Title: 3,8-DIAZA-BICYCLO[4.2.0]OCT-3-YL AMIDES

Abstract: The present invention relates to 3,8-diaza-bicyclo[4.2.0]oct-3-yl amide derivatives of formula (I), wherein the relative configuration of the diazabicyclooctane moiety is cis; and wherein Ar\(^1\) and Ar\(^2\) are as described in the description, to their preparation, to pharmaceutically acceptable salts thereof, and to their use as pharmaceuticals, to pharmaceutical compositions containing one or more compounds of formula (I), and especially to their use as orexin receptor antagonists.
3,8-Diaza-bicyclo[4.2.0]oct-3-yl amides

The present invention relates to 3,8-diaza-bicyclo[4.2.0]oct-3-yl amide derivatives of formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and especially their use as orexin receptor antagonists.

Orexins (orexin A or OX-A and orexin B or OX-B) are novel neuropeptides found in 1998 by two research groups, orexin A is a 33 amino acid peptide and orexin B is a 28 amino acid peptide (Sakurai T. et al., Cell, 1998, 92, 573-585). Orexins are produced in discrete neurons of the lateral hypothalamus and bind to the G-protein-coupled receptors (OX-1 and OX-2 receptors). The orexin-1 receptor (OX-1) is selective for OX-A, and the orexin-2 receptor (OX-2) is capable of binding OX-A as well as OX-B. Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behaviour (Sakurai T. et al., Cell, 1998, 92, 573-585). On the other hand, it was also observed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches to insomnia and other sleep disorders (Chemelli R.M. et al., Cell, 1999, 98, 437-451). Furthermore, in vitro and in vivo evidence for a critical role of orexin signaling in the ventral tegmental area in neural plasticity relevant to addiction has been published (S. L. Borgland et al. Neuron, 2006, 49, 589-601). In addition, several lines of evidence demonstrate a role of the orexin system as modulator of the stress response. For instance, stress (i.e. psychological stress or physical stress) is associated with increased arousal and vigilance which in turn is controlled by orexins (Sutcliffe, JG, de Lecea, L: The hypocretins: setting the arousal threshold. Nat Rev Neurosci, 3(5) (2002) 339-349). Orexin neurons are likely to be involved in the coordinated regulation of behavioral and physiological responses in stressful environments (Kuru, M, Ueta, Y, Serino, R, Nakazato, M, Yamamoto, Y, Shibuya, I, Yamashita, H; Centrally administered orexin/hypocretin activates HPA axis in rats. Neuroreport, 11(9) (2000) 1977-1980). For instance, cardiovascular responses to conditioned fear and novelty exposure could be attenuated by a dual orexin receptor antagonist in rats (Furlong, TM, Vianna, DM, Liu, L, Carrive, P; Hypocretin/orexin contributes to the expression of some but not all forms of stress and arousal. Eur J Neurosci, 30(8) (2009) 1603-1614). Stress response may lead to dramatic, usually time-limited physiological, psychological and behavioural changes that may affect appetite, metabolism and feeding behavior (Chrousos, GP, Gold, PW; The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA, 267(9) (1992), 1244-1252). The acute stress response may include behavioural, autonomic and endocrinological
changes, such as promoting heightened vigilance, decreased libido, increased heart rate and blood pressure, or a redirection of blood flow to fuel the muscles, heart and the brain (Majzoub, JA; Corticotropin-releasing hormone physiology European Journal of Endocrinology, 155 (suppM) (2006) S71-S76).

The compound (2R)-2-[(1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isooquinolin-2-yl]-N,N-dimethyl-2-phenyl-acetamide (WO2005/1 18548), a dual orexin receptor antagonist, is currently in clinical development for primary insomnia. In the rat, the compound has been shown for example to decrease alertness, characterized by decreases in both active wake and locomotion; and to dose-dependently increase the time spent in both REM and NREM sleep (F. Jenck et al., Nature Medicine 2007, 13, 150-155). The compound has also been shown to enhance memory function in a rat model (WO2007/105177) and is also active in an animal model of conditioned fear: the rat fear potentiated startle paradigm (WO2009/0047723) which relates to emotional states of fear and anxiety diseases such as anxieties including post traumatic stress disorders (PTSDs).

The present invention provides novel diazabicyclooctane derivatives, which are non-peptide antagonists of human orexin receptors. These compounds are in particular of potential use in the treatment of diseases or disorders related to the orexin system, especially comprising all types of sleep disorders, of stress-related syndromes, of addictions (especially psychoactive substance use, abuse, seeking and reinstatement), of cognitive dysfunctions in the healthy population and in psychiatric and neurologic disorders, of eating or drinking disorders.

1) A first aspect of the invention relates to compounds of the formula (I)

![Formula (I)](image)

wherein the relative configuration of the diazabicyclooctane moiety is cis;

wherein

- Ar₁ represents phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
  > one of said substituents is attached in orofro-position to the point of attachment of Ar₁ to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, di-, or tri-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of
alkyl, (C₄₋₄)alkoxy, halogen, cyano, (C₃₋₃)fluoroalkyl, and (C₃₋₃)fluoroalkoxy (especially (C₄₋₄)alkyl and halogen);
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and the other of said substituents, if present, is/are independently selected from the group consisting of (C₄₋₄)alkyl, (C₄₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₃₋₃)fluoroalkyl, and (C₃₋₃)fluoroalkoxy;

and
• Ar² represents 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
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one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
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and the other of said substituents, if present, is/are independently selected from the group consisting of (C₄₋₄)alkyl, (C₄₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₃₋₃)fluoroalkyl, and (C₃₋₃)fluoroalkoxy;

• or Ar² represents 8- to 10-membered bicyclic heteroaryl which is unsubstituted, or mono-, di-, or tri-substituted; wherein
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the substituents are independently selected from the group consisting of (C₄₋₄)alkyl, (C₄₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₃₋₃)fluoroalkyl, and (C₃₋₃)fluoroalkoxy.

Certain 3,8-diaza-bicyclo[4.2.0]oct-3-yl amide orexin receptor antagonists have been disclosed in WO2011/050200 which was published after the priority date of the present invention.

2) A second embodiment, thus, relates to the compounds of formula (I) according to embodiment 1) with the exception of the structurally overlapping scope of the compounds disclosed in WO2011/050200; wherein WO2011/050200 discloses the compounds of Formula X:

![Formula X](image)

wherein

R¹ is a member selected from the group consisting of:
A) phenyl substituted or unsubstituted with one or two R^a members, and substituted in the ortho position with R^b;
R^a is independently selected from the group consisting of: halo, -C_4 alkyl, and -C_4 alkoxy, wherein two adjacent R^a members may come together to form a six membered aromatic ring;
R^b is a member selected from the group consisting of:
  a) halo, -C_4 alkoxy, -CF_3, or -CF_2 CHF_2;
  b) 5-membered heteroaryl ring containing one oxygen or one sulfur members;
  c) 5-6 membered heteroaryl ring containing one to three nitrogen members, optionally containing one oxygen member, substituted or unsubstituted with halo, -C_4 alkyl, tetrahydropyran-2-yl, or -NH(CH_3)_2; and
  d) phenyl substituted or unsubstituted with -F, or -CH_3;
B) pyridine substituted or unsubstituted with one or two R^c members and substituted with R^d, wherein R^d is positioned adjacent to the point of attachment by R^1;
R^c is a member independently selected from the group consisting of: -C_4 alkyl, -CF_3, and -C_4 alkoxy;
R^d is a member selected from the group consisting of:
  a) 5-6 membered heteroaryl ring selected from the group consisting of: 1H-1,2,3-triazol-yl, 2H-1,2,3-triazol-2-yl, 1H- pyrazol-3-yl, and 6-methyl-pyridin-2-yl; and
  b) -CF_3, -Br, or -C_4 alkoxy;
C) 6-membered heteroaryl ring selected from the group consisting of: pyrimidin-yl or pyrazin-yl, substituted or unsubstituted with a member independently selected from -CH_3, -OCH_3, or phenyl;
D) 5-membered heteroaryl ring selected from the group consisting of: 2-methyl-1,3-thiazol-yl, 5-methyl-isoxazol-4-yl, 2H-pyrazol-3-yl, 1H-pyrazol-4-yl, isoxazolyl, and 1,3-oxazol-4-yl, each substituted with phenyl substituted or unsubstituted with -F or -Cl; and
E) 3-methylfuran-2-yl, 9H-fluorene, 9H-fluoren-9-one, 3,5'-biisoxazole, [3-methyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)isoxazol-4-yl], or naphthyridine;
R^2 is a member selected from the group consisting of:
A) 6-membered heteroaryl ring containing two nitrogen members substituted or unsubstituted with one or more members independently selected from the group consisting of: halo, -C_4 alkyl, -C_4 alkoxy, -CF_3, -NH_2, -NHCH_3, -N(C_4 alkyl)_1,2, -NH cyclopropyl, and phenyl;
B) pyridine substituted or unsubstituted with one or two members independently
selected from the group consisting of: -C^alkyl, -N(C^alkyl)_2, and -CF_3; and
C) quinoxalin-2-yl, benzoxazol-2-yl, or 5-chloro-1,3-benzoxazole;
and pharmaceutically acceptable salts of compounds of Formula X.

For avoidance of any doubt, for the compounds of formula X for example the term
"heteroaryl" refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle
(ring structure having ring atoms selected from carbon atoms and up to four heteroatoms
selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle
and the term "halo" represents chloro, fluoro, bromo or iodo; and, for the compounds of
formula X, the term "substituted" means that the specified group or moiety bears one or more
substituents, the term "unsubstituted" means that the specified group bears no substituents,
and the term "optionally substituted" means that the specified group is unsubstituted or
substituted by one or more substituents.

The compounds of formula (I) may contain one or more stereogenic or asymmetric centers,
such as one or more asymmetric carbon atoms. The compounds of formula (I) may thus be
present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of
stereoisomers may be separated in a manner known to a person skilled in the art.

The relative configuration of the diazabicyclooctane moiety is cis; i.e. the compounds of
formula (I) are either compounds of formula (1_E1), or compounds of formula (1_E2), or any
mixture thereof (such as racemates):

![Formula (1_E1)](image1)

![Formula (1_E2)](image2)

The relative configuration of stereoisomers is denoted as follows: for example, ((1/?^*,6^S^*)-8-
(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-
2-yl)phenyl)methanone, if not explicitly mentioned as racemate, denominates ((1R,6^S^)-8-(5-
chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone or ((1 S,6^R^)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]
octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone, or any mixture of these two
enantiomers (including the racemic mixture).

The present invention also includes isotopically labelled, especially 2^H (deuterium) labelled
compounds of formula (I), which compounds are identical to the compounds of formula (I)
except that one or more atoms have each been replaced by an atom having the same atomic
number but an atomic mass different from the atomic mass usually found in nature. Isotopically labelled, especially $^2$H (deuterium) labelled compounds of formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope $^2$H (deuterium) may lead to greater metabolic stability, resulting e.g. in increased in-vivo half-life or reduced dosage requirements, or may lead to reduced inhibition of cytochrome P450 enzymes, resulting e.g. in an improved safety profile. In one embodiment of the invention, the compounds of formula (I) are not isotopically labelled, or they are labelled only with one or more deuterium atoms. In a sub-embodiment, the compounds of formula (I) are not isotopically labelled at all. Isotopically labelled compounds of formula (I) may be prepared in analogy to the methods described hereinafter, but using the appropriate isotopic variation of suitable reagents or starting materials.

In this patent application, a dotted line shows the point of attachment of the radical drawn. For example, the radical drawn below

![Radical Diagram]

is the 3-(3-methyl-phenyl)pyrazin-2-yl group.

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference to compounds of formula (I) is to be understood as referring also to the salts (and especially the pharmaceutically acceptable salts) of such compounds, as appropriate and expedient.

The term "pharmaceutically acceptable salts" refers to non-toxic, inorganic or organic acid and/or base addition salts. Reference can be made to "Salt selection for basic drugs", Int. J. Pharm. (1986), 33, 201-217.

The term "halogen" means fluorine, chlorine, or bromine, preferably fluorine or chlorine.

The term "alkyl", used alone or in combination, refers to a saturated straight or branched chain alkyl group containing one to six carbon atoms. The term "(C$_{x-y}$)alkyl" (x and y each being an integer), refers to an alkyl group as defined before, containing x to y carbon atoms. For example a (C$_{1-4}$)alkyl group contains from one to four carbon atoms. Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec.-butyl and tert.-butyl. Preferred are methyl and ethyl. Most preferred is methyl.
The term "cycloalkyi", used alone or in combination, refers to a saturated cyclic alkyl group containing three to six carbon atoms. The term ",(C_\text{x-y})\text{cycloalkyl}" (x and y each being an integer), refers to a cycloalkyi group as defined before containing x to y carbon atoms. For example a (C_3-6)cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyi groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred is cyclopropyl.

The term "alkoxy", used alone or in combination, refers to an alkyl-O-group wherein the alkyl group is as defined before. The term "(C_y)x\text{alkoxy}" (x and y each being an integer) refers to an alkoxy group as defined before containing x to y carbon atoms. For example a (C_4)xalkoxy group means a group of the formula (C_4)xalkyl-O- in which the term "(C_4)xalkyl" has the previously given significance. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy. Preferred are ethoxy and especially methoxy.

The term "fluoroalkyl" refers to an alkyl group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_\text{x-y})\text{fluoroalkyl}" (x and y each being an integer) refers to a fluoroalkyl group as defined before containing x to y carbon atoms. For example a (C_3)xfluoroalkyl group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkyl groups include trifluoromethyl, 2-fluoroethyl, 2,2-difluoroethyl and 2,2,2-trifluoroethyl. Preferred are (C-i)fluoroalkyl groups such as trifluoromethyl.

The term "fluoroalkoxy" refers to an alkoxy group as defined before containing one to three carbon atoms in which one or more (and possibly all) hydrogen atoms have been replaced with fluorine. The term "(C_\text{x-y})\text{fluoroalkoxy}" (x and y each being an integer) refers to a fluoroalkoxy group as defined before containing x to y carbon atoms. For example a (C_3)xfluoroalkoxy group contains from one to three carbon atoms in which one to seven hydrogen atoms have been replaced with fluorine. Representative examples of fluoroalkoxy groups include trifluoromethoxy, difluoromethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy and 2,2,2-trifluoroethoxy. Preferred are (C-i)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy.

Particular examples of phenyl groups which are further substituted in ortho position as used for the group Ar^1 are 1,2-phenylene, 5-methyl-1,2-phenylene, 5-fluoro-1,2-phenylene, 6-fluoro-1,2-phenylene, 5-cyano-1,2-phenylene, 5-methoxy-1,2-phenylene, 5-trifluoromethyl-1,2-phenylene, 5-trifluoromethoxy-1,2-phenylene, 6-fluoro-5-methyl-1,2-phenylene, and 6-
fluoro-5-methoxy-1,2-phenylene; wherein in the above groups the carbonyl group is attached in position 1. In a sub-embodiment, particular examples are 5-cyano-1,2-phenylene, 5-trifluoromethyl-1,2-phenylene, and 5-trifluoromethoxy-1,2-phenylene; wherein in the above groups the carbonyl group is attached in position 1.

Examples of the particular phenyl groups which are substituents of the groups Ar\(^1\) or Ar\(^2\) are notably phenyl, 3-methyl-phenyl, 4-methyl-phenyl, 2-fluoro-phenyl, 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, and 4-chloro-phenyl. In a sub-embodiment, particular examples of phenyl groups which are substituents of the groups Ar\(^1\) are methyl substituted phenyl such as 3-methyl-phenyl, and 4-methyl-phenyl; or halogen substituted phenyl such as 3-fluoro-phenyl, 4-fluoro-phenyl, 3-chloro-phenyl, and 4-chloro-phenyl.

The term "heteroaryl", if not explicitly stated otherwise, means a 5- to 10-membered monocyclic or fused bicyclic aromatic ring containing 1 to a maximum of 4 heteroatoms independently selected from oxygen, nitrogen and sulfur. Examples of monocyclic heteroaryl groups are 5-membered monocyclic heteroaryl groups such as furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, and tetrazolyl; and 6-membered monocyclic heteroaryl such as pyridinyl, pyrimidinyl, pyridazinyl, and pyrazinyl. Examples of bicyclic heteroaryl groups comprise 8-membered bicyclic heteroaryl groups such as 4H-furo[3,2-b]pyrrolyl, pyrrolo[2,1-b]thiazolyl and imidazo[2,1-b]thiazolyl; 9-membered bicyclic heteroaryl groups such as indolyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, benzoxadiazolyl, benzothiadiazolyl, pyrazolo[1,5-a]pyridinyl, pyrazolo[1,5-a]pyrimidinyl, imidazo[1,2-a]pyridinyl, 1H-pyrrrolo[3,2-b]pyridinyl, and 1H-pyrrolo[2,3-b]pyridinyl; and 10-membered bicyclic heteroaryl groups such as quinolinyl, isoquinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, quinoxalinyl, and phthalazinyl.

Examples of the particular 5- or 6-membered heteroaryl groups which are further substituted in ortho position as used for the group Ar\(^1\) are notably oxazolyl, isoxazolyl, thiethyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl and pyrazinyl. In a sub-embodiment, examples are oxazolyl (in particular 2-methyl-oxazol-4,5-diyl), isoxazolyl (in particular 5-methyl-isoxazol-3,4-diyl), thiazolyl (in particular 2-methyl-thiazol-4,5-diyl), pyridinyl (in particular pyridin-2,3-diyl, 6-methyl-pyridin-2,3-diyl), pyrimidinyl (in particular pyrimidin-4,5-diyl, 2-methyl-pyrimidin-4,5-diyl), and pyrazinyl (in particular pyrazin-2,3-diyl). The above groups are preferably attached to the rest of the molecule (i.e. the carbonyl group) in position 4 of oxazolyl, isoxazolyl, or thiazolyl groups, in position 2 of pyridinyl or pyrazinyl groups, or in position 5 of pyrimidinyl groups.
Examples of 5- or 6-membered heteroaryl groups as used for the group Ar² are notably oxazolyl, isoxazolyl, thienyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl and pyrazinyl. In a sub-embodiment, examples are oxazolyl (in particular oxazol-2,4-diyl, oxazol-2,5-diyl, 4-methyl-oxazol-2,5-diyl, 5-methyl-oxazol-2,4-diyl, 4-cyano-oxazol-2,5-diyl, 4-difluoromethyl-oxazol-2,5-diyl) and thiazolyl (in particular thiazol-2,4-diyl, thiazol-2,5-diyl, 4-methyl-thiazol-2,5-diyl, 5-methyl-thiazol-2,4-diyl). The above groups are preferably attached to the rest of the molecule on a carbon atom next to a heteroatom (notably next to a nitrogen atom); especially in position 2 of oxazolyl or thiazolyl groups. In addition, the above groups carry a phenyl or 5- or 6-membered heteroaryl substituent which is preferably attached on a carbon atom in meta position to the point of attachment of the rest of the molecule (it being well understood that for 5-membered heteroaryl a meta connectivity means, depending on the atom numbering of said 5-membered heteroaryl, either a 1,3-diyl, a 1,4-diyl, a 2,4-diyl, or a 2,5-diyl connectivity). Particular examples of such groups are 4-(3-methyl-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-thiazol-2-yl, 5-(3-fluoro-phenyl)-thiazol-2-yl, 4-(3-chloro-phenyl)-thiazol-2-yl, 5-(3-chloro-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-oxazol-2-yl, 5-(3-fluoro-phenyl)-oxazol-2-yl, 5-(2-fluoro-phenyl)-oxazol-2-yl, 5-(4-fluoro-phenyl)-oxazol-2-yl, 4-(3-chloro-phenyl)-oxazol-2-yl, 4-(3-chloro-phenyl)-5-methyl-oxazol-2-yl, 4-(3-methyl-phenyl)-oxazol-2-yl, 4-methyl-5-(3-methyl-phenyl)-thiazol-2-yl, 5-methyl-4-(3-methyl-phenyl)-thiazol-2-yl, 5-(3-chloro-phenyl)-4-methyl-thiazol-2-yl, 5-(3-fluoro-phenyl)-4-methyl-thiazol-2-yl, 4-(3-fluorophenyl)-5-methyl-thiazol-2-yl, 4-(3-chloro-phenyl)-4-methyl-oxazol-2-yl, 5-(3-fluoro-phenyl)-5-methyl-oxazol-2-yl, 5-methyl-oxazol-2,4-diyl), 5-(3-fluoro-phenyl)-4-methyl-oxazol-2-yl, 5-(3-chloro-phenyl)-5-methyl-thiazol-2-yl, 4-(3-fluorophenyl)-5-methyl-thiazol-2-yl, 4-(3-chloro-phenyl)-4-methyl-thiazol-2-yl, 4-(3-fluorophenyl)-5-methyl-thiazol-2-yl, 4-(3-chloro-phenyl)-5-methyl-thiazol-2-yl, 4-difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl, and 4-cyano-5-(3-fluoro-phenyl)-oxazol-2-yl.

Examples of 8- to 10-membered bicyclic heteroaryl groups as used for the group Ar² are notably 9- or 10-membered bicyclic heteroaryl groups; examples are notably indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, quinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, and quinoxalinyml (in a sub-embodiment especially benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, and quinoxalinylnl; in another sub-embodiment especially indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolinyl, and quinolinyl). Particular examples are benzoxazol-2-yl, 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, 5-chloro-benzoxazol-2-yl, 6-chloro-benzoxazol-2-yl, benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-3-yl, 6-methyl-
benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl, benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, 6-chloro-benzo[d]isothiazol-3-yl, quinoxalin-2-yl, 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl. In a sub-embodiment, particular examples are 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, and 6-chloro-benzoxazol-2-yl. In another sub-embodiment, particular examples are especially benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-3-yl, 6-methyl-benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl, benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, 6-chloro-benzo[d]isothiazol-3-yl, 5-chloro-benzo[d]isothiazol-3-yl, 6-chloro-benzo[d]isothiazol-3-yl, 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl. In addition to the above-mentioned examples, further particular examples are 5-fluoro-quinoxalin-2-yl, 8-fluoro-quinoxalin-2-yl, 6-fluoro-7-methoxy-quinoxalin-2-yl, 7,8-difluoro-quinoxalin-2-yl, 5,6-difluoro-quinoxalin-2-yl, and quinazolin-2-yl.

Examples of the particular 5- or 6-membered heteroaryl groups which are substituents of the groups Ar¹ or Ar² are notably oxazolyl, isoxazolyl, oxadiazolyl, thiienyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl, pyridinyl, pyrimidinyl, and pyrazinyl (especially isoxazolyl, oxadiazolyl, pyrazolyl, triazolyl, pyridinyl, and pyrimidinyl). Particular examples are pyrazol-1-yl, 3-methyl-pyrazol-1-yl, [1,2,3]triazol-2-yl, 3-methyl-isoxazol-5-yl, 3-methyl-[1,2,4]oxadiazol-5-yl, pyridin-2-yl, and pyrimidin-2-yl. In a sub-embodiment, examples of the particular 5- or 6-membered heteroaryl groups which are substituents of the group Ar¹ are notably thiazolyl, isothiazolyl, and thiadiazolyl.

The heteroaryl groups as defined herein may be unsubstituted or substituted as explicitly defined.
Further embodiments of the invention are presented hereinafter:

3) Another embodiment relates to novel compounds according to embodiments 1) or 2), wherein $A_r^2$ is a group selected from the group consisting of any of the following groups:

a) 6-membered heteroaryl, wherein the 6-membered heteroaryl is mono-, di-, or tri-substituted; wherein

> one of said substituents is a group selected from the group consisting of any of the following groups:

i.) 5- or 6-membered heteroaryl; wherein said 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of ($C_{\text{i,3}}$)alkyl, ($C_{\text{1,3}}$)alkoxy, halogen, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{1,3}}$)fluoroalkoxy; and

ii.) phenyl; wherein said phenyl is mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of ($C_{\text{1,4}}$)alkyl, ($C_{\text{1,4}}$)alkoxy, halogen, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{3,6}}$)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of ($C_{\text{1,3}}$)alkyl, ($C_{\text{1,4}}$)alkoxy, ($C_{\text{3,6}}$)cycloalkyl, halogen, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{3,6}}$)fluoroalkoxy;

b) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of ($C_{\text{1,4}}$)alkyl, ($C_{\text{1,4}}$)alkoxy, halogen, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{1,3}}$)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of ($C_{\text{1,4}}$)alkyl, ($C_{\text{1,4}}$)alkoxy, ($C_{\text{3,6}}$)cycloalkyl, halogen, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{3,6}}$)fluoroalkoxy;

c) 8- to 10-membered bicyclic heteroaryl which is mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of ($C_{\text{1,4}}$)alkyl, ($C_{\text{1,4}}$)alkoxy, ($C_{\text{3,6}}$)cycloalkyl, cyano, ($C_{\text{1,3}}$)fluoroalkyl, and ($C_{\text{1,3}}$)fluoroalkoxy;

d) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl,
benzoisothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group is independently unsubstituted, or mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of

- (Ci₄)alkyl, (Ci₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (Ci₃)fluoroalkyl, and
- (Ci₃)fluoroalkoxy;

e) 8- to 10-membered bicyclic heteroaryl which is quinoxalinyl which is mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of

- (Ci₄)alkyl, (Ci₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (Ci₃)fluoroalkyl, and
- (Ci₃)fluoroalkoxy;

f) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is mono-substituted; wherein

> the substituent is selected from the group consisting of (C₁₋₄)alkyl,
- (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

and, in addition, fluoro; and

g) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of

- (Ci₄)alkyl, (Ci₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (Ci₃)fluoroalkyl, and
- (Ci₃)fluoroalkoxy;

wherein each of the above groups represents a separate sub-embodiment.

4) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein Ar² is a group selected from the group consisting of any of the following groups:

a) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein

said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (Ci₃)fluoroalkyl, and (Ci₃)fluoroalkoxy;

b) 8- to 10-membered bicyclic heteroaryl which is mono-, di-, or tri-substituted; wherein
the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

c) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group is independently unsubstituted, or mono-, di-, or tri-substituted; wherein
> the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

d) 8- to 10-membered bicyclic heteroaryl which is quinoxalinyl which is mono-, di-, or tri-substituted; wherein
> the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

e) 8- to 10-membered bicyclic heteroaryl which is benzoazolyl which is mono-substituted; wherein
> the substituent is selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and

f) 8- to 10-membered bicyclic heteroaryl which is benzoaxazolyl which is di-, or tri-substituted; wherein
> the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

wherein each of the above groups represents a separate sub-embodiment.

5) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein Ar\textsuperscript{2} is a group selected from the group consisting of any of the following groups:

a) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently
selected from the group consisting of \((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \) and \((\text{C}_1\text{-}3)\text{fluoroalkoxy};\)

b) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzo thiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group is independently unsubstituted, or mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of

\((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, (\text{C}_3\text{-}6)\text{cycloalkyl}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \) and \((\text{C}_1\text{-}3)\text{fluoroalkoxy};\)

c) 8- to 10-membered bicyclic heteroaryl which is quinoxaliny l which is mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of

\((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, (\text{C}_3\text{-}6)\text{cycloalkyl}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \) and \((\text{C}_1\text{-}3)\text{fluoroalkoxy};\)

d) 8- to 10-membered bicyclic heteroaryl which is benoxazolyl which is mono-substituted; wherein

> the substituent is selected from the group consisting of \((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, (\text{C}_3\text{-}6)\text{cycloalkyl}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \) and \((\text{C}_1\text{-}3)\text{fluoroalkoxy};\)

and, in addition, fluoro;

wherein each of the above groups represents a separate sub-embodiment.

6) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein \(\text{Ar}^2\) is a group selected from the group consisting of any of the following groups:

a) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein

said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of \((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \) and \((\text{C}_1\text{-}3)\text{fluoroalkoxy};\)
and the other of said substituents, if present, is/are independently selected from the group consisting of \((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, (\text{C}_3\text{-}6)\text{cycloalkyl}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \text{and} (\text{C}_1\text{-}3)\text{fluoroalkoxy};\) and

b) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of any of the following groups:

i.) 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, and 6-chloro-benzoxazol-2-yl;

ii.) benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-3-yl, 6-methyl-benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl, benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, and 6-chloro-benzo[d]isothiazol-3-yl; and

iii.) 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl; and (in a further embodiment in addition to the above-listed):

iv.) 5-fluoro-quinoxalin-2-yl, 8-fluoro-quinoxalin-2-yl, 6-fluoro-7-methoxy-quinoxalin-2-yl, 7,8-difluoro-quinoxalin-2-yl, 5,6-difluoro-quinoxalin-2-yl, and quinazolin-2-yl;

wherein each of the above groups represents a separate sub-embodiment.

7) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein \(A_{r2}\) represents a 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzothiazolyl, benzofuranyl, benzothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group is independently unsubstituted, or mono-, di-, or tri-substituted; wherein

> the substituents are independently selected from the group consisting of \((\text{C}_1\text{-}4)\text{alkyl}, (\text{C}_1\text{-}4)\text{alkoxy}, (\text{C}_3\text{-}6)\text{cycloalkyl}, \text{halogen}, \text{cyano}, (\text{C}_1\text{-}3)\text{fluoroalkyl}, \text{and} (\text{C}_1\text{-}3)\text{fluoroalkoxy}.\)

8) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein \(A_{r2}\) represents 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently
selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy;
> and the other of said substituents, if present, is/are independently selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, (C1-4)cycloalkyl, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy.

9) Another embodiment relates to compounds according to any one of embodiments 1) to 8), wherein Ar1 represents phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
> one of said substituents is attached in ortho-position to the point of attachment of Ar1 to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy (especially (C1-4)alkyl and halogen);
> and the other of said substituents, if present, is/are independently selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy.

10) Another embodiment relates to compounds according to any one of embodiments 1) to 9), wherein

- Ar1 represents phenyl, which is mono-, di-, or tri-substituted; wherein
> one of said substituents is attached in ortho-position to the point of attachment of Ar1 to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridinyl, or pyrimidinyl; especially 5-membered heteroaryl), which is independently unsubstituted, or mono-, or di-substituted (notably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy (notably (C1-4)alkyl and halogen);
> and the other of said substituents, if present, is/are independently selected from the group consisting of (C1-4)alkyl, (C1-4)alkoxy, halogen, cyano, (C1-3)fluoroalkyl, and (C1-3)fluoroalkoxy;
- or Ar1 represents 5- or 6-membered heteroaryl (notably oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyrimidinyl or pyrazinyl) which is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein
one of said substituents is attached in ortho-position to the point of attachment of Ar\(^1\) to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridinyl, or pyrimidinyl; in case Ar\(^1\) represents 5-membered heteroaryl it is especially phenyl; and in case Ar\(^1\) represents 6-membered heteroaryl it is especially phenyl or 5-membered heteroaryl), which is independently unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (Cl\(_4\))alkyl, (Cl\(_4\))alkoxy, halogen, cyano, (Cl\(_3\))fluoroalkyl, and (Cl\(_3\))fluoroalkoxy (especially (Cl\(_3\))alkyl);

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C\(_1\_4\))alkyl, (C\(_1\_4\))alkoxy, halogen, cyano, (C\(_1\_3\))fluoroalkyl, and (C\(_1\_3\))fluoroalkoxy (especially (C\(_1\_3\))alkyl).

Another embodiment relates to compounds according to any one of embodiments 1) to 10), wherein Ar\(^1\) represents phenyl, which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar\(^1\) to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridinyl, or pyrimidinyl; especially 5-membered heteroaryl), which is independently unsubstituted, or mono-, or di-substituted (notably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (Cl\(_4\))alkyl, (Cl\(_4\))alkoxy, halogen, cyano, (Cl\(_3\))fluoroalkyl, and (Cl\(_3\))fluoroalkoxy (notably (Cl\(_4\))alkyl and halogen);

> and the other of said substituents, if present, is/are independently selected from the group consisting of (Cl\(_4\))alkyl, (Cl\(_4\))alkoxy, halogen, cyano, (Cl\(_3\))fluoroalkyl, and (Cl\(_3\))fluoroalkoxy.

Another embodiment relates to compounds according to any one of embodiments 1) to 10), wherein Ar\(^1\) represents 5- or 6-membered heteroaryl (notably oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyrimidinyl or pyrazinyl) which is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar\(^1\) to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridinyl, or pyrimidinyl) (in a sub-embodiment, in case Ar\(^1\) represents 5-membered heteroaryl it is especially phenyl, and in case Ar\(^1\) represents 6-membered heteroaryl it is especially phenyl or
5-membered heteroaryl), which is independently unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, halogen, cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy (especially (Cl₄)alkyl);

> and the other of said substituents, if present, is/are independently selected from the group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, halogen, cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy (especially (Cl₄)alkyl).

