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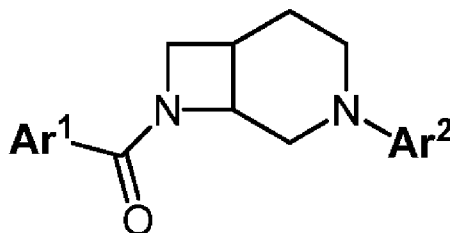
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(54) **Title:** 3,8-DIAZA-BICYCLO[4.2.0]OCT-8-YL AMIDES



Formula (I)

(57) **Abstract:** The present invention relates to 3,8-diaza-bicyclo[4.2.0]oct-8-yl amide derivatives of formula (I) wherein the relative configuration of the diazabicyclooctane moiety is *cis*; and wherein Ar¹, and Ar² 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.



WO 2012/085852 A1

3,8-Diaza-bicyclo[4.2.0]oct-8-yl amides

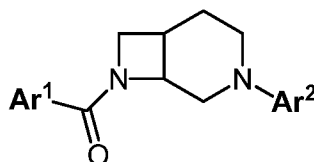
The present invention relates to 3,8-diaza-bicyclo[4.2.0]oct-8-yl amide derivatives of formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (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 (OX₁ and OX₂ receptors). The orexin-1 receptor (OX₁) is selective for OX-A, and the orexin-2 receptor (OX₂) is capable to bind 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 (suppl_1) (2006) S71-S76).

- 5 The compound (2R)-2-((1S)-6,7-dimethoxy-1-[2-(4-trifluoromethyl-phenyl)-ethyl]-3,4-dihydro-1H-isoquinolin-2-yl)-N-methyl-2-phenyl-acetamide (WO2005/118548), 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).
- 10
- 15 The present invention provides 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.
- 20

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



Formula (I)

wherein the relative configuration of the diazabicyclooctane moiety is cis;

25 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-, di-, or tri-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of

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(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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

and

- **Ar²** represents 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

- 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;

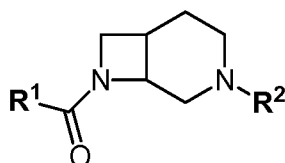
- and the other of said substituents, if present, is/are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

- or **Ar²** 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy.

Certain 3,8-diaza-bicyclo[4.2.0]oct-8-yl amide orexin receptor antagonists have been disclosed in WO2011/050202 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 WO2011/050202; wherein WO2011/050202 discloses the compounds of Formula X:



Formula X

wherein

R¹ is a member selected from the group consisting of:

A) phenyl substituted or unsubstituted with R^a, and substituted in the *ortho* position with R^b;

R^a is a member independently selected from the group consisting of: halo, -C₁₋₄alkyl, and -C₁₋₄alkoxy;

5 R^b is a member selected from the group consisting of:

a) halo or -C₁₋₄alkoxy,

b) thiophen-2-yl, 2H-1,2,3-triazole, 1H-1,2,3-triazol-1-yl, 1H-pyrazol-1-yl, 1H-pyrazol-5-yl, pyrimidin-2-yl, or 3-methyl-1,2,4-oxadiazol-5-yl, and

c) phenyl;

10 B) pyridine substituted or unsubstituted with one or two members independently selected from the group consisting of: C₁₋₄alkyl and 1H-1,2,3-triazol-1-yl, wherein the substituents are positioned adjacent to the point of attachment by R¹; and

C) methylthiazole substituted with 2-fluorophenyl;

R² is a member selected from the group consisting of:

15 A) 6-membered heteroaryl ring containing two nitrogen members substituted or unsubstituted with one or more members selected from the group consisting of: -C₁₋₄alkyl, -C₁₋₄alkoxy, -CF₃, halo, -N(C₁₋₄alkyl)₂, -NH₂, and phenyl;

B) pyridine substituted or unsubstituted with one or more members independently selected from the group consisting of: -CF₃ and -C₁₋₄alkyl;

20 C) quinoxalin-2-yl or quinoline substituted or unsubstituted with -C₁₋₄alkyl;

D) benzooxazol-2-yl substituted or unsubstituted with halo; and

E) 4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine;

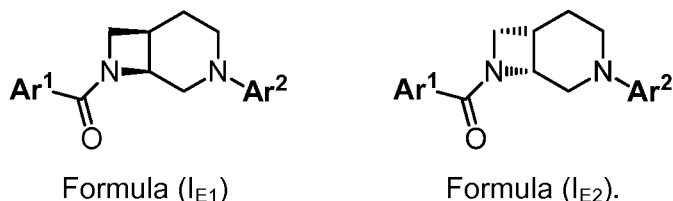
and pharmaceutically acceptable salts of compounds of formula X.

