1
65		418.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyridin-3-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Pyridin-3-yl-benzoic acid (commercially available)	419.1

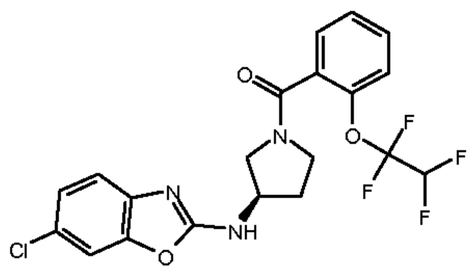
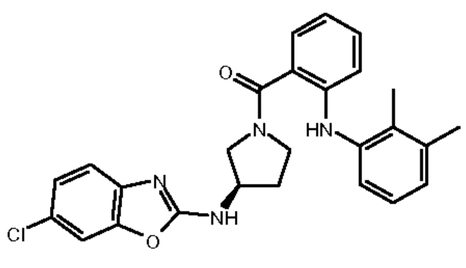
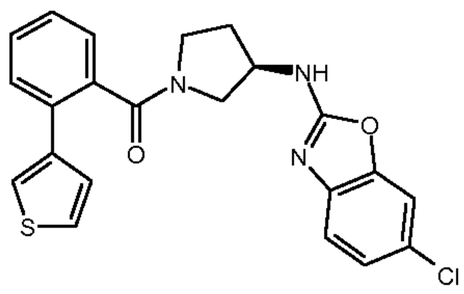
No.	structure	MW	name	starting materials	MW found (MH+)
66		419.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methanesulfonyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methanesulfonyl-benzoic acid (commercially available)	420.1
67		422.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Methyl-3-phenyl-isoxazole-4-carboxylic acid (commercially available)	423.1
68		423.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Methyl-2-trifluoromethyl-benzoic acid (commercially available)	424.1

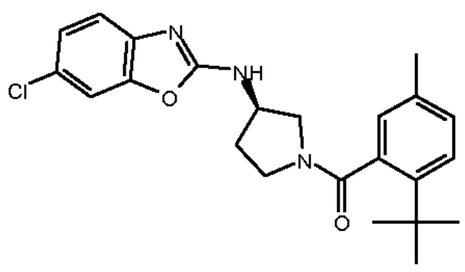
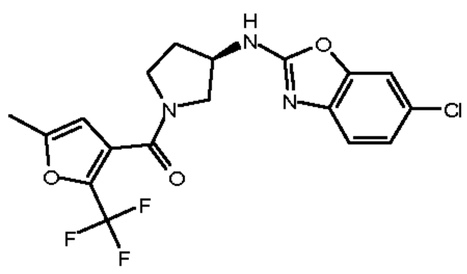
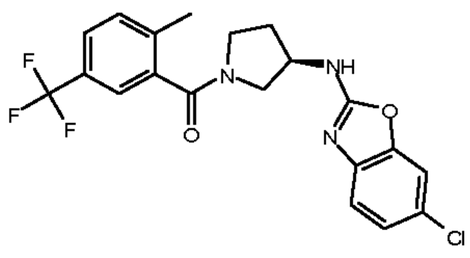
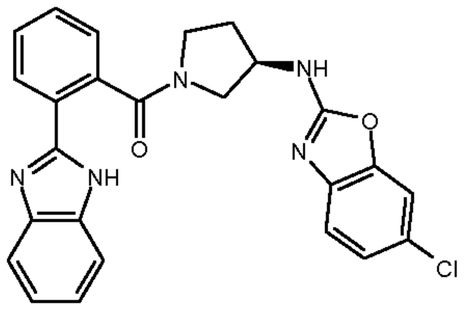
No.	structure	MW	name	starting materials	MW found (MH+)
69		423.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-benzoic acid (commercially available)	424.1
70		423.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-2-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Thiophen-2-yl-benzoic acid (commercially available)	424.1
71		425.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Trifluoromethoxy-benzoic acid (commercially available)	426.1

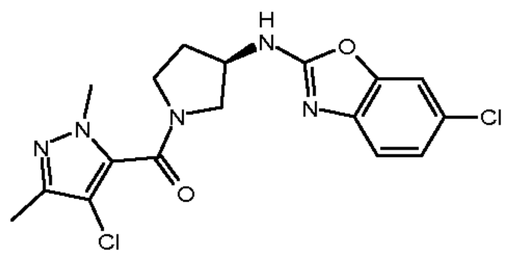
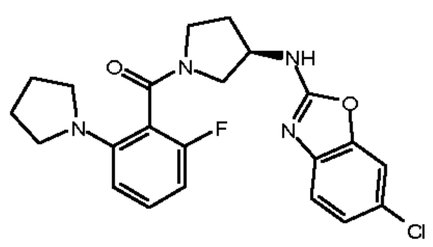
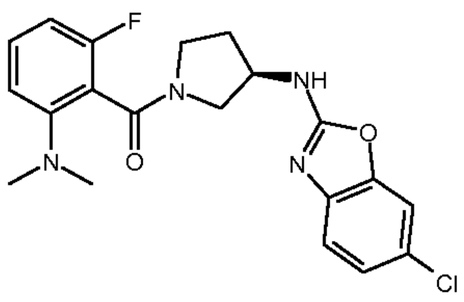
No.	structure	MW	name	starting materials	MW found (MH+)
72		427.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Fluoro-6-trifluoromethyl-benzoic acid (commercially available)	428.1
73		429.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-diethoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2,6-Diethoxy-benzoic acid (commercially available)	430.1
74		431.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2'-methyl-biphenyl-2-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2'-Methyl-biphenyl-2-carboxylic acid (commercially available)	432.1

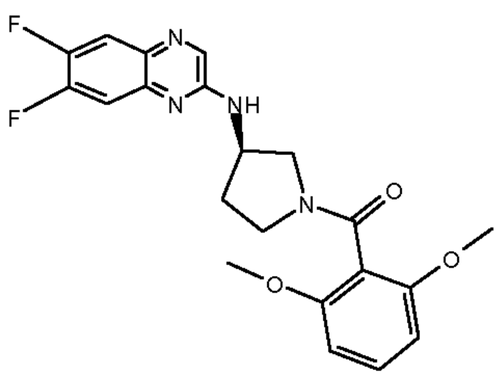
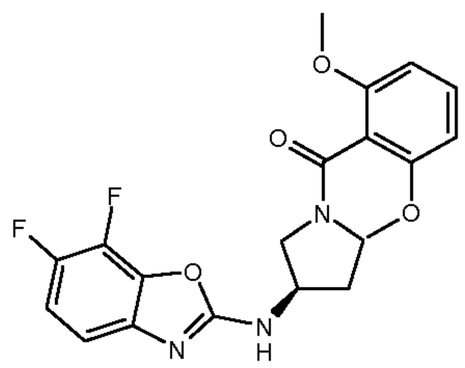
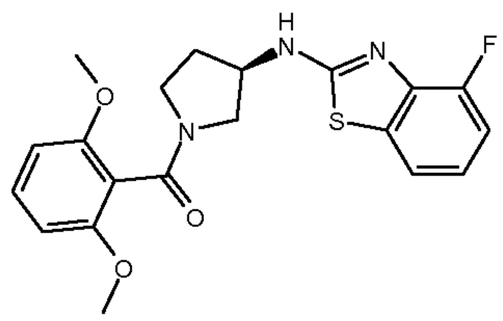
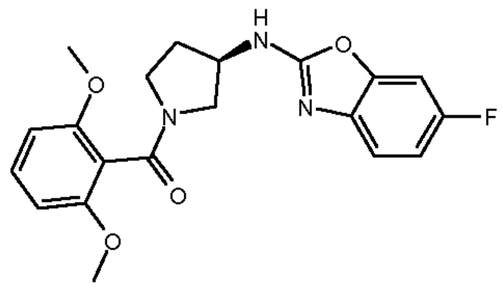
No.	structure	MW	name	starting materials	MW found (MH+)
75		431.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(3'-methyl-biphenyl-2-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 3'-Methyl-biphenyl-2-carboxylic acid (commercially available)	432.1
76		433.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-phenoxy-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Phenoxy-benzoic acid (commercially available)	434.1
77		435.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(4'-fluoro-biphenyl-2-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 4'-Fluoro-biphenyl-2-carboxylic acid (commercially available)	436.1
78		438.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-4-phenyl-thiazol-5-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methyl-4-phenyl-thiazole-5-carboxylic acid (commercially available)	439.1

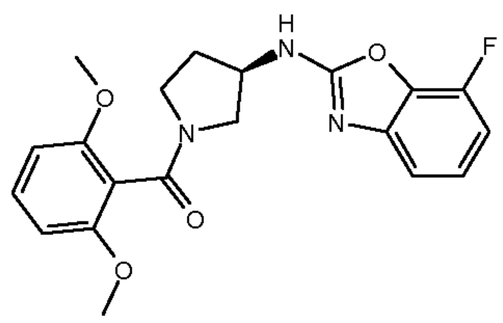
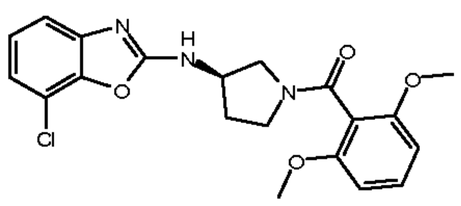
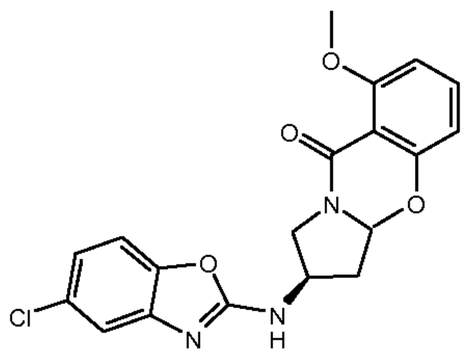
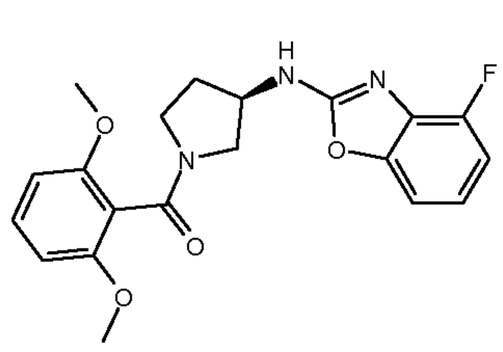
No.	structure	MW	name	starting materials	MW found (MH+)
79		444.2	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-trifluoromethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Chloro-6-trifluoromethyl-benzoic acid (commercially available)	444.1
80		447.9	(2-Benzyloxy-phenyl)-[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Benzyloxy-benzoic acid (commercially available)	448.1
81		457.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 3-(2-Chloro-phenyl)-5-methyl-isoxazole-4-carboxylic acid (commercially available)	457.1

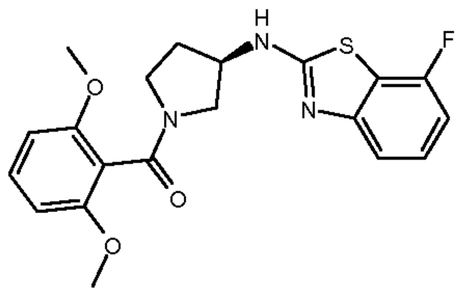
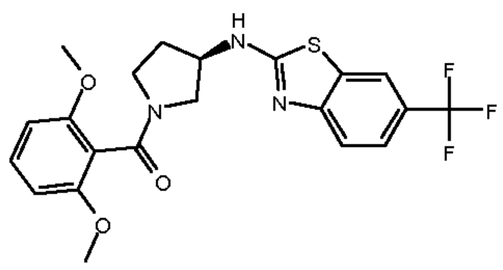
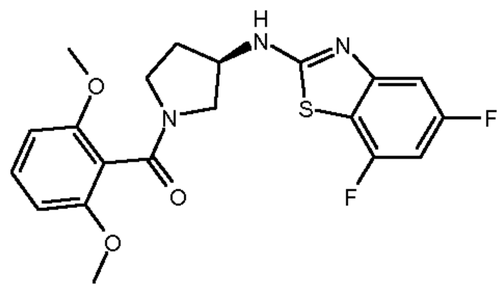
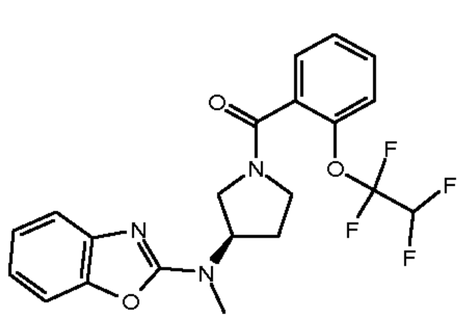
No.	structure	MW	name	starting materials	MW found (MH+)
82		457.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Pentafluoroethyloxy-benzoic acid (commercially available)	458.1
83		461.0	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(2,3-dimethyl-phenylamino)-phenyl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-(2,3-Dimethyl-phenylamino)-benzoic acid (commercially available)	461.2
84		423.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-3-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Thiophen-3-yl-benzoic acid (commercially available)	424.1

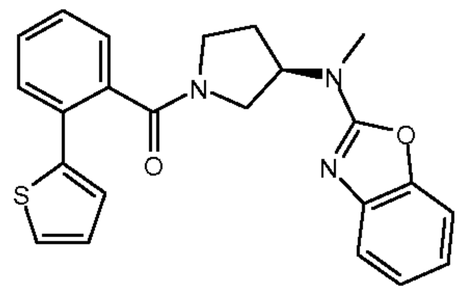
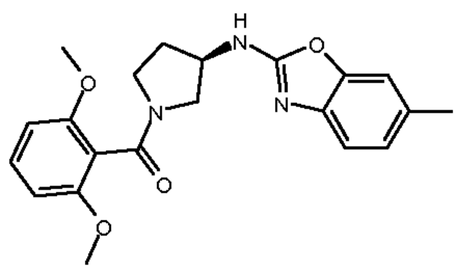
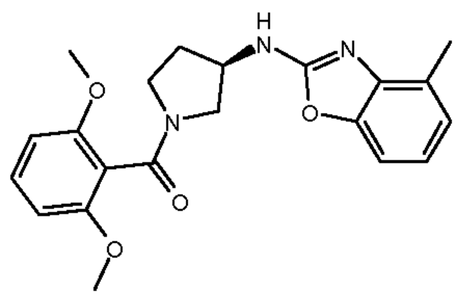
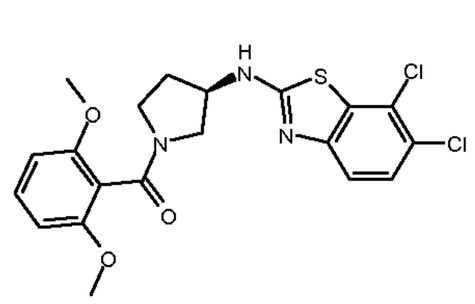
No.	structure	MW	name	starting materials	MW found (MH+)
85		411.9	(2-*tert*-Butyl-5-methyl-phenyl)-[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-tert-Butyl-5-methyl-benzoic acid (commercially available)	412.1
86		413.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-furan-3-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 5-Methyl-2-trifluoromethyl-furan-3-carboxylic acid (commercially available)	414.1
87		423.8	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-trifluoromethyl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Methyl-5-trifluoromethyl-benzoic acid (commercially available)	424.1
88		457.9	[2-(1*H*-Benzoimidazol-2-yl)-phenyl]-[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-(1H-Benzoimidazol-2-yl)-benzoic acid (commercially available)	458.1