13) Another embodiment relates to compounds according to embodiment 1), or any one of embodiments 2) to 8), wherein Ar¹ is a group selected from the group consisting of any of the following groups:

a) phenyl, which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar¹ to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridyl, or pyrimidyl; especially 5-membered heteroaryl), which is independently mono-, or di-substituted (especially mono-substituted), wherein the substituents are independently selected from the group consisting of (Cl₄)alkoxy, cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, and halogen;

b) phenyl, which is di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar¹ to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl (notably phenyl, oxadiazolyl, pyrazolyl, triazolyl, pyridyl, or pyrimidyl; especially 5-membered heteroaryl), which is independently unsubstituted, or mono-, or di-substituted (notably unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, halogen, cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy (notably (Cl₄)alkyl and halogen);

> and the other of said substituents, if present, is/are independently selected from the group consisting of cyano, (C₁₃)fluoroalkyl, and (C₁₃)fluoroalkoxy;

c) 6-membered heteroaryl selected from the group consisting of pyrimidinyl and pyrazinyl, which is mono-, di-, or tri-substituted; wherein
one of said substituents is attached in ortho-position to the point of attachment of Ar\textsubscript{1} to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

i.) phenyl which is mono-, or di-substituted (especially mono-substituted), wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy (especially (C\textsubscript{i-4})alkyl and halogen); and

ii.) 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy (especially (C\textsubscript{i-4})alkyl and halogen);

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

d) 6-membered heteroaryl which is pyridinyl, which is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein

one of said substituents is attached in ortho-position to the point of attachment of Ar\textsubscript{1} to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

i.) phenyl, which is unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy (especially (C\textsubscript{i-4})alkyl and halogen);

ii.) 6-membered heteroaryl which is unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy (especially halogen); and

iii.) 5-membered heteroaryl which is mono-, or di-substituted (especially mono-substituted), wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy (especially (C\textsubscript{i-4})alkyl);
and the other of said substituents, if present, is/are independently selected from the group consisting of \((\text{Cl}_4)\)alkyl, \((\text{Cl}_4)\)alkoxy, halogen, cyano, \((\text{Cl}_3)\)fluoroalkyl, and \((\text{Cl}_3)\)fluoroalkoxy (especially \((\text{Cl}_4)\)alkyl); and 
e) 5-membered heteroaryl (especially selected from the group consisting of oxazolyl, isoxazolyl, thienyl, thiazolyl, and isothiazolyl); which is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein
> one of said substituents is attached in ortho-position to the point of attachment of \(\text{Ar}^1\) to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

i.) phenyl which is mono-, or di-substituted (especially mono-substituted), wherein the substituents are independently selected from the group consisting of \((\text{C}_1\text{-}4)\)alkyl, \((\text{C}_1\text{-}4)\)alkoxy, cyano, \((\text{C}_1\text{-}3)\)fluoroalkyl, and \((\text{C}_1\text{-}3)\)fluoroalkoxy (especially \((\text{C}_1\text{-}4)\)alkyl); and

ii.) 5- or 6-membered heteroaryl which is mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of \((\text{Cl}_4)\)alkoxy, halogen, cyano, \((\text{Cl}_3)\)fluoroalkyl, and \((\text{Cl}_3)\)fluoroalkoxy;
> and the other of said substituents, if present, is/are independently selected from the group consisting of \((\text{Cl}_4)\)alkyl, \((\text{Cl}_4)\)alkoxy, halogen, cyano, \((\text{Cl}_3)\)fluoroalkyl, and \((\text{Cl}_3)\)fluoroalkoxy (especially \((\text{Cl}_4)\)alkyl); wherein each of the above groups represents a separate sub-embodiment.

14) Another embodiment relates to compounds according to any one of embodiments 1) to 10), wherein \(\text{Ar}^1\) is a group selected from the group consisting of:

![Chemical structures](https://example.com/structures.png)
or, in addition to the above listed groups, \( \text{Ar}^1 \) may be a group selected from the group consisting of:

\[
\begin{align*}
\text{Cl} & & \text{F} & & \text{and} & & \text{F} \\
\text{N} & & \text{O} & & \text{N} & & \text{O} \\
\text{F} & & \text{F} & & \text{and} & & \text{F} \\
\text{N} & & \text{O} & & \text{N} & & \text{O}
\end{align*}
\]

(wherein each of the above two lists forms a separate sub-embodiment).
15) Another embodiment relates to compounds according to embodiment 1), or any one of embodiments 2) to 10), wherein $\text{Ar}^1$ is a group selected from the group consisting of:

![Chemical structures](image)

$\text{Ar}^1$ represents 5- or 6-membered heteroaryl (especially 5-membered heteroaryl), wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein

- $\text{Ar}^2$ represents 5- or 6-membered heteroaryl (especially 5-membered heteroaryl), wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein

- one of said substituents is phenyl or 5- or 6-membered heteroaryl (especially said substituent is phenyl) [which is preferably attached in meta-position to the point of attachment of $\text{Ar}^2$ to the rest of the molecule]; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of $(\text{Ci}_4)$alkyl, $(\text{Ci}_4)$alkoxy, halogen, cyano, $(\text{Ci}_3)$fluoroalkyl, and $(\text{Ci}_3)$fluoroalkoxy (especially $(\text{Ci}_4)$alkyl and halogen);
> and the other of said substituents, if present, is/are independently selected from the group consisting of \((\text{Cl}_2) \text{alkyl}, (\text{Cl}_4) \text{alkoxy}, (C_{3-6}) \text{cycloalkyl}, \text{halogen}, \text{cyano}, (\text{Cl}_3) \text{fluoroalkyl}, \text{and} (\text{Cl}_3) \text{fluoroalkoxy} \) (notably \((\text{Cl}_2) \text{alkyl}, \text{cyano}, (\text{Cl}_3) \text{fluoroalkyl}; \) especially \((\text{Cl}_4) \text{alkyl})

- or \(\text{Ar}^2\) represents 8- to 10-membered bicyclic heteroaryl (especially 9 or 10-membered heteroaryl) which is unsubstituted, or mono-, di-, or tri-substituted (especially unsubstituted, or mono-, or di-substituted); wherein
  > the substituents are independently selected from the group consisting of \((\text{Cl}_2) \text{alkyl}, (\text{Cl}_4) \text{alkoxy}, (C_{3-6}) \text{cycloalkyl}, \text{cyano}, (\text{Cl}_3) \text{fluoroalkyl}, \text{and} (\text{C}_{1-3}) \text{fluoroalkoxy} \) (especially \((C_{1-3}) \text{alkyl} \) and \(\text{halogen})\)

17) Another embodiment relates to compounds according to any one of embodiments 1) to 15) [especially embodiments 2), 13) or 15]], wherein

- \(\text{Ar}^2\) represents 5-membered heteroaryl, which is mono- or di-substituted; wherein
  > one of said substituents is phenyl [which is preferably attached in \text{meta}-position to the point of attachment of \(\text{Ar}^2\) to the rest of the molecule]; wherein said phenyl is unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of \((\text{Cl}_2) \text{alkyl}, (\text{Cl}_4) \text{alkoxy}, \text{halogen, cyano, (Cl}_3) \text{fluoroalkyl, and (Cl}_3) \text{fluoroalkoxy (especially (Cl}_4) \text{alkyl and halogen})\)

20) > and the other of said substituents, if present, is/are independently selected from the group consisting of \((\text{Cl}_2) \text{alkyl}, (\text{Cl}_4) \text{alkoxy}, (C_{3-6}) \text{cycloalkyl, halogen, cyano, (Cl}_3) \text{fluoroalkyl, and (Cl}_3) \text{fluoroalkoxy (notably (Cl}_4) \text{alkyl, cyano, (Cl}_3) \text{fluoroalkyl; especially (Cl}_4) \text{alkyl})\)

- or \(\text{Ar}^2\) represents 9- or 10-membered bicyclic heteroaryl which is unsubstituted, or mono-, or di-substituted; wherein
  > the substituents are independently selected from the group consisting of \((C_{1-4}) \text{alkyl, (C}_{1-4}) \text{alkoxy, cyano, (C}_{1-3}) \text{fluoroalkyl, and (C}_{1-3}) \text{fluoroalkoxy (especially (C}_{1-4}) \text{alkyl and halogen})\)

30) 18) Another embodiment relates to compounds according to any one of embodiments 1) to 15) [especially embodiments 2), 13) or 15]], wherein \(\text{Ar}^2\) represents 5- or 6-membered heteroaryl (especially 5-membered heteroaryl), wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted (especially mono- or di-substituted); wherein
  > one of said substituents is phenyl or 5- or 6-membered heteroaryl (especially said substituent is phenyl) [which is preferably attached in \text{meta}-position to the point of
attachment of Ar² to the rest of the molecule]; wherein said phenyl or 5- or 6-
membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted
(epecially unsubstituted or mono-substituted), wherein the substituents are
independently selected from the group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, halogen,
cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy (especially (Cl₄)alkyl and halogen);
> and the other of said substituents, if present, is/are independently selected from the
group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano,
(Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy (especially (Cl₄)alkyl, cyano, (Cl₃)fluoroalkyl;
especially (Cl₄)alkyl).

19) Another embodiment relates to compounds according to any one of embodiments 1) to
15) [especially embodiments 2), 13) or 15]), wherein Ar² represents 8- to 10-membered
bicyclic heteroaryl (especially 9 or 10-membered heteroaryl) which is unsubstituted, or mono-,
di-, or tri-substituted (especially unsubstituted, or mono-, or di-substituted); wherein the
substituents are independently selected from the group consisting of (C₁₋₅)alkyl, (C₁₋₅)alkoxy,
(C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₅)alkyl and halogen).

20) Another embodiment relates to compounds according to any one of embodiments 1) to
19), wherein, in case Ar² represents 8- to 10-membered bicyclic heteroaryl, said 8- to 10-
membered heteroaryl is a group selected from the group consisting of indolyl,
benzofuranyl, benzothiophenyl, indazolyl, benzoazazolyl, benzisoxazolyl, benzothiazolyl,
benzoisothiazolyl, quinolinyl, naphthyridinyl, cinnolinyl, quinazolinyl, and quinoxalinyl
(epecially benzoxazolyl, benzisoxazolyl, benzothiazolyl, and quinoxalinyl); which group is
unsubstituted, or mono-, di-, or tri-substituted (especially unsubstituted, or mono-, or di-
substituted); wherein the substituents are independently selected from the group consisting
of (Cl₄)alkyl, (Cl₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (Cl₃)fluoroalkyl, and (Cl₃)fluoroalkoxy
(epecially (Cl₄)alkyl and halogen).

21) Another embodiment relates to compounds according to any one of embodiments 1) to
19), wherein, in case Ar² represents 8- to 10-membered bicyclic heteroaryl, said 8- to 10-
membered bicyclic heteroaryl is a group selected from the group consisting of benzoxazol-2-
yl, 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, 5-chloro-
benzoxazol-2-yl, 6-chloro-benzoxazol-2-yl, benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-
3-yl, 6-methyl-benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-
benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl,
benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-
benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, 6-chloro-
benzo[d]isothiazol-3-yl, quinoxalin-2-yl, 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl.

22) Another embodiment relates to compounds according to any one of embodiments 1) to 19), wherein, in case Ar2 represents 8- to 10-membered bicyclic heteroaryl, said 8- to 10-membered bicyclic heteroaryl is a group selected from the group consisting of any of the following groups, alone or in any combination:

a) benzooxazol-2-yl, and 5-chloro-benzooxazol-2-yl;
b) 5-fluoro-benzooxazol-2-yl, 6-fluoro-benzooxazol-2-yl, 4-chloro-benzooxazol-2-yl, and 6-chloro-benzooxazol-2-yl;
c) benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-3-yl, 6-methyl-benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl, benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, and 6-chloro-benzo[d]isothiazol-3-yl;
d) quinoxalin-2-yl;
e) 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl; and/or

f) 5-fluoro-quinoxalin-2-yl, 8-fluoro-quinoxalin-2-yl, 6-fluoro-7-methoxy-quinoxalin-2-yl, 7,8-difluoro-quinoxalin-2-yl, 5,6-difluoro-quinoxalin-2-yl, and quinazolin-2-yl.

23) Another embodiment relates to compounds according to any one of embodiments 1) to 22), wherein, in case Ar2 represents 5- or 6-membered heteroaryl which is at least mono-substituted with phenyl or 5- or 6-membered heteroaryl, said phenyl or 5- or 6-membered heteroaryl substituent is attached in meta-position to the point of attachment of Ar2 to the rest of the molecule (it being well understood that for 5-membered heteroaryl a meta connectivity means, depending on the atom numbering of said 5-membered heteroaryl, either a 1,3-diyl, a 1,4-diyl, a 2,4-diyl, or a 2,5-diyl connectivity).

24) Another embodiment relates to compounds according to any one of embodiments 1) to 22), wherein, in case Ar2 represents 5- or 6-membered heteroaryl (which is at least mono-substituted with phenyl or 5- or 6-membered heteroaryl as explicitly defined), said Ar2 is a group selected from the group consisting of:
i.e. said $A_r^2$ is a group selected from the group consisting of 4-(3-methyl-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-thiazol-2-yl, 5-(3-fluoro-phenyl)-thiazol-2-yl, 4-(3-chloro-phenyl)-thiazol-2-yl, 5-(3-chloro-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-oxazol-2-yl, 5-(3-fluoro-phenyl)-oxazol-2-yl, 5-(2-fluoro-phenyl)-oxazol-2-yl, 5-(4-fluoro-phenyl)-oxazol-2-yl, 4-(3-chloro-phenyl)-oxazol-2-yl, 4-(3-chloro-phenyl)-5-methyl-oxazol-2-yl, 4-(3-methyl-phenyl)-oxazol-2-yl, 4-(3-fluoro-phenyl)-thiazol-2-yl, 5-methyl-4-(3-methyl-phenyl)-thiazol-2-yl, 5-methyl-4-(3-methyl-phenyl)-thiazol-2-yl, 5-(3-
chloro-phenyl)-4-methyl-thiazol-2-yl, 5-(3-fluoro-phenyl)-4-methyl-thiazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-thiazol-2-yl, 4-(3-chloro-phenyl)-5-methyl-oxazol-2-yl, 5-(3-chloro-phenyl)-4-methyl-oxazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-oxazol-2-yl, 5-(2-fluoro-phenyl)-4-methyl-oxazol-2-yl, 5-(4-fluoro-phenyl)-4-methyl-oxazol-2-yl, 5-(3-methyl-phenyl)-thiazol-2-yl, 4-methyl-5-(3-methyl-phenyl)-oxazol-2-yl, 4-(3-chloro-phenyl)-5-methyl-thiazol-2-yl, 4-difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl, and 4-cyano-5-(3-fluoro-phenyl)-oxazol-2-yl.

25) Another embodiment relates to compounds according to any one of embodiments 1) to 24), which are also compounds of formula (I<sub>e1</sub>) wherein the absolute configuration of the 3,8-diaza-bicyclo[4.2.0]octane moiety is (1R,6S):

![Formula (I<sub>e1</sub>)](image)

26) Another embodiment relates to compounds according to any one of embodiments 1) to 24), which are also compounds of formula (I<sub>e2</sub>) wherein the absolute configuration of the 3,8-diaza-bicyclo[4.2.0]octane moiety is (1S,6R):

![Formula (I<sub>e2</sub>)](image)

27) Another embodiment relates to compounds of formula (I) according to any one of embodiments 1) to 3) selected from the group consisting of:

[(1'R<sup>+</sup>,6S<sup>+</sup>)-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(6-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(4-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(Benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1'R<sup>+</sup>,6S<sup>+</sup>)-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;]
[(1 R*,6S*)-8-(5-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-Benzo[d]isoxazol-3-yl-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Fluoro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Fluoro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Methyl-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Methyl-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Chloro-benzo[d]isothiazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Chloro-benzo[d]isothiazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(5-Methyl-benzo[d]isothiazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(6-Methyl-benzo[d]isothiazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(4-Methyl-5-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(3-Chloro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(4-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-(4-Methyl-5-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(4-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(2-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(5-methyl-2-1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[5-(4-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[5-(2-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
5-(3-Fluoro-phenyl)-2-[(1 R', 6S')-3-(5-methyl-2-[1,2,3]triazol-2-yl-benzoyl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-oxazole-4-carbonitrile;
{(1 R', 6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[5-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
5-(Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R', 6S')-8-(5-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
{(1 R', 6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R', 6S')-8-(4-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
{(1 R', 6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
5-(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R', 6S')-8-(4-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
{(1 R', 6S')-8-[4-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R', 6S')-8-[4-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1R*,6S*)-8-(5-Methyl-4-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1R*,6S*)-8-[4-(3-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1R*,6S*)-8-[4-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R*,6S*)-8-(4-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
[(1 R*,6S*)-8-(7-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6,7-Dichloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1S*,6R*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-[1,2,3]triazol-2-
yl-5-trifluoromethyl-phenyl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-[1,2,3]triazol-2-
yl-5-trifluoromethoxy-phenyl)-methanone;
3-[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]octane-3-carbonyl]-4-
[1,2,3]triazol-2-yl-benzonitrile;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(6-methyl-3-(3-
pyrazol-1-yl)-pyridin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(6-methyl-3-
pyrimidin-2-yl-pyridin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(6'-methyl-
[2,3']bipyridinyl-2'-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(6-methyl-
3-phenyl-pyridin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-3-p-tolyl-
isoaxoz-4-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-3-methyl-isoxazol-4-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-3-(3-methyl-isoxazol-5-yl)-pyridin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-3-(3-fluoro-phenyl)-2-methyl-oxazol-4-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(2-methyl-5-methyl-3-methyl-isoxazol-5-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(3-m-tolyl-pyrazin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(3-p-tolyl-pyrazin-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(2-methyl-4-methyl-pyrimidin-5-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(2-methyl-4-p-tolyl-pyrimidin-5-yl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Fluoro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(4-Methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-[6,7-Difluoro-quinoxalin-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
(1 \textit{R}',6\textit{S}')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(4-methyl-biphenyl-2-yl)-methanone;
[(1R,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R',6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

25 (2-Fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)=[(1R*,6S*)-8-[5-(3-fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone; and

(2-Fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)=[(1R*,6S*)-8-[4-(3-fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;

In a sub-embodiment of embodiment 27), the above listed compounds having the relative configuration (1R',6S') preferably are enantiomerically enriched, especially having the absolute configuration (1R,6S), corresponding to the compounds of formula (Ie,i) of embodiment 25).

28) Another embodiment relates to compounds of formula (I) according to any one of embodiments 1) to 3) selected from the group consisting of:
[(1 R*,6S*)-8-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R,6S)-8-(6-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R,6S)-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R,6S)-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(4-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R,6S)-8-[4-(Methyl-5-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[4-(3-Chloro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R,6S)-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(2-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R\(^*\),6S\(^*\))-8-(5-Methyl-4-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;

{(1 R\(^*\),6S\(^*\))-8-(4-(3-Fluoro-phenyl)-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;

{(1 R\(^*\),6S\(^*\))-8-(5-Methyl-4-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;

{(1 R\(^*\),6S\(^*\))-8-(7-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;

{(1 R\(^*\),6S\(^*\))-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl-(5-methyl-2-
[1,2,3]triazol-2-yl-phenyl)-methanone;

{(1 S\(^*\),6R\(^*\))-(2-[1,2,3]triazol-2-yl-5-trifluoromethyl-phenyl)-methanone;
3-[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]octane-3-carbonyl]-4-
[1,2,3]triazol-2-yl-benzonitrile;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[6-methyl-3-(3-
methyl-pyrazol-1-yl)-pyridin-2-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[6-methyl-3-
pyrimidin-2-yl-pyridin-2-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[6'-methyl-
[2,3']bipyridinyl-2'-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[6-methyl-3-
phenyl-pyridin-2-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[5-(methyl-
3-p-tolyl-isoxazol-4-yl)-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[5-(methyl-3-
phenyl-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-phenyl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[5-(fluoro-
phenyl)-2-methyl-oxazol-4-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[2-methyl-5-m-
tolyl-oxazol-4-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[2-(methyl-
3-p-tolyl-pyrazin-2-yl)-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[3-p-tolyl-
pyrimidin-5-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[2-methyl-4-
tolyl-pyrimidin-5-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[2-methyl-4-p-
tolyl-pyrimidin-5-yl]-methanone;
[(1R*,6S*)-8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[4-methyl-
biphenyl-2-yl]-methanone;
[(1 R,6S)-8-(5-Fluoro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
5
[(1 R',6S')-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
10
[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
15
[(1 R',6S')-8-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
20
[(1 R',6S')-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R,6S)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
25
[(1 R',6S')-8-(6,7-Dichloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R*,6S')-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(4-methyl-biphenyl-2-yl)-methanone;}
30
[(1 R',6S')-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}
[(1 R',6S')-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}
35
[(1 R',6S')-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
([(1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*,6S*)-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*,6S*)-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*,6S*)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*6S*)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R,6S)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R,6S)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
((1 R*6S*)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyridin-2-yl-phenyl)-methanone;
((1 R,6S)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyridin-2-yl-phenyl)-methanone;
((1 R*6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyridin-2-yl-phenyl)-methanone;
((1 R,6S)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]- (5-methyl-2-pyridin-2-yl-phenyl)-methanone;
In a sub-embodiment of embodiment 28), the above listed compounds having the relative configuration \((1 \, R^*, 6S^*)\) preferably are enantiomerically enriched, especially having the absolute configuration \((1 \, R, 6S)\), corresponding to the compounds of formula \((l_E)\) of embodiment 25).

29) In addition to the compounds listed in any of embodiments 27) and 28), further compounds of formula \((l)\) according to any one of embodiments 1) to 3) are selected from the group consisting of:
[1 R,6S\(^*\)\]-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[1 R,6S\(^*\)\]-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[1 R\(^*\),6S\(^*\)\]-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(8-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(6-Fluoro-7-methoxy-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(8-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(6-Fluoro-7-methoxy-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\)\]-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl\)-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R\(^*\),6S\(^*\))-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R,6S)-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;

[(1 R\(^*\),6S\(^*\))-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1 R,6S)-8-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1 R\(^*\),6S\(^*\))-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1 R,6S)-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

[(1 R*\(^*\),6S\(^*\))-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;

[(1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;

[(1 R*\(^*\),6S\(^*\))-8-(7,8-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;

[(1 R,6S)-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;
(3-Fluoro-4-methyl-biphenyl-2-yl)-[(1R,6S)-8-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
(3-Fluoro-4-methyl-biphenyl-2-yl)-[(1R,6S)-8-(5-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
5
[(1R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(2-fluoro-3-methyl-6-pyridin-2-yl-phenoxy)-methanone;
(2-Fluoro-3-methyl-6-pyridin-2-yl-phenoxy)-[(1R,6S)-8-(6-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
[(1R,6S)-8-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-[(2-fluoro-3-methyl-6-pyridin-2-yl-phenoxy)-methanone; and
(2-Fluoro-3-methyl-6-pyridin-2-yl-phenoxy)-[(1R,6S)-8-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone.
10
In a sub-embodiment of embodiment 29), the above listed compounds having the relative configuration (1R',6S') preferably are enantiomerically enriched, especially having the absolute configuration (1R,6S), corresponding to the compounds of formula (I), of embodiment 25).

The term "enriched", for example when used in the context of enantiomers is understood in the context of the present invention to mean especially that the respective enantiomer is present in a ratio (mutatis mutandis: purity) of at least 70:30, and notably of at least 90:10 (mutatis mutandis: purity of 70% / 90%) with respect to the respective other enantiomer. Preferably the term refers to the respective essentially pure enantiomer. The term "essentially", for example when used in a term such as "essentially pure" is understood in the context of the present invention to mean especially that the respective stereoisomer / composition / compound etc. consists in an amount of at least 90, especially of at least 95, and notably of at least 99 per cent by weight of the respective pure stereoisomer / composition / compound etc.

The compounds of formula (I) and their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical compositions for enteral or parental administration.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Remington, The Science and Practice of Pharmacy, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing the described compounds of formula
or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

The present invention also relates to a method for the prevention or treatment of a disease or disorder mentioned herein comprising administering to a subject a pharmaceutically active amount of a compound of formula (I).

For avoidance of any doubt, if compounds are described as useful for the prevention or treatment of certain diseases or disorders, such compounds are likewise suitable for use in the preparation of a medicament for the prevention or treatment of said diseases or disorders.

The compounds according to formula (I) are useful for the prevention or treatment of diseases or disorders related to the orexin system.

Such diseases or disorders related to the orexin system may be defined as comprising all types of sleep disorders, stress-related syndromes, addictions (especially psychoactive substance use, abuse, seeking and reinstatement), cognitive dysfunctions in the healthy population and in psychiatric and neurologic disorders, and eating or drinking disorders. Especially, such diseases or disorders related to the orexin system comprise all types of sleep disorders, stress-related syndromes, and addictions (especially psychoactive substance use, abuse, seeking and reinstatement).

In a sub-embodiment, such diseases or disorders related to the orexin system may be selected from the group consisting of sleep disorders that comprises all types of insomnias, sleep-related dystonias, restless leg syndrome, sleep apneas, jet-lag syndrome, shift-work syndrome, delayed or advanced sleep phase syndrome or insomnias related to psychiatric disorders (notably all types of insomnias, especially primary insomnia).

In another sub-embodiment, such diseases or disorders related to the orexin system may be selected from the group consisting of cognitive dysfunctions that comprise deficits in all types of attention, learning and memory functions occurring transiently or chronically in the normal, healthy, young, adult or aging population, and also occurring transiently or chronically in psychiatric, neurologic, cardiovascular and immune disorders.

In another sub-embodiment, such diseases or disorders related to the orexin system may be selected from the group consisting of eating disorders that comprise metabolic dysfunction; dysregulated appetite control; compulsive obesities; bulimia or anorexia nervosa.
In another sub-embodiment, such diseases or disorders related to the orexin system may be selected from the group consisting of all types of addictions (especially psychoactive substance use, abuse, seeking and reinstatement) that comprise all types of psychological or physical addictions and their related tolerance and dependence components.

Eating disorders may be defined as comprising metabolic dysfunction; dysregulated appetite control; compulsive obesities; emetobulimia or anorexia nervosa. Pathologically modified food intake may result from disturbed appetite (attraction or aversion for food); altered energy balance (intake vs. expenditure); disturbed perception of food quality (high fat or carbohydrates, high palatability); disturbed food availability (unrestricted diet or deprivation) or disrupted water balance. Drinking disorders include polydipsias in psychiatric disorders and all other types of excessive fluid intake.

Sleep disorders include all types of parasomnias, insomnias, sleep-related dystonias; restless leg syndrome; sleep apneas; jet-lag syndrome; shift-work syndrome, delayed or advanced sleep phase syndrome or insomnias related to psychiatric disorders.

Insomnias are defined as comprising sleep disorders associated with aging; intermittent treatment of chronic insomnia; situational transient insomnia (new environment, noise) or short-term insomnia due to stress; grief; pain or illness. Insomnia also include stress-related syndromes including post-traumatic stress disorders as well as other types and subtypes of anxiety disorders such as generalized anxiety, obsessive compulsive disorder, panic attacks and all types of phobic anxiety and avoidance.

Addictions may be defined as addiction to one or more rewarding stimuli, notably to one rewarding stimulus. Such rewarding stimuli may be of either natural or synthetic origin. Psychoactive substance use, abuse, seeking and reinstatement are defined as all types of psychological or physical addictions and their related tolerance and dependence components.

Cognitive dysfunctions include deficits in all types of attention, learning and memory functions occurring transiently or chronically in the normal, healthy, young, adult or aging population, and also occurring transiently or chronically in psychiatric, neurologic, cardiovascular and immune disorders.

Besides, any characteristics described in this invention for the compounds of formula (I) (whether for the compounds themselves, salts thereof, compositions containing the compounds or salts thereof, uses of the compounds or salts thereof, etc.) apply mutatis mutandis to compounds of formula (I_{1,1}) and formula (I_{1,2}).
**Preparation of compounds of formula (I):**

A further aspect of the invention is a process for the preparation of compounds of formula (I). Compounds according to formula (I) of the present invention can be prepared according to the general sequence of reactions outlined in the schemes below wherein $\text{Ar}^1$, and $\text{Ar}^2$ are as defined for formula (I). In the schemes below, the generic substituent $(\text{R})_n$ refers to optional substituents that may be present in the respective residues as explicitly defined for the compounds of formula (I). The compounds obtained may also be converted into salts thereof in a manner known per se.

In general, all chemical transformations can be performed according to well-known standard methodologies as described in the literature or as described in the procedures or in the experimental part below.

Diazabicyclooctanes - derivatives of formula (I) may be prepared according to schemes 1, or 2 as racemates or as single enantiomers. The starting materials for use in the scheme are commercially available or can be prepared according to known methods described in the literature: *J. Med. Chem.* 2006, 49(26), 7843-7853 ($n = 1$) - The diazabicyclooctane core templates 1 and 6 can be prepared racemic and/or enantiomerically pure according to the same reference. Compounds of formula (I) can be obtained according to Method A depicted in Scheme 1 or according to Method B depicted in Scheme 2.

**Method A:**

![Scheme 1: Preparation of compounds of formula (I)](image)

The starting material 1, available in racemic or enantiomerically enriched form, can be coupled with a carboxylic acid derivative $\text{Ar}^1$-COOH 2 via a peptidic coupling using TBTU as activating agent in the presence of a base such as DIPEA in CH$_3$CN at RT to afford intermediate 3. Boc-deprotection is usually achieved by reacting 3 with a solution of HCl 4 N in dioxane using dioxane as solvent or with a solution of HCl 2 N in Et$_2$O using Et$_2$O as solvent to give the amine's HCl salt 4. Further nucleophilic substitution of a suitable $\text{Ar}^2$-

Method B:

![Scheme 2: Preparation of compounds of formula (I)](image)

In analogy to the methods described above, the starting material 6, available in racemic or enantiomerically enriched form, can be reacted with the suitable Ar²-halogenide or equivalent, e.g. Ar²-Cl 5, via a nucleophilic substitution to afford intermediate 7. Boc-deprotection is achieved as before to give the amine's HCl salt 8. Ultimately 8 is coupled with the carboxylic acid derivative Ar¹-COOH 2 as described before to give the final compounds of formula (I).

In the following, particular methods for the synthesis of carboxylic acid derivatives of formula Ar¹-CO-OH and halogenides of formula Ar²-halogenide (such as Ar²-Cl) are described. These starting materials are well known in the art and/or commercially available; or they may be synthesized according to methods described in the literature. In addition, they may be synthesized in analogy to the methods given in the experimental part. In case Ar¹, Ar², or a substituent thereof is a heteroaryl moiety, such heteroaryl may be introduced using well known and generally commercially available building blocks (literature for precursors of heteroaryl-containing groups: see e.g. T. Eicher, S. Hauptmann "The chemistry of Heterocycles: Structure, Reactions, Syntheses, and Applications", 2nd Edition 2003, Wiley, ISBN 978-3-527-30720-3; A. R. Katritzky, C. W. Rees, E. F. V. Scriven (Eds.)
Preparation of building blocks of formula $\text{Ar}^1\text{-CO-OH}$:

Carboxylic acid derivatives of formula $\text{Ar}^1\text{-CO-OH}$ are well known in the art and/or commercially available; or they may be synthesized according to methods described in the literature (see for example Schemes 5-11, wherein $R^4$ and $R^5$ correspond to the respective optional substituents as defined for the compounds of formula(I)). In addition, they may be synthesized in analogy to the methods given in the experimental part.


Scheme 5: Preparation of building blocks of formula $\text{Ar}^1\text{-CO-OH}$; wherein $R^3$ is optionally substituted phenyl or 5- or 6-membered heteroaryl; $X$ is CH or N

Acids of structure 16 shown in Scheme 6 can be prepared following the procedures reported in WO2010/044054, WO2010/038200, and WO2010/004507.

Scheme 6: Preparation of building blocks of formula $\text{Ar}^1\text{-CO-OH}$; wherein $Y$ is O or S

Acids of structure 17a and 17b shown in Scheme 7 can be prepared following the procedures reported in WO2010/044054.
Preparation of building blocks of formula $\text{Ar}^1\text{-CO-OH}$

Building blocks of formula $\text{Ar}^2\text{-Cl}$ are well known in the art and/or commercially available, or they may be synthesized according to methods described in the literature. In addition, they may be synthesized in analogy to the methods given in the experimental part. General synthetic routes, which can be applied to several similar building blocks, are also shown in Schemes 8 through 11.

$\text{Ar}^2\text{-Cl}$ of structure 22 can be prepared according to general Method E depicted in Scheme 8.