For avoidance of any doubt, for the compounds of formula X for example the term
25 "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
30 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 (I_{E1}), or compounds of formula (I_{E2}), or any mixture thereof (such as racemates):

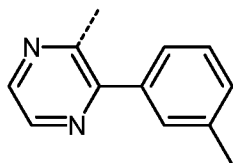


The relative configuration of stereoisomers is denoted as follows: for example, ((1*R**,6*S**)-3-(5-chlorobenzo[*d*]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone, if not explicitly mentioned as racemate, denominates ((1*R*,6*S*)-3-(5-chlorobenzo[*d*]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone or ((1*S*,6*R*)-3-(5-chlorobenzo[*d*]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-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 ²H (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 ²H (deuterium) labelled compounds of formula (I) and salts thereof are within the scope of the present invention. Substitution of hydrogen with the heavier isotope ²H (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



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.

- 5 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.*

- 10 *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.

- 15 For example a (C₁₋₄)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 "cycloalkyl", used alone or in combination, refers to a saturated cyclic alkyl group containing three to six carbon atoms. The term "(C_{x-y})cycloalkyl" (x and y each being an integer), refers to a cycloalkyl group as defined before containing x to y carbon atoms. For example a (C₃₋₆)cycloalkyl group contains from three to six carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Preferred is cyclopropyl.
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- 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_{x-y})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 (C₁₋₄)alkoxy group means a group of the formula (C₁₋₄)alkyl-O- in which the term "(C₁₋₄)alkyl" 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.
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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_{x-y})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 (C₁₋₃)fluoroalkyl 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 (C₁)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_{x-y})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 (C₁₋₃)fluoroalkoxy 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 (C₁)fluoroalkoxy groups such as trifluoromethoxy and difluoromethoxy.

Particular examples of phenyl groups which are further substituted in ortho position as used for the group Ar¹ 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, 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.

Examples of the particular phenyl groups which are substituents of the groups Ar¹ or Ar² 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 Ar¹ are 3-methyl-phenyl, 4-methyl-phenyl, 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-pyrrolo[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 Ar¹ are notably oxazolyl, isoxazolyl, thienyl, 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). In another sub-embodiment, examples are oxazolyl (in particular 2-methyl-oxazol-4,5-diyl), isoxazolyl (in particular 5-methyl-isoxazol-3,4-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-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-(3-fluoro-phenyl)-4-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; (especially 5-(3-fluoro-phenyl)-4-methyl-thiazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-thiazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-oxazol-2-yl, 5-(3-fluoro-phenyl)-4-methyl-oxazol-2-yl, and 4-difluoromethyl-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 quinoxalinyl (in a sub-embodiment especially benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, and quinoxalinyl; in another sub-embodiment especially indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolinyl, and quinazolinyl). 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 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, 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, 7,8-difluoro-quinoxalin-2-yl, and 5,6-difluoro-quinoxalin-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, thienyl, 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 oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyridinyl and pyrazinyl (especially 3-methyl-pyrazol-1-yl, 3-methyl-isoxazol-5-yl, and pyridin-2-yl).