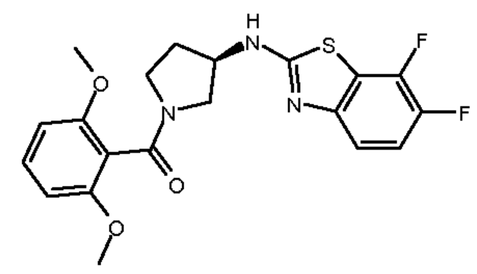
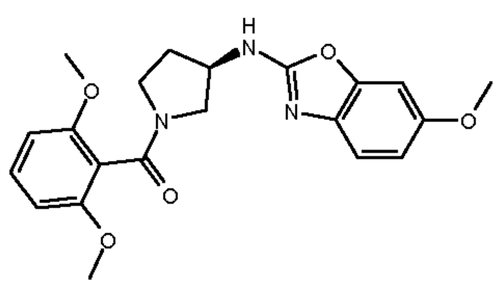
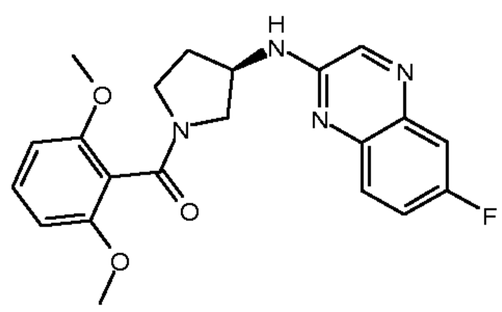
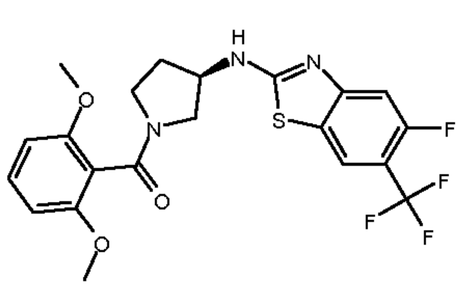
No.	structure	MW	name	starting materials	MW found (MH+)
89		394.3	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(4-chloro-2,5-dimethyl-2*H*-pyrazol-3-yl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 4-Chloro-2,5-dimethyl-2H-pyrazole-3-carboxylic acid (commercially available)	394.1
90		428.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-pyrrolidin-1-yl-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Fluoro-6-pyrrolidin-1-yl-benzoic acid (commercially available)	429.1
91		402.9	[(R)-3-(6-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-dimethylamino-6-fluoro-phenyl)-methanone	(6-Chloro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine, hydrochloride (intermediate 4) and 2-Dimethylamino-6-fluoro-benzoic acid (commercially available)	403.1

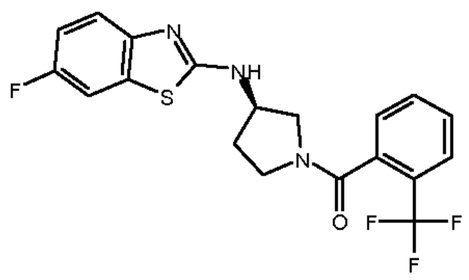
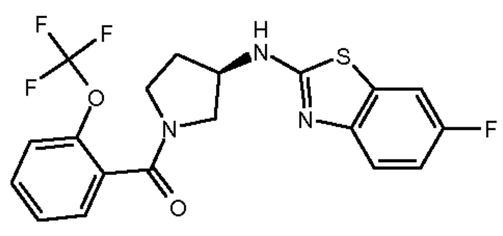
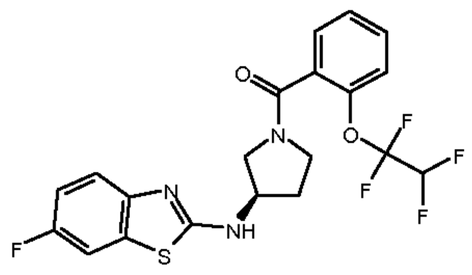
No.	structure	MW	name	starting materials	MW found (MH+)
92		414.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	415.1
93		403.4	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2-Chloro-6,7-difluoro-benzooxazole (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	404.1
94		401.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	402.1
95		385.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	386.1

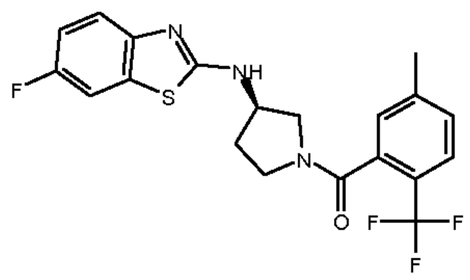
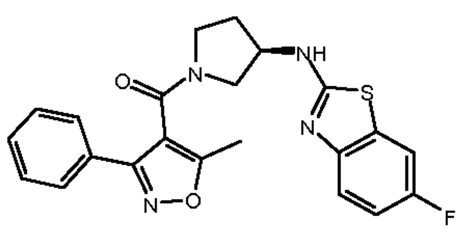
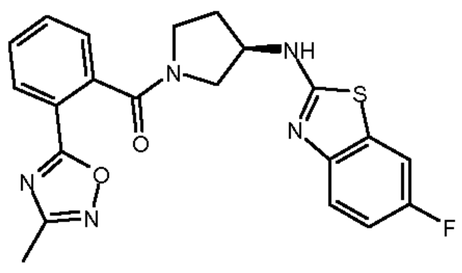
No.	structure	MW	name	starting materials	MW found (MH+)
96		385.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(7-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	386.1
97		401.8	[(R)-3-(7-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2,7-Dichlorobenzoxazole (WO8301448A1) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	402.1
98		401.8	[(R)-3-(5-Chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2,6-Dichlorobenzoxazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	402.1
99		385.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(4-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-4-fluoro-benzooxazole (intermediate 7) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	386.1

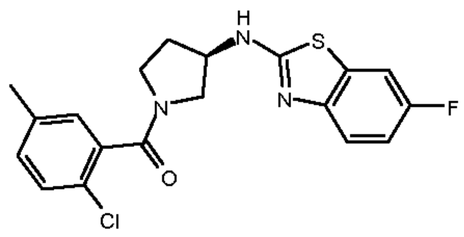
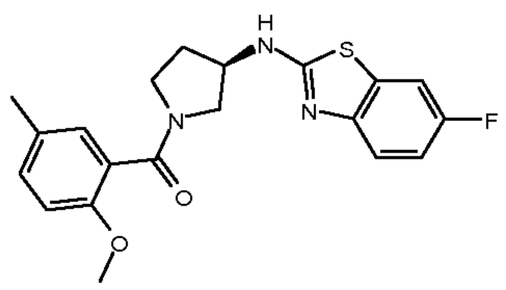
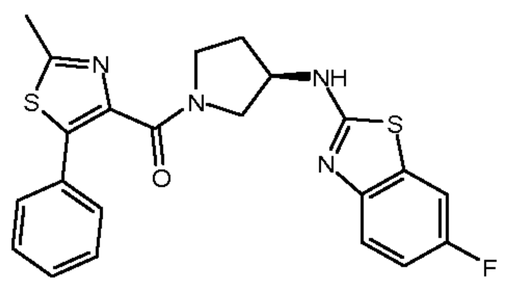
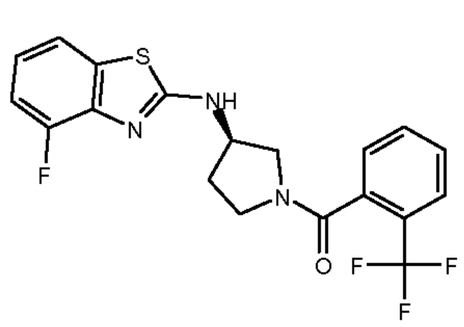
No.	structure	MW	name	starting materials	MW found (MH+)
100		401.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(7-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-7-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	402.1
101		451.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-trifluoromethylbenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	452.1
102		419.5	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	420.1
103		437.4	[(R)-3-(Benzooxazol-2-yl-methyl-amino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	Benzooxazol-2-yl-methyl-(R)-pyrrolidin-3-yl-amine (intermediate 8) and 2-(1,1,2,2-Tetrafluoro-ethoxy)-benzoic acid (commercially available)	438.2

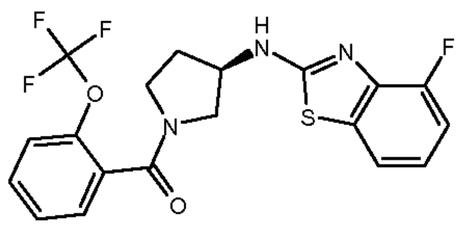
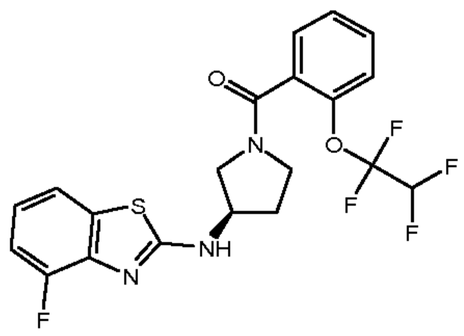
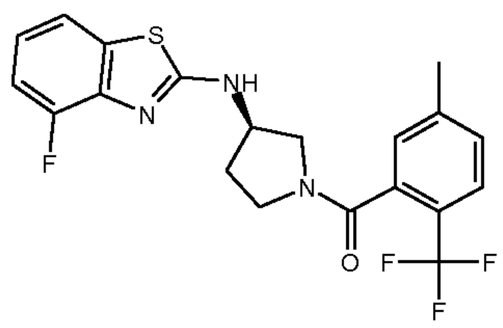
No.	structure	MW	name	starting materials	MW found (MH+)
104		403.5	[(R)-3-(Benzooxazol-2-yl-methyl-amino)-pyrrolidin-1-yl]-(2-thiophen-2-yl-phenyl)-methanone	Benzooxazol-2-yl-methyl-(R)-pyrrolidin-3-yl-amine (intermediate 8) and 2-Thiophen-2-yl-benzoic acid (commercially available)	404.2
105		381.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-methyl-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-methylbenzooxazole (Organic Process Research & Development, 1997, 1, 331) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	382.2
106		381.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(4-methyl-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-methylbenzooxazole (WO2008005368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	382.2
107		452.4	[(R)-3-(6,7-Dichloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2,6,7-Trichloro-benzothiazole (intermediate 9) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	452.1

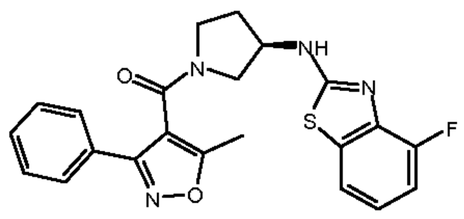
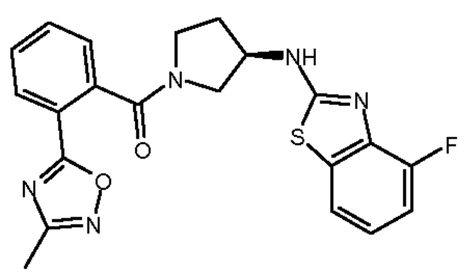
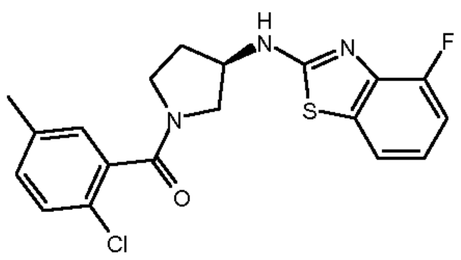
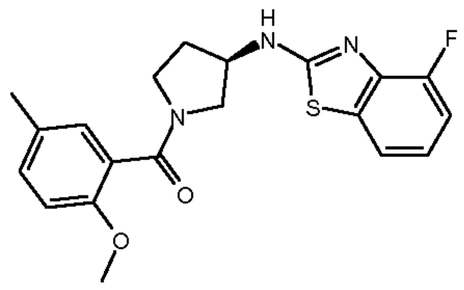
No.	structure	MW	name	starting materials	MW found (MH+)
108		419.5	[(R)-3-(6,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone	2-chloro-6,7-difluoro-benzthiazole (WO2007146066) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	420.1
109		397.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-methoxy-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-methoxybenzoxazole (EP621271) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	398.2
110		396.4	(2,6-Dimethoxy-phenyl)-[(R)-3-(6-fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-fluoroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	397.2
111		469.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(5-fluoro-6-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-5-fluoro-6-trifluoromethylbenzothiazole (WO2007023882) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	470.2

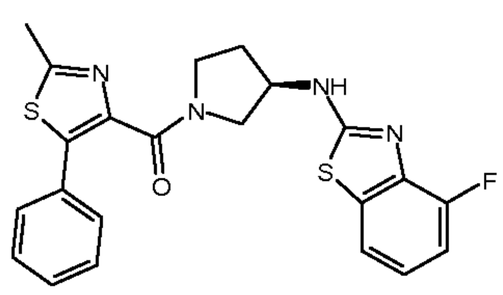
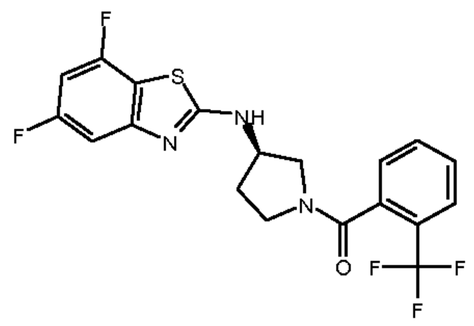
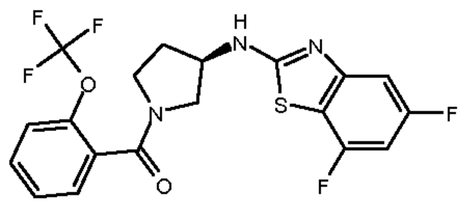
No.	structure	MW	name	starting materials	MW found (MH+)
112		409.4	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	410.1
113		425.4	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	426.1
114		457.4	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	458.2

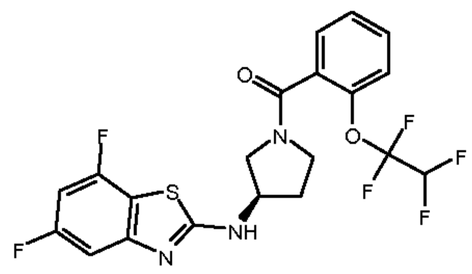
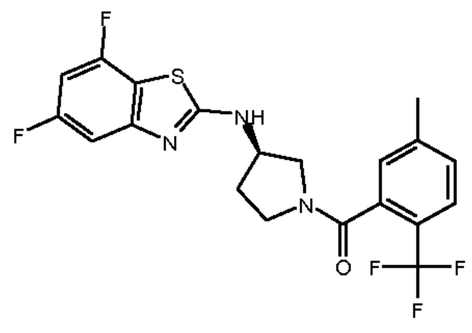
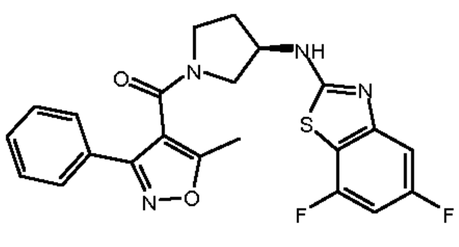
No.	structure	MW	name	starting materials	MW found (MH+)
115		423.4	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	424.1
116		422.5	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	423.2
117		423.5	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	424.1