**Method E:**

![Scheme 8: Preparation of building blocks of formula $\text{Ar}^1\text{-Cl}$; $\text{R}^6$ is H or alkyl](image)

Optionally, in case $\text{R}^6 = \text{CH}_3$, commercially available TOSMIC 18 can be alkylated in a first step, e.g. to methyl-TOSMIC 19 with Mel, in the presence of benzyltriethylammonium chloride (TEBA) and NaOH 30% at 0°C in DCM. Further condensation of 18 or 19 on commercially available aldehydes 20 in the presence of a base such as $\text{K}_2\text{CO}_3$ in MeOH at reflux affords the oxazoles 21. Chlorination of 21 can be performed at -78°C in THF with a base such as LiHMDS (1.0 M in THF) and hexachloroethane to give final compounds of structure 22.

$\text{Ar}^2\text{-Cl}$ of structure 26 can be prepared according to general Method F depicted in Scheme 9.
Method F:

\[
\begin{array}{c}
\text{23} \quad \text{OH} \\
\text{(R)}_n \\
\end{array} \quad \begin{array}{c}
\text{24} \quad \text{R}^7 \\
\text{(R)}_n \\
\end{array} \quad \begin{array}{c}
\text{25} \quad \text{NH}_2 \\
\text{(R)}_n \\
\end{array} \quad \begin{array}{c}
\text{26} \quad \text{Cl} \\
\text{(R)}_n \\
\end{array}
\]

Scheme 9: Preparation of building blocks of formula \( \text{Ai}^\text{Chi} \); \( R^7 \) is H or alkyl

In case \( R^7 \) is H, the commercially available alcohols 23 can be converted to aldehydes 24 e.g. with Dess-Martin periodinane in DCM at RT. Cyclization of 24 into the amino-thiazole 25 can be achieved in a two step sequence: bromination at -10°C with \( \text{Br}_2 \) in DCM followed by a treatment with thiourea in EtOH at reflux. Alternatively, 25 can also be obtained in one step if 24 is reacted with thiourea in pyridine at 80°C in the presence of \( \text{I}_2 \).

In case \( R^7 \) is alkyl, especially \( \text{CH}_3 \), the respective commercially available ketone 24 can be directly used to give 25 in the same manner as described above. Chlorination of 25 can finally be performed at RT in \( \text{CH}_3\text{CN} \) with \( \text{CuCl}_2 \) and \( \text{tBuN}_2 \) to give final compounds of structure 26.

When not readily accessible, alcohols 23 can, for example, be synthesized starting from the corresponding commercially available substituted arylbromides as follows: Reaction of substituted arylbromides with carbon monoxide in the presence of a base such as \( \text{CsCO}_3 \) (or TEA or DABCO), a ligand such as di-(1-adamantyl)-n-butylphosphine, and a catalyst such as \( \text{Pd(OAc)}_2 \) in toluene (or 1-methyl-pyrrolidin-2-one) as solvent at 100°C gives the corresponding aldehydes. Reduction of the aldehydes with a reducing agent such as \( \text{NaBH}_4 \) (or \( \text{Bu}_3\text{SnH} \)) in MeOH at RT to the corresponding alcohols followed by bromination in the presence bromine, 1H-imidazole and \( \text{PPh}_3 \) in DCM at RT affords the corresponding substituted benzylbromides. Further nucleophilic substitution of the benzylbromides with KCN in EtOH/H\(_2\)\(\text{O} \) at 80°C gives the corresponding substituted arylacetonitriles. The arylacetonitriles are subsequently converted to the alcohols 23 by first hydrolysis to the corresponding substituted arylacetic acids with \( \text{H}_2\text{SO}_4 \) in AcOH followed by reduction of the obtained acids to the alcohols with Borane-THF complex (or Borane-Me\(_2\)S complex) in THF at RT. The same methodology can be applied to substituted heteroaryl bromides.

Ketones 24 can be synthesized starting from the above described substituted arylacetic acids, which are first converted to their corresponding Weinreb amides using N,0-dimethylhydroxylamine hydrochloride in the presence of a base such as TEA, an activating
agent such as HOBT, and a peptidic coupling agent such as EDC in DMF at RT. Ketones 24 are obtained by reaction of these Weinreb amides with alkylmagnesium bromides in THF at RT. The same methodology can be applied to substituted heteroaryl bromides.

Ar^2-Cl of general formula 31 can be prepared according to general Method G depicted in Scheme 10. The commercially available phenylketone derivative 27 can be brominated with Br_2 in AcOH at RT to give 28, which can further be converted to 29 with HCOONa in MeOH at reflux. Cyclization of 29 into 30 can be achieved in 2-PrOH in the presence of AcOH and KOCN at 50°C. Chlorination of 30 can finally be performed with POCl_3 at 120°C in pyridine to give final compounds of structure 31.

When not readily accessible, ary1ketones 27 wherein R^8 = H can, for example, be synthesized starting from the corresponding commercially available substituted aryl bromides, which are reacted with acetic anhydride in the presence of magnesium (or isopropylmagnesium chloride) in THF at reflux. For R^8 = CH_3: ary1ketones 27 can, for example, be synthesized starting from the corresponding commercially available substituted aryl bromides, which are reacted with N-methoxy-N-methylpropionamide in the presence of magnesium (or isopropylmagnesium chloride) in THF at RT. The same methodologies can be applied to substituted heteroaryl bromides using isopropylmagnesium chloride to generate the Grignard reagents.

Method G:

\[
\begin{align*}
\text{27} & \rightarrow \text{28} & \rightarrow \text{29} \\
\text{30} & \rightarrow \text{31}
\end{align*}
\]

Scheme 10: Preparation of building blocks of formula Ar^2-Cl; R^8 = H or alkyl

Ar^2-Cl of structure 33 can be prepared according to general Method H depicted in Scheme 11.
**Method H:**

![Chemical structure](image)

Scheme 11: Preparation of building blocks of formula $\text{Ar}^2\text{Cl}$; $R^8 = \text{H}$ or alkyl

Similarly, phenylketone derivatives 27 can be brominated with $\text{Br}_2$ in $\text{AcOH}$ at RT to give 28, which can further be converted to 32 with $\text{NaSCN}$ in acetone at RT. 32 can then be cyclized in $\text{HCl} \ 4 \ N$ in dioxane at RT to give final compounds of structure 33.

Generally, bi-(hetero-)aryl-like structures can be synthesised using well-established Suzuki chemistry in analogy to scheme 12.

![Chemical structure](image)

Scheme 12: Synthesis of bi-(hetero-)aryl like structures; X is $\text{Br}$, $\text{I}$

Reaction of commercially available (hetero-)aryl-boronic acid derivatives (e.g. carboxylic acids or esters thereof) with commercially available (hetero-)aryl-bromides or (hetero-)aryl-iodides (or analogues thereof, such as chlorides, trifluoromethanesulfonates) in presence of a metal catalyst catalyst such as $\text{Pd(PPh}_3)_4$ or equivalent and a base such as $\text{Na}_2\text{CO}_3$ under heating in a solvent such as toluene, dioxane, THF provides the corresponding bi-(hetero-)aryl like structures.

$\text{Ar}^2\text{Cl}$ of structure 77 can be prepared according to general Method I depicted in Scheme 13.
Method I:

Scheme 13: Preparation of building blocks of formula $\text{Ar}^2\text{Cl}$: $R_n = \text{F}$ and/or $\text{OCH}_3$

The commercially available aniline derivative 69 (where $R_n$ represents, for example, one or two F) can be acetylated with acetic anhydride 70 at RT followed by nitration with nitric acid at RT to give 71. 74 is obtained via deacetylation of 71 into 72 in EtOH in the presence of HCl 6N at 100°C followed by nucleophilic substitution of 72 onto ethyl bromoacetate 73 in the presence of $\text{K}_2\text{CO}_3$ at 137°C. Cyclization of 74 into 75 can be achieved via a one pot 2 steps reaction: the nitro group is first reduced to the corresponding aniline with $\text{SnCl}_2\cdot2\text{H}_2\text{O}$ in EtOH at 80°C or with Fe in AcOH at reflux, which is followed by intramolecular cyclization. Oxidation of 75 into 76 is performed with ammoniacal silver nitrate in water at reflux or with $\text{H}_2\text{O}_2$ (3wt% in $\text{H}_2\text{O}$) in the presence of NaOH 50% at 100°C. Chlorination of 76 can finally be performed with neat $\text{POCl}_3$ at 110°C to give final compounds of structure 77.

When readily accessible, anilines 72 can directly be used as starting materials using the same sequence to get chloro quinoxalines of formula 77.

The compounds of formula (I) can be prepared as pure enantiomers using enantiomerically enriched core templates synthesized according to known methods described in the literature: J. Med. Chem. 2006, 49(26), 7843-7853 or as a mixture of enantiomers.

Whenever the compounds of formula (I) are obtained in the form of mixtures of enantiomers, the enantiomers can be separated using methods known to the one skilled in the art: e.g. by formation and separation of diastereomeric salts or by HPLC over a chiral stationary phase such a Daicel ChiralCel OD-H (5-10 µµ) column, a Daicel ChiralPak IC (5 µµ) column, or a
Daicel ChiralPak IA (5-10 µm) or AD-H (5 µm) column. Typical conditions of chiral HPLC are an isocratic mixture of eluent A (heptanes or CH₃CN) and eluent B (EtOH, MeOH, DCM or tBME in presence or absence of an amine such as TEA or DEA), at a flow rate of 0.8 to 150 mL/min.

5 Experimental Section

Abbreviations (as used herein and in the description above):

Ac Acetyl (such as in OAc = acetate, AcOH = acetic acid)
AcOH Acetic acid
anh. Anhydrous
aq. aqueous
atm Atmosphere
tBME tert-Butylmethylether
Boc ferf-Butoxycarbonyl
Boc₂O di-ferf-Butyl dicarbonate

15 BSA Bovine serum albumine
Bu Butyl such as tBu = ferf-butyl = tertiary butyl
n-BuLi n-Butyllithium
tBuNO₂ tert-Butylnitrite
CC Column Chromatography on silica gel

20 CHO Chinese Hamster Ovary
cone. Concentrated
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO 1,4-Diazabicyclo[2.2.2]octane
DCE 1,2-Dichloroethane

25 DCM Dichloromethane
DEA Diethylamine
Deoxo-Fluor Bis(2-methoxyethyl)aminosulfur trifluoride
DIBAL-H Diisobutylaluminium hydride
DIPEA Diisopropylethylamine

30 DMF N,N-Dimethylformamide
DMSO Dimethyl sulfoxide
ELSD Evaporative Light-Scattering Detection
eq Equivalent(s)
ES Electron spray

35 Et Ethyl
Diethyl ether
Ethyl acetate
Ethanol
Flash Chromatography on silica gel
Foetal calf serum
Fluorescent imaging plate reader
Hour(s)
Hank's balanced salt solution
Hydrogen chloride
4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
Nuclear magnetic resonance of the proton
High performance liquid chromatography
Sulfuric acid
Liquid chromatography - Mass Spectroscopy
Lithium bis(trimethylsilyl)amide
Literature
Exact mass (as used for LC-MS)
Methyl
Acetonitrile
mefa-Chloroperoxybenzoic acid
Methanol
Methyl iodide
Megahertz
Microliter
Minute(s)
Mass spectroscopy
Normality
Palladium diacetate
Tetrakis(triphenylphosphine)palladium(0)
Phenyl
Triphenylphosphine
Preparative
Isopropanol
reflux
Room temperature
Saturated
**I-Chemistry**

All temperatures are stated in °C. The commercially available starting materials were used as received without further purification. Compounds are purified by flash column chromatography on silica gel (FC) or by preparative HPLC. Compounds described in the invention are characterized by LC-MS (retention time \( t_R \) is given in min.; molecular weight obtained from the mass spectrum is given in g/mol, using the conditions listed below). If the mass is not detectable the compounds are also characterized by \(^1\text{H}-\text{NMR} \) (300 MHz: Varian Oxford; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; p = pentuplet, hex = hexet, hept = heptet, m = multiplet, br = broad, coupling constants are given in Hz).

**LC-MS with acidic conditions (conditions A)**

Apparatus: Agilent 1100 series with mass spectroscopy detection (MS : Finnigan single quadrupole). Column: Waters XBridge C18 (2.5 \( \mu \text{m} \), 4.6 x 30 mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B \( \rightarrow \) 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV/Vis + MS.

**LC-MS with basic conditions (conditions B)**

Apparatus: Agilent 1100 series with mass spectroscopy detection (MS : Finnigan single quadrupole). Column: Waters XBridge C18 (5 \( \mu \text{m} \), 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/l \( \text{NH}_3 \) in water [eluent B]. Gradient: 95% B \( \rightarrow \) 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV/Vis + MS.

**Preparative HPLC for purification of compounds (conditions C)**

Column: Waters XBridge (10 \( \mu \text{m} \), 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% \( \text{NH}_4\text{OH} \) (25% aq.) [eluent B]. Gradient: 90% B \( \rightarrow \) 5% B over 6.5 min. (flow: 75 ml/min.). Detection: UV + ELSD.
Preparative HPLC for purification of compounds (conditions D)
Column: Waters Atlantis T3 OBD (10 µm, 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCOOH [eluent B]; Gradient: 90% B → 5% B over 6.4 min. (flow: 75 ml/min.). Detection: UV + ELSD.

5 LC-MS with basic conditions (conditions E)
Apparatus: Agilent 1100 series with mass spectroscopy detection (MS: Finnigan single quadrupole). Column: Agilent Zorbax Extend-C18 (5 µm, 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/l NH₃ in water [eluent B]. Gradient: 95% B → 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV + MS.

10 LC-MS with acidic conditions (conditions F)
Apparatus: Agilent 1100 series with mass spectroscopy detection (MS: Finnigan single quadrupole). Column: Agilent Zorbax SB-Aq, (3.5 µm, 4.6 x 50mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B → 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV + MS.

The following examples illustrate the preparation of compounds of the invention but do not at all limit the scope thereof.

Preparation of precursors and intermediates:

A Preparation of building blocks of formula Ar¹-CO-OH:

In addition to commercially available building blocks, further particular building blocks of formula Ar¹-CO-OH are prepared as follows:
A.1 2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)benzoic acid 34

2-Fluoro-3-methyl-6-(2/-/-1,2,3-triazol-2-yl)benzoic acid 34 is synthesized in analogy to procedures reported in WO2008/069997.

In a dry Schlenk Tube at RT under nitrogen are successively charged 2-fluoro-6-iodo-3-methyl-benzoic acid (1.786 mmol, 1 eq), Cul (0.089 mmol, 0.05 eq), 1H-1,2,3-triazole (3.571 mmol, 2 eq), Cs₂CO₃ (3.571 mmol, 2 eq) and DMF (2.5 mL). The resulting blue suspension is stirred at 80°C overnight. The obtained reaction mixture is taken up in 1 M eq. HCl and extracted twice with EtOAc. The combined organic layers are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification is achieved by preparative HPLC (conditions D) to give the titled compound (246 mg) as a pale yellow solid. LC-MS (conditions A): tᵣ = 0.55 min, [M + 1]⁺ = 222.19.

A.2 5-Methoxy-2-(2H-1,2,3-triazol-2-yl)benzoic acid 35

The title compound is prepared in analogy to compound 34 starting from 2-iodo-5-methoxybenzoic acid (1.798 mmol, 1 eq). 35 (313 mg) is obtained as a yellow solid. LC-MS (conditions A): tᵣ = 0.49 min, [M + 1]⁺ = 220.07.

A.3 2-Fluoro-3-methoxy-6-(2H-1,2,3-triazol-2-yl)benzoic acid 36

The title compound is prepared in analogy to compound 34 starting from 2-fluoro-6-iodo-3-methoxy-benzoic acid (1.689 mmol, 1 eq). 36 (221 mg) is obtained as a pale yellow solid. LC-MS (conditions A): tᵣ = 0.48 min, [M + 1]⁺ = 238.18.

A.4 2-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)benzoic acid 37

The title compound is prepared in analogy to compound 34 starting from 2-iodo-5-trifluorobenzoic acid (1.582 mmol, 1 eq). 37 (268 mg, 66%) is obtained as a white solid. LC-MS (conditions A): tᵣ = 0.64 min, [M + 1]⁺ = 257.91.

A.5 2-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethoxy)benzoic acid 38

The title compound is prepared in analogy to compound 34 starting from 2-iodo-5-(trifluoromethoxy)benzoic acid (1.506 mmol, 1 eq). 38 (243 mg) is obtained as an off-white solid. LC-MS (conditions A): tᵣ = 0.66 min, [M + 1]⁺ = 273.69.

A.6 5-Cyano-2-(2H-1,2,3-triazol-2-yl)benzoic acid 39

The title compound is prepared in analogy to compound 34 starting from 5-cyano-2-iodobenzoic acid (1.831 mmol, 1 eq). 39 (214 mg) is obtained as a grey solid. LC-MS (conditions A): tᵣ = 0.46 min, [M + 1]⁺ = not detectable. ¹H NMR (D₆-DMSO): δ 13.49 (m, 1 H), 8.21 (m, 1 H), 8.18 (m, 2 H), 8.15 (m, 1 H), 8.03 (m, 1 H).
A.7 5-Methyl-2-(pyridin-2-yl)benzoic acid 40

a) In a dry Schlenk Tube at RT under nitrogen are successively charged 2-iodo-5-methylbenzoic acid methyl ester (13.765 mmol, 1 eq), Cul (2.753 mmol, 0.2 eq), CsF (27.529 mmol, 2 eq), 2-tributylstannylpyridine (20.647 mmol, 1.5 eq), Pd(PPh₃)₄ (1.376 mmol, 0.1 eq) and DMF (60 mL). The resulting suspension is stirred at 90°C overnight. The obtained reaction mixture is diluted with EtOAc and filtered through a short pad of Celite®. A solution of sat. aq. NaHCO₃ is then added to the filtrate and the aq. phase extracted with EtOAc (3 times). The combined organic layers are washed with H₂O and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification is achieved by FC (EtOAc/Heptane 1:4 to 3:7) to give methyl 5-methyl-2-(pyridin-2-yl)benzoate (2.64 g) as a brown oil. LC-MS (conditions A): tᵣ = 0.67 min, [M + 1]⁺ = 228.07.

b) To a solution of methyl 5-methyl-2-(pyridin-2-yl)benzoate (1.617 mmol, 1 eq) in MeOH (15 mL) and THF (17 mL) is added 1 M NaOH (23.233 mL, 2 eq). The resulting mixture is stirred at RT overnight. The volatiles are evaporated under reduced pressure and the remaining aq. phase is acidified with 2 M HCl to pH = 1-2 and extracted with DCM (3 times). The combined organic layers are dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-methyl-2-(pyridin-2-yl)benzoic acid 40 (2.65 g) as a pale brown foam. LC-MS (conditions A): tᵣ = 0.39 min, [M + 1]⁺ = 214.25.

A.8 2-Fluoro-3-methyl-6-(1H-pyrazol-1-yl)benzoic acid 78

The title compound is prepared in analogy to compound 34 replacing the 1H-1,2,3-triazole with 1H-pyrazole (25 mmol, 2 eq). 78 (1.86 g) is obtained as a light yellow solid. LC-MS (conditions F): tᵣ = 0.63 min, [M + 1]⁺ = 221.16.

A.9 2-Fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid 79

a) In a dry Schlenk Tube at RT under nitrogen are successively charged methyl 2-fluoro-6-iodo-3-methylbenzoate (9.18 mmol, 1 eq), Cul (1.84 mmol, 0.2 eq), CsF (18.4 mmol, 2 eq), 2-tributylstannylpyridine (9.18 mmol, 1 eq), Pd(PPh₃)₄ (0.918 mmol, 0.1 eq) and DMF (40 mL). The resulting suspension is stirred at 90°C overnight. The obtained reaction mixture is diluted with EtOAc and filtered through a short pad of Celite®. A solution of sat. aq. NaHCO₃ is then added to the filtrate and the aq. phase extracted with EtOAc (3 times). The combined organic layers are washed with H₂O and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification is achieved by FC (Teledyne Isco Combiflash Rf, SiO₂ cartridge 120 g; Heptane to EtOAc/Heptane 3:7) to give methyl 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoate as a brown oil. LC-MS (conditions F): tᵣ = 0.74 min, [M + 1]⁺ = 246.15.
b) To a solution of methyl 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoate (6.36 mmol, 1 eq) in MeOH (11.3 mL) is added NaOH 32% (6.27 mL). The resulting mixture is stirred at 60°C for 1 hour. The volatiles are evaporated under reduced pressure and the remaining aq. phase is acidified with 7 M HCl to pH = 1-2. The pink suspension is concentrated under reduced pressure and the obtained solid is purified by preparative HPLC (conditions D) to give 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid 79 (1.14 g) as a light pink solid. LC-MS (conditions F): t_R = 0.47 min, [M + 1]^+ = 232.17.

A.10 3-fluoro-4-methyl-1',1'-biphenyl]-2-carboxylic acid 80
a) In a dry Schlenk Tube at RT under nitrogen are successively charged methyl 2-fluoro-6-iodo-3-methylbenzoate (23.5 mmol, 1 eq), Pd(PPh_3)_4 (1.17 mmol, 0.05 eq) and Toluene (60 mL). The resulting mixture is stirred at RT for 15 minutes before a solution of phenylboronic acid (25.8 mmol, 1.1 eq) in EtOH (26 mL) and 2 M Na_2CO_3 (54 mL) are successively added. The resulting mixture is stirred at reflux overnight. The obtained reaction mixture is diluted with Et_2O and the solvents are removed under reduced pressure. The residue is purified by FC (Teledyne Isco CombiFlash Rf, SiO_2 cartridge 120 g; Heptane to EtOAc/Heptane 3:97) to give methyl 3-fluoro-4-methyl-[1',1'-biphenyl]-2-carboxylate as a light yellow oil. LC-MS (conditions F): t_R = 0.94 min, [M + 1]^+ = 245.19.

b) To a solution of methyl 3-fluoro-4-methyl-[1',1'-biphenyl]-2-carboxylate (23 mmol, 1 eq) in MeOH (42 mL) is added NaOH 32% (24 mL). The resulting mixture is stirred at 65°C for 2 hour. The volatiles are evaporated under reduced pressure and the remaining aq. phase is acidified with 7 M HCl to pH = 1-2. The resulting suspension is filtered under vacuum and the obtained solid dried under hight vacuum. 3-Fluoro-4-methyl-[1',1'-biphenyl]-2-carboxylic acid 80 (4.35 g) is obtained as a white solid. LC-MS (conditions F): t_R = 0.81 min, [M + 1]^+ = not detectable. ^1H NMR (D_6-DMSO): δ 13.37 (bs, 1 H), 7.40 (m, 5 H), 7.15 (m, 2 H), 2.48 (s, 3 H).

All other carboxylic acids used in the experimental part which are not described in the previous section are either commercially available or fully described in the literature listed in the introduction part.
B Preparation of building blocks of formula Ar²-Cl:

In addition to commercially available building blocks, further particular building blocks of  
formula Ar⁺-Cl are prepared as follows:
B.1 2-Chloro-5-(3-fluorophenyl)-4-methyloxazole 41

a) To a solution of TOSMIC (43.536 mmol, 1 eq) in DCM (85 mL) at 0°C under nitrogen are successively added benzyltriethylammonium chloride (8.707 mmol, 0.2 eq), Mel (87.072 mmol, 2 eq) and aq. NaOH (30%, 85 mL). The resulting mixture is stirred at 0°C for 3 h, diluted with H₂O and extracted with DCM (3 times). The combined organic layers are washed with H₂O (2 times) and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give rac-N-methyl-1-tosylethanamine (9.1 1 g) as a brown oil. The compound is clean enough to be used in the next step without further purification. ¹H NMR ([CDCl₃]: δ 7.88 (m, 2 H), 7.44 (d, J = 8.1 Hz, 2 H), 4.57 (m, 1 H), 2.49 (s, 3 H), 1.74 (d, J = 6.8 Hz, 3 H)

b) To a solution of 3-fluorobenzaldehyde (39.194 mmol, 1 eq) in MeOH (180 mL) at RT are successively added rac-N-methyl-1-tosylethanamine (39.194 mmol, 1 eq) and K₂CO₃ (47.033 mmol, 1.2 eq). The resulting mixture is refluxed for 3 h, cooled down to RT and further stirred at this temperature for an additional 16 h. Upon completion the reaction is concentrated under reduced pressure and the residue is diluted with H₂O. The aq. layer is extracted with Et₂O (3 times). The combined organic layers are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification is achieved by FC (EtOAc/Heptane 1:9) to give 5-(3-fluorophenyl)-4-methyloxazole (6.27 g) as a pale yellow solid. ¹H NMR ([CDCl₃]: δ 7.83 (s, 1 H), 7.40 (m, 2 H), 7.31 (m, 1 H), 7.02 (m, 1 H), 2.45 (s, 3 H).

c) To a solution of 5-(3-fluorophenyl)-4-methyloxazole (35.388 mmol, 1 eq) in THF (146 mL) at -78°C is added dropwise LiHMDS (1 M in THF, 44.235 mmol, 1.25 eq). The obtained reaction mixture is stirred at this temperature for 30 min before being transferred via a canula onto a suspension of hexachloroethane (70.776 mmol, 2 eq) in THF (10 mL) at -78°C. The resulting mixture is allowed to warm up to RT and is further stirred at this temperature overnight. Upon completion the reaction is quenched with sat. NH₄Cl and is extracted with Et₂O (2 times). The combined organic layers are dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification is achieved by FC (EtOAc/Heptane 5:95) to give the title compound 41 (6.50 g) as an orange oil. ¹H NMR ([CDCl₃]: δ 7.83 (s, 1 H), 7.40 (m, 2 H), 7.31 (m, 1 H), 7.02 (m, 1 H), 2.45 (s, 3 H).
B.2 2-Chloro-5-(4-fluorophenyl)-4-methyloxazole 42

a) Identical to B.1 a)

b) 5-(4-Fluorophenyl)-4-methyloxazole is prepared in analogy to 5-(3-fluorophenyl)-4-methyloxazole starting from 4-fluorobenzaldehyde (37.466 mmol, 1 eq). 5-(4-Fluorophenyl)-4-methyloxazole (5.71 g) is obtained as a yellow solid. LC-MS (conditions A): \( t_R = 0.71 \text{ min}, [M + 1]^+ = 178.21 \).

c) 2-Chloro-5-(4-fluorophenyl)-4-methyloxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methyloxazole 41 starting from 5-(4-fluorophenyl)-4-methyloxazole (32.171 mmol, 1 eq). 42 (6.33 g) is obtained as a brown solid. LC-MS (conditions A): \( t_R = 0.86 \text{ min}, [M + 1]^+ = \text{not detectable.} \)

1H NMR (CDCl₃): \( \delta 7.53 \text{ (m, 2 H), 7.14 \text{ (m, 2 H), 2.37 \text{ (m, 3 H).} } \)

B.3 2-Chloro-5-(2-fluorophenyl)-4-methyloxazole 43

a) Identical to B.1 a)

b) 5-(2-Fluorophenyl)-4-methyloxazole is prepared in analogy to 5-(3-fluorophenyl)-4-methyloxazole starting from 2-fluorobenzaldehyde (37.466 mmol, 1 eq). 5-(2-Fluorophenyl)-4-methyloxazole (6.01 g) is obtained as a yellow liquid. LC-MS (conditions A): \( t_R = 0.69 \text{ min}, [M + 1]^+ = 178.26 \).

c) 2-Chloro-5-(2-fluorophenyl)-4-methyloxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methyloxazole 41 starting from 5-(2-fluorophenyl)-4-methyloxazole (33.921 mmol, 1 eq). 43 (5.80 g) is obtained as an orange liquid. LC-MS (conditions A): \( t_R = 0.85 \text{ min}, [M + 1]^+ = 212.09 \).

B.4 2-Chloro-5-(3-chlorophenyl)-4-methyloxazole 44

a) Identical to B.1 a)

b) 5-(3-Chlorophenyl)-4-methyloxazole is prepared in analogy to 5-(3-fluorophenyl)-4-methyloxazole starting from 3-chlorobenzaldehyde (35.570 mmol, 1 eq). 5-(3-Chlorophenyl)-4-methyloxazole (2.29 g) is obtained as a brown solid. 1H NMR (CDCl₃): \( \delta 8.36 \text{ (s, 1 H), 7.51 \text{ (m, 4 H), 2.37 \text{ (s, 3 H).} } \)

c) 2-Chloro-5-(3-chlorophenyl)-4-methyloxazole is prepared in analogy to 2-chloro-5-(3-chlorophenyl)-4-methyloxazole 41 starting from 5-(3-chlorophenyl)-4-methyloxazole (1.775 mmol, 1 eq). 44 (2.09 g) is obtained as an orange liquid. LC-MS (conditions A): \( t_R = 1.26 \text{ min, } [M + 1]^+ = 228.12. \)

B.5 2-Chloro-4-methyl-5-(m-tolyl)oxazole 45

a) Identical to B.1 a)
b) 4-Methyl-5-(m-tolyl)oxazole is prepared in analogy to 5-(3-fluorophenyl)-4-methyloxazole starting from 3-methylbenzaldehyde (41.614 mmol, 1 eq). 4-Methyl-5-(m-tolyl)oxazole (2.39 g) is obtained as an orange liquid. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.82 (s, 1 H), 7.41 (m, 2 H), 7.33 (t, J = 7.5 Hz, 1 H), 7.15 (d, J = 7.5 Hz, 1 H), 2.44 (s, 3 H), 2.41 (s, 3 H).

c) 2-Chloro-4-methyl-5-(m-tolyl)oxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methyloxazole \(41\) starting from 4-methyl-5-(m-tolyl)oxazole (13.798 mmol, 1 eq). \(45\) (2.90 g) is obtained as an orange liquid. LC-MS (conditions A): \(t_R = 0.92\) min, [M + 1]\(^+\) = 208.13.

### 2-Chloro-5-(3-fluorophenyl)oxazole 46

a) To a solution of 3-fluorobenzaldehyde (40.246 mmol, 1 eq) in MeOH (200 ml) at RT are successively added TOSMIC (40.286 mmol, 1 eq) and \(K_2CO_3\) (48.343 mmol, 1.2 eq). The resulting mixture is refluxed for 3 h, cooled down to RT and further stirred at this temperature for an additional 16 h. Upon completion the reaction is concentrated under reduced pressure and the residue is diluted with \(H_2O\). The aq. layer is extracted with \(Et_2O\) (3 times). The combined organic layers are dried over \(Na_2SO_4\), filtered and concentrated under reduced pressure. Purification is achieved by FC (EtOAc/Heptane 1:9) to give 5-(3-fluorophenyl)oxazole (5.86 g) as a yellow solid. LC-MS (conditions A): \(t_R = 0.67\) min, [M + 1]\(^+\) = not detectable. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.92 (s, 1 H), 7.39 (m, 4 H), 7.04 (m, 1 H).

b) To a solution of 5-(3-fluorophenyl)oxazole (35.918 mmol, 1 eq) in THF (140 ml) at -78°C is added dropwise LiHMDS (1 M in THF, 44.897 mmol, 1.25 eq). The obtained reaction mixture is stirred at this temperature for 30 min before being transferred via a canula onto a suspension of hexachloroethane (71.835 mmol, 2 eq) in THF (20 ml) at -78°C. The resulting mixture is allowed to warm up to RT and is further stirred at this temperature overnight. Upon completion the reaction is quenched with sat. \(NH_4Cl\) and is extracted with \(Et_2O\) (2 times). The combined organic layers are dried over \(Na_2SO_4\), filtered and concentrated under reduced pressure. Purification is achieved by FC (EtOAc/Heptane 5:95) to give the title compound \(46\) (4.99 g) as a beige solid. LC-MS (conditions A): \(t_R = 0.82\) min, [M + 1]\(^+\) = not detectable. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.83 (s, 1 H), 7.39 (m, 2 H), 7.30 (s, 1 H), 7.26 (m, 1 H), 7.05 (m, 1 H).

### 2-Chloro-5-(4-fluorophenyl)oxazole 47

a) 5-(4-Fluorophenyl)oxazole is prepared in analogy to 5-(3-fluorophenyl)oxazole starting from 4-fluorobenzaldehyde (32.229 mmol, 1 eq). 5-(4-Fluorophenyl)oxazole (4.70 g) is obtained as a yellow solid. LC-MS (conditions A): \(t_R = 0.66\) min, [M + 1]\(^+\) = not detectable. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.90 (s, 1 H), 7.63 (m, 2 H), 7.29 (s, 1 H), 7.12 (t, J = 8.7 Hz, 2 H).

b) 2-Chloro-5-(4-fluorophenyl)oxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)oxazole \(46\) starting from 5-(4-fluorophenyl)oxazole (28.808 mmol, 1 eq). \(47\)
(4.30 g) is obtained as a pale yellow solid. LC-MS (conditions A): $t_R = 0.81$ min, $[M + 1]^+ = \text{not detectable}$. $^1H$ NMR (CDCl$_3$): $\delta 7.57$ (m, 2 H), 7.22 (s, 1 H), 7.12 (m, 2 H).