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 Ar² 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; and

ii.) phenyl; wherein said phenyl is mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- d) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnoliny, and quinazolinyl; which group 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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- e) 8- to 10-membered bicyclic heteroaryl which is quinoxaliny which is mono-, di-, or tri-substituted; wherein
- the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- f) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is mono-, di-, or tri-substituted; wherein
- the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; and
- g) 8- to 10-membered bicyclic heteroaryl which is quinoliny which is mono-, di-, or tri-substituted; wherein

- the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

5 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

10 ➤ 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;

15 ➤ 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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

20 ➤ the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

25 ➤ the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

30 ➤ the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

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

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

- the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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**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 (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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, and quinazolinyl; which group 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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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

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

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

- the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

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 **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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; and

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

- i.) 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; and
- ii.) 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):

- iii.) 5-fluoro-quinoxalin-2-yl, 8-fluoro-quinoxalin-2-yl, 6-fluoro-7-methoxy-quinoxalin-2-yl, 7,8-difluoro-quinoxalin-2-yl, and 5,6-difluoro-quinoxalin-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 **Ar²** represents 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolynyl, and quinazolinyl; which group 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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy.

8) Another embodiment relates to novel compounds according to any one of embodiments 1) to 3); wherein **Ar²** 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, (C₃₋₆)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 **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; in case **Ar¹** represents 5-membered heteroaryl it is especially phenyl; and in case **Ar¹** 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl);
 - 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 (especially (C₁₋₄)alkyl).

11) Another embodiment relates to compounds according to any one of embodiments 1) to 10), 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.

12) 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl);
- 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 (especially (C₁₋₄)alkyl).

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

- a) phenyl, which is 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 a group selected from the group consisting of any of the following groups:
 - i.) phenyl which is independently mono-, or di-substituted (notably 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);

ii.) pyridinyl; which is 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

iii.) pyrazolyl, triazolyl, or pyrimidinyl which is independently mono-, or di-substituted (notably 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, and halogen;

b) phenyl, which is di-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 is independently selected from the group consisting of cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

c) phenyl, which is 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 are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

5 d) 5- or 6-membered heteroaryl selected from the group consisting of oxazolyl, isoxazolyl, pyrimidinyl and pyrazinyl; which group is independently 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 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; in case Ar¹ represents 5-membered heteroaryl it is especially phenyl; and in case Ar¹ 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl);

- 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 (especially (C₁₋₄)alkyl);

20 e) 5-membered heteroaryl which is thiazolyl which is mono-substituted; wherein

- said substituent 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 phenyl), 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);

25 f) 5-membered heteroaryl which is thiazolyl which is di-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 phenyl), 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 the other of said substituents is independently selected from the group consisting of (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

g) 5-membered heteroaryl which is thiazolyl which is di-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 phenyl), 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, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl);

- and the other of said substituents is (C₁₋₄)alkyl;