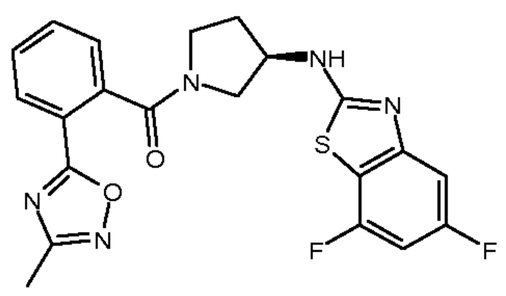
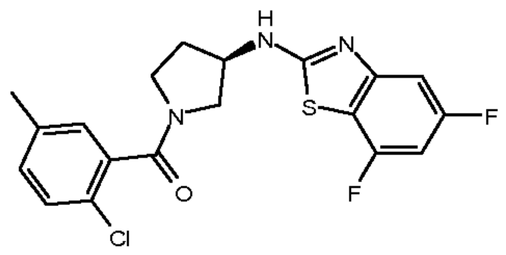
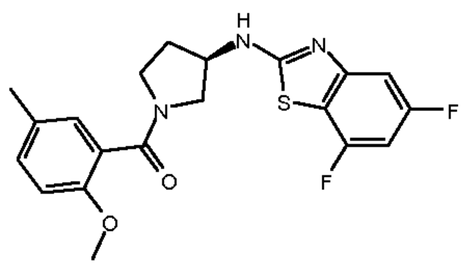
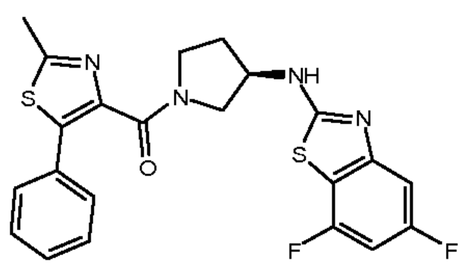
No.	structure	MW	name	starting materials	MW found (MH+)
118		389.9	(2-Chloro-5-methyl-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	390.1
119		385.5	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	386.1
120		438.5	[(R)-3-(6-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-6-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	439.1
121		409.4	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	410.1

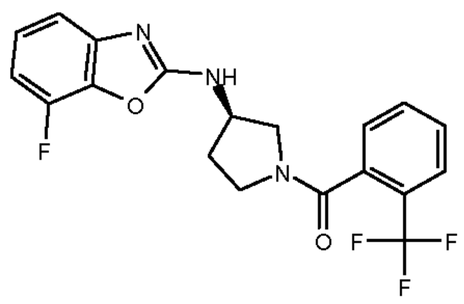
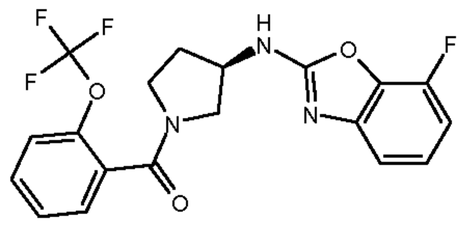
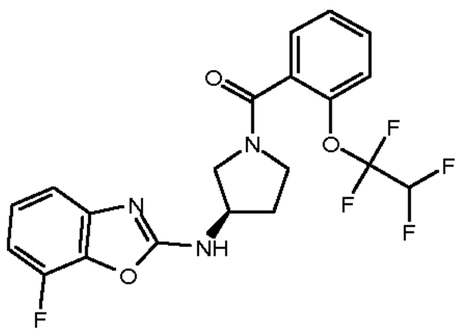
No.	structure	MW	name	starting materials	MW found (MH+)
122		425.4	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	426.1
123		457.4	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	458.1
124		423.4	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	424.1

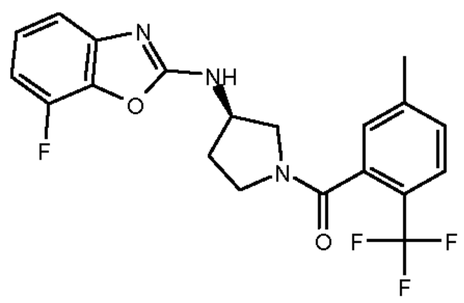
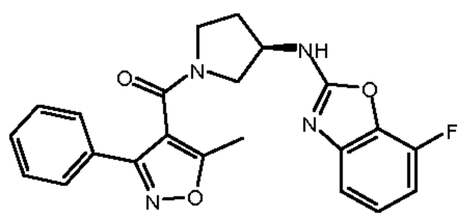
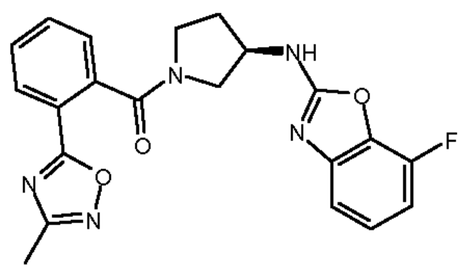
No.	structure	MW	name	starting materials	MW found (MH+)
125		422.5	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	423.1
126		423.5	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	424.1
127		389.9	(2-Chloro-5-methyl-phenyl)-[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	390.1
128		385.5	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	386.1

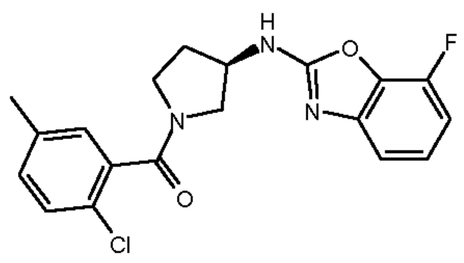
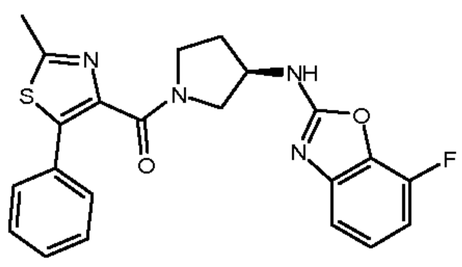
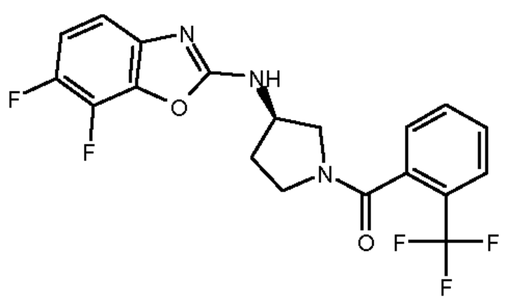
No.	structure	MW	name	starting materials	MW found (MH+)
129		438.5	[(R)-3-(4-Fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-4-fluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	439.1
130		427.4	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	428.1
131		443.4	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	444.1

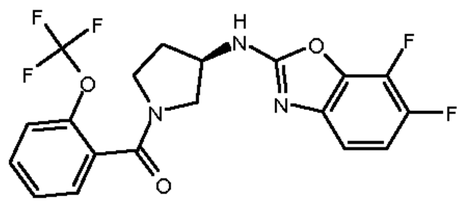
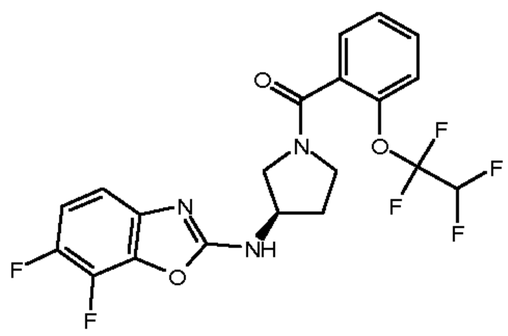
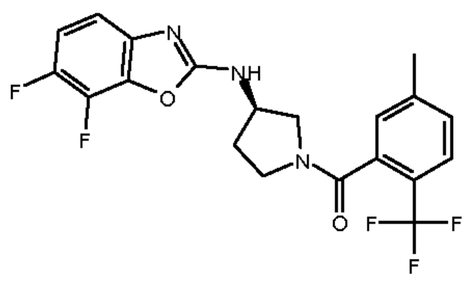
No.	structure	MW	name	starting materials	MW found (MH+)
132		475.4	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	476.2
133		441.4	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	442.1
134		440.5	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	441.1

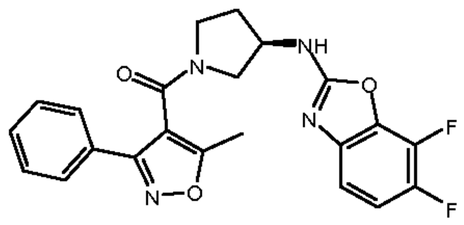
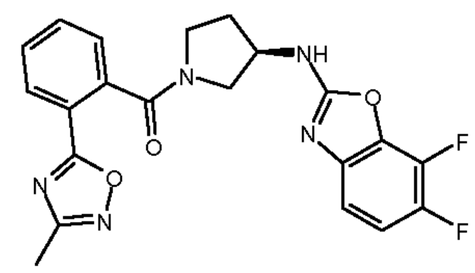
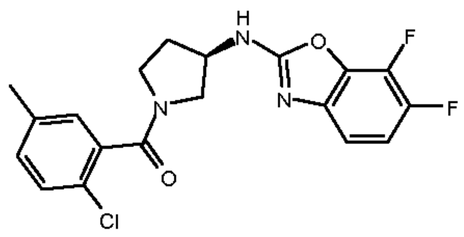
No.	structure	MW	name	starting materials	MW found (MH+)
135		441.5	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	442.2
136		407.9	(2-Chloro-5-methyl-phenyl)-[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	408.1
137		403.5	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	404.2
138		456.5	[(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-5,7-difluorobenzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	457.1

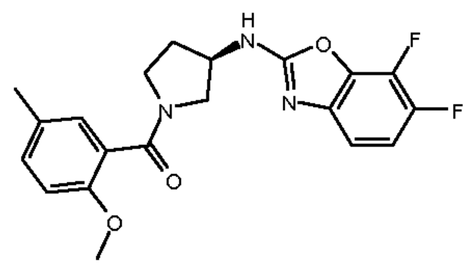
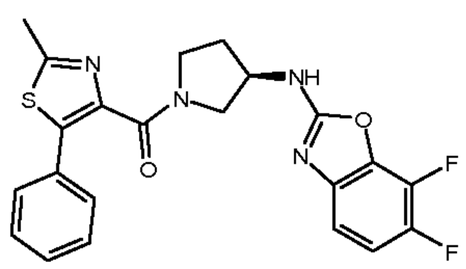
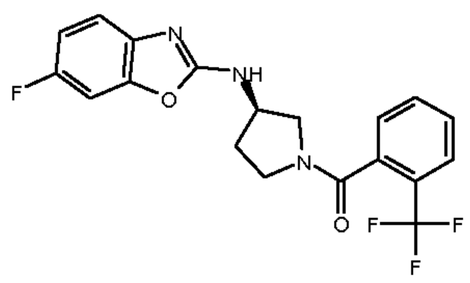
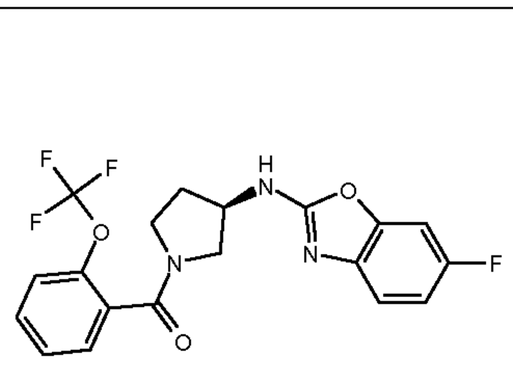
No.	structure	MW	name	starting materials	MW found (MH+)
139		393.3	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	394.1
140		409.3	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	410.1
141		441.4	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	442.1

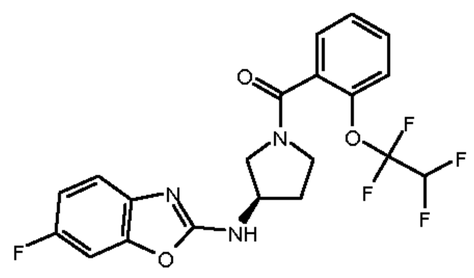
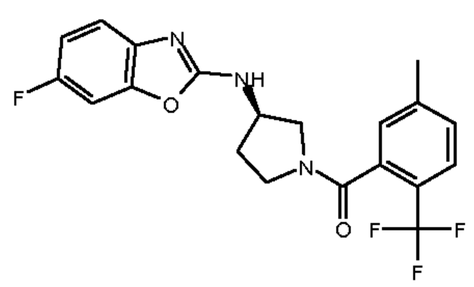
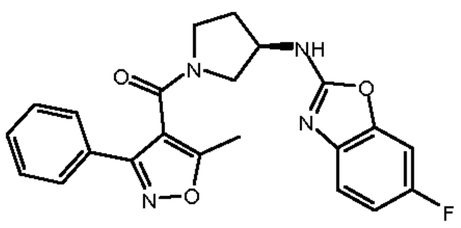
No.	structure	MW	name	starting materials	MW found (MH+)
142		407.4	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	408.2
143		406.4	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	407.2
144		407.4	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	408.2

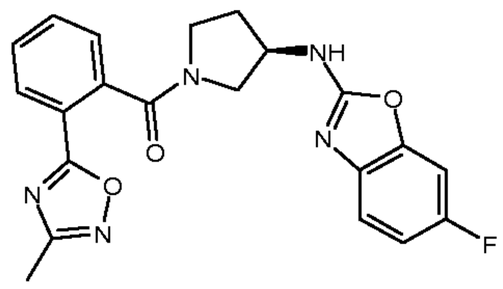
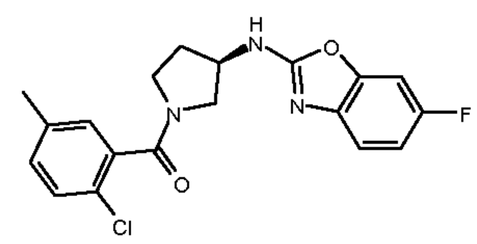
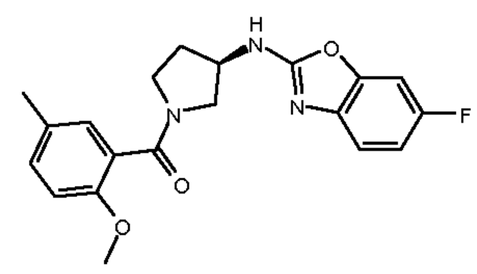
No.	structure	MW	name	starting materials	MW found (MH+)
145		373.8	(2-Chloro-5-methyl-phenyl)-[(R)-3-(7-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	374.1
146		422.5	[(R)-3-(7-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-7-fluorobenzooxazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	423.1
147		411.3	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	412.1