**B.8 2-Chloro-5-(2-fluorophenyl)oxazole 48**

a) 5-(2-Fluorophenyl)oxazole is prepared in analogy to 5-(3-fluorophenyl)oxazole starting from 2-fluorobenzaldehyde (40.286 mmol, 1 eq). 5-(2-Fluorophenyl)oxazole (5.72 g) is obtained as a yellow liquid. LC-MS (conditions A): $t_R = 0.67$ min, $[M + 1]^+ = \text{not detectable}$. $^1H$ NMR (CDCl$_3$): $\delta 7.57$ (m, 2 H), 7.22 (s, 1 H), 7.12 (m, 2 H).

b) 2-Chloro-5-(2-fluorophenyl)oxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)oxazole 46 starting from 5-(2-fluorophenyl)oxazole (35.06 mmol, 1 eq). 48 (5.80 g) is obtained as a brown liquid. LC-MS (conditions A): $t_R = 0.83$ min, $[M + 1]^+ = \text{not detectable}$. $^1H$ NMR (CDCl$_3$): $\delta 7.70$ (td, $J_1 = 7.6$ Hz, $J_2 = 1.6$ Hz, 1 H), 7.42 (d, $J = 3.7$ Hz, 1 H), 7.33 (m, 1 H), 7.19 (m, 2 H).

**B.9 2-Chloro-4-(difluoromethyl)-5-(3-fluorophenyl)oxazole 49**

![Chemical structure diagram]

a) To a solution of 3-fluorobenzoyl chloride (12.361 mmol, 1 eq) in THF (25 mL) at 0°C is added TEA (37.084 mmol, 3 eq). Ethyl isocyanoacetate (13.597 mmol, 1.1 eq) is then added dropwise, the mixture is warmed to RT, and stirred at this temperature overnight. Upon completion, the mixture is quenched with $H_2O$ and extracted with EtOAc (3 times). The combined organic phases are washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:4 to
1:1) to give ethyl 5-(3-fluorophenyl)oxazole-4-carboxylate (1.6 g) as a brown solid. LC-MS (conditions A): \( t_R = 0.73 \text{ min}, [M + 1]^+ = 235.75 \).

b) To a solution of ethyl 5-(3-fluorophenyl)oxazole-4-carboxylate (3.337 mmol, 1 eq) in THF (9 ml) at -78°C, is added dropwise a solution of DIBAL-H (1 M in Toluene, 6.675 mmol, 2 eq). The reaction mixture is allowed to proceed at -78°C for 1 h, before being warmed up to -20°C and further stirred at this temperature for 1 h. The reaction mixture is diluted with DCM (90 ml) and quenched with Rochelle salt (90 ml) at -20°C. This resulting mixture is stirred vigorously with gradual warming to RT overnight. After 16 h, the layers are separated, and the aq. layer is extracted with DCM (3 times). The combined organic layers are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:9 to 2:3) to yield 5-(3-fluorophenyl)oxazole-4-carbaldehyde (564 mg) as a yellow solid. LC-MS (conditions A): \( t_R = 0.78 \text{ min}, [M + 1]^+ = \text{not detectable} \). \(^1\)H NMR (CDCl₃): \( \delta 10.13 \) (s), 7.99 (m, 2 H), 7.95 (s, 1 H), 7.50 (td, \( J_1 = 8.2 \text{ Hz}, J_2 = 5.9 \text{ Hz}, 1 \text{ H} \)), 7.21 (m, 1 H).

c) To a solution of 5-(3-fluorophenyl)oxazole-4-carbaldehyde (3.547 mmol, 1 eq) in DCM (3 ml) at -78°C, are successively added methoxytrimethylsilane (7.094 mmol, 2 eq) and trimethylsilyl trifluoromethanesulfonate (0.177 mmol, 0.05 eq). The resulting reaction mixture is allowed to proceed with gradual warming to RT for 24 h. Upon completion the reaction is quenched with a sat. aq. solution of NaHCO₃ (10 ml), and extracted with with EtOAc (3 times). The combined organic layers are washed with \( \text{H}_2\text{O} \) and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 4-(dimethoxymethyl)-5-(3-fluorophenyl)oxazole (749 mg) as a yellow oil. The compound is clean enough to be used in the next step without further purification. LC-MS (conditions A): \( t_R = 0.82 \text{ min}, [M + 1]^+ = 238.20 \). \(^1\)H NMR (CDCl₃): \( \delta 7.89 \) (s, 1 H), 7.54 (m, 2 H), 7.41 (m, 1 H), 7.07 (m, 1 H), 5.55 (s, 1 H), 3.42 (m, 6 H).

d) To a solution of 4-(dimethoxymethyl)-5-(3-fluorophenyl)oxazole (3.157 mmol, 1 eq) in THF (13 ml) at -78°C is added dropwise a solution of LiHMDS (1 M in THF, 3.473 mmol, 1.1 eq). The reaction mixture is stirred at -78°C for 30 min. before hexachloroethane (3.473 mmol, 1.1 eq.) is added in one portion. The reaction is allowed to proceed with gradual warming to 5°C over a period of 5.5 h and quenched with a sat. aq. solution of NH₄Cl. The aq. layer is extracted with Et₂O (3 times). The combined organic layers are washed with \( \text{H}_2\text{O} \) and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 2-chloro-4-(dimethoxymethyl)-5-(3-fluorophenyl)oxazole (832 mg) as a brown oil. The compound is clean enough to be used in the next step without further purification. LC-MS (conditions A): \( t_R \)
= 0.97 min, [M + 1]^+ = not detectable. ^1H NMR (CDCl$_3$): $\delta$ 7.46 (m, 3 H), 7.09 (tdd, $J_1 = 8.3$ Hz, $J_2 = 2.6$ Hz, $J_3 = 1.1$ Hz, 1 H), 5.48 (m, 1 H).

e) A HCl solution (4 M in dioxane, 12.044 mmol, 4 eq.) is added to a solution of 2-chloro-4-(dimethoxymethyl)-5-(3-fluorophenyl)oxazole (3.011 mmol, 1 eq.) in THF (10 ml) / H$_2$O (5 ml). The reaction mixture is stirred at RT for 16 h, quenched with a sat. aq. Sol. of Na$_2$CO$_3$. The aq. layer is extracted with Et$_2$O (3 times). The combined organic layers are washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:9) to give 2-chloro-5-(3-fluorophenyl)oxazole-4-carbaldehyde (521 mg) as a beige solid. LC-MS (conditions A): $t_R = 0.88$ min, [M + 1]^+ = not detectable. ^1H NMR (CDCl$_3$): $\delta$ 10.0 (m, 1 H), 7.93 (m, 2 H), 7.50 (m, 1 H), 7.23 (m, 1 H).

1) To a solution of 2-chloro-5-(3-fluorophenyl)oxazole-4-carbaldehyde (2.309 mmol, 1 eq.) in DCM (7 ml) at 0°C, is added Deoxo-Flur (3.464 mmol, 1.5 eq.). The reaction is stirred at 0°C for 2 h, and 1 h at RT. The reaction mixture is quenched with H$_2$O and extracted with DCM (3 times). The combined organic layers are washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:9) to give 49 (215 mg) as a white solid. LC-MS (conditions A): $t_R = 0.94$ min, [M + 1]^+ = not detectable. ^1H NMR (CDCl$_3$): $\delta$ 7.47 (m, 2 H), 7.39 (m, 1 H), 7.15 (m, 1 H), 6.71 (t, $J = 54$ Hz, 1 H).

**B.10 2-Chloro-5-(3-fluorophenyl)oxazole-4-carbonitrile 50**

a) To a solution of 5-(3-fluorophenyl)oxazole (B.6a, 13.914 mmol, 1 eq) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1/-)-pyrimidinone (18 ml) in THF (25 ml) at -78°C is added dropwise a solution of LiHMDS (1 M in THF, 16.696 mmol, 1.2 eq). The reaction mixture is stirred at -78°C for 1 h before addition Br$_2$ (13.914 mmol, 1 eq). The reaction mixture is further stirred at this temperature for 1 h and poured onto a mixture of Et$_2$O / aq. 10% Na$_2$SO$_3$ solution. The layers are separated and the organic phase is washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 5:95) to give 4-bromo-5-(3-fluorophenyl)oxazole (2.27 g) as a pale yellow. LC-MS (conditions A): $t_R = 0.81$ min, [M + 1]^+ = not detectable. ^1H NMR (D$_6$-DMSO): $\delta$ 8.60 (m, 1 H), 7.65 (m, 4 H), 7.32 (m, 1 H).
b) A mixture of 4-bromo-5-(3-fluorophenyl)oxazole (8.469 mmol, 1 eq), Zn(CN)$_2$ (9.316 mmol, 1.1 eq.), and Pd(PPh$_3$)$_4$ (0.423 mmol, 0.05 eq) in DMF (20 mL), is heated in a microwave at 160°C for 15 min. The reaction mixture is cooled to RT, diluted with EtOAc, filtered through a short pad of Celite®, washed with H$_2$O and brine, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 5:95 to 1:4) to give 5-(3-fluorophenyl)oxazole-4-carbonitrile (1.27 g) as a white solid. LC-MS (conditions A): $t_R$ = 0.84 min, [M + 1]$^+$ = not detectable. $^1$H NMR (CDCl$_3$): $\delta$ 7.94 (s, 1 H), 7.80 (m, 1 H), 7.63 (m, 1 H), 7.52 (m, 1 H), 7.22 (m, 1 H).

c) To a solution of 5-(3-fluorophenyl)oxazole-4-carbonitrile (6.750 mmol, 1 eq) in THF (21 mL) at -78°C is added dropwise a solution of LiHMDS (1 M in THF, 7.425 mmol, 1.1 eq). The reaction mixture is stirred at -78°C for 30 min. before hexachloroethane (6.75 mmol, 1.1 eq.) is added in one portion. The reaction is allowed to proceed with gradual warming to RT overnight. The reaction mixture is quenched with H$_2$O before heptane is added. The solid formed is filtered and the filtrate is diluted with EtOAc. The organic layer is washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 5:95 to 1:4) to give 50 (770 mg) as a white solid. LC-MS (conditions A): $t_R$ = 0.93 min, [M + 1]$^+$ = not detectable. $^1$H NMR (CDCl$_3$): $\delta$ 7.75 (m, 1 H), 7.59 (m, 1 H), 7.51 (m, 1 H), 7.22 (m, 1 H).

**B.11 2-Chloro-5-(3-fluorophenyl)-4-methylthiazole 51**

a) To a solution of 3-fluorophenylacetone (16.101 mmol, 1 eq) in pyridine (14 mL) at RT is added thiourea (16.101 mmol, 1 eq) followed by I$_2$ (16.101 mmol, 1 eq). The reaction mixture is stirred at 80°C for 16 h, and allowed to cool down to RT. The resulting suspension is filtered and washed with EtOAc. The filtrate is concentrated in vacuo, the residue redissolved in EtOAc, washed with a sat. aq. solution of NaHCO$_3$ (2 times) and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give 5-(3-fluorophenyl)-4-methylthiazol-2-amine (2.99 g) as a brown oil. The compound is clean enough to be used in the next step without further purification. LC-MS (conditions B): $t_R$ = 0.79 min, [M + 1]$^+$ = 209.20.

b) To a suspension of CuCl$_2$ anhydrous (12.577 mmol, 1.2 eq) in dry CH$_3$CN (25 mL) is added dropwise tert-Butyl nitrite (15.721 mmol, 1.5 eq), followed by a solution of 5-(3-fluorophenyl)-4-methylthiazol-2-amine (10.481 mmol, 1 eq) in dry CH$_3$CN (40 mL). The reaction mixture is stirred at RT for 3 h, poured onto an aq. solution of 0.5 N HCl and diluted with EtOAc. The separated organic layer is washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:99 to 2:98) to give 51 (1.21 g) as a yellow liquid. LC-MS (conditions B): $t_R$
\[ H^+ = 1.02 \text{ min, } [M + 1]^+ \text{ not detectable.} \]

B.12 2-Chloro-5-(3-chlorophenyl)-4-methylthiazole 52

a) 5-(3-Chlorophenyl)-4-methylthiazol-2-amine is prepared in analogy to 5-(3-fluorophenyl)-4-methylthiazol-2-amine starting from 3-chlorophenylacetone (13.936 mmol, 1 eq). 5-(3-Chlorophenyl)-4-methylthiazol-2-amine (949 mg) is obtained as a red oil. LC-MS (conditions B): \( t_R = 0.84 \text{ min, } [M + 1]^+ = 225.07. \)

b) 2-Chloro-5-(3-chlorophenyl)-4-methylthiazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methylthiazole starting from 5-(3-chlorophenyl)-4-methylthiazol-2-amine (7.001 mmol, 1 eq). 52 (949 mg) is obtained as a yellow liquid. LC-MS (conditions B): \( t_R = 1.08 \text{ min, } [M + 1]^+ \text{ not detectable.} \)

B.13 2-Chloro-4-methyl-5-(m-tolyl)thiazole 53

a) 4-Methyl-5-(m-tolyl)thiazol-2-amine is prepared in analogy to 5-(3-fluorophenyl)-4-methylthiazol-2-amine starting from 3-methylphenylaceton (13.936 mmol, 1 eq). 4-Methyl-5-(m-tolyl)thiazol-2-amine (2.96 g) is obtained as a brown oil. LC-MS (conditions B): \( t_R = 0.82 \text{ min, } [M + 1]^+ = 205.21. \)

b) 2-Chloro-4-methyl-5-(m-tolyl)thiazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methylthiazole starting from 4-methyl-5-(m-tolyl)thiazol-2-amine (8.403 mmol, 1 eq). 53 (876 mg) is obtained as a yellow liquid. LC-MS (conditions B): \( t_R = 1.08 \text{ min, } [M + 1]^+ \text{ not detectable.} \)

B.14 2-Chloro-5-(3-fluorophenyl)thiazole 54

a) Dess-Martin periodinane (16.781 mmol, 1.2 eq) is added to a solution of 3-fluorophenethyl alcohol (13.984 mmol, 1 eq) in DCM (32 mL). The resulting reaction mixture is stirred at RT for 4 h. The solvent is then partially evaporated, and the residue filtered through a short pad of Celite®. The filtrate is concentrated under reduced pressure and the residue purified by FC (EtOAc/heptane, 5:95). Crude 2-(3-fluorophenyl)acetaldehyde is obtained as a colorless oil (2.58 g). The compound is used in the next step without further purification. \( H^+ \text{ NMR (CDCl}_3)\): \( \delta 7.30 \text{ (m, 1 H), 7.16 (m, 3 H), 2.43 (s, 3 H), 2.39 (s, 3 H).} \)

b) A solution of bromine (13.984 mmol, 1 eq) in DCM (3 mL) is slowly added to a -10°C cooled solution of 2-(3-fluorophenyl)acetaldehyde (13.984 mmol, 1 eq) in DCM (20 mL). The resulting solution is allowed to slowly warm up to RT, and is further stirred at this temperature for 2 h. Upon completion the reaction is quenched with a sat. eq. solution of NaHCO\textsubscript{3} and
extracted DCM (3 times). The separated organic layer is dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue is dissolved in EtOH (28 mL) before thiourea (27.968 mmol, 2 eq) is added. The obtained mixture is heated to reflux for 16 h, cooled down to RT and concentrated in vacuo. The residue is partitioned between EtOAc and a sat. aq. solution of NaHCO₃. The separated organic layer is washed with H₂O and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-(3-fluorophenyl)thiazol-2-amine (1.35 g) as a brown solid. The compound is used in the next step without further purification. LC-MS (conditions B): t_R = 0.77 min, [M + 1]^+ = 195.20.

c) To a suspension of CuCl₂ anhydrous (8.341 mmol, 1.2 eq) in dry CH₃CN (19 mL) is added dropwise tert-Butyl nitrite (10.426 mmol, 1.5 eq), followed by a solution of 5-(3-fluorophenyl)thiazol-2-amine (6.95 mmol, 1 eq) in dry CH₃CN (12 mL). The reaction mixture is stirred at RT for 3 h, poured onto an aq. solution of 0.5 N HCl and diluted with EtOAc. The separated organic layer is washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:99) to give 54 (722 mg) as a yellow liquid. LC-MS (conditions B): t_R = 0.98 min, [M + 1]^+ = not detectable. ¹H NMR (CDCl₃): δ 7.72 (s, 1 H), 7.39 (m, 1 H), 7.25 (m, 1 H), 7.18 (m, 1 H), 7.05 (m, 1 H).

B.15 2-Chloro-5-(3-chlorophenyl)thiazole 55

a) 2-(3-Chlorophenyl)acetaldehyde is prepared in analogy to 2-(3-fluorophenyl)acetaldehyde starting from 3-chlorophenethyl alcohol (14.048 mmol, 1 eq). 2-(3-Chlorophenyl)acetaldehyde (1.21 g) is obtained as a colorless oil. ¹H NMR (CDCl₃): δ 7.75 (t, J = 2.1 Hz, 1 H), 7.30 (m, 2 H), 7.21 (m, 1 H), 7.10 (m, 1 H), 3.68 (d, J = 2.1 Hz, 2 H).

b) 5-(3-Chlorophenyl)thiazol-2-amine is prepared in analogy to 5-(3-fluorophenyl)thiazol-2-amine starting from 2-(3-chlorophenyl)acetaldehyde (7.827 mmol, 1 eq). 5-(3-Chlorophenyl)thiazol-2-amine (980 mg) is obtained as a yellow solid. LC-MS (conditions A): t_R = 0.52 min, [M + 1]^+ = 211.08.

c) 2-Chloro-5-(3-chlorophenyl)thiazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)thiazole starting from 5-(3-Chlorophenyl)thiazol-2-amine (4.177 mmol, 1 eq). 2-Chloro-5-(3-chlorophenyl)thiazole 55 (546 mg) is obtained as a yellow liquid. LC-MS (conditions B): t_R = 1.03 min, [M + 1]^+ = not detectable. ¹H NMR (CDCl₃): δ 7.72 (s, 1 H), 7.47 (m, 1 H), 7.34 (m, 3 H).

B.16 2-Chloro-5-(m-tolyl)thiazole 56

a) 2-(m-Tolyl)acetaldehyde is prepared in analogy to 2-(3-fluorophenyl)acetaldehyde starting from 2-(3-methylphenyl)ethanol (14.048 mmol, 1 eq). 2-(m-Tolyl)acetaldehyde (1.66 g) is
obtained as a colorless oil. $^1$H NMR (CDCl$_3$): $\delta$ 9.74 (t, $J = 2.4$ Hz, 1 H), 7.26 (m, 1 H), 7.12 (m, 1 H), 7.02 (m, 2 H), 3.64 (d, $J = 2.4$ Hz, 2 H), 2.36 (s, 3 H).

b) 5-(m-Tolyl)thiazol-2-amine is prepared in analogy to 5-(3-fluorophenyl)thiazol-2-amine starting from 2-(m-tolyl)acetaldehyde (5.567 mmol, 1 eq). 5-(m-Tolyl)thiazol-2-amine (659 mg) is obtained as a brown solid. LC-MS (conditions B): $t_R = 0.79$ min, [M + 1]$^+$ = 191.21.

c) 2-Chloro-5-(m-tolyl)thiazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)thiazole starting from 5-(m-tolyl)thiazol-2-amine (6.228 mmol, 1 eq). 2-Chloro-5-(m-tolyl)thiazole (730 mg) is obtained as a yellow liquid. LC-MS (conditions B): $t_R = 1.03$ min, [M + 1]$^+$ = not detectable.$^1$H NMR (CDCl$_3$): $\delta$ 7.69 (s, 1 H), 7.29 (m, 3 H), 7.17 (m, 1 H), 2.39 (s, 3 H).

### B.17 2-Chloro-4-(3-fluorophenyl)-5-methyloxazole 57

a) To a stirred solution of 3’-fluoropropiophenone (26.287 mmol, 1 eq) in AcOH (35 mL) at RT is slowly added a solution of Br$_2$ (26.287 mL, 1 eq) in DCM (10 mL). The resulting light yellow solution is stirred at RT overnight, concentrated under reduced pressure and the residue diluted with sat. NaHCO$_3$. The aq. phase is extracted with EtOAc (3 times). The combined organic layers are washed with with sat. NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give 2-bromo-1-(3-fluorophenyl)propan-1-one (5.82 g) as a light yellow oil. The crude is used in the next step without further purification. LC-MS (conditions A): $t_R = 0.82$ min, [M + 1]$^+$ = not detectable.$^1$H NMR (D$_6$-DMSO): $\delta$ 7.87 (m, 1 H), 7.80 (m, 1 H), 7.61 (m, 1 H), 7.52 (m, 1 H), 5.79 (t, $J = 6.0$ Hz, 1 H), 1.77 (d, $J = 6.0$ Hz, 3 H).

b) To a solution of 2-bromo-1-(3-fluorophenyl)propan-1-one (25.188 mmol, 1 eq) in MeOH (50 mL) at RT is added HCOONa (100.752 mmol, 4 eq) and the resulting mixture is refluxed for 8 h. Upon completion the reaction is concentrated under reduced pressure and the residue dissolved in EtOAc. The organic phase is washed with H$_2$O, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:4) to give 1-(3-fluorophenyl)-2-hydroxypropan-1-one (3.26 g) as a yellow oil. LC-MS (conditions A): $t_R = 0.53$ min, [M + 1]$^+$ = not detectable.$^1$H NMR (D$_6$-DMSO): $\delta$ 7.82 (m, 1 H), 7.73 (m, 1 H), 7.57 (m, 1 H), 7.46 (m, 1 H), 5.41 (d, $J = 6.0$ Hz, 1 H), 4.99 (qt, J = 6.0 Hz, 1 H), 1.29 (d, J = 6.0 Hz, 3 H).

c) To a solution of 1-(3-fluorophenyl)-2-hydroxypropan-1-one (19.326 mmol, 1 eq) and KOCN (38.652 mmol, 2 eq) in 2-PrOH (50 mL) at 50°C is slowly added AcOH (2.65 mL, 46.383 mmol, 2.4 eq). The reaction is further stirred at this temperature for 5 h, poured onto ice cooled H$_2$O and the resulting precipitate is collected by filtration. 4-(3-Fluorophenyl)-5-methyloxazol-2(3H)-one (1.48 g) is obtained as a white solid. LC-MS (conditions A): $t_R = 0.61$
min, [2M + 1] + = 386.1. 1H NMR (D$_6$-DMSO): δ 7.48 (m, 1 H), 7.28 (m, 2 H), 7.14 (m, 1 H), 2.27 (s, 3 H).

d) To a mixture of 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one (7.661 mmol, 1 eq) in POCl$_3$ (45.968 mmol, 6 eq) is added pyridine (0.62 mL, 7.661 mmol, 1 eq.) at RT. The reaction mixture is heated at 120°C and stirred at this temperature for 2.5 h. The reaction is cooled down to RT, carefully poured onto H$_2$O and the aq. phase is extracted with EtOAc (2 times). The combined organic layers are washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The residue is purified by FC (EtOAc/heptane, 1:9) to give 57 (1.00 g) as a yellow oil. LC-MS (conditions A): $t_R = 0.89$ min, [M + 1]$^+$ = 212.02. 1H NMR (D$_6$-DMSO): δ 7.49 (m, 2 H), 7.39 (m, 1 H), 7.19 (m, 1 H), 2.54 (s, 3 H).

**B.18 2-Chloro-4-(3-fluorophenyl)-5-methyloxazole 58**

a) 2-Bromo-1-(3-chlorophenyl)propan-1-one is prepared in analogy to 2-bromo-1-(3-fluorophenyl)propan-1-one starting from 1-(3-chlorophenyl)propan-1-one (23.722 mmol, 1 eq). 2-Bromo-1-(3-chlorophenyl)propan-1-one (5.68 g) is obtained as a yellow oil. LC-MS (conditions A): $t_R = 0.89$ min, [M + 1]$^+$ = not detectable. 1H NMR (D$_6$-DMSO): δ 8.03 (m, 1 H), 7.98 (m, 1 H), 7.73 (m, 1 H), 7.58 (m, 1 H), 5.85 (t, $J = 6.0$ Hz, 1 H), 1.77 (d, $J = 6.0$ Hz, 3 H).

b) 1-(3-Chlorophenyl)-2-hydroxypropan-1-one is prepared in analogy to 1-(3-fluorophenyl)-2-hydroxypropan-1-one starting from 2-bromo-1-(3-chlorophenyl)propan-1-one (22.948 mmol, 1 eq). 1-(3-Chlorophenyl)-2-hydroxypropan-1-one (3.49 g) is obtained as a light yellow oil. LC-MS (conditions A): $t_R = 0.61$ min, [M + 1]$^+$ = not detectable. £ 1H NMR (D$_6$-DMSO): δ 7.97 (m, 1 H), 7.91 (m, 1 H), 7.67 (m, 1 H), 7.54 (m, 1 H), 5.43 (d, $J = 6.0$ Hz, 1 H), 4.99 (qt, $J = 6.0$ Hz, 1 H), 1.27 (d, $J = 6.0$ Hz, 3 H).

c) 4-(3-Chlorophenyl)-5-methylazol-2(3/-/-)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methylazol-2(3H)-one starting from 1-(3-chlorophenyl)-2-hydroxy-propan-1-one (18.904 mmol, 1 eq). 4-(3-Chlorophenyl)-5-methylazol-2(3/-/-)-one (1.44 g) is obtained as a white solid. LC-MS (conditions A): $t_R = 1.00$ min, [2M + 1]$^+$ = 418.9. 1H NMR (D$_6$-DMSO): δ 57.48 (m, 1 H), 7.44 (m, 1 H), 7.39 (m, 2 H), 2.23 (s, 3 H).

d) 2-Chloro-4-(3-chlorophenyl)-5-methylazole 58 is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylazole 57 starting from 4-(3-chlorophenyl)-5-methylazol-2(3/-/-)-one (6.855 mmol, 1 eq). 58 (680 mg) is obtained as a yellow oil. LC-MS (conditions A): $t_R = 0.96$ min, [2M + 1]$^+$ = 454.58. 1H NMR (D$_6$-DMSO): δ 7.62 (m, 1 H), 7.58 (m, 1 H), 7.48 (m, 1 H), 7.41 (m, 1 H), 2.55 (s, 3 H).
B.19 2-Chloro-5-methyl-4-(m-tolyl)oxazole 59

a) 2-Bromo-1-(m-tolyl)propan-1-one is prepared in analogy to 2-bromo-1-(3-fluorophenyl)propan-1-one starting from 1-(m-tolyl)propan-1-one (26.990 mmol, 1 eq). 2-Bromo-1-(m-tolyl)propan-1-one (5.75 g) is obtained as a yellow oil. LC-MS (conditions A): \( t_R = 0.86 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR (\(D_6\)-DMSO): \( \delta 7.82 \) (m, 2 H), 7.44 (m, 2 H), 5.77 (q, \( J = 6.5 \) Hz, 1 H), 2.37 (s, 3 H), 1.76 (d, \( J = 6.5 \) Hz, 3 H).

b) 2-Hydroxy-1-(m-tolyl)propan-1-one is prepared in analogy to 1-(3-fluorophenyl)-2-hydroxypropan-1-one starting from 2-bromo-1-(m-tolyl)propan-1-one (25.319 mmol, 1 eq). 2-Hydroxy-1-(m-tolyl)propan-1-one (2.98 g) is obtained as a light yellow oil. LC-MS (conditions A): \( t_R = 0.59 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR (\(D_6\)-DMSO): \( \delta 7.77 \) (m, 2 H), 7.40 (m, 2 H), 5.22 (d, \( J = 6.5 \) Hz, 1 H), 5.01 (qt, \( J = 6.5 \) Hz, 1 H), 2.37 (s, 3 H), 1.26 (d, \( J = 6.5 \) Hz, 3 H).

c) 5-Methyl-4-(m-tolyl)oxazol-2(3/-/-)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one starting from 2-hydroxy-1-(m-tolyl)propan-1-one (18.087 mmol, 1 eq). 5-Methyl-4-(m-tolyl)oxazol-2(3H)-one (1.44 g) is obtained as a white solid. LC-MS (conditions A): \( t_R = 0.65 \) min, \([2M + 1]^+ = 379.1 \).

d) 2-Chloro-5-methyl-4-(m-tolyl)oxazole 59 is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methyloxazole 57 starting from 5-methyl-4-(m-tolyl)oxazol-2(3/-/-)-one (7.610 mmol, 1 eq). 59 (727 mg) is obtained as a yellow oil. LC-MS (conditions A): \( t_R = 0.93 \) min, \([M + 1]^+ = 208.09 \). \(^1\)H NMR (\(D_6\)-DMSO): \( \delta 7.41 \) (m, 2 H), 7.32 (m, 1 H), 7.16 (m, 1 H), 2.52 (s, 3 H), 2.36 (s, 3 H).

B.20 2-chloro-4-(3-fluorophenyl)oxazole 60

a) 2-Bromo-1-(3-fluorophenyl)ethanone is prepared in analogy to 2-bromo-1-(3-fluorophenyl)propan-1-one starting from 1-(3-fluorophenyl)ethanone (21.717 mmol, 1 eq). 2-Bromo-1-(3-fluorophenyl)ethanone (4.68 g) is obtained as a yellow oil. LC-MS (conditions A): \( t_R = 0.74 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR (\(D_6\)-DMSO): \( \delta 7.84 \) (m, 1 H), 7.78 (m, 1 H), 7.62 (m, 1 H), 7.53 (m, 1 H), 4.92 (s, 2 H).

b) 1-(3-Fluorophenyl)-2-hydroxyethanone is prepared in analogy to 1-(3-fluorophenyl)-2-hydroxypropan-1-one starting from 2-bromo-1-(3-fluorophenyl)ethanone (10.92 mmol, 1 eq). 1-(3-Fluorophenyl)-2-hydroxyethanone (854 mg) is obtained as a pale yellow solid. LC-MS (conditions A): \( t_R = 0.45 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR (\(D_6\)-DMSO): \( \delta 7.76 \) (m, 1 H), 7.68 (m, 1 H), 7.57 (m, 1 H), 7.48 (m, 1 H), 5.15 (t, \( J = 6.0 \) Hz, 1 H), 4.76 (d, \( J = 6.0 \) Hz, 2 H).
c) 4-(3-Fluorophenyl)oxazol-2(3H)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one starting from 1-(3-fluorophenyl)-2-hydroxyethanone (5.514 mmol, 1 eq). 4-(3-Fluorophenyl)oxazol-2(3H)-one (540 mg) is obtained as a light orange solid. LC-MS (conditions A): \( t_R = 0.55 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 11.35 \) (s, 1 H), 7.77 (s, 1 H), 7.43 (m, 3 H), 7.16 (m, 1 H).

d) 2-Chloro-4-(3-fluorophenyl)oxazole 60 is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methyloxazole 57 starting from 4-(3-fluorophenyl)oxazol-2(3H)-one (3.014 mmol, 1 eq). 60 (225 mg) is obtained as a yellow solid. LC-MS (conditions A): \( t_R = 0.84 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 8.80 \) (s, 1 H), 7.53 (m, 3 H), 7.17 (m, 1 H).

\textbf{B.21 2-Chloro-4-(3-chlorophenyl)oxazole 61}

a) 2-Bromo-1-(3-chlorophenyl)ethanone is prepared in analogy to 2-bromo-1-(3-fluorophenyl)propan-1-one starting from 1-(3-chlorophenyl)ethanone (12.937 mmol, 1 eq). 2-Bromo-1-(3-chlorophenyl)ethanone (3.00 g) is obtained as a light yellow oil. LC-MS (conditions A): \( t_R = 0.80 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 8.00 \) (m, 2 H), 7.93 (m, 1 H), 7.73 (m, 1 H), 7.57 (m, 1 H), 4.98 (s, 2 H).

b) 1-(3-Chlorophenyl)-2-hydroxyethanone is prepared in analogy to 1-(3-fluorophenyl)-2-hydroxypropan-1-one starting from 2-bromo-1-(3-chlorophenyl)ethanone (13.277 mmol, 1 eq). 1-(3-Chlorophenyl)-2-hydroxyethanone (1.46 g) is obtained as a pale yellow solid. LC-MS (conditions A): \( t_R = 0.55 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 7.87 \) (m, 2 H), 7.69 (m, 1 H), 7.53 (m, 1 H), 5.15 (t, \( J = 6.0 \) Hz, 1 H), 4.76 (d, \( J = 6.0 \) Hz, 2 H).

c) 4-(3-Chlorophenyl)oxazol-2(3H)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one starting from 1-(3-chlorophenyl)-2-hydroxyethanone (8.50 mmol, 1 eq). 4-(3-Chlorophenyl)oxazol-2(3H)-one (922 mg) is obtained as a light red solid. LC-MS (conditions A): \( t_R = 0.62 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 11.34 \) (s, 1 H), 7.78 (m, 1 H), 7.67 (m, 1 H), 7.51 (m, 1 H), 7.44 (m, 1 H), 7.37 (m, 1 H).

d) 2-Chloro-4-(3-chlorophenyl)oxazole 61 is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methyloxazole 57 starting from 4-(3-chlorophenyl)oxazol-2(3H)-one (4.714 mmol, 1 eq). 61 (371 mg) is obtained as a yellow solid. LC-MS (conditions A): \( t_R = 0.92 \) min, [M + 1]^+ = not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta 8.82 \) (s, 1 H), 7.79 (m, 1 H), 7.69 (m, 1 H), 7.45 (m, 2 H).