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

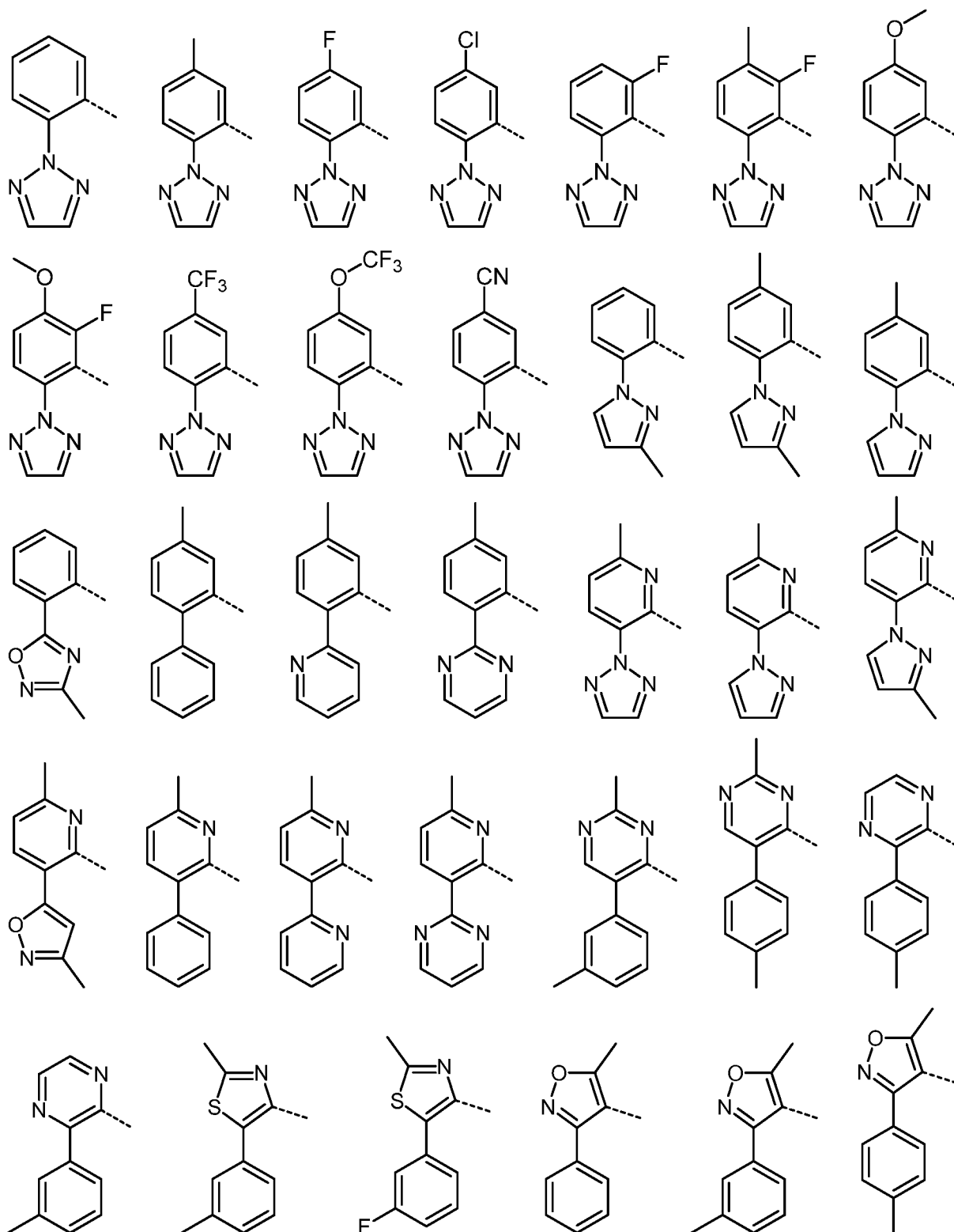
- one of said substituents is attached in *ortho*-position to the point of attachment of Ar¹ to the rest of the molecule, wherein said substituent is a group selected from the group consisting of
- (especially) phenyl,
 - oxadiazolyl, pyrazolyl, pyridinyl, or pyrimidinyl; and
 - [1,2,3]-triazole-2-yl;

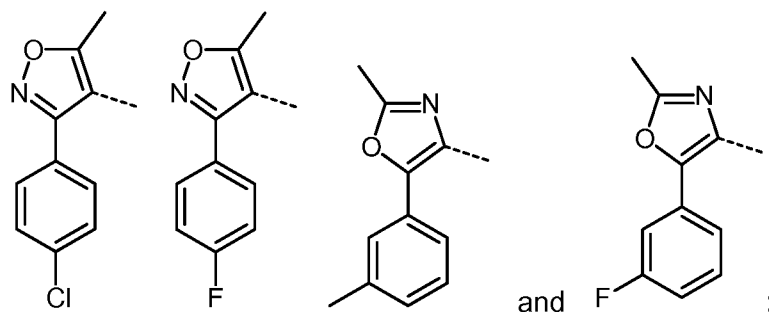
which group is independently unsubstituted, or mono-, or di-substituted (especially unsubstituted or mono-substituted), wherein the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl);

- and 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 (especially (C₁₋₄)alkyl);

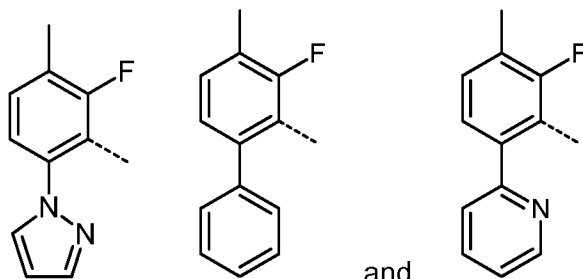
wherein each of the above groups represents a separate sub-embodiment.