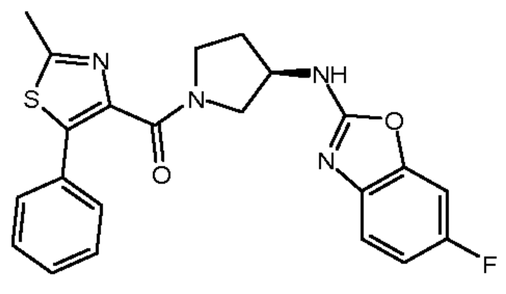
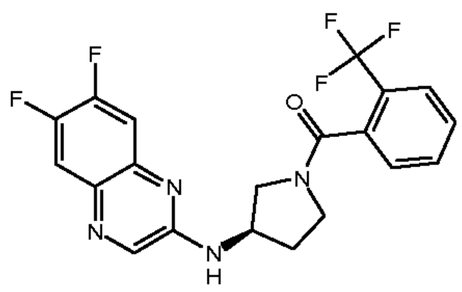
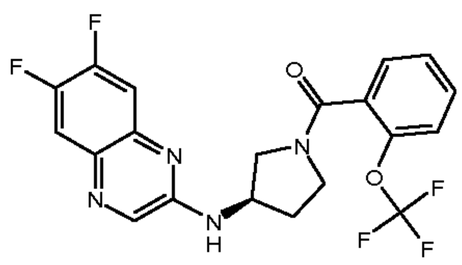
No.	structure	MW	name	starting materials	MW found (MH+)
148		427.3	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	428.1
149		459.3	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	460.2
150		425.4	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	426.1

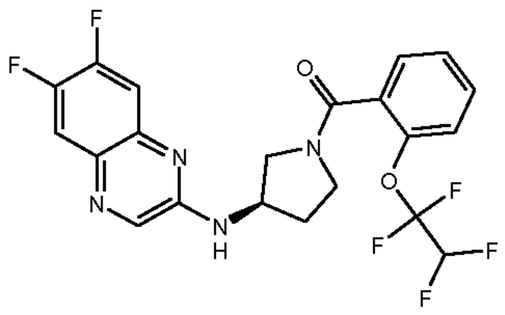
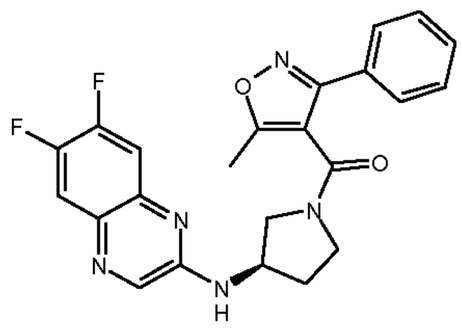
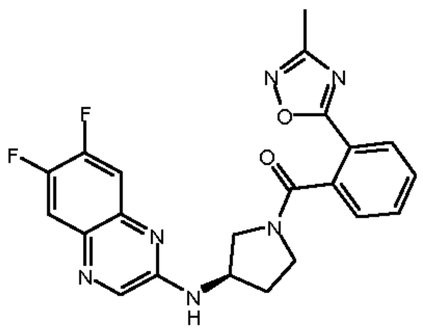
No.	structure	MW	name	starting materials	MW found (MH+)
151		424.4	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	425.2
152		425.4	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	426.2
153		391.8	(2-Chloro-5-methyl-phenyl)-[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	392.1

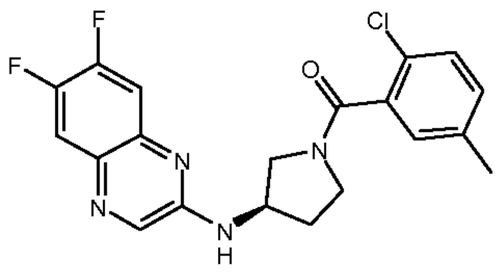
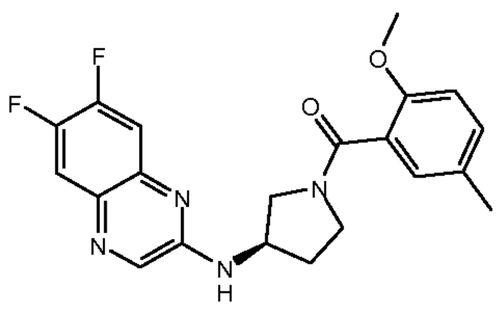
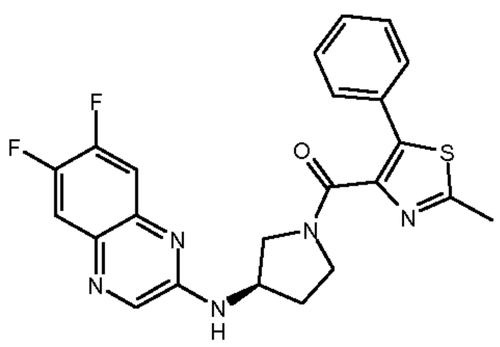
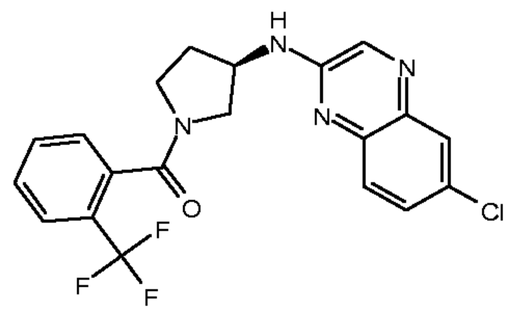
No.	structure	MW	name	starting materials	MW found (MH+)
154		387.4	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	388.2
155		440.5	[(R)-3-(6,7-Difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	(6,7-Difluoro-benzooxazol-2-yl)-(R)-pyrrolidin-3-yl-amine (intermediate 6) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	441.1
156		393.3	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	394.1
157		409.3	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	410.1

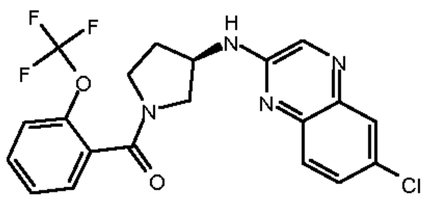
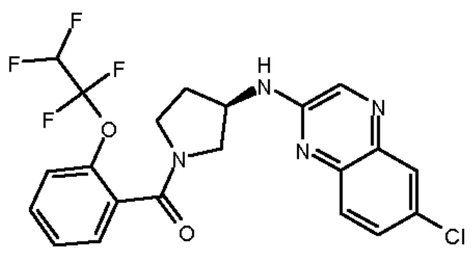
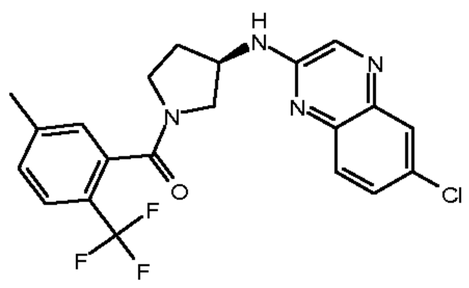
No.	structure	MW	name	starting materials	MW found (MH+)
158		441.4	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	442.1
159		407.4	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	408.2
160		406.4	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	407.2

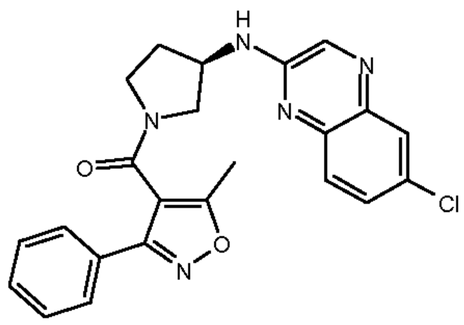
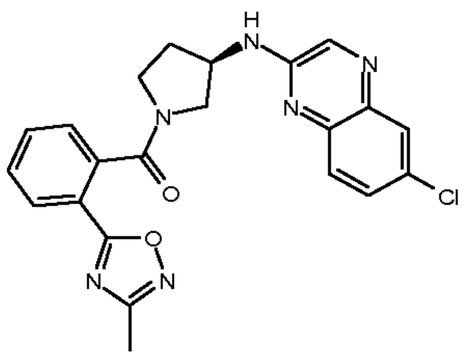
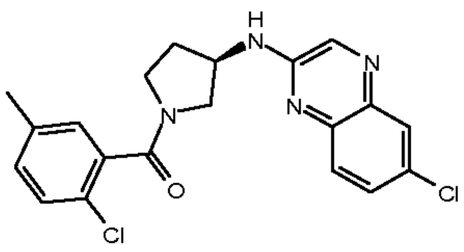
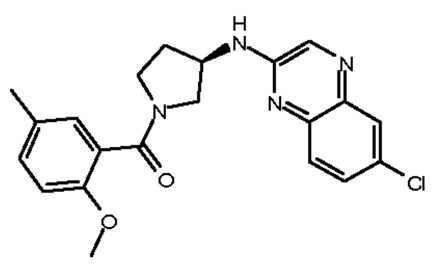
No.	structure	MW	name	starting materials	MW found (MH+)
161		407.4	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	408.2
162		373.8	(2-Chloro-5-methyl-phenyl)-[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	374.1
163		369.4	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	370.2

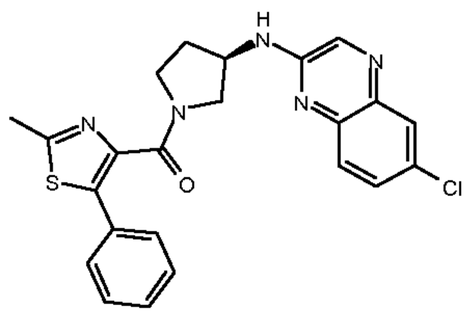
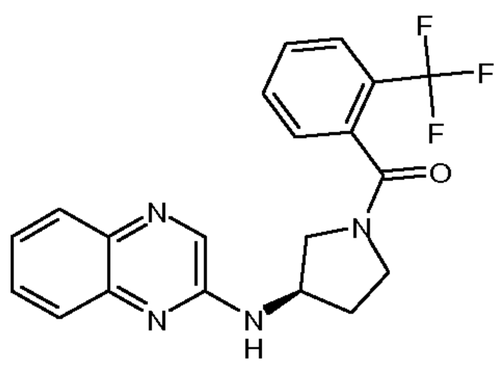
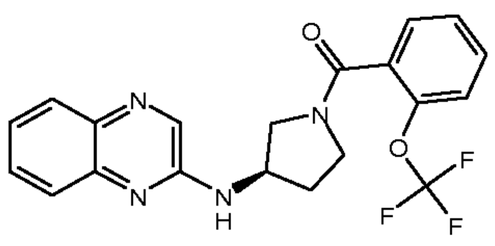
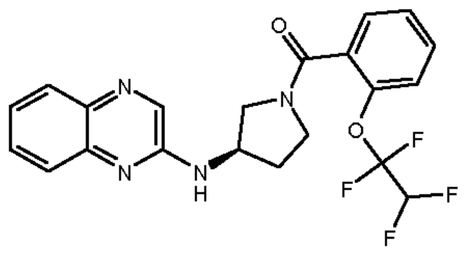
No.	structure	MW	name	starting materials	MW found (MH+)
164		422.5	[(R)-3-(6-Fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-6-fluorobenzothiazole (Bioorganic & Medicinal Chemistry Letters 2007, 17, 4689) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	423.1
165		422.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	423.2
166		438.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	439.2

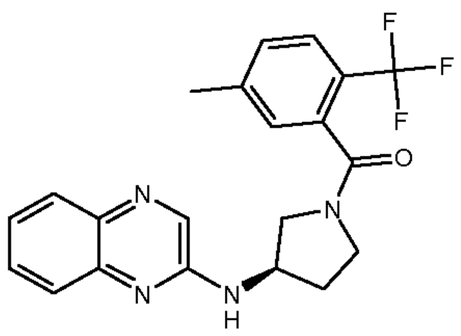
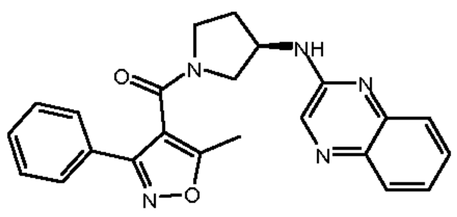
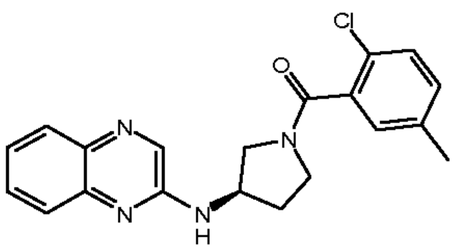
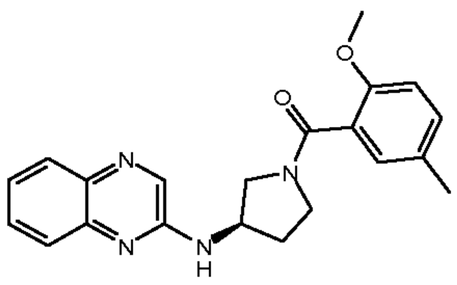
No.	structure	MW	name	starting materials	MW found (MH+)
167		470.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	471.3
168		435.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	436.2
169		436.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	437.2

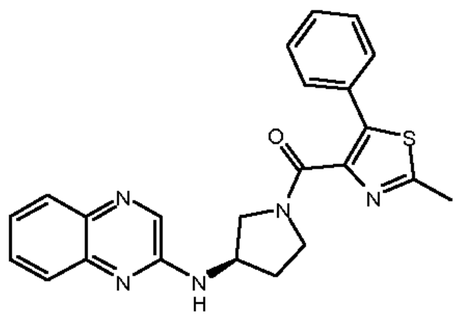
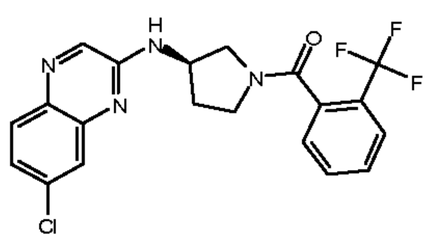
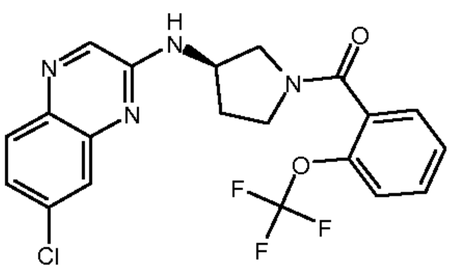
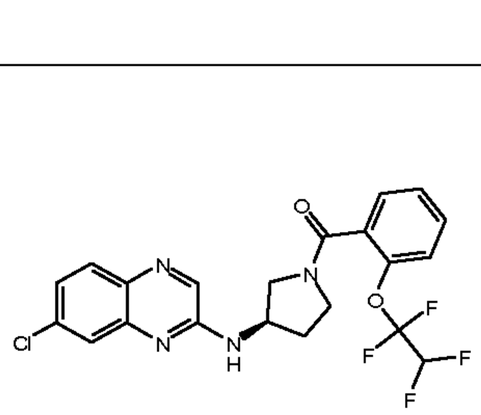
No.	structure	MW	name	starting materials	MW found (MH+)
170		402.8	(2-Chloro-5-methyl-phenyl)-[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	403.2
171		398.4	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	399.2
172		451.5	[(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2-Chloro-6,7-difluoroquinoxaline (WO2003051368) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	452.2
173		420.8	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	421.2