\textbf{B.22 2-Chloro-4-(m-tolyl)oxazole 62}

a) 2-Bromo-1-(m-tolyl)ethanone is prepared in analogy to 2-bromo-1-(3-fluorophenyl)propan-1-one starting from 1-(m-tolyl)ethanone (14.906 mmol, 1 eq). 2-Bromo-1-(m-tolyl)ethanone...
(3.25 g) is obtained as a light yellow oil. LC-MS (conditions A): \( t_R = 0.77 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 7.80 \) (m, 2 H), 7.46 (m, 2 H), 4.87 (s, 2 H), 2.34 (s, 3 H).

b) 2-Hydroxy-1-(m-tolyl)ethanone is prepared in analogy to 1-(3-fluorophenyl)-2-hydroxypropan-1-one starting from 2-bromo-1-(m-tolyl)ethanone \((15.253 \text{ mmol, } 1 \text{ eq})\). 2-Hydroxy-1-(m-tolyl)ethanone \((1.22 \text{ g})\) is obtained as a pale yellow solid. LC-MS (conditions A): \( t_R = 0.53 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 7.70 \) (m, 2 H), 7.41 (m, 2 H), 4.99 (t, \( J = 6.0 \text{ Hz} \), 1 H), 4.76 (d, \( J = 6.0 \text{ Hz} \), 2 H), 2.35 (s, 3 H).

c) 4-(m-Tolyl)oxazol-2(3H)-one is prepared in analogy to 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(m-tolyl)ethanone \((8.09 \text{ mmol, } 1 \text{ eq})\). 4-(m-Tolyl)oxazol-2(3H)-one \((740 \text{ mg})\) is obtained as a light red solid. LC-MS (conditions A): \( t_R = 0.61 \) min, \([2M + 1]^+ = 351.0\). \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 11.23 \) (s, 1 H), 7.62 (s, 1 H), 7.38 (m, 1 H), 7.30 (m, 2 H), 7.14 (m, 1 H), 2.30 (s, 3 H).

d) 2-Chloro-4-(m-tolyl)oxazole \((62 \text{ mg})\) is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole \((57 \text{ mmol, } 1 \text{ eq})\) starting from 4-(m-tolyl)oxazol-2(3H)-one \((4.196 \text{ mmol, } 1 \text{ eq})\). 2-Chloro-4-(m-tolyl)oxazole \((255 \text{ mg})\) is obtained as a yellow oil. LC-MS (conditions A): \( t_R = 0.89 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 8.72 \) (s, 1 H), 7.57 (m, 1 H), 7.51 (m, 1 H), 7.31 (m, 1 H), 7.17 (m, 1 H), 2.33 (s, 3 H).

\section*{B.23 2-Chloro-4-(3-fluorophenyl)-5-methylthiazole \(63\)}

a) To a solution of 2-bromo-1-(3-fluorophenyl)propan-1-one \((6.167 \text{ mmol, } 1 \text{ eq})\) in acetone \((10 \text{ mL})\) at RT is added NaSCN \((6.167 \text{ mmol, } 1 \text{ eq})\) and the resulting mixture is stirred at RT for 2 h. Upon completion the reaction is concentrated under reduced pressure and the residue is purified by FC \((\text{EtOAc}/\text{heptane}, 5:95 \text{ to } 3:7)\) to give 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one \((1.14 \text{ g})\) as a light yellow oil. LC-MS (conditions A): \( t_R = 0.75 \) min, \([M + 1]^+ = \) not detectable. \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 7.88 \) (m, 2 H), 7.59 (m, 2 H), 5.35 (q, \( J = 6.0 \text{ Hz} \), 1 H), 1.64 (d, \( J = 6.0 \text{ Hz} \), 3 H).

b) 1-(3-Fluorophenyl)-2-thiocyanatopropan-1-one \((5.448 \text{ mmol, } 1 \text{ eq})\) is dissolved in HCl \((4 \text{ M in dioxane, } 10 \text{ mL})\) and the resulting mixture is stirred at RT for 2 h. Upon completion the reaction mixture is concentrated under reduced pressure and the residue is purified by FC \((\text{EtOAc}/\text{heptane}, 5:95)\) to give 63 \((763 \text{ mg})\) as a colorless oil. LC-MS (conditions A): \( t_R = 0.94 \) min, \([M + 1]^+ = 228.06\). \(^1\)H NMR \((\text{D}_6\text{-DMSO})\): \( \delta 7.47 \) (m, 3 H), 7.21 (m, 1 H), 2.53 (s, 3 H).

\section*{B.24 2-Chloro-4-(3-chlorophenyl)-5-methylthiazole \(64\)}

a) 1-(3-Chlorophenyl)-2-thiocyanatopropan-1-one is prepared in analogy to 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(3-chlorophenyl)propan-1-
one (B18.a, 5.858 mmol, 1 eq). 1-(3-Chlorophenyl)-2-thiocyanatopropan-1-one (1.24 g) is obtained as a yellow solid. LC-MS (conditions A): t_R = 0.81 min, [M + 1]^+ not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \(\delta 8.09 \text{ (m, 1 H), 7.99 (m, 1 H), 7.77 (m, 1 H), 7.60 (m, 1 H), 5.37 (q, J = 6.0 Hz, 1 H), 1.62 (d, J = 6.0 Hz, 3 H).}

5 b) 2-Chloro-4-(3-chlorophenyl)-5-methylthiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 1-(3-chlorophenyl)-2-thiocyanatopropan-1-one (5.494 mmol, 1 eq). 64 (843 mg) is obtained as a white solid. LC-MS (conditions A): t_R = 1.01 min, [M + 1]^+ = 243.95. \(^1\)H NMR (D\(_6\)-DMSO): £7.64 (m, 1 H), 7.59 (m, 1 H), 7.47 (m, 2 H), 2.52 (s, 3 H).

10 \(\text{B.25 2-Chloro-5-methyl-4-}-(\text{m-tolyl})\text{thiazole 65}\)

a) 2-Thiocyanato-1-(m-tolyl)propan-1-one is prepared in analogy to 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(m-tolyl)propan-1-one (B19.a, 6.297 mmol, 1 eq). 2-Thiocyanato-1-(m-tolyl)propan-1-one (1.18 g) is obtained as a colorless oil. LC-MS (conditions A): t_R = 0.80 min, [M + 1]^+ not detectable. \(^1\)H NMR (D\(_6\)-DMSO): £7.84 (m, 2 H), 7.48 (m, 2 H), 5.41 (q, J = 6.0 Hz, 1 H), 2.36 (s, 3 H), 1.62 (d, J = 6.0 Hz, 3 H).

15 b) 2-Chloro-5-methyl-4-(m-tolyl)thiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 2-thiocyanato-1-(m-tolyl)propan-1-one (5.305 mmol, 1 eq). 65 (994 mg) is obtained as a light yellow oil. LC-MS (conditions A): t_R = 0.99 min, [M + 1]^+ = 224.01. \(^1\)H NMR (D\(_6\)-DMSO): £7.38 (m, 3 H), 7.18 (m, 1 H), 2.50 (s, 3 H), 2.35 (s, 3 H).

20 \(\text{B.26 2-chloro-4-}-(\text{3-fluorophenyl})\text{thiazole 66}\)

a) 1-(3-Fluorophenyl)-2-thiocyanatoethanone is prepared in analogy to 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(3-fluorophenyl)ethanone (B20.a, 4.953 mmol, 1 eq). 1-(3-Fluorophenyl)-2-thiocyanatoethanone (697 mg) is obtained as a yellow solid. LC-MS (conditions A): t_R = 0.70 min, [M + 1]^+ not detectable. \(^1\)H NMR (D\(_6\)-DMSO): £7.82 (m, 2 H), 7.60 (m, 2 H), 5.02 (s, 2 H).

25 b) 2-Chloro-4-(3-fluorophenyl)thiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 1-(3-fluorophenyl)-2-thiocyanatoethanone (3.535 mmol, 1 eq). 66 (714 mg) is obtained as a white solid. LC-MS (conditions A): t_R = 0.91 min, [M + 1]^+ not detectable. \(^1\)H NMR (D\(_6\)-DMSO): £8.21 (s, 1 H), 7.74 (m, 2 H), 7.50 (m, 1 H), 7.21 (m, 1 H).

30 \(\text{B.27 2-Chloro-}-(\text{3-chlorophenyl})\text{thiazole 67}\)

a) 1-(3-Chlorophenyl)-2-thiocyanatoethanone is prepared in analogy to 1-(3-chlorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(3-chlorophenyl)ethanone (B21.a, 6.703 mmol, 1 eq). 1-(3-Chlorophenyl)-2-thiocyanatoethanone (856 mg) is obtained as a yellow...
solid. LC-MS (conditions A): \( t_R = 0.76 \) min, [M + 1]\(^+\) not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta \) 8.04 (m, 1 H), 7.95 (m, 1 H), 7.77 (m, 1 H), 7.60 (m, 1 H), 4.97 (s, 2 H).

b) 2-Chloro-4-(3-chlorophenyl)thiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 1-(3-chlorophenyl)-2-thiocyanatoethanone (4.016 mmol, 1 eq). 67 (845 mg) is obtained as a white solid. LC-MS (conditions A): \( t_R = 0.98 \) min, [M + 1]\(^+\) not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta \) 8.27 (s, 1 H), 7.97 (m, 1 H), 7.86 (m, 1 H), 7.48 (m, 2 H).

**B.28 2-Chloro-4-(m-tolyl)thiazole 68**

a) 2-Thiocyanato-1-(m-tolyl)ethanone is prepared in analogy to 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one starting from 2-bromo-1-(m-tolyl)ethanone (B22.a, 7.744 mmol, 1 eq.). 2-Thiocyanato-1-(m-tolyl)ethanone (971 mg) is obtained as a yellow solid. LC-MS (conditions A): \( t_R = 0.75 \) min, [M + 1]\(^+\) not detectable. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta \) 7.81 (m, 2 H), 7.47 (m, 2 H), 5.03 (s, 2 H), 2.33 (s, 3 H).

b) 2-Chloro-4-(m-tolyl)thiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 2-thiocyanato-1-(m-tolyl)ethanone (5.046 mmol, 1 eq). 68 (926 mg) is obtained as a light yellow oil. LC-MS (conditions A): \( t_R = 0.95 \) min, [M + 1]\(^+\) = 210.09. \(^1\)H NMR (D\(_6\)-DMSO): \( \delta \) 8.07 (s, 1 H), 7.71 (m, 1 H), 7.67 (m, 1 H), 7.32 (m, 1 H), 7.17 (m, 1 H), 2.34 (s, 3 H).

Syntheses of further quinoxalines of formula A\(^\text{CI}\):

\[
\begin{align*}
81 & & 82 & & 83 & & 84 & & 85 \\
\text{F} & & \text{F} & & \text{Cl} & & \text{Cl} & & \text{O} \\
\text{F} & & \text{F} & & \text{N} & & \text{N} & & \text{F} \\
\text{F} & & \text{F} & & \text{Cl} & & \text{Cl} & & \text{F} \\
\end{align*}
\]

**B.29 2-Chloro-5,6-difluoroquinoxaline 81**

a) A mixture of 2,3-difluoro-6-nitroaniline (159 mmol, 1 eq), ethylbromo acetate (1.59 mol, 10 eq) and K\(_2\)CO\(_3\) (254 mmol, 1.6 eq) is stirred at 137°C under nitrogen till completion. The resulting reaction mixture is cooled down to RT, carefully quenched with 1 N NaOH (215 mL) and stirred for 10 minutes. The aqueous phase is extracted with DCM (3 times). The combined organic layers are dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The residue is purified by FC (DCM/heptane, 1:9) to give ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate (16 g) as a light yellow solid. LC-MS (conditions F): \( t_R = 0.87 \) min, [M + 1]\(^+\) = 261.21.
b) A solution of ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate (38.4 mmol, 1 eq) and tin(II) chloride dihydrate (150 mmol, 3.9 eq) in EtOH (202 ml) is refluxed for 1 h. Upon completion the reaction is concentrated under reduced pressure and the residue basified to pH = 11 with NaOH 1N (300 ml). The resulting white suspension is extracted with DCM (3 times). The combined organic layers are dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by FC (Teledyne Isco Combiflash Rt, SiO₂ cartridge 40 g; DCM/MeOH, 100:0 to 95:5) to give 5,6-difluoro-3,4-dihydroquinoxalin-2 (1H)-one (4.2 g) as a yellow solid. LC-MS (conditions F): tᵣ = 0.60 min, [M + 1 + CH₃CN]⁺ = 226.14.

c) A suspension of 5,6-difluoro-3,4-dihydroquinoxalin-2 (1H)-one (33.9 mmol, 1 eq), H₂O₂ (3 wt% in H₂O, 78.2 mmol, 2.3 eq) and NaOH 50% (4.29 ml.) is heated at 100°C for 3 hours, cooled down to 0°C and acidified with AcOH (81.3 mmol, 4.65 ml, 2.3 eq). The solid formed is filtered, washed several times with ice cold water and dried under vacuum at 50°C. 5,6-Difluoroquinoxalin-2 (1H)-one (4.21 g) is obtained as a brown solid. LC-MS (conditions F): tᵣ = 0.55 min, [M + 1 + CH₃CN]⁺ = 224.17.

d) A mixture of 5,6-difluoroquinoxalin-2(1/-)-one (23.1 mmol, 1 eq) and POCl₃ (461 mmol, 20 eq) is stirred at 100°C for 15 minutes. Upon completion, the reaction is cooled down to RT and excess POCl₃ removed under reduced pressure. The residual POCl₃ is carefully quenched with H₂O at RT and the aq. phase is extracted with DCM (3 times). The combined organic layers are washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue is purified by FC (Teledyne Isco Combiflash Rt, SiO₂ cartridge 80 g; Heptane to EtOAc/Heptane 9:1) to give 81 (3.4 g) as a white solid. LC-MS (conditions F): tᵣ = 0.79 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃):  δ 8.84 (s, 1 H), 7.84 (dm, 1 H), 7.71 (m, 1 H).

B.30 2-Chloro-7,8-difluoroquinoxaline 82

a) Ethyl 2-((3,4-difluoro-2-nitrophenyl)amino)acetate is prepared in analogy to ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate starting from 3,4-difluoro-2-nitroaniline (11.5 mmol, 1 eq). Ethyl 2-((3,4-difluoro-2-nitrophenyl)amino)acetate (1.34 g) is obtained as a red solid. LC-MS (conditions F): tᵣ = 0.86 min, [M + 1]⁺ = 261.10.

b) 7,8-Difluoro-3,4-dihydroquinoxalin-2 (1H)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2 (1H)-one starting from ethyl 2-((3,4-difluoro-2-nitrophenyl)amino)acetate (5.15 mmol, 1 eq). 7,8-Difluoro-3,4-dihydroquinoxalin-2 (1H)-one (0.85 g) is obtained as a beige solid. LC-MS (conditions F): tᵣ = 0.56 min, [M + 1 + CH₃CN]⁺ = 226.21.

c) 7,8-difluoroquinoxalin-2 (1H)-one is prepared in analogy to 5,6-difluoroquinoxalin-2 (1H)-one starting from 7,8-difluoro-3,4-dihydroquinoxalin-2 (1H)-one (4.62 mmol, 1 eq). 7,8-
Difluoroquinoxalin-2(1H)-one (572 mg) is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.54$ min, [M + 1 + CH$_3$CN]$^+$ = 224.02.

d) 2-Chloro-7,8-difluoroquinoxaline 82 is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline 81 starting from 7,8-difluoro-3,4-dihydroquinoxalin-2(1H)-one (3.09 mmol, 1 eq). 82 (300 mg) is obtained as a white solid. LC-MS (conditions F): $t_R = 0.52$ min, [M + 1]$^+$ = not detectable. $^1$H NMR (CDCl$_3$): $\delta$ 8.79 (s, 1 H), 7.93 (d, 1 H), 7.65 (m, 1 H).

**B.31 2-Chloro-7,8-difluoroquinoxaline 83**

a) Ethyl 2-((2-fluoro-6-nitrophenyl)amino)acetate is prepared in analogy to ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate starting from 2-fluoro-6-nitroaniline (12.8 mmol, 1 eq). Ethyl 2-((2-fluoro-6-nitrophenyl)amino)acetate (1.35 g) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.84$ min, [M + 1]$^+$ = 243.3.

b) 5-Fluoro-3,4-dihydroquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2(1H)-one starting from ethyl 2-((2-fluoro-6-nitrophenyl)amino)acetate (5.57 mmol, 1 eq). 5-Fluoro-3,4-dihydroquinoxalin-2(1H)-one (862 mg) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.53$ min, [M + 1 + CH$_3$CN]$^+$ = 208.32.

c) 5-Fluorquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1H)-one starting from 5-fluoro-3,4-dihydroquinoxalin-2(1H)-one (5.19 mmol, 1 eq). 5-Fluorquinoxalin-2(1H)-one (572 mg) is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.50$ min, [M + 1 + CH$_3$CN]$^+$ = 206.31.

d) 2-Chloro-5-fluoroquinoxaline 83 is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline 81 starting from 5-fluorquinoxalin-2(1H)-one (4.39 mmol, 1 eq). 83 (416 mg) is obtained as a white solid. LC-MS (conditions F): $t_R = 0.73$ min, [M + 1]$^+$ = not detectable. $^1$H NMR (CDCl$_3$): $\delta$ 8.82 (s, 1 H), 7.85 (m, 1 H), 7.75 (m, 1 H), 7.49 (m, 1 H).

**B.32 2-Chloro-7,8-difluoroquinoxaline 84**

a) Ethyl 2-((3-fluoro-2-nitrophenyl)amino)acetate is prepared in analogy to ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate starting from 3-fluoro-2-nitroaniline (19.2 mmol, 1 eq). Ethyl 2-((3-fluoro-2-nitrophenyl)amino)acetate (1.60 g) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.84$ min, [M + 1]$^+$ = 243.23.

b) 8-Fluoro-3,4-dihydroquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2(1H)-one starting from ethyl 2-((3-fluoro-2-nitrophenyl)amino)acetate (6.61 mmol, 1 eq). 8-Fluoro-3,4-dihydroquinoxalin-2(1H)-one (1.05 g) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.52$ min, [M + 1 + CH$_3$CN]$^+$ = 208.22.
c) 8-Fluoroquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1H)-one starting from 8-fluoro-3,4-dihydroquinoxalin-2(1H)-one (41.5 mmol, 1 eq). 8-Fluoroquinoxalin-2(1H)-one (5.15 g) is obtained as a brown solid. LC-MS (conditions F): t_R = 0.50 min, [M + 1 + CH_3CN]^+ = 206.16.

d) 2-Chloro-8-fluoroquinoxaline 84 is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline 81 starting from 8-fluoroquinoxalin-2(1H)-one (31.4 mmol, 1 eq). 84 (4.36 g) is obtained as a light yellow solid. LC-MS (conditions F): t_R = 0.75 min, [M + 1 + CH_3CN]^+ = 224.1.

**B.33 2-Chloro-6-fluoro-7-methoxyquinoxaline 85**

a) Acetic anhydride (159 mmol, 1.495 eq) is added to 3-fluoro-4-methoxyaniline (106 mmol, 1 eq) at RT and the resulting mixture is stirred at this temperature for 30 minutes. Nitric acid (156 mmol, 1.57 eq) is then added dropwise and the resulting suspension is stirred at RT for 3 h. Water is added to quench the reaction, the resulting solid collected by filtration and dried under vacuum. A/-((5-Fluoro-4-methoxy-2-nitrophenyl)acetamide (24.2 g) is obtained as a yellow solid. LC-MS (conditions F): t_R = 0.71 min, [M + 1 + CH_3CN]^+ = 270.25.

b) HCl 6N (200 mL) is added to a solution of A/-((5-fluoro-4-methoxy-2-nitrophenyl)acetamide (106 mmol, 1 eq) in EtOH (80 mL) at RT and the resulting suspension is stirred at 100°C for 1 hour before being cooled to 0°C with an ice bath. The resulting solid is collected by filtration, washed several times with water and dried under vacuum. 5-Fluoro-4-methoxy-2-nitroaniline (13.66 g) is obtained as a red solid. LC-MS (conditions F): t_R = 0.73 min, [M + 1]^+ = 187.26.

c) Ethyl 2-((5-fluoro-4-methoxy-2-nitrophenyl)amino)acetate is prepared in analogy to ethyl 2-((2,3-difluoro-6-nitrophenyl)amino)acetate starting from 5-fluoro-4-methoxy-2-nitroaniline (66.1 mmol, 1 eq). Ethyl 2-((5-fluoro-4-methoxy-2-nitrophenyl)amino)acetate (2.78 g) is obtained as an orange solid. LC-MS (conditions F): t_R = 0.86 min, [M + 1]^+ = 273.29.

d) 6-Fluoro-7-methoxy-3,4-dihydroquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2(1H)-one starting from ethyl 2-((5-fluoro-4-methoxy-2-nitrophenyl)amino)acetate (2.13 mmol, 1 eq). 6-Fluoro-7-methoxy-3,4-dihydroquinoxalin-2(1H)-one (106 mg) is obtained as a yellow solid. LC-MS (conditions F): t_R = 0.54 min, [M + 1 + CH_3CN]^+ = 238.33.

e) 6-Fluoro-7-methoxyquinoxalin-2(1H)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1H)-one starting from 6-fluoro-7-methoxy-3,4-dihydroquinoxalin-2(1H)-one (3.01 mmol, 1 eq). 6-Fluoro-7-methoxyquinoxalin-2(1H)-one (550 mg) is obtained as a brown solid. LC-MS (conditions F): t_R = 0.58 min, [M + 1]^+ = 195.18.
f) 2-Chloro-6-fluoro-7-methoxyquinoxaline 85 is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline 81 starting from 6-fluoro-7-methoxyquinoxalin-2(1H)-one (2.83 mmol, 1 eq). 85 (120 mg) is obtained as a light yellow solid. LC-MS (conditions F): \( t_R = 0.82 \text{ min} \), [M + 1]+ = 213.22.

All other groups Al^+-Cl used in the experimental part which are not described in this section are commercially available and/or fully described in the literature.

C Preparation of precursors:

**General Method A: Nucleophilic substitution**

To a solution of 1 mmol of secondary amine 1, 4, 6 or 14 (Schemes 1 + 2 +3 + 4) in DMF (7 ml.) are successively added \( \text{K}_2\text{C}_6\text{O}_3 \) (2.5 mmol for the free amine; 3.5 mmol when HCl salt is present) and \( \text{R}^1\text{-Cl} \) or \( \text{R}^2\text{-Cl} \) (1.05 mmol). The resulting suspension is stirred at 60 °C overnight. Upon completion \( \text{H}_2\text{O} \) is added and the aq. phase is extracted with EtOAc (3 times). The combined organic phases are washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The residue is purified by column chromatography or by preparative HPLC (conditions C).

**General Method B: Nucleophilic substitution**

To a solution of 1 mmol of secondary amine 1, 4, 6 or 14 (Schemes 1 + 2 +3 + 4) in pyridine (5.5 ml.) are successively added DBU (2.5 mmol for the free amine; 3.5 mmol when HCl salt is present) and \( \text{R}^1\text{-Cl} \) or \( \text{R}^2\text{-Cl} \) (1.2 mmol). The resulting suspension is stirred at 110 °C overnight. Upon completion \( \text{H}_2\text{O} \) is added and the aq. phase is extracted with EtOAc (3 times). The combined organic phases are washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The residue is purified by column chromatography or by preparative HPLC (conditions C).

**General Method C: Boc-deprotection**

To a solution of 1 mmol of Boc-protected amine 3, 7, 10 or 13 (Schemes 1 + 2 +3 + 4) in dioxane (1.5 ml.) is added HCl 4 M in dioxane (7.5 ml). The resulting reaction mixture is stirred at RT overnight and concentrated under reduced pressure. The residue is taken up in MeOH, sonicated and concentrated in vacuum. This operation is repeated 3 times to get rid of all HCl gas. The compound is obtained as foam or solid and is used in the next step without further purification.

**General Method D: Boc-deprotection**

To a solution of 1 mmol of Boc-protected amine 3, 7, 10 or 13 (Schemes 1 + 2 +3 + 4) in \( \text{Et}_2\text{O} \) (2.5 ml.) at 0°C is added HCl 2 M in \( \text{Et}_2\text{O} \) (2.5 ml.). The resulting white suspension is stirred at RT for 2 h, cooled down to 0°C diluted with \( \text{Et}_2\text{O} \) (1.25 ml.) and treated again with
HCI 2 M in Et$_2$O (1.25 mL). The resulting reaction mixture is further stirred at RT for an additional 2 h, diluted with cold EtOAc (3 mL) and filtered. The HCl salt is washed with EtOAc and pentane. The compound is obtained as a solid, which is used in the next step without further purification.

**General Method E**: Peptidic coupling

To a mixture of R$^1$-OH or R$^2$-OH (1 mmol) and TBTU (1.05 mmol) in CH$_3$CN (5.5 mL) at RT is added DIPEA (5 mmol). The resulting solution is stirred at RT for 15 minutes before addition of a solution of 1 mmol of secondary amine 1, 6, 8, or 11 (Schemes 1 + 2 +3 + 4) in CH$_3$CN (2 mL). The resulting reaction mixture is stirred at RT overnight. Upon completion aq. Sat. NaHCO$_3$ is added and the aq. phase is extracted with EtOAc (3 times). The combined organic phases are washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue is purified by FC or by preparative HPLC (conditions C).

**C.1 rac-(1R*,6S$^3$,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-$^2$,3-triazol-2-yI)phenyl)methanone hydrochloride**

a) rac-(1 R*,6S$^3$)-tert-Butyl 3-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R*,6S$^3$)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/069997) following **General Method E**. rac-(1R*,6S$^3$)-tert-Butyl 3-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after CC(DCM/MeOH 99:1 to 96:4). LC-MS (conditions A): rotamers $t_{R_1} = 0.72$ min / $t_{R_2} = 0.75$ min, [M + 1]$^+$ = 398.08.

b) rac-(1 R*,6S$^3$)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting rac-(1R*,6S$^3$)-tert-butyl 3-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following **General Method C**. rac-(1R*,6S$^3$)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a light orange foam. LC-MS (conditions A): rotamers $t_{R_1} = 0.37$ min / $t_{R_2} = 0.44$ min, [M + 1 - HCl]$^+$ = 298.1 11.

**C.1a (1R,6S$^3$)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1$^1$,3-triazol-2-yI)phenyl)methanone hydrochloride**

a) (1R,6S$^3$)-tert-Butyl 3-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1R,6S$^3$)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/069997) following **General Method E**. (1R,6S$^3$)-tert-Butyl 3-(5-methyl-2-(2H-
1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, Si0.2, DCM/MeOH 100:0 to 95:5). LC-MS (conditions F): rotamers t<sub>r1</sub> = 0.80 min / t<sub>r2</sub> = 0.83 min, [M + 1]<sup>+</sup> = 398.08.

b) (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting (1R,6S)-tert-butyl 3-(5-methyl-2-(2/-/-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a beige foam. LC-MS (conditions F): rotamers t<sub>r1</sub> = 0.80 min / t<sub>r2</sub> = 0.82 min, [M + 1 - HCl]<sup>+</sup> = 298.31.

10 C.4 rac-2-((1R*,6R*)-3,8-Diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[d]oxazole hydrochloride

a) rac-(1R<sup>*</sup>,6R<sup>*</sup>)-tert-Butyl 8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting rac-(1R<sup>*</sup>,6R<sup>*</sup>)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-3-carboxylate (6—) with 2,5-dichlorobenzo[c]oxazole (commercially available) following General Method A. rac-(1R<sup>*</sup>,6R<sup>*</sup>)-tert-Butyl 8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a pale yellow foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions B): t<sub>R</sub> = 0.93 min, [M + 1]<sup>+</sup> = 363.99.

b) rac-2-((1R<sup>*</sup>,6R<sup>*</sup>)-3,8-Diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride is obtained by reacting rac-(1R<sup>*</sup>,6R<sup>*</sup>)-tert-butyl 8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following General Method C. rac-2-((1R<sup>*</sup>,6R<sup>*</sup>)-3,8-Diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride is obtained as a beige solid. LC-MS (conditions B): t<sub>R</sub> = 0.74 min, [M + 1 - HCl]<sup>+</sup> = 264.03.

C.7 rac-(1R<sup>*</sup>,6S<sup>*</sup>)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride

a) rac-(1R<sup>*</sup>,6S<sup>*</sup>)-tert-Butyl 3-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R<sup>*</sup>,6S<sup>*</sup>)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1-1) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following General Method E. rac-(1R<sup>*</sup>,6S<sup>*</sup>)-tert-Butyl 3-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a beige oil after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): rotamers t<sub>r1</sub> = 0.85 min / t<sub>r2</sub> = 0.88 min, [M + 1]<sup>+</sup> = 407.18.

b) rac-(1R<sup>*</sup>,6S<sup>*</sup>)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride is obtained by reacting rac-(1R<sup>*</sup>,6S<sup>*</sup>)-tert-butyl 3-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C.
rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1',1'-biphenyl]-2-yl)methanone hydrochloride is obtained as a beige foam. LC-MS (conditions A): t_R = 0.54 min, [M + 1 - HCl]^+ = 307.22.

C.7a (1R,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1',1'-biphenyl]-2-yl)methanone hydrochloride

a) (1R,6S*)-tert-Butyl 3-(4-methyl-[1',1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1/R,6S*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 4-methyl-[1',1'-biphenyl]-2-carboxylic acid (commercially available) following General Method E. (1R,6S*)-tert-Butyl 3-(4-methyl-[1',1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO₂, DCM/MeOH 100:0 to 95:5). LC-MS (conditions F): rotamers t_R1 = 0.91 min / t_R2 = 0.93 min, [M + 1]^+ = 407.15.

b) (1R,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1',1'-biphenyl]-2-yl)methanone hydrochloride is obtained by reacting (1/R,6S*)-tert-butyl 3-(4-methyl-[1',1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. (1R,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1',1'-biphenyl]-2-yl)methanone hydrochloride is obtained as a white foam. LC-MS (conditions F): t_R = 0.62 min, [M + 1 - HCl]^+ = 307.09.

C.9 rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride

a) rac-(1 R*,6S*)-tert-Butyl 3-(5-methyl-2-(1 H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R*,6S*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1-) with 5-methyl-2-(1 H-pyrazol-1-yl)benzoic acid (commercially available) following General Method E. rac-(1R*,6S*)-tert-Butyl 3-(5-methyl-2-(1 H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): rotamers t_R1 = 0.70 min / t_R2 = 0.72 min, [M + 1]^+ = 397.15.

b) rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1 H-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained by reacting rac-(1R*,6S*)-tert-butyl 3-(5-methyl-2-(1 H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1 H-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained as a beige foam. LC-MS (conditions B): rotamers t_R1 = 0.64 min / t_R2 = 0.67 min, [M + 1 - HCl]^+ = 297.16.
**C.9a (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride**

a) (1R,6S)-tert-Butyl 3-(5-methyl-2-(1H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 5-methyl-2-(1H-pyrazol-1-yl)benzoic acid (commercially available) following **General Method E**. (1R,6S)-tert-Butyl 3-(5-methyl-2-(1H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco Combiflash RF, SiO\textsubscript{2}, DCM/MeOH 100:0 to 95:5). LC-MS (conditions A): rotamers \( t_{R1} = 0.70 \) min / \( t_{R2} = 0.72 \) min, \([M + 1]^+ = 397.15\).

b) (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained by reacting (1R,6S)-tert-butyl 3-(5-methyl-2-(1H-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following **General Method C**. (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained as a white foam. LC-MS (conditions F): \( t_R = 0.48 \) min, \([M + 1 - HCl]^+ = 297.31\).