14) Another embodiment relates to compounds according to any one of embodiments 1) to 10), wherein **Ar¹** is a group selected from the group consisting of:



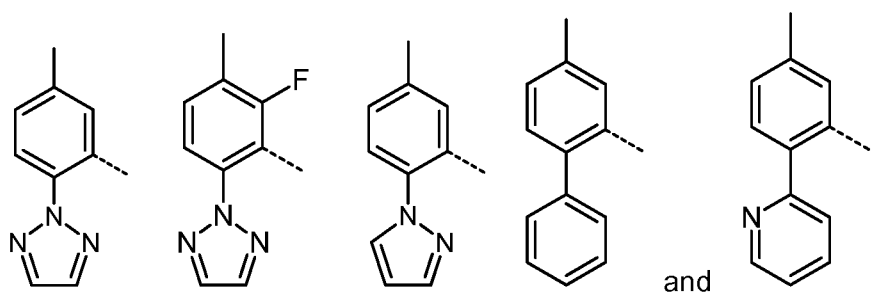


or, in addition to the above listed groups, **Ar**¹ may be a group selected from the group

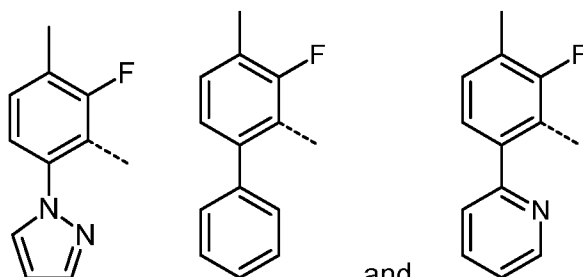


wherein each of the above lists form a separate sub-embodiment.

- 5 15) Another embodiment relates to compounds according to any one of embodiments 1) to 10), wherein **Ar**¹ is a group selected from the group consisting of:

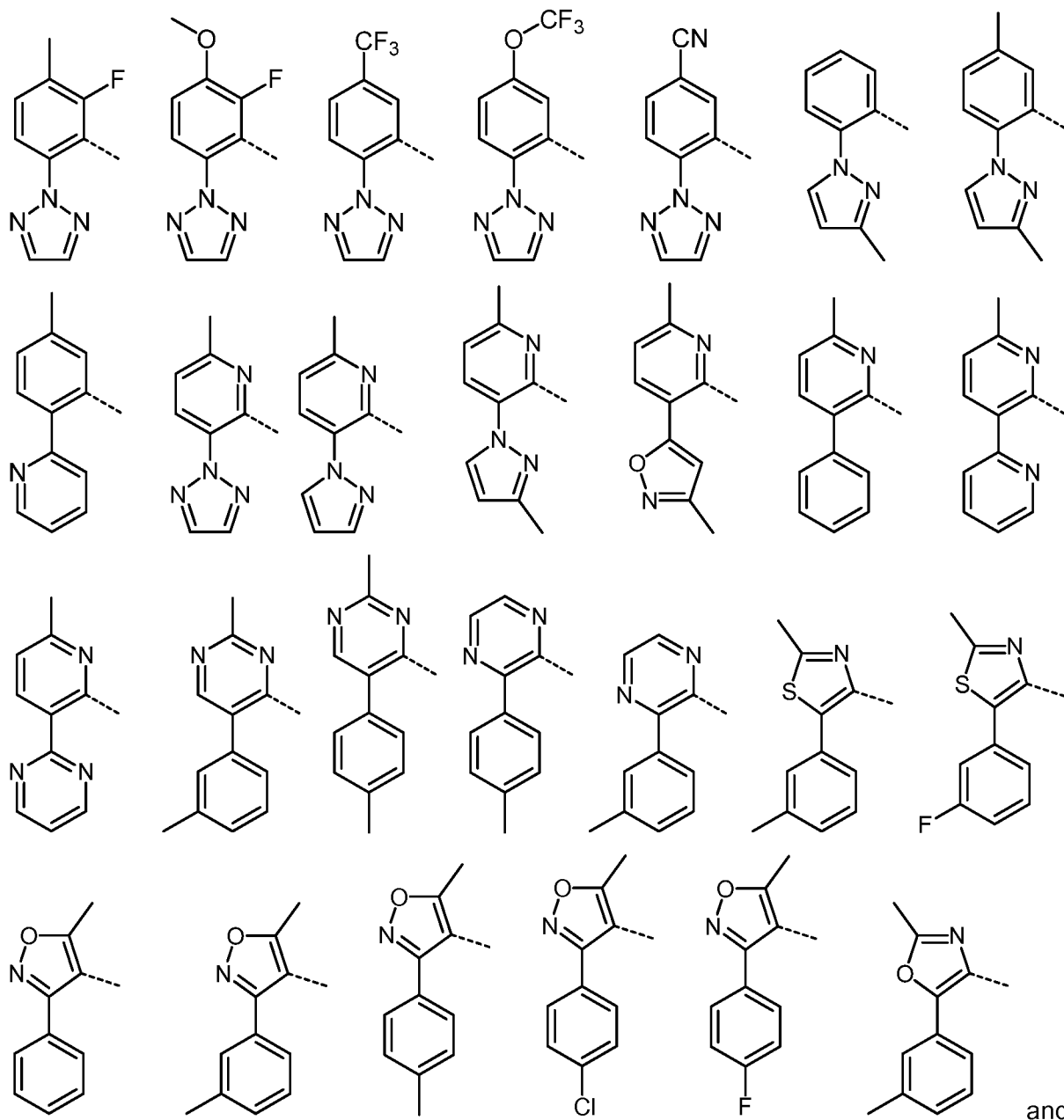


or, in addition to the above listed groups, **Ar**¹ may be a group selected from the group

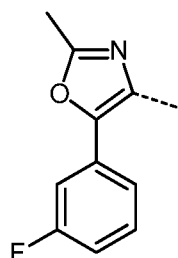


10 form a separate sub-embodiment.

- 16) Another embodiment relates to compounds according to embodiment 1), or any one of embodiments 2) to 10), wherein **Ar**¹ is a group selected from the group consisting of:



and



17) Another embodiment relates to compounds according to any one of embodiments 1) to 16) [especially embodiments 2), 13) or 16)], wherein

- **Ar²** 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 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 (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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (notably (C₁₋₄)alkyl, cyano, (C₁₋₃)fluoroalkyl; especially (C₁₋₄)alkyl);
- or **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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl and halogen).

18) Another embodiment relates to compounds according to any one of embodiments 1) to 16) [especially embodiments 2), 13) or 16)], wherein

- **Ar²** represents 5-membered heteroaryl, which is mono- or di-substituted; wherein
 - one of said substituents is phenyl [which is preferably attached in *meta*-position to the point of attachment of Ar² 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 (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, (C₃₋₆)cycloalkyl, halogen,

cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (notably (C₁₋₄)alkyl, cyano, (C₁₋₃)fluoroalkyl; especially (C₁₋₄)alkyl);

- or **Ar²** represents 9- or 10-membered bicyclic heteroaryl which is unsubstituted, or mono-, or di-substituted; wherein

5 ➤ the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl and halogen).

19) Another embodiment relates to compounds according to any one of embodiments 1) to 16) [especially embodiments 2), 13) or 16)], wherein **Ar²** 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

- 15 ➤ 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 **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 (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);
- 20 ➤ 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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (notably (C₁₋₄)alkyl, cyano, (C₁₋₃)fluoroalkyl; especially (C₁₋₄)alkyl).

20) Another embodiment relates to compounds according to any one of embodiments 1) to 16) [especially embodiments 2), 13) or 16)], 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl and halogen).

30 21) Another embodiment relates to compounds according to any one of embodiments 1) to 20), wherein, in case **Ar²** represents 8- to 10-membered bicyclic heteroaryl (or, respectively 9- or 10-membered heteroaryl), said 8- to 10-membered bicyclic heteroaryl is a group selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, quinolinyl, naphthyridinyl, 35 cinnolinyl, quinazolinyl, and quinoxalinyl (especially benzoxazolyl, benzisoxazolyl,

benzothiazolyl, and quinoxaliny); 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy (especially (C₁₋₄)alkyl and halogen).