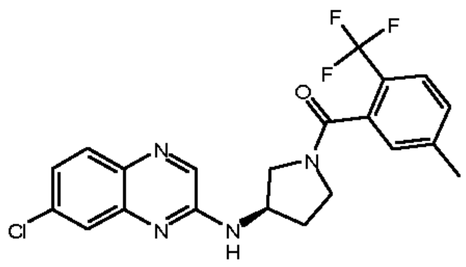
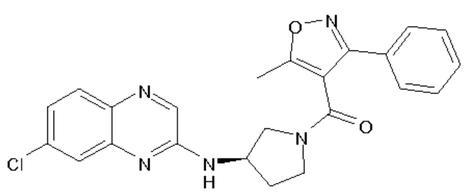
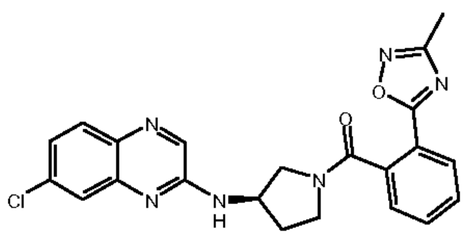
No.	structure	MW	name	starting materials	MW found (MH+)
174		436.8	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	437.2
175		468.8	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	469.2
176		434.8	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	435.2

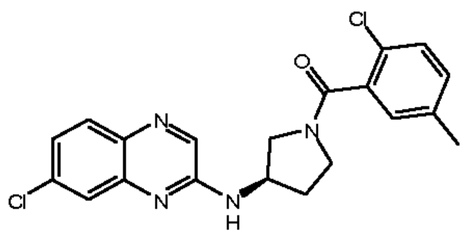
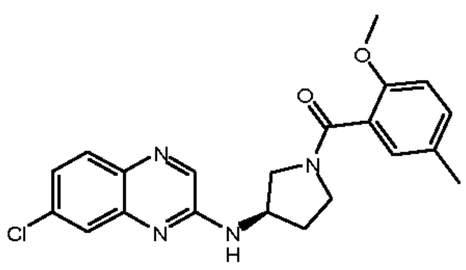
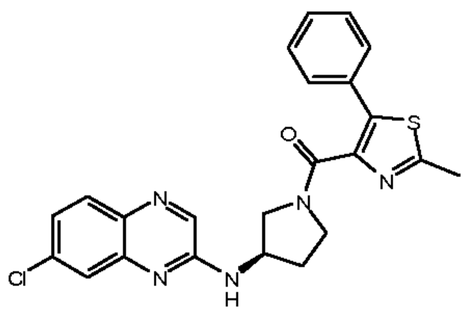
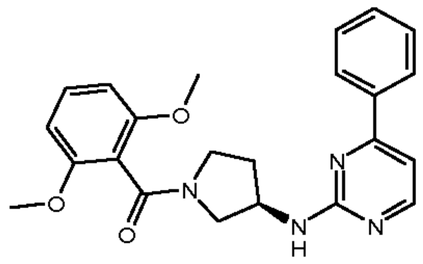
No.	structure	MW	name	starting materials	MW found (MH+)
177		433.9	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	434.2
178		434.9	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	435.2
179		401.3	(2-Chloro-5-methyl-phenyl)-[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	401.2
180		396.9	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	397.2

No.	structure	MW	name	starting materials	MW found (MH+)
181		450.0	[(R)-3-(6-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2,6-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	450.2
182		386.4	[(R)-3-(Quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	387.2
183		402.4	[(R)-3-(Quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	403.2
184		434.4	[(R)-3-(Quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	435.2

No.	structure	MW	name	starting materials	MW found (MH+)
185		400.4	(5-Methyl-2-trifluoromethyl-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	401.2
186		399.5	(5-Methyl-3-phenyl-isoxazol-4-yl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	400.3
187		366.9	(2-Chloro-5-methyl-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	367.2
188		362.4	(2-Methoxy-5-methyl-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	363.2

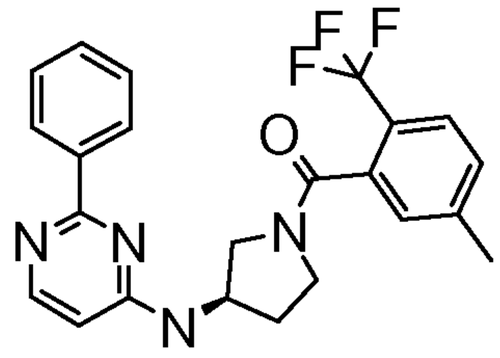
No.	structure	MW	name	starting materials	MW found (MH+)
189		415.5	(2-Methyl-5-phenyl-thiazol-4-yl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	416.2
190		420.8	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethyl-phenyl)-methanone (intermediate 10)	421.2
191		436.8	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-trifluoromethoxy-phenyl)-methanone (intermediate 11)	437.2
192		468.8	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone (intermediate 12)	469.2

No.	structure	MW	name	starting materials	MW found (MH+)
193		434.8	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13)	435.2
194		433.9	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone (intermediate 14)	434.2
195		434.9	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone (intermediate 15)	435.2

No.	structure	MW	name	starting materials	MW found (MH+)
196		401.3	(2-Chloro-5-methyl-phenyl)-[(R)-3-(7-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-chloro-5-methyl-phenyl)-methanone (intermediate 16)	401.2
197		396.9	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methoxy-5-methyl-phenyl)-methanone (intermediate 17)	397.2
198		450.0	[(R)-3-(7-Chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone	2,7-Dichloroquinoxaline (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2-methyl-5-phenyl-thiazol-4-yl)-methanone (intermediate 18)	450.2
199		404.5	(2,6-Dimethoxy-phenyl)-[(R)-3-(4-phenyl-pyrimidin-2-ylamino)-pyrrolidin-1-yl]-methanone	2-Chloro-4-phenylpyrimidine (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (intermediate 5)	405.2

Example 200

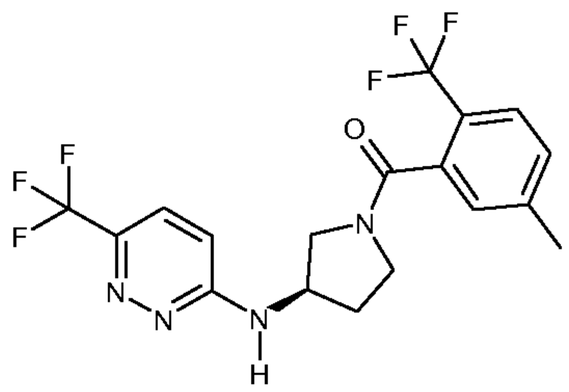
(5-Methyl-2-trifluoromethyl-phenyl)-[(R)-3-(2-phenyl-pyrimidin-4-ylamino)-pyrrolidin-1-yl]-methanone



A solution of 30 mg (0.16 mmol) 4-chloro-2-phenyl-pyrimidine (CAS: 14790-42-2), 42.8 mg (0.16 mmol) ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13), 54.3 mg (0.39 mmol) K_2CO_3 and 6.5 mg (0.039 mmol) KI in 1 mL N,N-dimethylacetamide was heated in a 60 °C for 2 h, and at 100 °C for 23 h. The solvent was removed in vacuo. The residue was dissolved in ethyl acetate and washed twice with water. The organic layer was dried with Na_2SO_4 and filtered. The mixture was concentrated and purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 31 mg (46 %) of the titled compound as a light yellow solid. MS(m/e): 427.2 ($M+H^+$).

Example 201

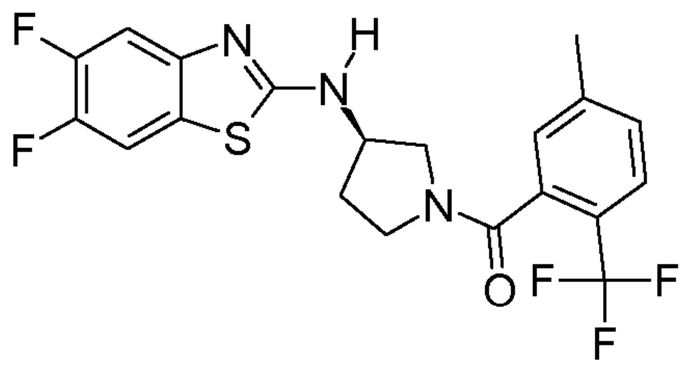
(5-Methyl-2-trifluoromethyl-phenyl)-[(R)-3-(6-trifluoromethyl-pyridazin-3-ylamino)-pyrrolidin-1-yl]-methanone



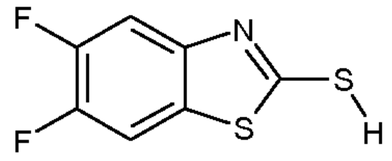
In analogy to the procedure described for example 200, the title compound was prepared from ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13) and 3-chloro-6-trifluoromethyl-pyridazine (commercially available). (MH^+) 419.3.

Example 202

[(R)-3-(5,6-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

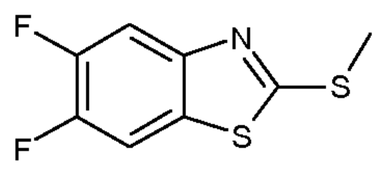


a) step 1: 5,6-Difluoro-benzothiazole-2-thiol



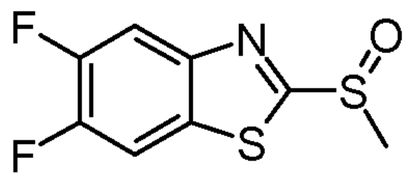
A mixture of 1 g (6.80 mmol) 2,4,5-trifluoroaniline and 1.33 g (8.16 mmol) potassium ethylxanthogenate in 5 mL dry N,N-dimethylformamide was heated in a 95 °C oil bath for 7 h. The reaction mixture was cooled to room temperature and diluted with water (15 mL). The mixture was acidified with aqueous HCl 2N. The precipitate was collected by filtration, washed with water and dried to provide 0.55 g (40 %) of the titled compound as a light yellow solid. MS(m/e): 201.9 ($M-H^+$).

b) step 2: 5,6-Difluoro-2-methylsulfanyl-benzothiazole



A suspension (0 °C) of 300 mg (1.476 mmol) 5,6-difluoro-benzothiazole-2-thiol and 306 mg (2.214 mmol) potassium carbonate in 6 mL N,N-dimethylformamide under nitrogen, were added 110.5 L (1.77 mmol) iodomethane. The mixture was stirred at 0 °C for 1 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate. The combined extracts were washed with water and brine , dried over Na_2SO_4, filtered and concentrated in vacuo to provide 294 mg (91.7 %) of the title compound as a solid. MS(m/e): 218.3 ($M+H^+$).

c) step 3: rac-5,6-Difluoro-2-methanesulfinyl-benzothiazole



To a solution of 240 mg (1.1 mmol) 5,6-difluoro-2-methylsulfanyl-benzothiazole in 8 mL methanol under nitrogen at 0-5 °C, was added drop wise a solution of 1.019 g (1.658 mmol) oxone in 4 mL water. The reaction mixture was stirred at 0 °C for 1 h. The suspension was diluted with water (10mL). The solid was filtered, washed with water and dissolved in dichloromethane. The solution was dried over Na_2SO_4, filtered,

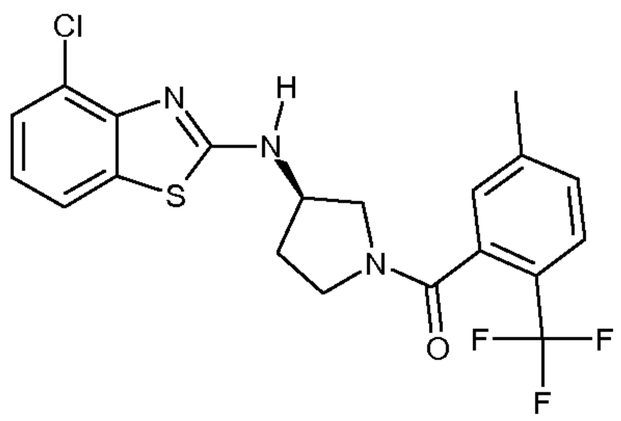
concentrated in vacuo and purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 130 mg (50.6 %) of the title compound as white solid. MS(m/e): 234.1 ($M+H^+$).

d) step 4: [(R)-3-(5,6-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

A mixture of 30 mg (0.129 mmol) rac-5,6-difluoro-2-methanesulfinyl-benzothiazole and 70.3 mg (0.258 mmol) ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13) in 540 µL dimethyl sulfoxide was heated in a 100 °C oil-bath for 4 h. The solution was cooled to room temperature, diluted with water and basified with a saturated $NaHCO_3$ solution. The mixture was stirred for 1 h. The solid was filtered, washed with water and dissolved in dichloromethane. The solution was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude compound was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 27 mg (47.6 %) of the title compound as a white solid. MS(m/e): 442.2 ($M+H^+$).

Example 203

(R)-3-(4-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: rac-4-chloro-2-methanesulfinyl-benzothiazole

In analogy to the procedure described for example 202, step 1-3, the title compound was prepared from 2-amino-3-chloro-benzenethiol. ($M+H^+$) 232.1.

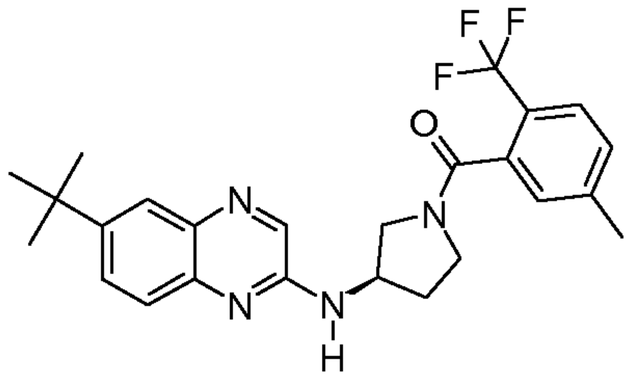
step 2: (R)-3-(4-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

In analogy to the procedure described for example 202, step 4, the title compound was prepared from rac-4-chloro-2-methanesulfinyl-benzothiazole and ((R)-3-Amino-

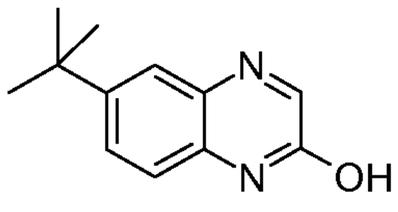
pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 440.2.