**C.11 rac-(1R\*,6S\*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride**

a) rac-(1R\*,6S\*)-tert-Butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1-1) with 5-methyl-2-(pyridin-2-yl)benzoic acid (40, A.7) following **General Method E**. rac-(1R\*,6S\*)-tert-Butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a beige foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions B): rotamers \( t_{R1} = 0.83 \) min / \( t_{R2} = 0.85 \) min, \([M + 1]^+ = 408.23\).

b) rac-(1R\*,6S\*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained by reacting rac-(1R\*,6S\*)-tert-butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following **General Method D**. rac-(1R\*,6S\*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained as an off-white powder. LC-MS (conditions A): \( t_R = 0.40 \) min, \([M + 1 - HCl]^+ = 308.28\).

**C.11a (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride**

a) (1R,6S)-tert-Butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 5-methyl-2-(pyridin-2-yl)benzoic acid (40, A.7) following **General Method...
E. (1R,6S)-tert-Butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a pale pink foam after FC (Teledyne Isco CombiFlash Rf, SiO₂, DCM/MeOH 100:0 to 95:5). LC-MS (conditions B): tᵣ = 0.69 min, [M + 1]⁺ = 408.15.

b) (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting (1/?,6S)-tert-butyl 3-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method D. (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions F): tᵣ = 0.49 min, [M + 1 - HCl]⁺ = 308.07.

C.13 rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride

a) rac-(1 R*,6S*)-tert-Butyl 3-(2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R*,6S*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1-) with 2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)benzoic acid (34, A.1) following General Method E. rac-(1R*,6S*)-tert-Butyl 3-(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): rotamers tᵣ₁ = 0.73 min / tᵣ₂ = 0.76 min, [M + 1]⁺ = 416.23.

b) rac-(1 R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting rac-(1R*,6S*)-tert-butyl 3-(2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method D. rac-(1R*,6S*)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions A): 2 sets of rotamers tᵣ₁ = 0.38 min / tᵣ₂ = 0.40 min and tᵣ₃ = 0.44 min / tᵣ₄ = 0.46 min, [M + 1 - HCl]⁺ = 316.24.

C.13a (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride

a) (1R,6S)-tert-Butyl 3-(2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1/?,6S)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 2-fluoro-3-methyl-6-(2H-1 ,2,3-triazol-2-yl)benzoic acid (34, A.1) following General Method E. (1R,6S)-tert-Butyl 3-(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO₂, DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): rotamers tᵣ₁ = 0.82 min / tᵣ₂ = 0.85 min, [M + 1]⁺ = 416.05.
b) (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a white solid. LC-MS (conditions F): $t_R = 0.59$ min, $[M + 1 - \text{HCl}]^+ = 293.18$.

C.15 rac-[1,1'-Biphenyl]-2-yl((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride

a) rac-(1R*,6S*)-tert-Butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R*,6S*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with [1,1'-biphenyl]-2-carboxylic acid (commercially available) following General Method E. rac-(1R*,6S*)-tert-Butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. rac-[1,1'-Biphenyl]-2-yl((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride is obtained as a white foam after FC (Teledyne Isco Combiflash Rf, SiO$_2$, DCM/MeOH 100:0 to 98:2DCM/MeOH 99:1 to 98:2). LC-MS (conditions F): $t_R = 0.93$ min, $[M + 1]^+ = 393.09$.

b) rac-[[1,1'-biphenyl]-2-yl((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride is obtained by reacting rac-(1R*,6S*)-tert-butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. rac-[1,1'-Biphenyl]-2-yl((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride is obtained as a white solid. LC-MS (conditions F): $t_R = 0.59$ min, $[M + 1 - \text{HCl}]^+ = 293.17$.

C.15a [1,1'-Biphenyl]-2-yl((1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride

a) (1R,6S)-tert-Butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1/?,6S)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with [1,1'-biphenyl]-2-carboxylic acid (commercially available) following General Method E. (1R,6S)-tert-Butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco Combiflash Rf, SiO$_2$, DCM/MeOH 100:0 to 98:2). LC-MS (conditions F): $t_R = 0.88$ min, $[M + 1]^+ = 393.11$.

b) [1,1'-Biphenyl]-2-yl((1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride is obtained by reacting (1R,6S)-tert-butyl 3-[[1,1'-biphenyl]-2-carbonyl]-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. [1,1'-Biphenyl]-2-yl((1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride is obtained as a white solid. LC-MS (conditions F): $t_R = 0.59$ min, $[M + 1 - \text{HCl}]^+ = 293.18$. 
C.16 rac-(1R^6S^-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-y1)phenyl)methanone hydrochloride

a) rac-(1 R^1,6S^-)-tert-Butyl 3-(2-fluoro-3-methyl-6-(1 H-pyrazol-1 -yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R^1,6S^-)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 2-fluoro-3-methyl-6-(1 H-pyrazol-1-yl)benzoic acid (78, A.8) following General Method E. rac-(1R^-1,6S^-)-tert-Butyl 3-(2-fluoro-3-methyl-6-(1 H-pyrazol-1 -yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a beige foam after FC (Teledyne Isco CombiFlash Rf, SiO 2, DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): rotamers t\textsubscript{r1} = 0.81 min / t\textsubscript{r2} = 0.84 min, [M + 1]^+ = 415.08.

b) rac-(1R^*,6S^-)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1 H-pyrazol-1 -yl)phenyl)methanone hydrochloride is obtained by reacting rac-(1R^*,6S^-)-tert-butyl 3-(2-fluoro-3-methyl-6-(1 H-pyrazol-1 -yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. rac-(1R^*,6S^-)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1 H-pyrazol-1 -yl)phenyl)methanone hydrochloride is obtained as a white foam. LC-MS (conditions F): rotamers t\textsubscript{r1} = 0.51 min / t\textsubscript{r2} = 0.56 min, [M + 1 - HCl]^+ = 315.06.

C.17 rac-(1R^*,6S^-3,8-Diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1, 1'-biphenyl]-2-yl)methanone hydrochloride

a) rac-(1R^-1,6S^-)-tert-Butyl 3-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1R^-1,6S^-)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (80, A.10) following General Method E. rac-(1R^-1,6S^-)-tert-Butyl 3-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO 2, DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): rotamers t\textsubscript{r1} = 0.92 min / t\textsubscript{r2} = 0.94 min, [M + 1]^+ = 425.08.

b) rac-(1 R^1,6S^-)-3,8-Diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride is obtained by reacting rac-(1R^-1,6S^-)-tert-butyl 3-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method C. rac-(1R^-1,6S^-)-3,8-Diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride is obtained as a beige foam. LC-MS (conditions F): rotamers t\textsubscript{r1} = 0.60 min / t\textsubscript{r2} = 0.63 min, [M + 1-HCl]^+ = 324.71.

C.17a (1R,6S^-3,8-Diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride

a) (1R,6S^-)-tert-Butyl 3-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1R,6S^-)-tert-butyl 3,8-
diazabicyclo[4.2.0]octane-8-carboxylate \((1)\) with 3-fluoro-4-methyl-[1',1'-biphenyl]-2-carboxylic acid \((80, A.10)\) following General Method E. \((1R,6S)\)-tert-Butyl 3-(3-fluoro-4-methyl-[1',1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO\(_2\), DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): rotamers \(t_{R1} = 0.92\) min / \(t_{R2} = 0.94\) min, [M + 1]\(^+\) = 425.08.

b) \((1R,6S)\)-3,8-Diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1',1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO\(_2\), DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): \(t_{R1} = 0.61\) min / \(t_{R2} = 0.64\) min, [M + 1-HCl]\(^+\) = 325.02.

C.18 \(\text{rac-(1R}^*,6S^*)\)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride

a) \(\text{rac-(1 R}^*,6S^*)\)-tert-Butyl 3-(2-fluoro-3-methyl-6-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting \(\text{rac-(1R}^*,6S^*)\)-tert-butyl 3-(2-fluoro-3-methyl-6-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate \((1)\) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid \((79, A.9)\) following General Method E. \(\text{rac-(1R}^*,6S^*)\)-tert-Butyl 3-(2-fluoro-3-methyl-6-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a white foam after FC (Teledyne Isco CombiFlash Rf, SiO\(_2\), DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): \(t_{R} = 0.54\) min, [M + 1 - HCl]\(^+\) = 326.08.

b) \(\text{rac- (1R}^*,6S^*)\)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained by reacting \(\text{rac-(1R}^*,6S^*)\)-tert-butyl 3-(2-fluoro-3-methyl-6-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following General Method D. \(\text{rac- (1R}^*,6S^*)\)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions F): \(t_{R} = 0.54\) min, [M + 1 - HCl]\(^+\) = 326.08.
FC (Teledyne Isco Combiflash Rf, SiO\textsubscript{2}, DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): rotamers t\textsubscript{R1} = 0.77 min / t\textsubscript{R2} = 0.79 min, [M + 1]\textsuperscript{+} = 426.10.

b) (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained by reacting (1/?1,6S)-tert-butyl 3-(2-fluoro-3-methyl-6-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octan-8-carboxylate with HCl following General Method D. (1R,6S)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained as a off-white solid. LC-MS (conditions F): t\textsubscript{R} = 0.54 min, [M + 1 - HCl]\textsuperscript{+} = 326.10.

**Preparation of Examples**

The General Methods referred to in this section are the same as those described under section C. All final compounds are purified by column chromatography or by preparative HPLC (conditions C).

**Reference Example 1:** rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,5-dichlorobenzo[c]oxazole (commercially available) following General Method A or by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/069997) following General Method E. LC-MS (conditions B): rotamers t\textsubscript{R1} = 0.85 min / t\textsubscript{R2} = 0.87 min, [M + 1]\textsuperscript{+} = 449.10.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \)m; 20’250 mm) column, Heptane/EtOH + 0.1% DEA 50:50, flow rate = 16 mL/min.

**Reference Example 1a (enantiomer 1):**

\((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or \((1S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2/-/-1,2,3-triazol-2-yl)phenyl)methanone:

t\textsubscript{R} = 10.73 min.

**Reference Example 1b (enantiomer 2):**

\((1S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or \((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2/-/-1,2,3-triazol-2-yl)phenyl)methanone:

t\textsubscript{R} = 14.18 min.
Reference Example 2: rac-((1f?,6S*)-8-(Benzo[d]oxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2-
H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl-
(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-
chlorobenzo[c]oxazole (commercially available) following General Method A. LC-MS
(conditions B): rotamers \( t_{R1} = 0.79 \text{ min} / t_{R2} = 0.82 \text{ min}, [M + 1]^+ = 415.15. \)

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \eta \);
30°250 mm) column, Heptane/EtOH + 0.1% DEA 20:80, flow rate = 34 mL/min.

Reference Example 2a (enantiomer 1):

\(((1R,6S)-8-(Benzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,
2,3-triazol-2-yl)phenyl)methanone\) or \(((1S,6R)-8-(Benzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]
/octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: \( t_R = 9.40 \text{ min}. \)

Reference Example 2b (enantiomer 2):

\(((1R,6S)-8-(Benzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-
triazol-2-yl)phenyl)methanone\) or \(((1S,6R)-8-(Benzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]
 octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: \( t_R = 14.83 \text{ min}. \)

Example 3: rac-((1^6S*)-8-(6-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-
3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,6-
dichlorobenzo[c]oxazole (commercially available) following General Method A. LC-MS
(conditions B): rotamers \( t_{R1} = 0.86 \text{ min} / t_{R2} = 0.88 \text{ min}, [M + 1]^+ = 449.03. \)

Example 4: rac-((1f?,6S*)-8-(6-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-
3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-6-
fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS
(conditions B): rotamers \( t_{R1} = 0.81 \text{ min} / t_{R2} = 0.84 \text{ min}, [M + 1]^+ = 433.16. \)

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 \( \mu \eta \);
30°250 mm) column, DCM/CH \(_3\)CN + 0.1% DEA 10:90, flow rate = 34 mL/min.
**Example 4a** (enantiomer 1):

\[ ((1R,6S)-8-(6-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \text{ or } ((1S,6R)-8-(6-Fluorobenzo[c]oxazol-2-yl)-3,8-diaza bicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: t_R = 7.36 \text{ min.} \]

**Example 4b** (enantiomer 2):

\[ ((1R,6S)-8-(6-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \text{ or } ((1S,6R)-8-(6-Fluorobenzo[c]oxazol-2-yl)-3,8-diaza bicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: t_R = 9.12 \text{ min.} \]

**Example 5**:

\[ \text{rac-((1f^*},6S^*)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone} \]

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following **General Method A**. LC-MS (conditions B): rotamers \( t_{R_1} = 0.81 \text{ min} / t_{R_2} = 0.84 \text{ min, } [M + 1]^+ = 433.18. \)

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \eta \); 20°250 mm) column, Heptane/EtOH + 0.1% DEA 40:60, flow rate = 16 mL/min.

**Example 5a** (enantiomer 1):

\[ ((1R,6S)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \text{ or } ((1S,6R)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diaza bicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: t_R = 9.66 \text{ min.} \]

**Example 5b** (enantiomer 2):

\[ ((1R,6S)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \text{ or } ((1S,6R)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diaza bicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: t_R = 13.63 \text{ min.} \]

**Example 6**:

\[ \text{rac-((1f^*},6S^*)-8-(4-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone} \]

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,4-dichlorobenzo[c]oxazole (commercially available) following **General Method A**. LC-MS (conditions B): rotamers \( t_{R_1} = 0.84 \text{ min} / t_{R_2} = 0.88 \text{ min, } [M + 1]^+ = 449.07. \)
Example 7: rac-((1/?*,6S*)-8-(Benzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chlorobenzo[c/thiazole] (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.83$ min / $t_{r2} = 0.85$ min, $[M + 1]^+ = 431.06$.

Example 8: rac-((1^6S*)-8-(6-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,6-dichlorobenzo[c/thiazole] (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.89$ min, $[M + 1]^+ = 465.05$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ; 20*250 mm) column, CH$_3$CN/tBu Methyl Ether 95:5, flow rate = 16 mL/min.

Example 8a (enantionmer 1):

((1R,6S)-8-(6-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(6-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 11.10$ min.

Example 8b (enantionmer 2):

((1R,6S)-8-(6-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(6-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 13.45$ min.

Example 9: rac-((1^6S*)-8-(5-Chlorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,5-dichlorobenzo[c/thiazole] (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.90$ min, $[M + 1]^+ = 465.05$.

Example 10: rac-((1/?*,6S*)-8-(6-Fluorobenzo[c/thiazol-2-yl])-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-6-fluorobenzo[c/thiazole] (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.84$ min / $t_{r2} = 0.87$ min, $[M + 1]^+ = 449.06$. 
Example 11: rac-((1/?*,6S*)-8-(5-Fluorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-fluorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.84$ min / $t_{R2} = 0.87$ min, $[M + 1]^+ = 449.11$.

Example 12: rac-((1f/?*,6S*)-8-(Benzo[d]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3-chlorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.82$ min / $t_{R2} = 0.85$ min, $[M + 1]^+ = 415.14$.

Example 13: rac-((1f/?*,6S*)-8-(5-Chlorobenzo[d]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3,5-dichlorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.87$ min / $t_{R2} = 0.92$ min, $[M + 1]^+ = 449.06$.

Example 14: rac-((1f/?*,6S*)-8-(6-Chlorobenzo[d]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3,6-dichlorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.89$ min / $t_{R2} = 0.91$ min, $[M + 1]^+ = 449.07$.

Example 15: rac-((1/?*,6S*)-8-(5-Fluorobenzo[c]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3-chloro-5-fluorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.83$ min / $t_{R2} = 0.87$ min, $[M + 1]^+ = 433.09$.

Example 16: rac-((1f/?*,6S*)-8-(6-Fluorobenzo[d]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3-chloro-6-
fluorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.84$ min / $t_{R2} = 0.87$ min, $[M + 1]^+ = 433.09$.

**Example 17:** rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1fR*,6S*)-8-(5-methylbenzo[c]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3-chloro-5-methylbenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.85$ min / $t_{R2} = 0.89$ min, $[M + 1]^+ = 429.07$.

**Example 18:** rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1fR*,6S*)-8-(6-methylbenzo[c]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3-chloro-6-methylbenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.86$ min / $t_{R2} = 0.89$ min, $[M + 1]^+ = 429.11$.

**Example 19:** rac-((1fR*,6S*)-8-(5-Chlorobenzo[c]isothiazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3,5-dichlorobenzo[c]isothiazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.95$ min / $t_{R2} = 0.99$ min, $[M + 1]^+ = 465.01$.

**Example 20:** rac-((1fR*,6S*)-8-(6-Chlorobenzo[c]isothiazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 3,6-dichlorobenzo[c]isothiazole (commercially available) following General Method B. LC-MS (conditions B): rotamers $t_{R1} = 0.94$ min / $t_{R2} = 1.00$ min, $[M + 1]^+ = 465.01$.

**Example 21:** rac-((1fR*,6S*)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.85$ min / $t_{R2} = 0.90$ min, $[M + 1]^+ = 473.14$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 µm; 20`250 mm) column, Heptane/EtOH + 0.1% DEA 50:50, flow rate = 16 mL/min.
Example 21a (enantiomer 1):

\((1R,6S)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone or \((1S,6R)-8-(5-(3-Fluorophenyl)-4-
methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone: \(t_R = 12.76\) min.

Example 21b (enantiomer 2):

\((1R,6S)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone or \((1S,6R)-8-(5-(3-Fluorophenyl)-4-
methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone: \(t_R = 15.57\) min.

Example 22:

\(\text{rac-}\((1/?*,6S*)-8-(5-(3-Chlorophenyl)-4-methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone\)

The title compound is prepared by reacting \(\text{rac-(1R*,6S*)-3,8-
diazabicyclo[4.2.0]octan-3-yl}(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-
chlorophenyl)-4-methyloxazole (B.4 - 44) following General Method A. LC-MS (conditions B): rotamers \(t_{R1} = 0.89\) min / \(t_{R2} = 0.94\) min, \([M + 1]^+ = 488.94\).

Example 23:

\(\text{rac-}((5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1f/?*,6S*)-8-(4-methyl-5-(m-
tolyl)oxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)methanone\)

The title compound is prepared by reacting \(\text{rac-(1R*,6S*)-3,8-
diazabicyclo[4.2.0]octan-3-yl}(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-methyl-
5-(m-tolyl)oxazole (B.5 - 45) following General Method A. LC-MS (conditions B): rotamers \(t_{R1} = 0.88\) min / \(t_{R2} = 0.93\) min, \([M + 1]^+ = 469.14\).

Example 24:

\(\text{rac-}((1/?*,6S*)-8-(5-(4-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone\)

The title compound is prepared by reacting \(\text{rac-(1R*,6S*)-3,8-
diazabicyclo[4.2.0]octan-3-yl}(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(4-
fluorophenyl)-4-methyloxazole (B.2 - 42) following General Method A. LC-MS (conditions B): rotamers \(t_{R1} = 0.85\) min / \(t_{R2} = 0.89\) min, \([M + 1]^+ = 473.09\).

Example 25:

\(\text{rac-}((1/?*,6S*)-8-(5-(2-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-
diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-
yl)phenyl)methanone\)

The title compound is prepared by reacting \(\text{rac-(1R*,6S*)-3,8-
diazabicyclo[4.2.0]octan-3-yl}(5-
methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(2-
fluorophenyl)-4-methyloxazole (B.3 - 43) following General Method A. LC-MS (conditions B): rotamers \(t_{R1} = 0.85\) min / \(t_{R2} = 0.89\) min, \([M + 1]^+ = 473.00\).
The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 µη; 30°250 mm) column, CH₃CN/DCM + 0.1% DEA 95:5, flow rate = 34 mL/min.

**Example 25a (enantiomer 1):**

((1R,6S)-8-(5-(2-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(5-(2-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: tᵣ = 8.34 min.

**Example 25b (enantiomer 2):**

((1R,6S)-8-(5-(2-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(5-(2-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: tᵣ = 9.36 min.

**Example 26:** rac-((1/?*,6S*)-8-(5-(3-Fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-fluorophenyl)oxazole (B.6-46) following General Method A. LC-MS (conditions B): rotamers tᵣ₁ = 0.83 min / tᵣ₂ = 0.88 min, [M + 1]+ = 459.29.

**Example 27:** rac-((1/?*,6S*)-8-(5-(4-Fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(4-fluorophenyl)oxazole (B.7-47) following General Method A. LC-MS (conditions B): rotamers tᵣ₁ = 0.83 min / tᵣ₂ = 0.87 min, [M + 1]+ = 459.27.

**Example 28:** rac-((1/?*,6S*)-8-(5-(2-Fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(2-fluorophenyl)oxazole (B.8-48) following General Method A. LC-MS (conditions B): rotamers tᵣ₁ = 0.84 min / tᵣ₂ = 0.88 min, [M + 1]+ = 459.29.

**Example 29:** rac-((1/?*,6S*)-8-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-((1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-
(difluoromethyl)-5-(3-fluorophenyl)oxazole (B.9 - 49) following General Method A. LC-MS (conditions B): rotamers $t_{R_1} = 0.87$ min / $t_{R_2} = 0.92$ min, [M + 1]$^+$ = 509.01.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 $\mu\eta$; 30°250 mm) column, Heptane/EtOH + 0.1% DEA 55:45, flow rate = 34 mL/min.

Example 29a (enantiomer 1):

$((1R,6S)-8-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1 R,6S)-8-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 12.23$ min.

Example 29b (enantiomer 2):

$((1R,6S)-8-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 14.68$ min.

Example 30: rac-5-(3-Fluorophenyl)-2-((1S,6R*)-3-(5-methyl-2-(2H-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octan-8-yl)oxazole-4-carbonitrile

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-fluorophenyl)oxazole-4-carbonitrile (B.10 - 50) following General Method A. LC-MS (conditions B): rotamers $t_{R_1} = 0.87$ min / $t_{R_2} = 0.91$ min, [M + 1]$^+$ = 484.07.

Example 31a (enantiomer 1):

$((1R,6S)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1 S,6R)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 14.48$ min.
**Example 31b (enantiomer 2):**

\[(1R,6S)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\] or \[(1S,6R)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\]: \( t_\text{R} = 17.34 \text{ min.} \)

**Example 32:** rac-\((1f^*?,6S^*)-8-(5-(3-Chlorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-chlorophenyl)-4-methylthiazole (B.12 - 52) following General Method A. LC-MS (conditions B): rotamers \( t_{\text{R1}} = 0.97 \text{ min} \)/\( t_{\text{R2}} = 0.99 \text{ min}, \ [M + 1]^+ = 505.16. \)

**Example 33:** rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1f^*?,6S^*)-8-(4-methyl-5-(m-tolyl)thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-methyl-5-(m-tolyl)thiazole (B.13 - 53) following General Method A. LC-MS (conditions B): rotamers \( t_{\text{R1}} = 0.95 \text{ min} \)/\( t_{\text{R2}} = 0.98 \text{ min}, \ [M + 1]^+ = 485.26. \)

**Example 34:** rac-\((1f^*?,6S^*)-8-(5-(3-Fluorophenyl)thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-fluorophenyl)thiazole (B.14 - 54) following General Method A. LC-MS (conditions B): rotamers \( t_{\text{R1}} = 0.90 \text{ min} \)/\( t_{\text{R2}} = 0.92 \text{ min}, \ [M + 1]^+ = 475.22. \)

**Example 35:** rac-\((1f^*?,6S^*)-8-(5-(3-Chlorophenyl)thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(3-chlorophenyl)thiazole (B.15 - 55) following General Method A. LC-MS (conditions B): rotamers \( t_{\text{R1}} = 0.95 \text{ min} \)/\( t_{\text{R2}} = 0.97 \text{ min}, \ [M + 1]^+ = 491.09. \)

**Example 36:** rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1f^*?,6S^*)-8-(5-(m-tolyl)thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-(m-...
Example 37: rac-((1/?*,6S*)-8-(4-(3-Fluorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.17 - 57) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.90 \text{ min} / t_{R2} = 0.93 \text{ min}, \ [M + 1]^+ = 473.08. \)

Example 38: rac-((1/?*,6S*)-8-(4-(3-Chlorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-chlorophenyl)-5-methylthiazole (B.18 - 58) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.95 \text{ min} / t_{R2} = 0.97 \text{ min}, \ [M + 1]^+ = 488.90. \)

Example 39: rac-((5-Methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(5-methyl-4-(m-tolyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-methyl-4-(m-tolyl)oxazole (B.19 - 59) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.92 \text{ min} / t_{R2} = 0.94 \text{ min}, \ [M + 1]^+ = 469.12. \)

Example 40: rac-((1/?*,6S*)-8-(4-(3-Fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-fluorophenyl)oxazole (B.20 - 60) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.88 \text{ min} / t_{R2} = 0.90 \text{ min}, \ [M + 1]^+ = 458.93. \)

Example 41: rac-((1/?*,6S*)-8-(4-(3-Chlorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-chlorophenyl)oxazole (B.21 - 61) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.93 \text{ min} / t_{R2} = 0.95 \text{ min}, \ [M + 1]^+ = 475.00. \)
Example 42: rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1R*,6S*)-8-(4-(m-tolyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(m-tolyl)oxazole (B.22 - 62) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.90 \) min / \( t_{R2} = 0.92 \) min, [M + 1] = 455.10.

Example 43: rac-((1/?*,6S*)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following General Method A. LC-MS (conditions B): rotamers \( t_{R1} = 0.95 \) min / \( t_{R2} = 0.97 \) min, [M + 1] = 488.87.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \)m; 30’250 mm) column, Heptane/EtOH + 0.1% DEA 80:20, flow rate = 34 mL/min.

Example 43a (enantiomer 1):

\( ((1R,6S)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \) or \((1S,6R)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: \( t_R = 29.05 \) min.

Example 43b (enantiomer 2):

\( ((1R,6S)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone \) or \((1S,6R)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: \( t_R = 35.37 \) min.

Example 44: rac-((1f/?*,6S*)-8-(4-(3-Chlorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-4-(3-chlorophenyl)-5-methylthiazole (B.24 - 64) following General Method A. LC-MS (conditions B): \( t_R = 1.00 \) min, [M + 1] = 505.02.

Example 45: rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1f/?*,6S*)-8-(5-methyl-4-(m-tolyl)thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5-methyl-
4-(m-tolyl)thiazole (B.25 - 65) following General Method A. LC-MS (conditions B): \( t_R = 0.98 \) min, \([M + 1]^+ = 485.04\).

**Example 46: rac-\((-((1\text{f}^*\text{R},6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\)**

The title compound is prepared by reacting rac-\((-((1\text{R}^*,6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\) hydrochloride (C.1) with 2-chloro-4-(3-fluorophenyl)thiazole (B.26 - 66) following General Method A. LC-MS (conditions B): rotamers \( t_{R_1} = 0.94 \) min / \( t_{R_2} = 0.96 \) min, \([M + 1]^+ = 475.04\).

**Example 47: rac-\((-((1\text{f}^*\text{R},6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\)**

The title compound is prepared by reacting rac-\((-((1\text{R}^*,6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\) hydrochloride (C.1) with 2-chloro-4-(3-chlorophenyl)thiazole (B.27 - 67) following General Method A. LC-MS (conditions B): rotamers \( t_{R_1} = 0.98 \) min / \( t_{R_2} = 1.01 \) min, \([M + 1]^+ = 490.81\).

**Example 48: rac-\((-((5\text{Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl})\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{methanone}\)**

The title compound is prepared by reacting rac-\((-((1\text{R}^*,6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\) hydrochloride (C.1) with 2-chloro-4-(m-tolyl)thiazole (B.28 - 68) following General Method A. LC-MS (conditions B): rotamers \( t_{R_1} = 0.96 \) min / \( t_{R_2} = 0.98 \) min, \([M + 1]^+ = 471.08\).

**Reference Example 49: rac-\((-((5\text{Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl})\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{methanone}\)**

The title compound is prepared by reacting rac-\((-((1\text{R}^*,6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\) hydrochloride (C.1) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers \( t_{R_1} = 0.78 \) min / \( t_{R_2} = 0.81 \) min, \([M + 1]^+ = 425.80\).

**Example 50: rac-\((-((1\text{f}^*\text{R},6\text{S}^*)\text{-}8-(7\text{-Fluoroquinoxalin-2-yl})\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\)**

The title compound is prepared by reacting rac-\((-((1\text{R}^*,6\text{S}^*)\text{-}3,8\text{-diazabicyclo}[4.2.0]\text{octan} \text{-}3\text{-yl})\text{(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone}\) hydrochloride (C.1) with 2-chloro-7-fluoroquinoxaline (WO201 0/0841 52A1) following General Method A. LC-MS (conditions B): rotamers \( t_{R_1} = 0.81 \) min / \( t_{R_2} = 0.85 \) min, \([M + 1]^+ = 444.08\).
Example 51: rac-((1f?*,6S*)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers t_R1 = 0.81 min / t_R2 = 0.85 min, [M + 1]^+ = 444.10.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 µm; 30*250 mm) column, CH_3CN/tBME + 0.1% DEA 98:2, flow rate = 34 mL/min.

Example 51a (enantiomer 1):

((1R,6S)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

Example 51b (enantiomer 2):

((1R,6S)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

Example 52: rac-((1f?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers t_R1 = 0.84 min / t_R2 = 0.87 min, [M + 1]^+ = 462.02.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 µm; 30*250 mm) column, CH_3CN/tBME + 0.1% DEA 98:2, flow rate = 34 mL/min.

Example 52a (enantiomer 1):

((1R,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

Example 52b (enantiomer 2):

((1R,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
Example 53: rac-((1R*,6S*)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.87$ min / $t_{R2} = 0.89$ min, [M + 1]$^+$ = 460.01.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 $\mu$m; 30°250 mm) column, CH$_3$CN/tBME + 0.1% DEA 98:2, flow rate = 34 mL/min.

Example 53a (enantiomer 1):

((1R,6S)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 12.35$ min.

Example 53b (enantiomer 2):

((1R,6S)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 16.58$ min.

Example 54: rac-((1R*,6S*)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,6-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.87$ min / $t_{R2} = 0.89$ min, [M + 1]$^+$ = 460.02.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 $\mu$m; 30°250 mm) column, CH$_3$CN/tBME + 0.1% DEA 98:2, flow rate = 34 mL/min.

Example 54a (enantiomer 1):

((1R,6S)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 12.31$ min.

Example 54b (enantiomer 2):

((1R,6S)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone or ((1S,6R)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 17.17$ min.
Example 55: rac-((1R*,6S*)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2,6,7-trichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): \( t_R = 0.95 \) min, \([M + 1]^+ = 493.99 \).

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \) \eta); 30°250 mm) column, CH\(_3\)CN/tBME + 0.1% DEA 98:2, flow rate = 34 mL/min.

Example 55a (enantiomer 1):

\(((1R,6S)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\) or \(((1S,6R)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\): \( t_R = 12.68 \) min.

Example 55b (enantiomer 2):

\(((1R,6S)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\) or \(((1S,6R)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone\): \( t_R = 20.33 \) min.

Reference Example 56: rac-(2-(2H-1,2,3-Triazol-2-yl)phenyl)((1/?*,6S*)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (WO201 0/04801 2) following General Method E. LC-MS (conditions B): rotamers \( t_{R1} = 0.82 \) min / \( t_{R2} = 0.84 \) min, \([M + 1]^+ = 435.00 \).

Reference Example 57: rac-(5-Chloro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1/?*,6S*)-8-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[d]oxazole hydrochloride (C.4) with 5-chloro-2-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/00851 7 A2) following General Method E. LC-MS (conditions B): rotamers \( t_{R1} = 0.87 \) min / \( t_{R2} = 0.89 \) min, \([M + 1]^+ = 468.91 \).

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \) \eta); 30°250 mm) column, Heptane/EtOH + 0.1% DEA 50:50, flow rate = 34 mL/min.

Reference Example 57a (enantiomer 1):

\((5-Chloro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1R,6S)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone\) or \((5-Chloro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,6R)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone\).
(yl)phenyl)((1S,6R)-8-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone: \( t_R = 9.08 \) min.

**Reference Example 57b (enantiomer 2):**
(5-Chloro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1R,6S)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone or (5-Chloro-2-(2H-1,2,3-triazol-2-yl)phenyl)((1S,6R)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone: \( t_R = 12.43 \) min.

**Reference Example 58:** rac-((1/?,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-fluoro-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-fluoro-2-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/008517 A2) following **General Method E**. LC-MS (conditions B): rotamers \( t_{R1} = 0.84 \) min / \( t_{R2} = 0.86 \) min, \([M + 1]^+ = 453.02\).

**Reference Example 59:** rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-fluoro-6-(2H-1,2,3-triazol-2-yl)benzoic acid (WO2008/008517 A2) following **General Method E**. LC-MS (conditions B): rotamers \( t_{R1} = 0.84 \) min / \( t_{R2} = 0.86 \) min, \([M + 1]^+ = 453.02\).

**Reference Example 60:** rac-((1/?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(6-methyl-3-(2H-1,2,3-triazol-2-yl)pyridin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 6-methyl-3-(2H-1,2,3-triazol-2-yl)picolinic acid (WO2011/063662) following **General Method E**. LC-MS (conditions B): rotamers \( t_{R1} = 0.77 \) min / \( t_{R2} = 0.80 \) min, \([M + 1]^+ = 450.43\).

**Reference Example 61:** rac-((1/?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)benzoic acid (A.1 - 34) following **General Method E**. LC-MS (conditions A): 2 sets of rotamers \( t_{R1} = 0.75 \) min / \( t_{R2} = 0.77 \) min - \( t_{R3} = 0.79 \) min / \( t_{R4} = 0.80 \) min, \([M + 1]^+ = 467.20\).
Reference Example 62: rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methoxy-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone
The title compound is prepared by reacting rac-2-((l R\*6R\*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methoxy-2-(2/-/-1,2,3-triazol-2-yl)benzoic acid (A.2 - 35) following General Method E. LC-MS (conditions A): rotamers \( t_{R1} = 0.72 \text{ min} / t_{R2} = 0.75 \text{ min}, [M + 1]^+ = 465.11 \).

Reference Example 63: rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methoxy-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone
The title compound is prepared by reacting rac-2-((l R\*6R\*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-fluoro-3-methoxy-6-(2/-/-1,2,3-triazol-2-yl)benzoic acid (A.3 - 36) following General Method E. LC-MS (conditions A): rotamers \( t_{R1} = 0.71 \text{ min} / t_{R2} = 0.76 \text{ min}, [M + 1]^+ = 483.19 \).

Example 64: rac-(2-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethyl)phenyl)((1f?*,6S*)-8-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone
The title compound is prepared by reacting rac-2-((l R\*6R\*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-(2/-/-1,2,3-triazol-2-yl)-5-(trifluoromethyl)benzoic acid (A.4 - 37) following General Method E. LC-MS (conditions A): rotamers \( t_{R1} = 0.81 \text{ min} / t_{R2} = 0.84 \text{ min}, [M + 1]^+ = 503.24 \).

Example 65: rac-(2-(2H-1,2,3-Triazol-2-yl)-5-(trifluoromethoxy)phenyl)((1f?*,6S*)-8-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone
The title compound is prepared by reacting rac-2-((l R\*6R\*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-(2/-/-1,2,3-triazol-2-yl)-5-(trifluoromethoxy)benzoic acid (A.5 - 38) following General Method E. LC-MS (conditions A): rotamers \( t_{R1} = 0.83 \text{ min} / t_{R2} = 0.86 \text{ min}, [M + 1]^+ = 519.14 \).

Example 66: rac-3-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-3-carbonyl)-4-(2H-1,2,3-triazol-2-yl)benzonitrile
The title compound is prepared by reacting rac-2-((l R\*6R\*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-cyano-2-(2H-1,2,3-triazol-2-yl)benzoic acid (A.6 - 39) following General Method E. LC-MS (conditions A): rotamers \( t_{R1} = 0.70 \text{ min} / t_{R2} = 0.74 \text{ min}, [M + 1]^+ = 460.16 \).
Reference Example 67: rac-((1R*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methyl-2-(1H-pyrazol-1-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): $t_R = 0.86$ min, $[M + 1]^+ = 448.03$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 µm; 30’250 mm) column, Heptane/ EtOH + 0.1% DEA 50:50, flow rate = 34 mL/min.

Reference Example 67a (enantiomer 1):

\[((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone~\]

Reference Example 67b (enantiomer 2):

\[((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone~\]

Reference Example 68: rac-(2-(1H-Pyrazol-1-yl)phenyl)((1/?*,6S*)-8-(5-chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-(1H-pyrazol-1-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 434.10$.

Reference Example 69: rac-((1R*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(3-methyl-1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methyl-2-(3-methyl-1H-pyrazol-1-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 462.05$.

Reference Example 70: rac-((1R*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-(3-methyl-1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-(3-methyl-1H-pyrazol-1-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): $t_R = 0.85$ min, $[M + 1]^+ = 448.03$. 
Reference Example 71: rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(6-methyl-3-(1H-pyrazol-1-yl)pyridin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 6-methyl-3-(1H-pyrazol-1-yl)picolinic acid (WO2010/063662) following General Method E. LC-MS (conditions B): rotamers $t_{R1} = 0.77$ min / $t_{R2} = 0.78$ min, [M + 1]$^+$ = 449.02.

Example 72: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(6-methyl-3-(3-methyl-1H-pyrazol-1-yl)pyridin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 6-methyl-3-(3-methyl-1H-pyrazol-1-yl)picolinic acid (WO2010/063662) following General Method E. LC-MS (conditions B): $t_R = 0.80$ min, [M + 1]$^+$ = 463.16.

Reference Example 73: rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[d]oxazole hydrochloride (C.4) with 5-methyl-2-(pyrimidin-2-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): rotamers $t_{R1} = 0.82$ min / $t_{R2} = 0.85$ min, [M + 1]$^+$ = 460.00.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 µm; 30¥250 mm) column, CH$_3$CN/DCM 95:5, flow rate = 34 mL/min.

Reference Example 73a (enantiomer 1):

((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone or ((1S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone: $t_R = 12.29$ min.

Reference Example 73b (enantiomer 2):

((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone or ((1S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyrimidin-2-yl)phenyl)methanone: $t_R = 22.60$ min.

Example 74: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(6-methyl-3-(pyrimidin-2-yl)pyridin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 6-methyl-3-(pyrimidin-2-yl)picolinic acid...
(WO20 10/063662) following General Method E. LC-MS (conditions B): rotamers \( t_{R1} = 0.74 \) min / \( t_{R2} = 0.78 \) min, \([M + 1]^+ = 461.20\).

**Reference Example 75:** rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]/oxazole hydrochloride (C.4) with 5-methyl-2-(pyridin-2-yl)benzoic acid (A.7 - 40) following General Method E. LC-MS (conditions B): \( t_R = 0.86 \) min, \([M + 1]^+ = 459.03\).

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \) \eta ; 30’250 mm) column, Heptane/EtOH + 0.1% DEA 50:50, flow rate = 34 mL/min.

**Reference Example 75a (enantiomer 1):**

((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

**Reference Example 75b (enantiomer 2):**

((1S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone: \( t_R = 11.22 \) min.

**Reference Example 77:** rac-((1f?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]/oxazole hydrochloride (C.4) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): \( t_R = 0.89 \) min, \([M + 1]^+ = 458.17\).

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 \( \mu \) \eta ; 30’250 mm) column, Heptane/EtOH + 0.1% DEA 50:50, flow rate = 34 mL/min.
Reference Example 77a (enantiomer 1):

\[(1\,R,6S)-8-(5\text{-Chlorobenzo}[c\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(4\text{-methyl-[1,1}'-biphenyl]-2-yl)\text{methanone or } (1\,S,6R)-8-(5\text{-Chlorobenzo}[c\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(4\text{-methyl-[1,1}'-biphenyl]-2-yl)\text{methanone: } t_R = 8.05 \text{ min.}

Reference Example 77b (enantiomer 2):

\[(1\,R,6S)-8-(5\text{-Chlorobenzo}[d\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(4\text{-methyl-[1,1}'-biphenyl]-2-yl)\text{methanone: } t_R = 10.74 \text{ min.}

Example 78: rac-\((1/?*,6S*)-8-(5\text{-Chlorobenzo}[c\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(6\text{-methyl-3-phenylpyridin-2-yl})\text{methanone}

The title compound is prepared by reacting rac-2-\((1R*,6R*)-3,8\text{-diazabicyclo}[4.2.0]octan-8-yl)-5\text{-chlorobenzo}[c\text{-}]oxazole hydrochloride (C.4) with 6\text{-methyl-3-phenylpicolinic acid (WO20 10/072722) following General Method E. LC-MS (conditions B): } t_R = 0.75 \text{ min, } [M + 1]^+ = 459.17.

Reference Example 79: rac-\((1f/?*,6S*)-8-(5\text{-Chlorobenzo}[d\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(5\text{-methyl-3-phenylisoxazol-4-yl})\text{methanone}

The title compound is prepared by reacting rac-2-\((1R*,6R*)-3,8\text{-diazabicyclo}[4.2.0]octan-8-yl)-5\text{-chlorobenzo}[c\text{-}]oxazole hydrochloride (C.4) with 5\text{-methyl-3-phenylisoxazole-4-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): } t_R = 0.87 \text{ min, } [M + 1]^+ = 448.99.

Reference Example 80: rac-\((1f/?*,6S*)-8-(5\text{-Chlorobenzo}[d\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(3\text{-}-(4\text{-fluorophenyl})-5\text{-methylisoxazol-4-yl})\text{methanone}

The title compound is prepared by reacting rac-2-\((1R*,6R*)-3,8\text{-diazabicyclo}[4.2.0]octan-8-yl)-5\text{-chlorobenzo}[c\text{-}]oxazole hydrochloride (C.4) with 3\text{-}-(4\text{-fluorophenyl})-5\text{-methylisoxazole-4-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): } t_R = 0.88 \text{ min, } [M + 1]^+ = 466.97.

Reference Example 81: rac-\((1f/?*,6S*)-8-(5\text{-Chlorobenzo}[d\text{-}]oxazol-2-yl)-3,8\text{-diazabicyclo}[4.2.0]octan-3-yl)(3\text{-}-(4\text{-chlorophenyl})-5\text{-methylisoxazol-4-yl})\text{methanone}

The title compound is prepared by reacting rac-2-\((1R*,6R*)-3,8\text{-diazabicyclo}[4.2.0]octan-8-yl)-5\text{-chlorobenzo}[c\text{-}]oxazole hydrochloride (C.4) with 3\text{-}-(4\text{-chlorophenyl})-5\text{-methylisoxazole-4-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): } t_R = 0.92 \text{ min, } [M + 1]^+ = 482.99.
Example 82: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-3-(p-tolyl)isoxazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methyl-3-(p-tolyl)isoxazol-4-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): t\textsubscript{R} = 0.90 min, [M + 1]\textsuperscript{+} = 463.00.

Example 83: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-3-(m-tolyl)isoxazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-methyl-3-(m-tolyl)isoxazol-4-carboxylic acid (commercially available) following General Method E. LC-MS (conditions B): t\textsubscript{R} = 0.90 min, [M + 1]\textsuperscript{+} = 463.06.

Example 84: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(6-methyl-3-(3-methylisoxazol-5-yl)pyridin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 6-methyl-3-(3-methylisoxazol-5-yl)picolinic acid (WO2010/063663) following General Method E. LC-MS (conditions B): rotamers t\textsubscript{R1} = 0.76 min / t\textsubscript{R2} = 0.82 min, [M + 1]\textsuperscript{+} = 464.04.

Example 85: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-(3-methyl-1,2,4-oxadiazol-5-yl)phenyl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-(3-methyl-1,2,4-oxadiazol-5-yl)benzoic acid (commercially available) following General Method E. LC-MS (conditions B): rotamers t\textsubscript{R1} = 0.80 min / t\textsubscript{R2} = 0.84 min, [M + 1]\textsuperscript{+} = 450.03.

Example 86: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-(3-fluorophenyl)-2-methyloxazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-(3-fluorophenyl)-2-methyloxazol-4-carboxylic acid (WO2010/004507) following General Method E. LC-MS (conditions B): t\textsubscript{R} = 0.85 min, [M + 1]\textsuperscript{+} = 467.04.
Example 87: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)oxazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-methyl-5-(m-toly1)oxazol-4-carboxylic acid (WO20 10/038200) following General Method E. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 463.04$.

Reference Example 88: rac-((1/?*,6S*)-8-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-(3-fluorophenyl)-2-methylthiazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 5-(3-fluorophenyl)-2-methylthiazole-4-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 482.98$.

Example 89: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)thiazol-4-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-methyl-5-(m-tolyl)thiazole-4-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): $t_R = 0.90$ min, $[M + 1]^+ = 479.03$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IC (5 µ m); 30˚250 mm) column, CH$_3$CN/EtOH 90:10 + 0.1% DEA, flow rate = 34 mL/min.

Example 89a (enantiomer 1):

((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)thiazol-4-yl)methanone or ((1 S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)thiazol-4-yl)methanone: $t_R = 7.55$ min.

Example 89b (enantiomer 2):

((1R,6S)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)thiazol-4-yl)methanone or ((1 S,6R)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-5-(m-tolyl)thiazol-4-yl)methanone: $t_R = 9.36$ min.

Example 90: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(3-(m-tolyl)pyrazin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1R*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 3-(m-tolyl)pyrazine-2-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): $t_R = 0.86$ min, $[M + 1]^+ = 460.02$. 
Example 91: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(3-(p-tolyl)pyrazin-2-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 3-(p-tolyl)pyrazine-2-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): \( t_R = 0.86 \) min, \([M + 1]^+ = 460.09\).

Example 92: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-4-(m-tolyl)pyrimidin-5-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-methyl-4-(m-tolyl)pyrimidine-5-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): \( t_R = 0.86 \) min, \([M + 1]^+ = 474.19\).

Example 93: rac-((1/?*,6S*)-8-(5-Chlorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-methyl-4-(p-tolyl)pyrimidin-5-yl)methanone

The title compound is prepared by reacting rac-2-((1/?*,6R*)-3,8-diazabicyclo[4.2.0]octan-8-yl)-5-chlorobenzo[c]oxazole hydrochloride (C.4) with 2-methyl-4-(p-tolyl)pyrimidine-5-carboxylic acid (WO20 10/044054) following General Method E. LC-MS (conditions B): \( t_R = 0.86 \) min, \([M + 1]^+ = 474.02\).

Example 94: rac-((1/?*,6S*)-8-(5-Chlorobenzo[d]isoxazol-3-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 3,5-dichlorobenzo[c]isoxazole (commercially available) following General Method B. LC-MS (conditions B): rotamers \( t_{R1} = 0.97 \) min / \( t_{R2} = 1.01 \) min, \([M + 1]^+ = 458.00\).

Example 95: rac-((1/?*,6S*)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS (conditions B): \( t_R = 0.92 \) min, \([M + 1]^+ = 442.19\).

Example 95a: ((1f?*,6S*)-8-(5-Fluorobenzo[d]isoxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1/?*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-5-
Example 96: rac-((1/?*,6S*)-8-(6-Chlorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl) methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl) methanone hydrochloride (C.7) with 2,6-dichlorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): t_R = 0.95 min, [M + 1]^+ = 474.09.

Example 97: rac-((1/?*,6S*)-8-(6-Fluorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl) methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl) methanone hydrochloride (C.7) with 2-chloro-6-fluorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): t_R = 1.00 min, [M + 1]^+ = 458.45.

Example 98: rac-((1/?*,6S*)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl) methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl) methanone hydrochloride (C.7) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 51) following General Method A. LC-MS (conditions B): rotamers t_R = 0.96 min / t_R2 = 0.99 min, [M + 1]^+ = 482.17.

Example 99: rac-((1/?*,6S*)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl) methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl) methanone hydrochloride (C.7) with 2-chloro-5-(3-fluorophenyl)-4-methylthiazole (B.1 1 - 51) following General Method A. LC-MS (conditions B): rotamers t_R1 = 1.02 min / t_R2 = 1.03 min, [M + 1]^+ = 498.15.

Example 100: rac-((1/?*,6S*)-8-(4-(3-Fluorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl) methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl) methanone hydrochloride (C.7) with 2-chloro-4-(3-fluorophenyl)-5-methyloxazole (B.1 7 - 57) following General Method A. LC-MS (conditions B): rotamers t_R = 1.00 min, [M + 1]^+ = 482.16.
Example 1.01: rac-((1f?,6S*)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 1.05 \text{ min} / t_{R2} = 1.07 \text{ min}, [M + 1]^+ = 498.19$.

Example 1.02: rac-((1/?*,6S*)-8-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-4-(difluoromethyl)-5-(3-fluorophenyl)oxazole (B.9 - 49) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.97 \text{ min} / t_{R2} = 1.00 \text{ min}, [M + 1]^+ = 518.34$.

Example 1.03: rac-((1f?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.96 \text{ min}, [M + 1]^+ = 471.14$.

Example 1.03a: ((1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1/?*,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): $t_R = 0.94 \text{ min}, [M + 1]^+ = 471.37$.

Example 1.04: rac-((1f?*,6S*)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.93 \text{ min}, [M + 1]^+ = 453.17$.

Example 1.04a: ((1f?,6S)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1/?*,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-6-fluoroquinoxaline
Example 105: rac-((1/?*,6S*)-8-(6,7-Dichloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2,6,7-trichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): t_R = 1.06 min, [M + 1]^+ = 503.10.

Example 106: rac-((1 f?*,6S*)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): t_R = 0.99 min, [M + 1]^+ = 469.15.

Example 107: rac-((1f?*,6S*)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2,6-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): t_R = 0.98 min, [M + 1]^+ = 469.15.

Example 108: rac-((1/?*,6S*)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1 H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS (conditions B): t_R = 0.81 min, [M + 1]^+ = 432.22.

Example 108a: ((1f?,6S)-8-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1 H-pyrazol-1 -yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9a) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following General Method A. LC-MS (conditions F): t_R = 0.80 min, [M + 1]^+ = 432.29.
Example 109: rac-((1/?*,6S*)-8-(6-Chlorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2,6-dichlorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.89$ min, $[M + 1]^+ = 464.1$.

Example 110: rac-((1/?*,6S*)-8-(6-Fluorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-6-fluorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.84$ min / $t_{r2} = 0.86$ min, $[M + 1]^+ = 448.10$.

Example 111: rac-((1/?*,6S*)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.86$ min / $t_{r2} = 0.89$ min, $[M + 1]^+ = 472.24$.

Example 112: rac-((1f/?*,6S*)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-5-(3-fluorophenyl)-4-methylthiazole (B.1 - 51) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.91$ min / $t_{r2} = 0.93$ min, $[M + 1]^+ = 488.15$.

Example 113: rac-((1f/?*,6S*)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following General Method A. LC-MS (conditions B): rotamers $t_{r1} = 0.95$ min / $t_{r2} = 0.97$ min, $[M + 1]^+ = 488.14$.

Example 114: rac-((1/?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-6,7-
difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.84$ min, $[M + 1]^+ = 461.15$.

**Example 114a:** ((1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 461.36$.

**Example 115:** rac-((1f?*,6S*)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.81$ min / $t_{R2} = 0.82$ min, $[M + 1]^+ = 443.16$.

**Example 115a:** ((1f?,6S)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9a) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.78$ min / $t_{R2} = 0.80$ min, $[M + 1]^+ = 443.32$.

**Example 116:** rac-((1f?*,6S*)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.86$ min, $[M + 1]^+ = 459.01$.

**Example 116a:** ((1f?,6S)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9a) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions E): rotamers $t_{R1} = 0.83$ min / $t_{R2} = 0.84$ min, $[M + 1]^+ = 459.34$. 
Example 117: rac-((1f?*,6S*)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9) with 2,6-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): \( t_R = 0.86 \) min, \([M + 1]^+ = 459.05\).

Example 117a: ((1f?,6S)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting (1/?*,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.9a) with 2,6-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers \( t_{R1} = 0.82 \) min / \( t_{R2} = 0.84 \) min, \([M + 1]^+ = 459.34\).

Example 118: rac-((1/?*,6S*)-8-(5-Fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS (conditions B): \( t_R = 0.82 \) min, \([M + 1]^+ = 443.11\).

Example 118a: ((1f?,6S)-8-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting (1/?*,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1a) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS (conditions F): \( t_R = 0.71 \) min, \([M + 1]^+ = 443.33\).

Example 119: rac-((1f?*,6S*)-8-(6-Chlorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2,6-dichlorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): \( t_R = 0.90 \) min, \([M + 1]^+ = 475.08\).

Example 120: rac-((1/?*,6S*)-8-(6-Fluorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-6-
fluorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.85$ min, [M + 1]$^+$ = 459.07.

**Example 121**: rac-((1R*,6S*)-8-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following General Method A. LC-MS (conditions B): $t_R = 0.89$ min, [M + 1]$^+$ = 483.16.

**Example 122**: rac-((1f?*,6S*)-8-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-5-(3-fluorophenyl)-4-methylthiazole (B.1 - 51) following General Method A. LC-MS (conditions B): $t_R = 0.92$ min, [M + 1]$^+$ = 499.16.

**Example 123**: rac-((1f?*,6S*)-8-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following General Method A. LC-MS (conditions B): $t_R = 0.96$ min, [M + 1]$^+$ = 499.17.

**Example 124**: rac-((1/?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.85$ min, [M + 1]$^+$ = 472.17.

**Example 124a**: (1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): $t_R = 0.74$ min, [M + 1]$^+$ = 472.37.
Example 125: rac-((1f?,6S*)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.81$ min, $[M + 1]^+ = 454.15$.

Example 125a: ((1f?,6S)-8-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting (1/?6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1a) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): $t_R = 0.70$ min, $[M + 1]^+ = 454.37$.

Example 126: rac-((1f?,6S*)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 470.14$.

Example 126a: ((1f?,6S)-8-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting (1/?6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1a) with 2,7-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions E): $t_R = 0.74$ min, $[M + 1]^+ = 470.37$.

Example 127: rac-((1/?*,6S*)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1) with 2,6-dichloroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 470.13$.

Example 127a: ((1f?,6S)-8-(6-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone
The title compound is prepared by reacting (1/?6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.1 1a) with 2,6-dichloroquinoxaline...
Example 128: rac-(2-Fluoro-3-methyl-6-(2H,1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(5-fluorobenzo[c]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-5-fluorobenzo[c]oxazole (commercially available) following General Method A. LC-MS (conditions E): $t_R = 0.70$ min, $[M + 1]^+ = 470.38$.

Example 129: rac-(2-Fluoro-3-methyl-6-(2H,1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(6-fluorobenzo[c]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-6-fluorobenzo[c]thiazole (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.82$ min / $t_{R2} = 0.85$ min, $[M + 1]^+ = 451.13$.

Example 130: rac-((1f?,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(2H,1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.86$ min / $t_{R2} = 0.89$ min, $[M + 1]^+ = 480.17$.

Example 130a: ((1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(2H,1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions E): rotamers $t_{R1} = 0.85$ min / $t_{R2} = 0.89$ min, $[M + 1]^+ = 480.18$.

Example 131: rac-(2-Fluoro-3-methyl-6-(2H,1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(6-fluorquinokxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-6-fluorquinokxalin (commercially available) following General Method A. LC-MS (conditions B): rotamers $t_{R1} = 0.82$ min / $t_{R2} = 0.86$ min, $[M + 1]^+ = 462.16$. 

Note: The conditions for each example are specified as conditions E or B, which may refer to specific LC-MS conditions or methods used in the preparation.
Example 131a: (2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1f?,6S)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1f?,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13a) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers $t_R^1 = 0.79$ min / $t_R^2 = 0.84$ min, [M + 1]$^+$ = 462.19.

Example 132: rac-(2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(5-(3-fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following General Method A. LC-MS (conditions B): rotamers $t_R^1 = 0.86$ min / $t_R^2 = 0.91$ min, [M + 1]$^+$ = 491.08.

Example 133: rac-(2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1f?*,6S*)-8-(4-(3-fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following General Method A. LC-MS (conditions B): rotamers $t_R^1 = 0.96$ min / $t_R^2 = 1.00$ min, [M + 1]$^+$ = 507.30.

Reference Example 134: rac-(4-Methyl-[1,1'-biphenyl]-2-yl)((1f?*,6S*)-8-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-[1,1'-biphenyl]-2-yl((1f?*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride (C.15) with 2-chloroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): $t_R = 0.79$ min, [M + 1]$^+$ = 421.07.

Reference Example 134a: (4-Methyl-[1,1'-biphenyl]-2-yl)((1f?,6S)-8-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting [1,1'-biphenyl]-2-yl((1f?,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone hydrochloride (C.15a) with 2-chloroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): $t_R = 0.79$ min, [M + 1]$^+$ = 421.07.

Example 135: rac-(1f?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-5,6-
difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.82 \text{ min} / t_{R2} = 0.85 \text{ min}$, $[M + 1]^+ = 462.31$.

**Example 135a:** ((1f?,6S)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.81 \text{ min} / t_{R2} = 0.85 \text{ min}$, $[M + 1]^+ = 462.08$.

**Reference Example 136:** rac-((1f?*,6S*)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.76 \text{ min} / t_{R2} = 0.81 \text{ min}$, $[M + 1]^+ = 444.08$.

**Reference Example 136a:** ((1f?*,6S*)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1a) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.76 \text{ min} / t_{R2} = 0.81 \text{ min}$, $[M + 1]^+ = 444.05$.

**Example 137:** rac-((1f?*,6S*)-8-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.79 \text{ min} / t_{R2} = 0.84 \text{ min}$, $[M + 1]^+ = 444.04$.

**Example 138:** rac-((1/?*,6S*)-8-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(2 H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloro-7,8-difluoroquinoxaline (82, B.30) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.82 \text{ min} / t_{R2} = 0.87 \text{ min}$, $[M + 1]^+ = 462.37$. 


Example 139: \( \text{rac-}((1R^*,6S^*)-8-(8\text{-Fluoroquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(5\text{-methyl-2-(1 H-pyrazol-1-y1)phenyl})\text{methanone} \)

The title compound is prepared by reacting \( \text{rac-}(1R^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(5\text{-methyl-2-(1H-pyrazol-1-yl)phenyl})\text{methanone hydrochloride (C.9)} \) with 2-chloro-7,8-difluorouinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.79 \text{ min} \)/ \( t_R^2 = 0.82 \text{ min}, [M + 1]^+ = 443.05. \)

Example 140: \( \text{rac-}((1f^*,6S^*)-8-(5\text{-Fluoroquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(5\text{-methyl-2-(1 H-pyrazol-1-y1)phenyl})\text{methanone} \)

The title compound is prepared by reacting \( \text{rac-}(1R^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(5\text{-methyl-2-(1H-pyrazol-1-yl)phenyl})\text{methanone hydrochloride (C.9)} \) with 2-chloro-7,8-difluorouinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.76 \text{ min} \)/ \( t_R^2 = 0.78 \text{ min}, [M + 1]^+ = 443.03. \)

Example 141: \( \text{rac-}((1/?^*,6S^*)-8-(5,6\text{-Difluoroquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(5\text{-methyl-2-(1 H-pyrazol-1-yl)phenyl})\text{methanone} \)

The title compound is prepared by reacting \( \text{rac-}(1/?^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(5\text{-methyl-2-(1H-pyrazol-1-yl)phenyl})\text{methanone hydrochloride (C.9)} \) with 2-chloro-5,6-difluorouinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.82 \text{ min} \)/ \( t_R^2 = 0.83 \text{ min}, [M + 1]^+ = 461.25. \)

Example 141a: \( ((1/?^*,6S^*)-8-(5,6\text{-Difluoroquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(5\text{-methyl-2-(1 H-pyrazol-1-yl)phenyl})\text{methanone} \)

The title compound is prepared by reacting \( (1/?^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(5\text{-methyl-2-(1H-pyrazol-1-yl)phenyl})\text{methanone hydrochloride (C.7a)} \) with 2-chloro-5,6-difluorouinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.82 \text{ min} \)/ \( t_R^2 = 0.83 \text{ min}, [M + 1]^+ = 461.24. \)

Example 142: \( \text{rac-}((1/?^*,6S^*)-8-(6\text{-Fluoro-7-methoxyquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(4\text{-methyl-[1,1'-biphenyl]-2-yl})\text{methanone} \)

The title compound is prepared by reacting \( \text{rac-}(1R^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(4\text{-methyl-[1,1'-biphenyl]-2-yl})\text{methanone hydrochloride (C.7)} \) with 2-chloro-6-fluoro-7-methoxyquinoxaline (85, B.33) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.89 \text{ min} \)/ \( t_R^2 = 0.91 \text{ min}, [M + 1]^+ = 483.20. \)

Example 142a: \( (1/?^*,6S^*)-8-(6\text{-Fluoro-7-methoxyquinoxalin-2-yl})-3,8\text{-diazabicyclo[4.2.0]octan-3-yl})(4\text{-methyl-[1,1'-biphenyl]-2-yl})\text{methanone} \)

The title compound is prepared by reacting \( (1/?^*,6S^*)\text{-3,8-diazabicyclo[4.2.0]octan-3-yl}(4\text{-methyl-[1,1'-biphenyl]-2-yl})\text{methanone hydrochloride (C.7a)} \) with 2-chloro-6-fluoro-7-methoxyquinoxaline (85, B.33) following General Method A. LC-MS (conditions F): rotamers \( t_R^1 = 0.89 \text{ min} \)/ \( t_R^2 = 0.91 \text{ min}, [M + 1]^+ = 483.24. \)
methoxyquinoxaline (85, B.33) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.89$ min / $t_{R2} = 0.91$ min, [M + 1]$^+$ = 483.10.

Example 143: rac-((1f?,6S*)-8-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.91$ min / $t_{R2} = 0.92$ min, [M + 1]$^+$ = 453.28.

Example 143a: ((1f?,6S*)-8-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): $t_{R} = 0.89$ min, [M + 1]$^+$ = 453.27.

Example 144: rac-((1f?,6S*)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): $t_{R} = 0.89$ min, [M + 1]$^+$ = 453.30.

Example 144a: ((1f?,6S*)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): $t_{R} = 0.89$ min, [M + 1]$^+$ = 453.30.

Example 145: rac-((1/?*,6S*)-8-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1′-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1R’,6S’)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1′-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-7,8-difluoroquinoxaline (82, B.30) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.93$ min / $t_{R2} = 0.95$ min, [M + 1]$^+$ = 471.25.
Example 145a: ((1f?,6S)-8-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1/?,,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-7,8-difluoroquinoxaline (82, B.30) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.93$ min / $t_{R2} = 0.95$ min, [M + 1]$^+$ = 471.21.

Example 146: rac-((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): $t_{R} = 0.93$ min, [M + 1]$^+$ = 471.23.

Example 146a: ((1f?,6S)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1/?,,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.7a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): $t_{R} = 0.93$ min, [M + 1]$^+$ = 471.20.

Example 147: rac-((1/?*,6S*)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.11) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): $t_{R} = 0.68$ min, [M + 1]$^+$ = 454.12.

Example 147a: ((1f?,6S)-8-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting (1/?,,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.11a) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): $t_{R} = 0.68$ min, [M + 1]$^+$ = 454.09.

Example 148: rac-((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.11) with 2-chloro-5,6-
difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): $t_R = 0.73$ min, [M + 1]$^+$ = 472.30.

**Example 148a:** ((1f?,6S)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.11a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): $t_R = 0.73$ min, [M + 1]$^+$ = 472.27.

**Example 149:** rac-((1/?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.16) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.85$ min / $t_{R2} = 0.88$ min, [M + 1]$^+$ = 479.16.

**Example 150:** rac-(2-Fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)((1f?*,6S*)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.16) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.80$ min / $t_{R2} = 0.83$ min, [M + 1]$^+$ = 461.21.

**Example 151:** rac-((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.16) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.83$ min / $t_{R2} = 0.87$ min, [M + 1]$^+$ = 479.19.

**Example 152:** rac-(2-Fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)((1f?*,6S*)-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.16) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers $t_{R1} = 0.81$ min / $t_{R2} = 0.83$ min, [M + 1]$^+$ = 461.18.
Example 153: rac- (2-Fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)((1f^?,6S^*)-8-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1(R^?,6S^*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)methanone hydrochloride (C.16) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.78 min / t_R2 = 0.81 min, [M + 1]^+ = 461.18.

Example 156: rac-((1/?^*,6S^*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1(R^?,6S^*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.84 min / t_R2 = 0.88 min, [M + 1]^+ = 480.20.

Example 156a: ((1f^?,6S^*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting (1/?^?,6S^*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.83 min / t_R2 = 0.87 min, [M + 1]^+ = 480.17.

Example 157: rac-(2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1?^F,6S^*)-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1(R^?,6S^*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.80 min / t_R2 = 0.86 min, [M + 1]^+ = 462.23.

Example 157a: (2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1?^f,6S^*)-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1/?^?,6S^*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13a) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.80 min / t_R2 = 0.86 min, [M + 1]^+ = 462.02.
Example 158: rac-(2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1FT,6S*)-8-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.13) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.78 min / t_R2 = 0.83 min, [M + 1]^+ = 462.16.

Example 159: rac-((1/?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.94 min / t_R2 = 0.97 min, [M + 1]^+ = 489.24.

Example 159a: ((1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1f?,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.94 min / t_R2 = 0.97 min, [M + 1]^+ = 489.19.

Example 160: rac-(3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1f?,6S*)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.90 min / t_R2 = 0.93 min, [M + 1]^+ = 471.23.

Example 160a: (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1f?,6S*)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1f?,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17a) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.90 min / t_R2 = 0.93 min, [M + 1]^+ = 471.22.