Example 204

(R)-3-(6-tert-Butyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

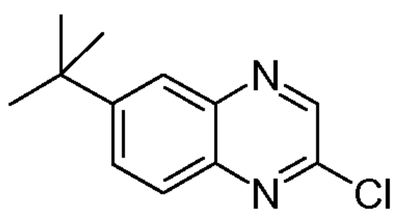


step 1: 6-tert-Butyl-quinoxalin-2-ol



To a solution of 2 g (12.18 mmol) 4-tert-butyl-1,2-diaminobenzene in 20 mL ethanol under argon at room temperature, was added 3.139 mL (15.83 mmol) ethyl glyoxalate (50 % in toluene). The reaction mixture was stirred at room temperature for 4 h. The resulting suspension was filtered and washed with ethanol. The powder was dried to provide 257 mg (10.4 %) of the title compound as a white solid. MS(m/e): 201.0 (M-H).

step 2: 6-tert-Butyl-2-chloro-quinoxaline



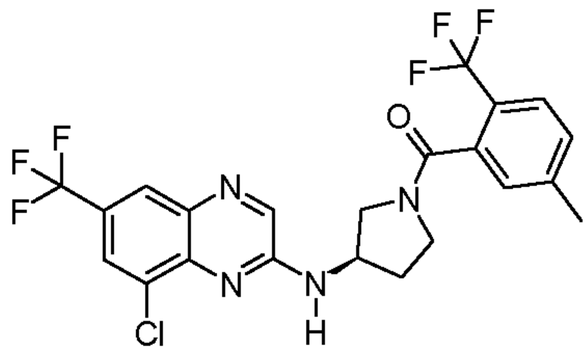
A solution of 250 mg (1.236 mmol) of 6-tert-Butyl-quinoxalin-2-ol in 1.07 mL (11.43 mmol) phosphorus oxychloride under nitrogen was heated at 110 °C for 3 h. The solution was cooled to room temperature and added drop wise to water (10-15 °C). Ethyl acetate was added. The aqueous layer was extracted with ethylacetate. The combined organic phases were washed with water, dried over Na_2SO_4 and concentrated. The crude compound was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 219 mg (80.3 %) of the title compound as a green solid. MS(m/e): 220 ($M+H^+$).

step 3: (R)-3-(6-tert-Butyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

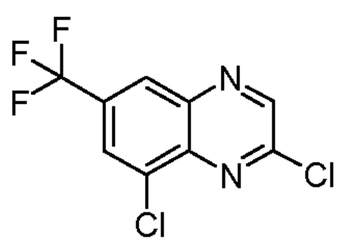
In analogy to the procedure described for example 200, the title compound was prepared from ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13) and 6-tert-Butyl-2-chloro-quinoxaline. (MH^+) 457.3.

Example 205

(R)-3-(8-Chloro-6-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2,8-dichloro-6-trifluoromethyl-quinoxaline



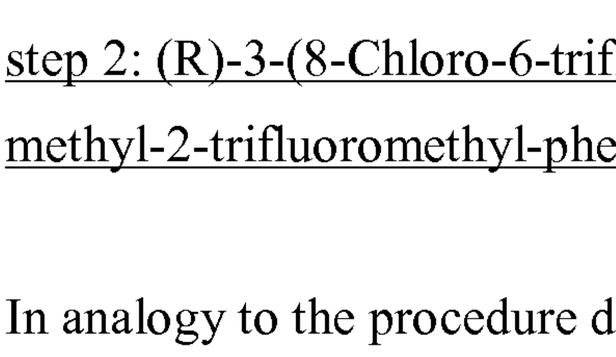
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 3-chloro-5-trifluoromethyl-benzene-1,2-diamine. (M^+) 266.

step 2: (R)-3-(8-Chloro-6-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

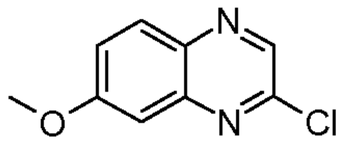
In analogy to the procedure described for example 200, the title compound was prepared from 2,8-dichloro-6-trifluoromethyl-quinoxaline and ((R)-3-Amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone. ($M-H^+$) 501.1.

Example 206

(R)-3-(7-Methoxy-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2-Chloro-7-methoxy-quinoxaline



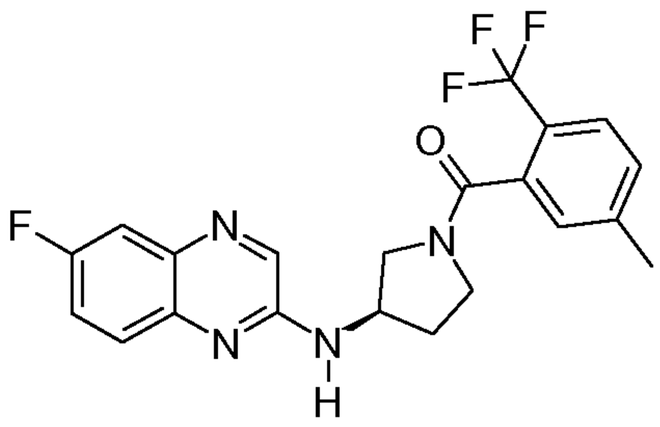
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-methoxy-benzene-1,2-diamine. ($M+H^+$) 195.2.

step 2: (R)-3-(7-Methoxy-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

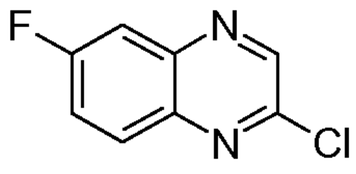
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-7-methoxy-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M-H^+$) 431.3.

Example 207

(R)-3-(6-Fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2-Chloro-6-fluoro-quinoxaline



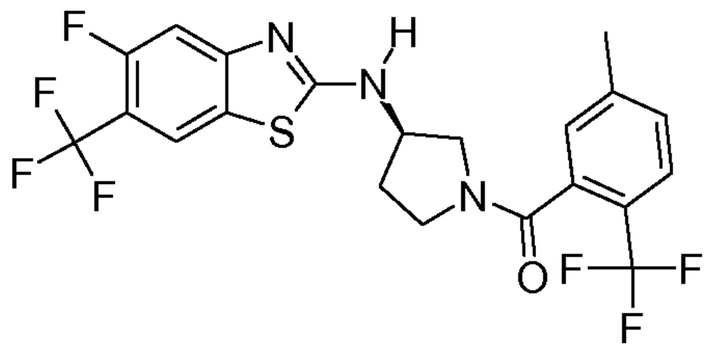
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-fluoro-benzene-1,2-diamine. ($M+H^+$) 182.0.

step 2: (R)-3-(6-Fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

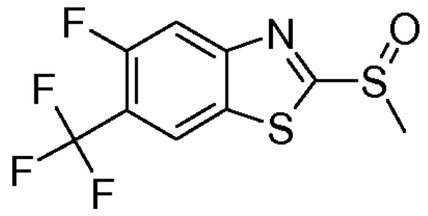
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-6-fluoro-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13), ($M-H^+$) 419.3.

Example 208

(R)-3-(5-Fluoro-6-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: rac-5-Fluoro-2-methanesulfinyl-6-trifluoromethyl-benzothiazole



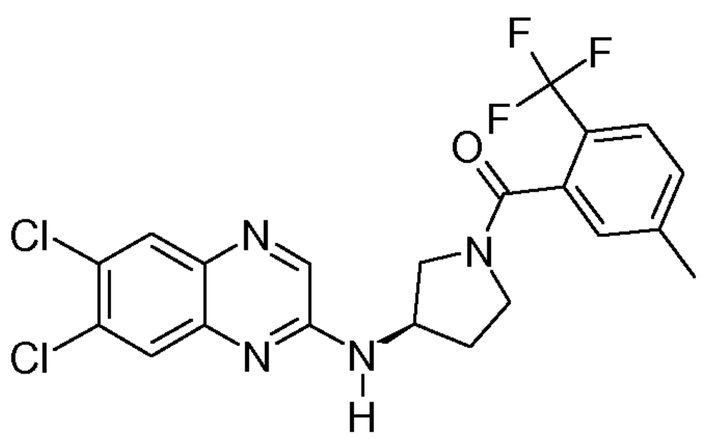
In analogy to the procedure described for example 202, step 1-3, the title compound was prepared from 2-amino-4-fluoro-5-trifluoromethyl-benzenethiol. ($M+H^+$) 284.0.

step 2: (R)-3-(5-Fluoro-6-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

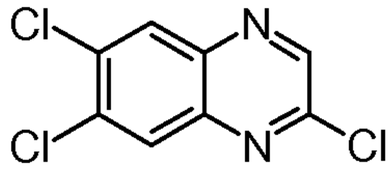
In analogy to the procedure described for example 202, step 4, the title compound was prepared from rac-5-fluoro-2-methanesulfinyl-6-trifluoromethyl-benzothiazole and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 492.2.

Example 209

(R)-3-(6,7-Dichloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2 trifluoromethyl-phenyl)-methanone



step 1: 2,6,7-Trichloro-quinoxaline



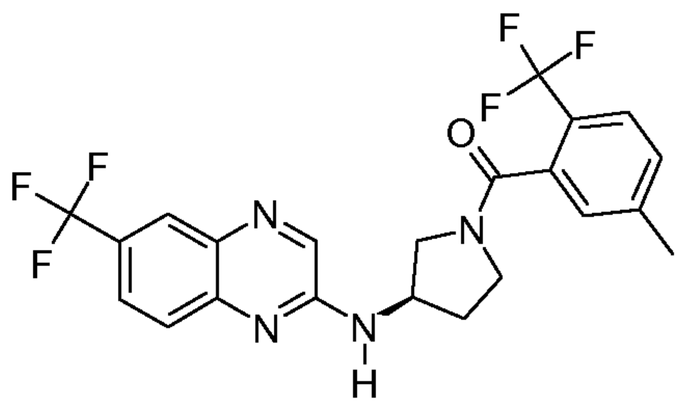
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4,5-dichloro-benzene-1,2-diamine. ($M+H^+$) 182.0

step 2: (R)-3-(6,7-Dichloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2 trifluoromethyl-phenyl)-methanone

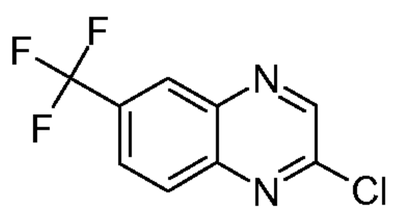
In analogy to the procedure described for example 200, the title compound was prepared from 2,6,7-trichloro-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M-H^+$) 469.2.

Example 210

(5-Methyl-2-trifluoromethyl-phenyl)-(R)-3-(6-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone



step 1: 2-Chloro-6-trifluoromethyl-quinoxaline



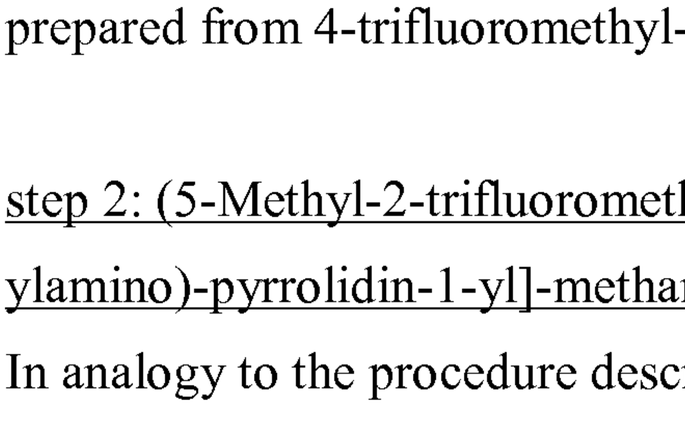
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-trifluoromethyl-benzene-1,2-diamine. ($M+H^+$) 232.

step 2: (5-Methyl-2-trifluoromethyl-phenyl)-[(R)-3-(6-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

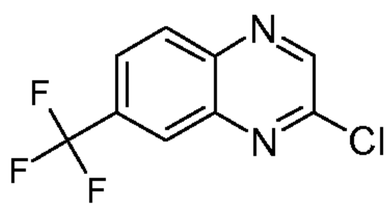
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-6-trifluoromethyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 469.2.

Example 211

(5-Methyl-2-trifluoromethyl-phenyl)-(R)-3-(7-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone



step 1: 2-Chloro-7-trifluoromethyl-quinoxaline



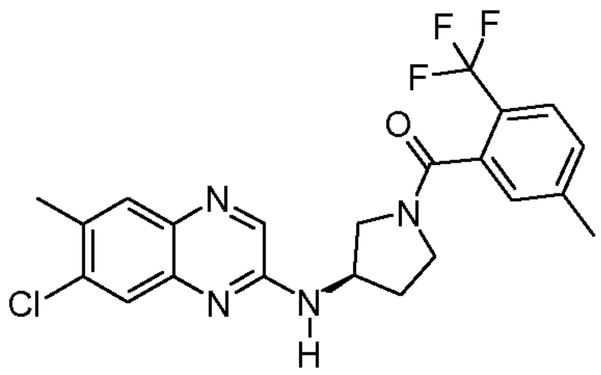
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-trifluoromethyl-benzene-1,2-diamine. ($M+H^+$) 232.

step 2: (5-Methyl-2-trifluoromethyl-phenyl)-[(R)-3-(7-trifluoromethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

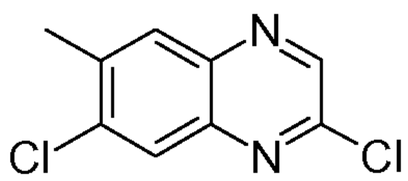
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-7-trifluoromethyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 469.2.

Example 212

(R)-3-(7-Chloro-6-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2,7-Dichloro-6-methyl-quinoxaline



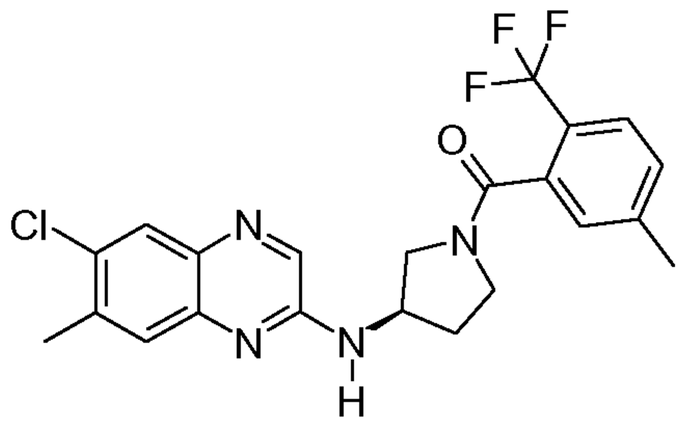
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-chloro-5-methyl-benzene-1,2-diamine. ($M-H^+$) 212.

step 2: (R)-3-(7-Chloro-6-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

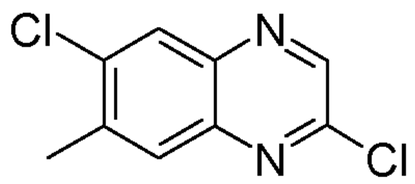
In analogy to the procedure described for example 200, the title compound was prepared from 2,7-dichloro-6-methyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 449.2.

Example 213

(R)-3-(6-Chloro-7-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2,6-Dichloro-7-methyl-quinoxaline



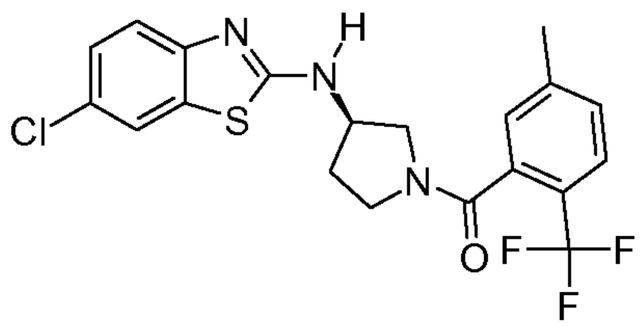
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4-chloro-5-methyl-benzene-1,2-diamine. ($M-H^+$) 212.

step 2: (R)-3-(6-Chloro-7-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

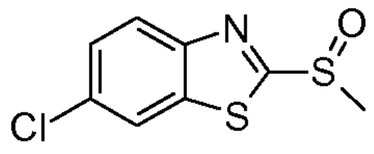
In analogy to the procedure described for example 200, the title compound was prepared from 2,6-dichloro-7-methyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 449.2.

Example 214

(R)-3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: rac- 6-Chloro-2-methanesulfinyl-benzothiazole



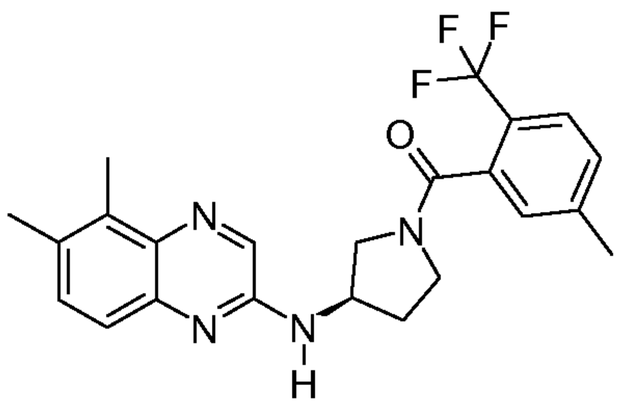
In analogy to the procedure described for example 202, step 1-3, the title compound was prepared from 2-amino-5-chloro-benzenethiol. ($M+H^+$) 232.1.

step 2: (R)-3-(6-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

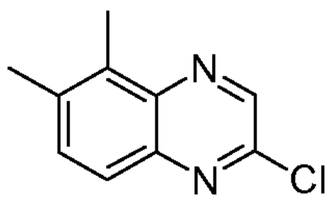
In analogy to the procedure described for example 202, step 4, the title compound was prepared from rac- 6-chloro-2-methanesulfinyl-benzothiazole and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). $(M+H^+)$ 440.2.

Example 215

(R)-3-(5,6-Dimethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2-Chloro-5,6-dimethyl-quinoxaline



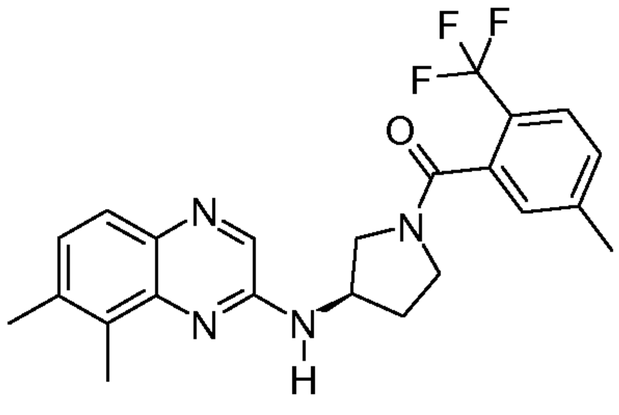
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 3,4-dimethyl-benzene-1,2-diamine. $(M+H^+)$ 193.

step 2: (R)-3-(5,6-Dimethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

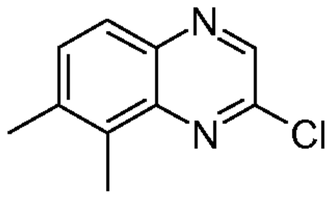
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-5,6-dimethyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). $(M+H^+)$ 429.3.

Example 216

(R)-3-(7,8-Dimethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2-Chloro-7,8-dimethyl-quinoxaline



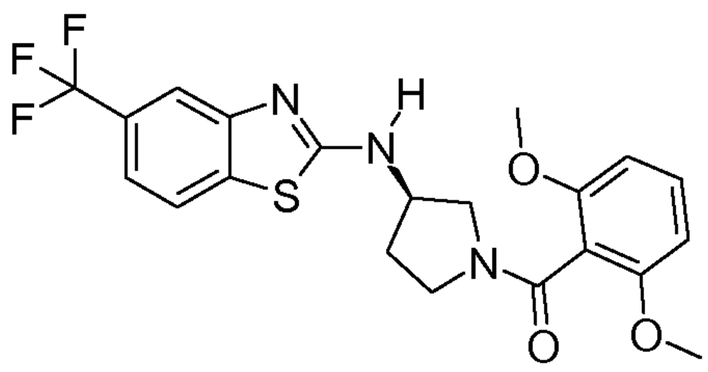
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 3,4-dimethyl-benzene-1,2-diamine. ($M+H^+$) 193.

step 2: (R)-3-(7,8-Dimethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

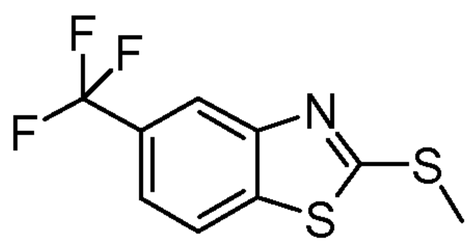
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-7,8-dimethyl-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 429.3.

Example 217

(2,6-Dimethoxy-phenyl)-(R)-3-(5-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone



step 1: 2-Methylsulfanyl-5-trifluoromethyl-benzothiazole



In analogy to the procedure described for example 202, step 1-2, the title compound was prepared from 2-amino-4-trifluoromethyl-benzenethiol, ($M+H^+$) 250.1

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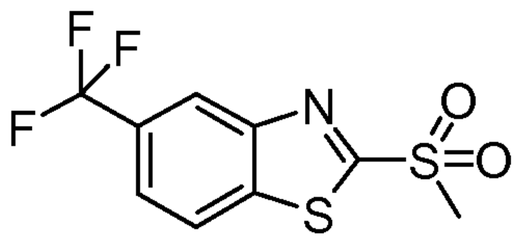
step 2: 2-Methanesulfonyl-5-trifluoromethyl-benzothiazole



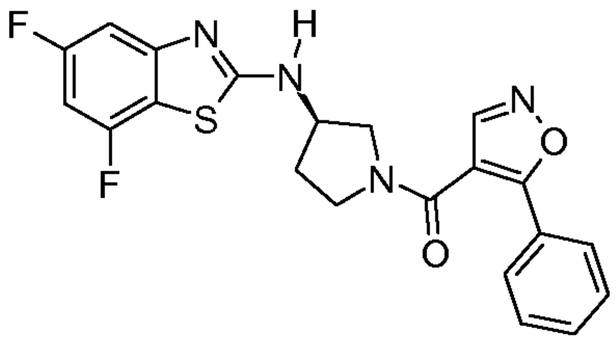
In analogy to the procedure described for example 202, step 3, the title compound was prepared from 2-methylsulfanyl-5-trifluoromethyl-benzothiazole. ($M+H^+$) 282.0.

step 3: (2,6-Dimethoxy-phenyl)-[(R)-3-(5-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

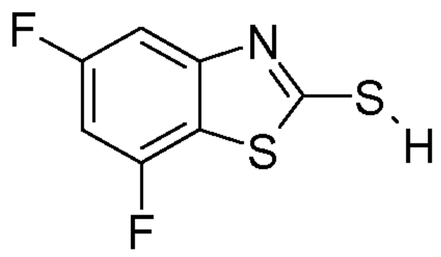
In analogy to the procedure described for example 202, step 4, the title compound was prepared from 2-methanesulfonyl-5-trifluoromethyl-benzothiazole and ((R)-3-Amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (Intermediate 5). ($M+H^+$) 452.2.

Example 218

(R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone

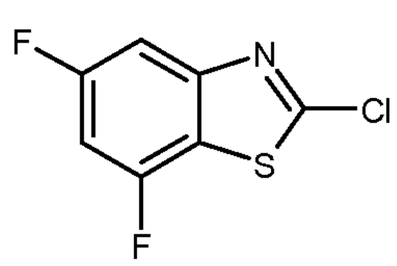


step 1: 5,7-Difluoro-benzothiazole-2-thiol



In analogy to the procedure described for example 202, step 1, the title compound was prepared from 2-amino-4,6-difluoro-benzenethiol. ($M-H^+$) 201.9.

step 2: 2-Chloro-5,7-difluoro-benzothiazole



To a suspension of 2 g (9.841 mmol) 5,7-difluoro-benzothiazole-2-thiol in 10.7 mL (147.6 mmol) thionyl chloride was added drop wise 215 L N,N-dimethylformamide at

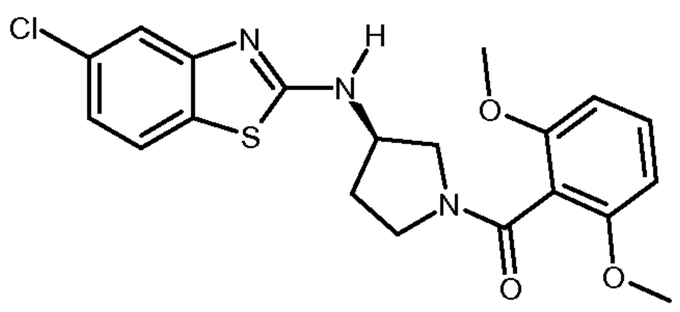
room temperature. The mixture was stirred at room temperature for 2 days. The solvent was removed in vacuo. The crude compound was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 659 mg (32.6 %) of the title compound as an off-white solid. MS(m/e): 205 ($M+H^+$).

step 3: (R)-3-(5,7-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone

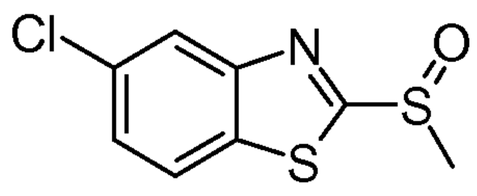
To a solution of 30 mg (0.146 mmol) 2-chloro-5,7-difluoro-benzothiazole and 45 mg (0.175 mmol) ((R)-3-Amino-pyrrolidin-1-yl)-(5-phenyl-isoxazol-4-yl)-methanone (intermediate 19) in 0.5 mL DMF were added 50 µL (0.292 mmol) N-ethyldiisopropylamine. The mixture was heated in a 90 °C oil-bath for 20 minutes. The solvent was removed under reduced pressure. The crude gum was purified with flash column chromatography on silica eluting with a gradient formed from n-heptane and ethyl acetate to provide 13.2 mg (21 %) of the title compound as a light yellow solid. MS(m/e): 427.1 ($M+H^+$).

Example 219

(R)-3-(5-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone



step 1: rac-5-Chloro-2-methanesulfinyl-benzothiazole



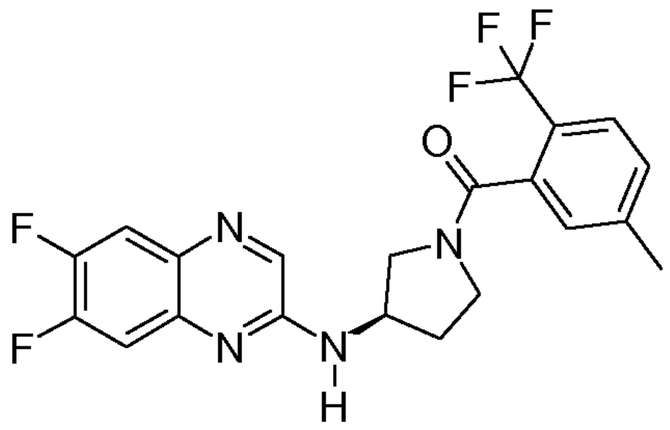
In analogy to the procedure described for example 202, step 1-3, the title compound was prepared from 2-amino-4-chloro-benzenethiol. ($M+H^+$) 232.1.

step 2: (R)-3-(5-Fluoro-6-trifluoromethyl-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

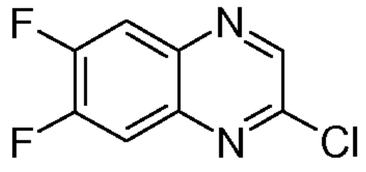
In analogy to the procedure described for example 202, step 4, the title compound was prepared from rac-5-chloro-2-methanesulfinyl-benzothiazole and ((R)-3-amino-pyrrolidin-1-yl)-(2,6-dimethoxy-phenyl)-methanone (Intermediate 5). ($M+H^+$) 418.3.

Example 220

(R)-3-(6,7-Difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: 2-Chloro-6,7-difluoro-quinoxaline



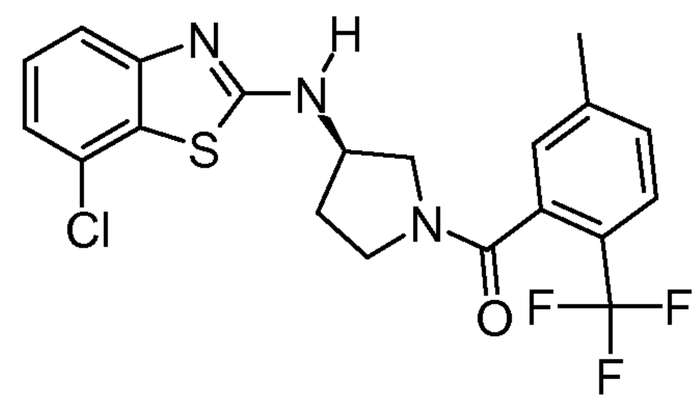
In analogy to the procedure described for example 204, step 1-2, the title compound was prepared from 4,5-difluoro-benzene-1,2-diamine. ($M+H^+$) 200.

step 2: (R)-3-(5,6-Dimethyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

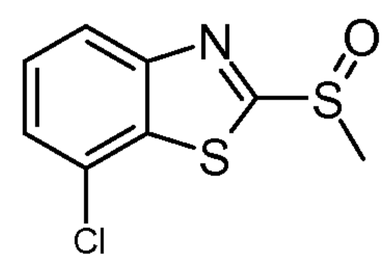
In analogy to the procedure described for example 200, the title compound was prepared from 2-chloro-6,7-difluoro-quinoxaline and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). ($M+H^+$) 437.3.

Example 221

(R)-3-(7-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



step 1: rac-7-Chloro-2-methanesulfinyl-benzothiazole



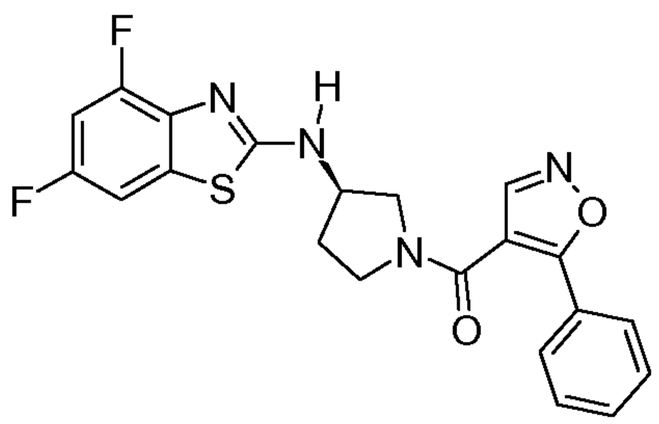
In analogy to the procedure described for example 202, step 1-3, the title compound was prepared from 2-amino-6-chloro-benzenethiol. ($M+H^+$) 232.1.

step 2: (R)-3-(7-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

In analogy to the procedure described for example 202, step 4, the title compound was prepared from rac-7-chloro-2-methanesulfinyl-benzothiazole and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). (M-H^+) 438.1.