Example 161: rac-((1/?*,6S*)-8-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-7,8-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.90 min / t_R2 = 0.93 min, [M + 1]^+ = 471.22.
difluoroquinoxahne (82, B.30) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.94 \text{ min} / t_R^2 = 0.98 \text{ min}, [M + 1]^+ = 489.16. \)

**Example 162:** rac- ((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.93 \text{ min} / t_R^2 = 0.96 \text{ min}, [M + 1]^+ = 489.24. \)

**Example 162a:** ((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.93 \text{ min} / t_R^2 = 0.96 \text{ min}, [M + 1]^+ = 489.17. \)

**Example 163:** rac-(3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1/?*,6S*)-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.92 \text{ min} / t_R^2 = 0.95 \text{ min}, [M + 1]^+ = 471.24. \)

**Example 163a:** (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1/?*,6S*)-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17a) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.92 \text{ min} / t_R^2 = 0.95 \text{ min}, [M + 1]^+ = 471.19. \)

**Example 164:** rac-(3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1/?*,6S*)-8-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R*,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl-(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.17) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers
\( t_R^1 = 0.89 \text{ min} / t_R^2 = 0.91 \text{ min}, [M + 1]^+ = 471.25. \)
Example 164a: (3-Fluoro-4-methyl-[1 ,1’-biphenyl]-2-yl)(1/? ,6S)-8-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1/? ,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(3-fluoro-4-methyl-[1 ,1’-biphenyl]-2-yl)methanone hydrochloride (C.17a) with 2-chloro-7,8-difluoroquinoxaline (83, B.31) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.89 min / t_R2 = 0.91 min, [M + 1]^+ = 471.20.

Example 165: rac-((1/?*,6S*)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R* ,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.80 min / t_R2 = 0.82 min, [M + 1]^+ = 490.23.

Example 165a: (1f?,6S)-8-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting (1/? ,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18a) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.81 min / t_R2 = 0.83 min, [M + 1]^+ = 489.93.

Example 166: rac-(2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1/?*,6S*)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting rac-(1R* ,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.76 min / t_R2 = 0.78 min, [M + 1]^+ = 472.24.

Example 166a: (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1f?,6S)-8-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone

The title compound is prepared by reacting (1/? ,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18a) with 2-chloro-6-fluoroquinoxaline (commercially available) following General Method A. LC-MS (conditions F): rotamers t_R1 = 0.77 min / t_R2 = 0.80 min, [M + 1]^+ = 471.94.

Example 167: rac-((1/?*,6S*)-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting rac-(1R* ,6S*)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18) with 2-chloro-5,6-
difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers 
\( t_{R1} = 0.78 \text{ min} / t_{R2} = 0.81 \text{ min}, [M + 1]^+ = 490.22. \)

**Example 167a:** (1f\(^{-}\),6S\(^{-}\))-8-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone 

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18a) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following General Method A. LC-MS (conditions F): rotamers 
\( t_{R1} = 0.79 \text{ min} / t_{R2} = 0.82 \text{ min}, [M + 1]^+ = 489.94. \)

**Example 168:** rac-(2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1f\(^{-}\),6S\(^{-}\))-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone 

The title compound is prepared by reacting rac-(1R\(^{+}\),6S\(^{+}\))-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers 
\( t_{R1} = 0.78 \text{ min} / t_{R2} = 0.83 \text{ min}, [M + 1]^+ = 472.22. \)

**Example 168a:** (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1f\(^{-}\),6S\(^{-}\))-8-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone 

The title compound is prepared by reacting (1R,6S)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone hydrochloride (C.18a) with 2-chloro-7,8-difluoroquinoxaline (84, B.32) following General Method A. LC-MS (conditions F): rotamers 
\( t_{R1} = 0.77 \text{ min} / t_{R2} = 0.82 \text{ min}, [M + 1]^+ = 471.93. \)

**Example 169:** rac-(5-Methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)((1f\(^{-}\),6S\(^{-}\))-8-(quinazolin-2-yl)-3,8-diazabicyclo[4.2.0]octan-3-yl)methanone 

The title compound is prepared by reacting rac-(1R\(^{+}\),6S\(^{+}\))-3,8-diazabicyclo[4.2.0]octan-3-yl(5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.1) with 2-chloroquinazoline (commercially available) following General Method A. LC-MS (conditions F): rotamers 
\( t_{R1} = 0.78 \text{ min} / t_{R2} = 0.81 \text{ min}, [M + 1]^+ = 425.79. \)

**II-Biological assays**

Antagonistic activities on both orexin receptors have been measured for each example compound using the following procedure:

**In vitro assay: Intracellular calcium measurements:**

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor and the human orexin-2 receptor, respectively, are grown in culture medium (Ham F-12 with L-Glutamine)
containing 300 μg/ml G418, 100 U/ml penicillin, 100 μg/ml streptomycin and 10 % heat
inactivated fetal calf serum (FCS). The cells are seeded at 20000 cells / well into 384-well
black clear bottom sterile plates (Greiner). The seeded plates are incubated overnight at
37°C in 5% CO₂.

Human orexin-A as an agonist is prepared as 1 mM stock solution in MeOH: water (1:1),
diluted in HBSS containing 0.1 % bovine serum albumin (BSA), NaHCO₃: 0.375g/l and 20
mM HEPES for use in the assay at a final concentration of 3 nM.

Antagonists are prepared as 10 mM stock solution in DMSO, then diluted in 384-well plates
using DMSO followed by a transfer of the dilutions into in HBSS containing 0.1 % bovine
serum albumin (BSA), NaHCO₃: 0.375g/l and 20 mM HEPES. On the day of the assay, 50 μl
of staining buffer (HBSS containing 1% FCS, 20 mM HEPES, NaHCO₃: 0.375g/l, 5 mM
probenecid (Sigma) and 3 μM of the fluorescent calcium indicator fluo-4 AM (1 mM stock
solution in DMSO, containing 10% pluronic) is added to each well. The 384-well cell-plates
are incubated for 50 min at 37° C in 5% CO₂ followed by equilibration at RT for 30 min
before measurement.

Within the Fluorescent Imaging Plate Reader (FLIPR Tetra, Molecular Devices), antagonists
are added to the plate in a volume of 10 μl/well, incubated for 120 min and finally 10 μl/well
of agonist is added. Fluorescence is measured for each well at 1 second intervals, and the
height of each fluorescence peak is compared to the height of the fluorescence peak induced
by 3 nM orexin-A with vehicle in place of antagonist. The IC₅₀ value (the concentration of
compound needed to inhibit 50 % of the agonistic response) is determined and may be
normalized using the obtained IC₅₀ value of a on-plate reference compound. Optimized
conditions were achieved by adjustment of pipetting speed and cell splitting regime. The
calculated IC₅₀ values may fluctuate depending on the daily cellular assay performance.

Fluctuations of this kind are known to those skilled in the art.

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Compounds of the present invention may be further characterized with regard to their general pharmacokinetic and pharmacological properties using conventional assays well known in the art; for example relating to their bioavailability in different species (such as rat or dog); or relating to their ability to cross the blood-brain barrier, using for example a human P-glycoprotein 1 (MDR 1) substrate assay, or an in vivo assay to determine drug concentrations in the brain, e.g. in rats after oral dosing; or relating to their functional behavior in different disease related animal models (for example: the sedative effect of the compound using Electroencephalography (EEG) and Electromyography (EMG) signal measurements [F. Jenck et al., Nature Medicine 2007, 13, 150-155]; the effect of the compound in the fear-potentiated startle paradigm [Fendt M et al., Neuroscience Biobehav Rev. 1999, 23, 743-760; WO2009/0047723]; the effect of the compound on stress-induced hyperthermia [Vinkers CH et al., European J Pharmacol. 2008, 585, 407-425]; the effect of the compound on morphine-induced locomotor sensitization [Vanderschuren LJMJ et al., in Self DW, Staley JK (eds.) "Behavioral Neuroscience of Drug Addiction", Current Topics in Behavioral Neurosciences 3 (2009), 179-195]; or for their properties with regard to drug

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safety and/or toxicological properties using conventional assays well known in the art, for example relating to cytochrome P450 enzyme inhibition and time dependent inhibition, pregnane X receptor (PXR) activation, glutathione binding, or phototoxic behavior.

**P-glycoprotein substrate assay in MDR1 overexpressing MDCKI cells**

The purpose of this assay is to assess the potential of a compound to be a substrate for the human P-glycoprotein (MDR-1) by determining its apparent permeability across a confluent MDR1-MDCKI cell monolayer in apical to basolateral (A-B) and basolateral to apical (B-A) direction.

Polarized MDR1-MDCKI cells are cultured in a filter insert of 12-well transwell plates that separates apical (A) and basolateral (B) compartments. The cells are grown on the plates for 7 to 11 days to obtain confluent monolayers. The test compound is added either to the apical (A) or basolateral (B) compartment at a final concentration of 1 or 5 µM in Hank's balanced salt solution supplemented with glucose containing maximally 1% DMSO. Bovine serum albumin (1%) is added to the receiver compartment. The experiment is conducted in duplicate at pH 7.4 and 37 °C. Samples from both sides are collected after 120 min incubation and the concentration of test compound is determined using an LC-MS/MS method with a seven point calibration curve. The quality of the cell monolayer is verified by a TEER measurement and by measuring the apparent permeability of control compounds (digoxin, atenolol and propranolol) before monolayers are used. Recovery of the test compound is determined in each individual experiment.

**Time-dependent CYP3A4 inhibition assay**

The CYP3A4 pre-incubation assay is performed by also using human liver microsomes and testosterone 6β-hydroxylation as P450 isoform-specific marker. It consists of two independent experiments in which the effect of various test compound concentrations on CYP3A4 activity is assessed with and without a pre-incubation.

**Assay without pre-incubation:** in a total volume of 100 µL, the test compound at final concentrations of 0, 0.0032, 0.016, 0.08, 0.4, 1.0, 2.0, 5.0, 10, 20, 50 and 100 µM (1 µL of the respective 100-fold concentrated stock solution in DMSO) is incubated in a 100 mM phosphate buffer (pH 7.4) in a 96-well PCR plate with 0.3 mg/mL of human liver microsomes in an Eppendorf thermomixer at 37 °C and 400 rpm. After 35 min at 37°C, testosterone at a final concentration of 300 µM (2 µL of a 15 mM stock solution in acetonitrile) is added and the reaction is initiated by addition of 10 µL of the NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase and terminated after 10 min with a 50 µL-3iGvoi of ice-
cold methanol containing 1.4 µM of cortisone. After sealing the PCR plate with aluminum foil and centrifugation at 465 g at 4 °C for 20 min, a 20 µL-aliquot of the supernatant is submitted to LC-MS/MS analysis according to the analytical method described below.

Assay with pre-incubation: in a total volume of 100 µL, a 1.0 µL-3i aliquot of a 100-fold concentrated test compound stock solution in DMSO is added at final concentrations of 0, 0.0032, 0.016, 0.08, 0.4, 1.0, 2.0, 5.0, 10, 20, 50 and 100 µM to a 100 mM sodium phosphate buffer (pH 7.4) and incubated in a 96-well PCR plate with 0.3 mg/mL of human liver microsomes in an Eppendorf thermomixer at 37 °C and 400 rpm. The reaction is initiated after 5 min of equilibration at 37°C by addition of 10 µL of the NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase. At the end of the 30 min pre-incubation period, 2 µL of the 15 mM testosterone stock solution in acetonitrile are added to yield a final concentration of 300 µM. The reaction is terminated after 10 min with a 50 µL-aliquot of ice-cold methanol containing 1.4 µM of cortisone. After sealing the 96-well PCR plate with aluminum foil and centrifugation at 465 g at 4 °C for 20 min, a 5 µL-3i aliquot of the supernatant is submitted to LC-MS/MS analysis according to the analytical method described below.

Mibebradil is run in parallel as a positive control at final concentrations of 0, 0.0032, 0.016, 0.08, 0.4, 1.0, 2.0, 5.0, 10, 20, 50 and 100 µM according to the protocol above.

The chromatographic analysis of 6β-hydroxytestosterone is achieved on a Phenomenex Luna C18 column (5 µm, 2.0 x 20 mm ID) at room temperature with a flow rate of 0.8 mL/min. Mobile phases consist of 0.1 % aqueous formic acid (phase A) and methanol (phase B). The applied gradient method is described below. Using these chromatographic conditions, 6β-hydroxytestosterone and cortisone exhibit retention times of 0.95 min and 0.98 min, respectively.

<table>
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<th>time [min]</th>
<th>0.00</th>
<th>0.5</th>
<th>1</th>
<th>1.2</th>
<th>1.25</th>
<th>1.5</th>
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<tbody>
<tr>
<td>phase B [%]</td>
<td>30</td>
<td>65</td>
<td>100</td>
<td>100</td>
<td>30</td>
<td>30</td>
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The quantification of 6β-hydroxytestosterone is carried out using an API4000 triple stage quadrupole mass spectrometer equipped with an electrospray interface operating in positive ion mode. The parameters of the mass detector are set as follows: capillary voltage 5.5 kV, ion source gas 20 psi, auxiliary ion source gas 50 psi, collision gas 5 mTorr, and heated
nebulizer temperature 600 °C. The mass transition used for 6β-hydroxytestosterone is 305.2 to 269.2 with a scan time of 30 ms and for cortisone 361.1 to 163.1 with a scan time of 30 ms.
Claims

1. A compound of formula (I)

wherein the relative configuration of the diazabicyclooctane moiety is cis; wherein

- $\text{Ar}^1$ represents phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
  > one of said substituents is attached in ortho-position to the point of attachment of $\text{Ar}^1$ to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C$_4$)alkyl, (C$_4$)alkoxy, halogen, cyano, (C$_3$)fluoroalkyl, and (C$_3$)fluoroalkoxy;

- and the other of said substituents, if present, is/are independently selected from the group consisting of (C$_4$)alkyl, (C$_4$)alkoxy, (C$_3$)cycloalkyl, halogen, cyano, (C$_3$)fluoroalkyl, and (C$_3$)fluoroalkoxy;

- $\text{Ar}^2$ represents 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
  > one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C$_4$)alkyl, (C$_4$)alkoxy, halogen, cyano, (C$_3$)fluoroalkyl, and (C$_3$)fluoroalkoxy;

- or $\text{Ar}^2$ represents 8- to 10-membered bicyclic heteroaryl which is unsubstituted, or mono-, di-, or tri-substituted; wherein
  > the substituents are independently selected from the group consisting of (C$_4$)alkyl, (C$_4$)alkoxy, (C$_3$)cycloalkyl, halogen, cyano, (C$_3$)fluoroalkyl, and (C$_3$)fluoroalkoxy.
with the exception of the compounds of Formula X:

![Formula X diagram]

wherein

5 \( R^1 \) is a member selected from the group consisting of:

A) phenyl substituted or unsubstituted with one or two \( R^a \) members, and substituted in the ortho position with \( R^b \);

\( R^a \) is independently selected from the group consisting of: halo, \(-\text{C}_4\text{alkyl}\), and \(-\text{C}_4\text{alkoxy}\), wherein two adjacent \( R^a \) members may come together to form a six

10 membered aromatic ring;

\( R^b \) is a member selected from the group consisting of:

a) halo, \(-\text{C}_4\text{alkoxy}\), \(-\text{CF}_3\), or \(-\text{CF}_2\text{CHF}_2\);

b) 5-membered heteroaryl ring containing one oxygen or one sulfur members;

c) 5-6 membered heteroaryl ring containing one to three nitrogen members, optionally containing one oxygen member, substituted or unsubstituted with halo, \(-\text{C}_4\text{alkyl}\), tetrahydropyran-2-yl, or \(-\text{N(CH}_3)_2\); and

d) phenyl substituted or unsubstituted with \(-\text{F}\), or \(-\text{CH}_3\);

B) pyridine substituted or unsubstituted with one or two \( R^c \) members and substituted with \( R^d \), wherein \( R^d \) is positioned adjacent to the point of attachment by \( R^1 \);

20 \( R^c \) is a member independently selected from the group consisting of: \(-\text{C}_4\text{alkyl}\), \(-\text{CF}_3\), and \(-\text{C}_4\text{alkoxy}\);

\( R^d \) is a member selected from the group consisting of:

a) 5-6 membered heteroaryl ring selected from the group consisting of: 1H-1,2,3-triazol-1-yl, 2H-1,2,3-triazol-2-yl, 1H pyrazol-3-yl, and 6-methyl-pyridin-2-yl; and

25 b) \(-\text{CF}_3\), \(-\text{Br}\), or \(-\text{d}^n\text{alkoxy}\);

C) 6-membered heteroaryl ring selected from the group consisting of: pyrimidin-yl or pyrazin-yl, substituted or unsubstituted with a member independently selected from \(-\text{CH}_3\), \(-\text{OCH}_3\), or phenyl;

30 D) 5-membered heteroaryl ring selected from the group consisting of: 2-methyl-1,3-thiazol-yl, 5-methyl-isonoxazol-4-yl, 2H-pyrazol-3-yl, 1H-pyrazol-4-yl, isoxazolyl, and 1,3-oxazol-4-yl, each substituted with phenyl substituted or unsubstituted with \(-\text{F}\) or \(-\text{Cl}\); and
E) 3-methylfuran-2-yl, 9H-fluorene, 9H-fluoren-9-one, 3,5'-biisoxazole, [3-methyl-5-(4-
methyl-1,2,3-thiadiazol-5-yl)isoxazol-4-yl], or naphthyridine;

R² is a member selected from the group consisting of:

A) 6-membered heteroaryl ring containing two nitrogen members substituted or
unsubstituted with one or more members independently selected from the group
consisting of: halo, -d^alkyl, -C^alkoxy, -CF₃, -NH₂, -NHCH₃, -N(Cl₄alkyl)₁₂, 
-NHcyclopropyl, and phenyl;

B) pyridine substituted or unsubstituted with one or two members independently
selected from the group consisting of: -C^alkyl, -N(C₄alkyl)₂, and -CF₃; and

C) quinoxalin-2-yl, benzooxazol-2-yl, or 5-chloro-1,3-benoxazole;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1

\[
\text{Ar}^1 \begin{array}{c}
\text{O} \\
\text{N} \\
\text{N} \\
\text{Ar}^2
\end{array}
\]

wherein the relative configuration of the diazabicyclooctane moiety is cis;

wherein

- \text{Ar}^1 represents phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or 5- or 6-
  membered heteroaryl independently is mono-, di-, or tri-substituted; wherein
  > one of said substituents is attached in orffro-position to the point of attachment
  of \text{Ar}^1 to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-
  membered heteroaryl, which is independently unsubstituted, or mono-, di-, or
  tri-substituted, wherein the substituents are independently selected from the
  group consisting of (Cl₄)alkyl, (Cl₄)alkoxy, halogen, cyano, (Cl₃)fluoroalkyl, 
  and (Cl₃)fluoroalkoxy;

  > and the other of said substituents, if present, is/are independently selected
  from the group consisting of (C₁₄)alkyl, (C₁₄)alkoxy, (C₃₆)cycloalkyl, halogen,
  cyano, (C₁₃)fluoroalkyl, and (C₁₃)fluoroalkoxy; and

- \text{Ar}² is a group selected from the group consisting of any of the following groups:
  a) 6-membered heteroaryl, wherein the 6-membered heteroaryl is mono-, di-, or tri-
  substituted; wherein
    > one of said substituents is a group selected from the group consisting of any
    of the following groups:
i) 5- or 6-membered heteroaryl; wherein said 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, halogen, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy; and

ii) phenyl; wherein said phenyl is mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, halogen, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy; and the other of said substituents, if present, is/are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, (C-3-6)cycloalkyl, halogen, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy;

b) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, halogen, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy; and the other of said substituents, if present, is/are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, (C-3-6)cycloalkyl, halogen, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy;

c) 8- to 10-membered bicyclic heteroaryl which is mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of (Ci-4)alkyl, (Ci-4)alkoxy, (C-3-6)cycloalkyl, cyano, (Ci-3)fluoroalkyl, and (Ci-3)fluoroalkoxy;

d) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group is independently unsubstituted, or mono-, di-, or tri-substituted; wherein the substituents are independently selected from the group consisting of (C-1-4)alkyl, (C-1-4)alkoxy, (C-3-6)cycloalkyl, halogen, cyano, (C-1-3)fluoroalkyl, and (C-1-3)fluoroalkoxy;

e) 8- to 10-membered bicyclic heteroaryl which is quinoxalinyl which is mono-, di-, or tri-substituted; wherein
> the substituents are independently selected from the group consisting of
(C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and
(C\textsubscript{1-3})fluoroalkoxy;

f) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is mono-
substituted; wherein
> the substituent is selected from the group consisting of (C\textsubscript{1-4})alkyl,
(C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, cyano, (C\textsubscript{1-3})fluoroalkyl, (C\textsubscript{1-3})fluoroalkoxy; and
fluoro; and

g) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is di-, or tri-
substituted; wherein
> the substituents are independently selected from the group consisting of
(C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and
(C\textsubscript{1-3})fluoroalkoxy;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claims 1 or 2; wherein Ar\textsuperscript{2} is a group selected from the group
consisting of any of the following groups:

a) 5-membered heteroaryl, wherein the 5-membered heteroaryl independently is mono-,
di-, or tri-substituted; wherein
> one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein
said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or
mono-, di-, or tri-substituted, wherein the substituents are independently
selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;
> and the other of said substituents, if present, is/are independently selected
from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

b) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of
indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl,
benzoisothiazolyl, naphthyridinyl, cinnolinyl, quinolinyl, and quinazolinyl; which group
is independently unsubstituted, or mono-, di-, or tri-substituted; wherein
> the substituents are independently selected from the group consisting of
(C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, (C\textsubscript{3-6})cycloalkyl, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy;

c) 8- to 10-membered bicyclic heteroaryl which is quinoxalinyl which is mono-, di-, or tri-
substituted; wherein
> the substituents are independently selected from the group consisting of
(\(\text{Cl}_4\))alkyl, (\(\text{Cl}_4\))alkoxy, (\(\text{C}_3\))cycloalkyl, halogen, cyano, (\(\text{Cl}_3\))fluoroalkyl, and
(\(\text{Cl}_3\))fluoroalkoxy;

d) and 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is mono-
substituted; wherein
> the substituent is selected from the group consisting of (\(\text{Cl}_4\))alkyl,
(\(\text{Cl}_4\))alkoxy, (\(\text{C}_3\))cycloalkyl, cyano, (\(\text{Cl}_3\))fluoroalkyl, (\(\text{Cl}_3\))fluoroalkoxy; and
fluoro;

or a pharmacetically acceptable salt thereof.

4. A compound according to any one of claims 1 to 3; wherein, in case \(\text{Ar}^2\) represents 5- or
6-membered heteroaryl which is at least mono-substituted with phenyl or 5- or 6-membered
heteroaryl, said phenyl or 5- or 6-membered heteroaryl substituent is attached in meta-
position to the point of attachment of \(\text{Ar}^2\) to the rest of the molecule;
or a pharmacetically acceptable salt thereof.

5. A compound according to any one of claims 1 to 3; wherein \(\text{Ar}^2\) is a group selected from
the group consisting of any of the following groups:

a) 5-membered heteroaryl which is selected from the group consisting of any of the
following groups:
b) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of any of the following groups:

i.) 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, and 6-chloro-benzoxazol-2-yl;

ii.) benzo[d]isoxazol-3-yl, 5-methyl-benzo[d]isoxazol-3-yl, 6-methyl-benzo[d]isoxazol-3-yl, 5-fluoro-benzo[d]isoxazol-3-yl, 6-fluoro-benzo[d]isoxazol-3-yl, 5-chloro-benzo[d]isoxazol-3-yl, 6-chloro-benzo[d]isoxazol-3-yl, benzothiazol-2-yl, 5-fluoro-benzothiazol-2-yl, 6-fluoro-benzothiazol-2-yl, 5-chloro-benzothiazol-2-yl, 6-chloro-benzothiazol-2-yl, 5-chloro-benzo[d]isothiazol-3-yl, and 6-chloro-benzo[d]isothiazol-3-yl; and

iii.) 6-fluoro-quinoxalin-2-yl, 7-fluoro-quinoxalin-2-yl, 6-chloro-quinoxalin-2-yl, 7-chloro-quinoxalin-2-yl, 6,7-difluoro-quinoxalin-2-yl, and 6,7-dichloro-quinoxalin-2-yl;

or a pharmaceutically acceptable salt thereof.

6. A compound according to any one of claims 1 to 5; wherein

- Ar^1 represents phenyl, which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar^1 to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-
membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (Cl)alkyl, (Cl)alkoxy, halogen, cyano, (Cl)fluoroalkyl, and (Cl)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (Cl)alkyl, (Cl)alkoxy, halogen, cyano, (Cl)fluoroalkyl, and (Cl)fluoroalkoxy;

- or Ar represents 5- or 6-membered heteroaryl which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C)alkyl, (C)alkoxy, halogen, cyano, (C)fluoroalkyl, and (C)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C)alkyl, (C)alkoxy, halogen, cyano, (C)fluoroalkyl, and (C)fluoroalkoxy.

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 5; wherein Ar is a group selected from the group consisting of any of the following groups:

a) phenyl, which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C)alkoxy, cyano, (C)fluoroalkyl, and (C)fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C)alkyl, (C)alkoxy, and halogen;

b) phenyl, which is di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar to the rest of the molecule, wherein said substituent is phenyl or 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the
group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

5 c) 6-membered heteroaryl selected from the group consisting of pyrimidinyl and pyrazinyl, which is mono-, di- or tri-substituted; wherein

> one of said substituents is attached in orffro-position to the point of attachment of Ar\textsuperscript{1} to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

10 i.) phenyl which is mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy; and

ii.) 5- or 6-membered heteroaryl, which is independently unsubstituted, or mono-, or di-substituted wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

> and the other of said substituents, if present, is/are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

20 d) 6-membered heteroaryl which is pyridinyl, which is mono-, di- or tri-substituted; wherein

> one of said substituents is attached in orffro-position to the point of attachment of Ar\textsuperscript{1} to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

25 i.) phenyl, which is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkyl, (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{i-3})fluoroalkoxy;

ii.) 6-membered heteroaryl which is unsubstituted, or mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C\textsubscript{i-4})alkoxy, halogen, cyano, (C\textsubscript{i-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and

iii.) 5-membered heteroaryl which is mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of
(C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and the other of said substituents, if present, is/are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and

e) 5-membered heteroaryl; which is mono-, di-, or tri-substituted; wherein

> one of said substituents is attached in ortho-position to the point of attachment of Ar\textsuperscript{1} to the rest of the molecule, wherein said substituent is a group selected from the group consisting of any of the following groups:

i.) phenyl which is mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and

ii.) 5- or 6-membered heteroaryl which is mono-, or di-substituted, wherein the substituents are independently selected from the group consisting of (C\textsubscript{1-4})alkoxy, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and the other of said substituents, if present, is/are independently selected from the group consisting of (C\textsubscript{1-4})alkyl, (C\textsubscript{1-4})alkoxy, halogen, cyano, (C\textsubscript{1-3})fluoroalkyl, and (C\textsubscript{1-3})fluoroalkoxy; and

or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 5; wherein Ar\textsuperscript{1} is a group selected from the group consisting of:
or a pharmaceutically acceptable salt thereof.

9. A compound according to any one of claims 1 to 8; which is also a compound of formula (I_{E1}) wherein the absolute configuration of the 3,8-diaza-bicyclo[4.2.0]octane moiety is (1R,6S):

\[
\text{Formula (I}_{E1}\text{);}
\]

or a pharmaceutically acceptable salt thereof.
10. A compound according to claim 1 selected from the group consisting of:

[(1 \(R^{'},6S^*\))-8-(6-Chloro-benzoazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-(6-Fluoro-benzoazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(5-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(4-Chloro-benzoazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-Benzo[d]isoxazol-3-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(6-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-(6-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(5-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(6-Fluoro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-(6-Fluoro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(5-Methyl-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R^{'},6S^*\))-8-(6-Methyl-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[(1 \(R,6S\))-8-(5-Chloro-benzo[d]isothiazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-\((5\text{-methyl-2-}[1,2,3]\text{triazol-2-yl-phenyl})\)-methanone;
[1 R', 6S']-8-[(4-Methyl-5-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R,6S)-8-[(5-(3-Chloro-phenyl)-4-methyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-4-methyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(2-Chloro-phenyl)-4-methyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-4-methyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

[(1 R',6S')-8-[(5-(3-Chloro-phenyl)-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R*, 6S')-8-(5-Methyl-4-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R', 6S')-8-(4-m-tolyl-oxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
(1 R, 6S)-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(5-Methyl-2-[1,2,3]triazol-2-yl-phenyl)-[(1 R', 6S')-8-(4-m-tolyl-thiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-methanone;
(1 R, 6S)-8-[4-(3-Fluoro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R', 6S')-8-[4-(3-Chloro-phenyl)-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(1 R, 6S)-8-(6,7-Dichloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
(15'S, 6R'-)8-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl)-(2-[1,2,3]triazol-2-yl-5-trifluoromethyl-phenyl)-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-[1,2,3]triazol-2-yl-5-trifluoromethoxy-phenyl}-methanone;
3-[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]octane-3-carbonyl]-4-[1,2,3]triazol-2-yl-benzenitrile;

5 [(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-3-(3-methyl-pyrazol-1-yl)-pyridin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-3-pyrimidin-2-yl-pyridin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-[1,2,3]triazol-2-yl-benzenitrile};

10 [(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-2,3’bipyridinyl-2’-y]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-3-phenyl-pyridin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-3-p-tolyl-isoxazol-4-yl]-methanone;
[(1 R,6S)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-[1,2,4]oxadiazol-5-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{5-(3-fluoro-phenyl)-2-methyl-oxazol-4-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-5-m-tolyl-oxazol-4-yl]-methanone;

15 [(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{5-methyl-3-m-tolyl-isoxazol-4-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{6-methyl-3-(3-methyl-isoxazol-5-yl)-pyridin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-[1,2,4]oxadiazol-5-yl]-methanone;

20 [(1 R,6S)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-5-m-tolyl-thiazol-4-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{3-m-tolyl-pyrazin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{3-p-tolyl-pyrazin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-4-m-tolyl-pyrimidin-5-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-4-p-tolyl-pyrimidin-5-yl]-methanone;

25 [(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{4-methyl-biphenyl-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{3-m-tolyl-pyrazol-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{3-p-tolyl-pyrazol-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-4-m-tolyl-pyrimidin-5-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-4-p-tolyl-pyrimidin-5-yl]-methanone;

30 [(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{2-methyl-4-m-tolyl-pyrimidin-5-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{3-m-tolyl-pyrazin-2-yl]-methanone;
[(1 R*,6S*)-8-(5-Chloro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{4-methyl-isoxazol-3-yl]-methanone;
[(1 R',6S')-8-(5-Fluoro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R,6S)-8-(5-Fluoro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R',6S')-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6,7-Dichloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1 R*,6S*)-8-(6-Fluoro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
[(1 R,6S)-8-(5-Fluoro-benzoxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
[(1 R',6S')-8-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

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[(1 R',6S')-8-{5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-{5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R,6S)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R,6S)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R,6S)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R,6S)-8-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;}

[(1 R',6S')-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R,6S)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-(5-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}

[(1 R',6S')-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl]-{(5-methyl-2-pyridin-2-yl-phenyl)-methanone;}
{(1 R*,6S*)-8-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(6J-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R*,6S*)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2O]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;
{(1 R,6S)-8-(6-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-3-yl}-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

A pharmaceutical composition containing, as active principle, one or more compounds according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, and at least one therapeutically inert excipient.
12. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use as a medicament.

13. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for the prevention or treatment of diseases selected from the group consisting of sleep disorders, stress-related syndromes, addictions, cognitive dysfunctions in the healthy population and in psychiatric and neurologic disorders, and eating or drinking disorders.

14. A compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, for use in the preparation of a medicament for the prevention or treatment of diseases selected from the group consisting of sleep disorders, stress-related syndromes, addictions, cognitive dysfunctions in the healthy population and in psychiatric and neurologic disorders, and eating or drinking disorders.
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D471/04 A61K31/4353 A61P25/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>COLEMAN P J ET AL: &quot;Design and synthesis of conformatively constrained N,N-di substituted 1,4-di azepanes as potent orexin receptor antagonists&quot;., BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, ELSEVIER SCIENCE, GB, vol. 20, no. 7, 1 April 2010 (2010-04-01), pages 2311-2315, XP026971068, ISSN: 0960-894X [retrieved on 2010-02-08] table 1</td>
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* Further documents are listed in the continuation of Box C.  

**CITATION**

Date of the actual completion of the international search  
23 March 2012

Date of mailing of the international search report  
03/04/2012

Name and mailing address of the ISA/  
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Authorized officer  
Bakboord, Joan

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