Example 222

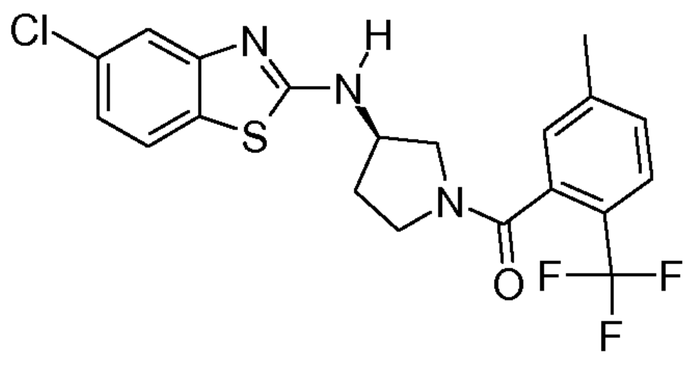
(R)-3-(4,6-Difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone



In analogy to the procedure described for example 217, step 3, the title compound was prepared from 2-chloro-4,6-difluoro-benzothiazole (commercially available) and ((R)-3-Amino-pyrrolidin-1-yl)-(5-phenyl-isoxazol-4-yl)-methanone (intermediate 19), (M-H^+) 427.1.

Example 223

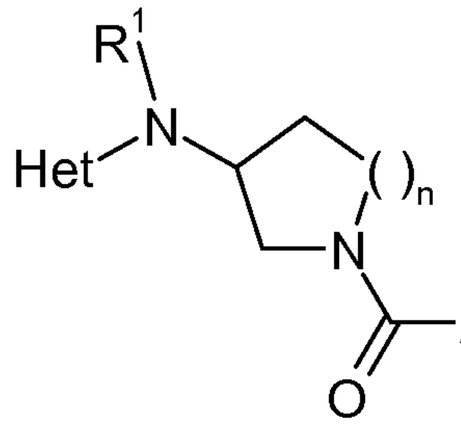
(R)-3-(5-Chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone



In analogy to the procedure described for example 202, step 4, the title compound was prepared from 5-chloro-2-methanesulfinyl-benzothiazole (example 219, step 1) and ((R)-3-amino-pyrrolidin-1-yl)-(5-methyl-2-trifluoromethyl-phenyl)-methanone (intermediate 13). (M+H^+) 440.2.

Claims

1. A compound of formula



I

wherein

Ar is an unsubstituted or substituted aryl or heteroaryl group, wherein the aryl and the heteroaryl group may be substituted by one or more substituents R^2;

R^2 is hydroxy, halogen, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, lower alkoxy substituted by halogen, C(O)-lower alkyl, nitro, NR'R'', cyano, S-lower alkyl, SO_2-lower alkyl, cycloalkyl, heterocycloalkyl, phenyloxy, benzyloxy, phenyl, NH-phenyl or heteroaryl, wherein the phenyl and heteroaryl group is unsubstituted or substituted by one or more substituents selected from lower alkyl or halogen;

R'/R'' are independently from each other hydrogen or lower alkyl;

R^1 is hydrogen or lower alkyl;

Het is a heteroaryl group, unsubstituted or substituted by one or more substituents selected from R^3;

R^3 is hydroxy, halogen, =O, lower alkyl, lower alkyl substituted by halogen, lower alkoxy, phenyl, lower alkoxy substituted by halogen, nitro, cyano, SO_2-lower alkyl, cycloalkyl or heterocycloalkyl;

n is 1 or 2;

or pharmaceutically suitable acid addition salts optically pure enantiomers, racemates or diastereomeric mixtures thereof.

2. A compound of formula I according to claim 1, wherein Het is benzooxazolyl, unsubstituted or substituted by one or more substituents selected from R^3.

3. A compound of formula I according to claim 2, wherein Ar is an unsubstituted or R^2-substituted aryl.

4. A compound of formula I according to claim 2, wherein Ar is an unsubstituted or R^2-substituted heteroaryl.

5. A compound of formula I according to claim 2, wherein the compounds are
[3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyrrol-1-yl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dichloro-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-methyl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethyl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-ethoxy-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methylsulfanyl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-difluoromethoxy-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-furan-2-yl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-phenyl-isoxazol-4-yl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(2*H*-[1,2,4]triazol-3-yl)-phenyl]-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-pyridin-3-yl-phenyl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-2-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-diethoxy-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(3'-methyl-biphenyl-2-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-4-phenyl-thiazol-5-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-chloro-6-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-thiophen-3-yl-phenyl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-furan-3-yl)-methanone

[(R)-3-(6-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-fluoro-6-pyrrolidin-1-yl-phenyl)-methanone

[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(7-chloro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

(2,6-dimethoxy-phenyl)-[(R)-3-(4-methyl-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(7-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone
[(R)-3-(6,7-difluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or
[(R)-3-(6-fluoro-benzooxazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone.

6. A compound of formula I according to claim 1, wherein Het is quinoxalinyl unsubstituted or substituted by one or more substituents selected from R^3.

7. A compound of formula I according to claim 6, wherein Ar is an unsubstituted or R^2-substituted aryl.

8. A compound of formula I according to claim 6, wherein Ar is an unsubstituted or R^2-substituted heteroaryl

9. A compound of formula I according to claim 6, wherein the compounds are
(2,6-dimethoxy-phenyl)-[3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone
[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methoxy-5-methyl-phenyl)-methanone

[(R)-3-(6,7-difluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

(5-methyl-2-trifluoromethyl-phenyl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone

(2-methyl-5-phenyl-thiazol-4-yl)-[(R)-3-(quinoxalin-2-ylamino)-pyrrolidin-1-yl]-methanone
[(R)-3-(7-chloro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone
(R)-3-(6-tert-butyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone
(R)-3-(6-fluoro-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone
(R)-3-(7-chloro-6-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or
(R)-3-(6-Chloro-7-methyl-quinoxalin-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone.

10. A compound of formula I according to claim 1, wherein Het is benzothiazolyl, unsubstituted or substituted by one or more substituents selected from R^3.

11. A compound of formula I according to claim 10, wherein Ar is an unsubstituted or R^2-substituted aryl.

12. A compound of formula I according to claim 10, wherein Ar is an unsubstituted or R^2-substituted heteroaryl.

13. A compound of formula I according to claim 10, wherein the compounds are
[3-(6-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
[(R)-3-(6-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
[(R)-3-(4-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone
(2,6-dimethoxy-phenyl)-[(R)-3-(7-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2,6-dimethoxy-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

(2-chloro-5-methyl-phenyl)-[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-methanone

[(R)-3-(6-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-methyl-5-phenyl-thiazol-4-yl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(2-trifluoromethoxy-phenyl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone

[(R)-3-(4-fluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(1,1,2,2-tetrafluoro-ethoxy)-phenyl]-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-3-phenyl-isoxazol-4-yl)-methanone

[(R)-3-(5,7-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-[2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone

[(R)-3-(5,6-difluoro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone or

(R)-3-(4-chloro-benzothiazol-2-ylamino)-pyrrolidin-1-yl]-(5-methyl-2-trifluoromethyl-phenyl)-methanone.

14. A compound of formula I according to claim 1, wherein Het is pyrimidinyl, unsubstituted or substituted by one or more substituents selected from R^3.

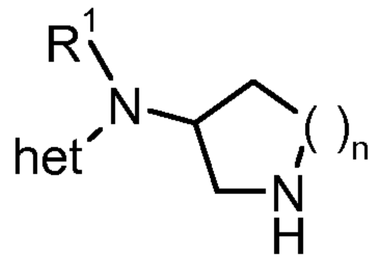
15. A compound of formula I according to claim 14, wherein Ar is an unsubstituted or R^2-substituted aryl.

16. A compound of formula I according to claim 14, wherein Ar is an unsubstituted or R^2-substituted heteroaryl

17. A compound of formula I according to claim 14, wherein the compound is (5-methyl-2-trifluoromethyl-phenyl)-[(R)-3-(2-phenyl-pyrimidin-4-ylamino)-pyrrolidin-1-yl]-methanone.

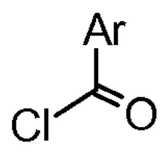
18. A process for preparation of compounds of formula I, which process comprises

a) reacting a compound of formula



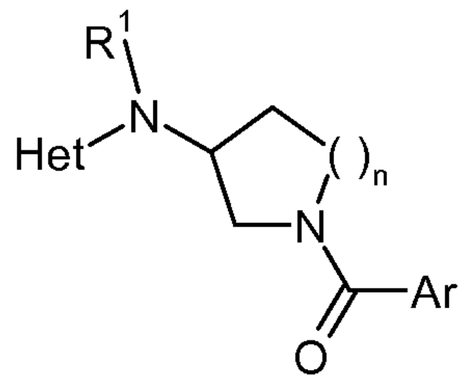
II

with an acid choride of formula



III

to the compound of formula



I

wherein the substituents are as described in claim 1, and

if desired, converting the compounds obtained into pharmaceutically acceptable acid addition salts.

19. A compound of formula I according to claim 1, whenever prepared by a process as claimed in claim 18 or by an equivalent method.

20. A medicament containing one or more compounds of formula I and pharmaceutically acceptable excipients.

21. A medicament as claimed in claim 20 for the treatment of sleep disorders including sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder, restless leg syndrome, psychiatric, neurological and neurodegenerative disorders including anxiety, depression, manic depression, obsessive compulsive disorders, affective neurosis, depressive neurosis, anxiety neurosis, mood disorder, delirium, panic-attack disorder, posttraumatic stress disorders, sexual dysfunction, schizophrenia, psychosis, cognitive disorders, Alzheimer's and Parkinson's diseases, dementia, mental retardation, dyskinesias such as Huntington's disease and Tourette syndrome, addictions, craving associated with drug abuse, seizure disorders, epilepsy, metabolic diseases such as obesity, diabetes, eating disorders including anorexia and bulimia, asthma, migraine, pain, neuropathic pain, sleep disorders associated with psychiatric, neurological and neurodegenerative disorders, neuropathic pain, enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia, acute pain, burn pain, back pain, complex regional pain syndrome I and II, arthritic pain, post-stroke pain, post-operative pain, neuralgia, pain associated with HIV infection, post-chemotherapy pain or irritable bowel syndrome.

22. A medicament as claimed in claim 21 for the treatment of sleep disorders, wherein the sleep disorders are sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome and sleep disorders associated with neuropsychiatric diseases.

23. The use of a compound of formula I according to claim 1 for the preparation of a medicament for the treatment of sleep disorders including sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder, restless leg syndrome, psychiatric, neurological and neurodegenerative disorders including anxiety, depression, manic depression, obsessive compulsive disorders, affective neurosis,

depressive neurosis, anxiety neurosis, mood disorder, delirium, panic-attack disorder, posttraumatic stress disorders, sexual dysfunction, schizophrenia, psychosis, cognitive disorders, Alzheimer's and Parkinson's diseases, dementia, mental retardation, dyskinesias such as Huntington's disease and Tourette syndrome, addictions, craving associated with drug abuse, seizure disorders, epilepsy, metabolic diseases such as obesity, diabetes, eating disorders including anorexia and bulimia, asthma, migraine, pain, neuropathic pain, sleep disorders associated with psychiatric, neurological and neurodegenerative disorders, neuropathic pain, enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia, acute pain, burn pain, back pain, complex regional pain syndrome I and II, arthritic pain, post-stroke pain, post-operative pain, neuralgia, pain associated with HIV infection, post-chemotherapy pain or irritable bowel syndrome.

24. The use of a compound of formula I according to claim 23, wherein the sleep disorders are sleep apnea, narcolepsy, insomnia, parasomnia, jet lag syndrome, circadian rhythms disorder or sleep disorders associated with neurological diseases,

25. The invention as herein before described.

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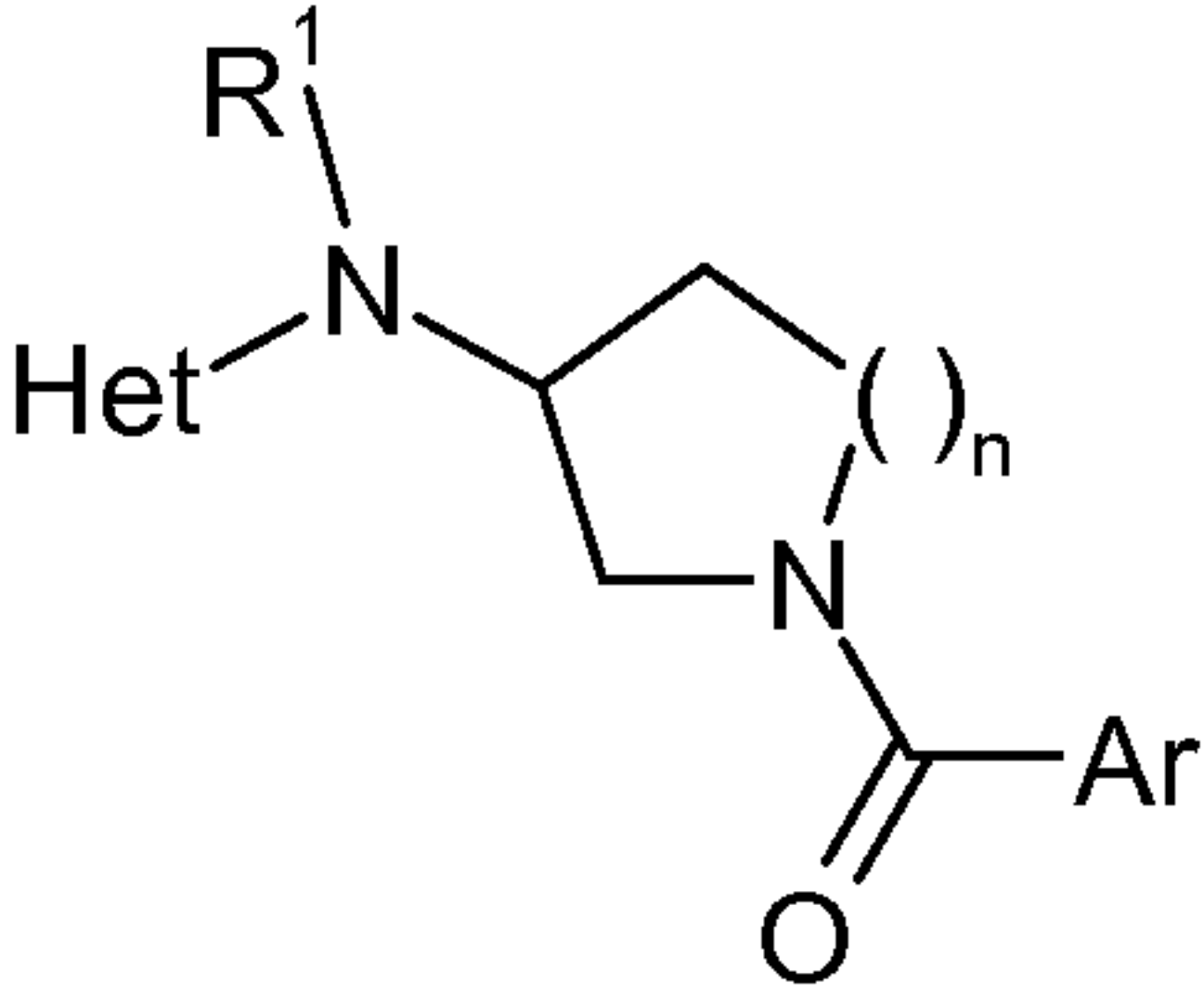

(I)