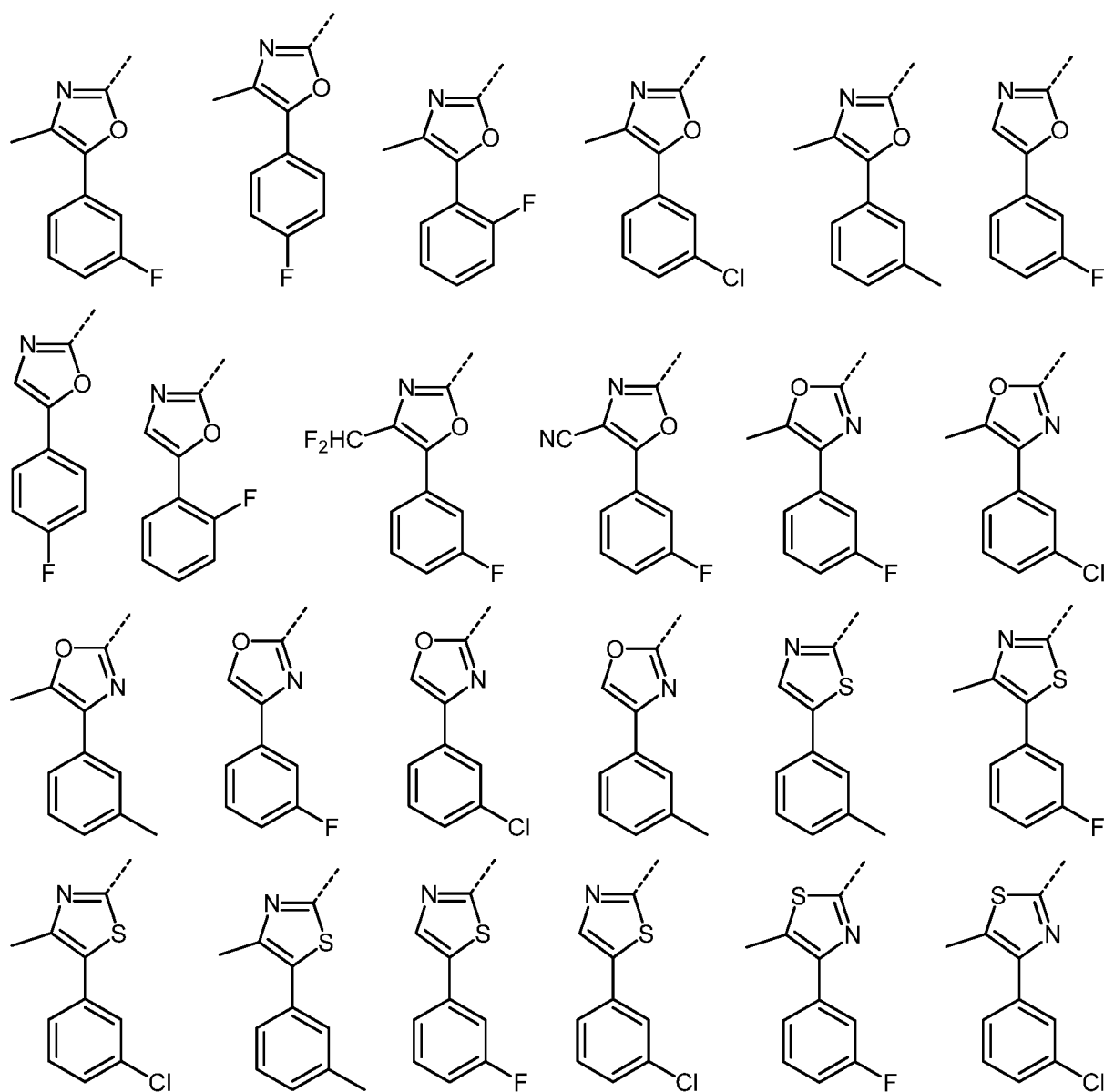
22) Another embodiment relates to compounds according to any one of embodiments 1) to 20), wherein, in case **Ar**² represents 8- to 10-membered bicyclic heteroaryl, said 8- to 10-membered bicyclic heteroaryl is a group selected from the group consisting of benzoxazol-2-yl, 5-fluoro-benzoxazol-2-yl, 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.

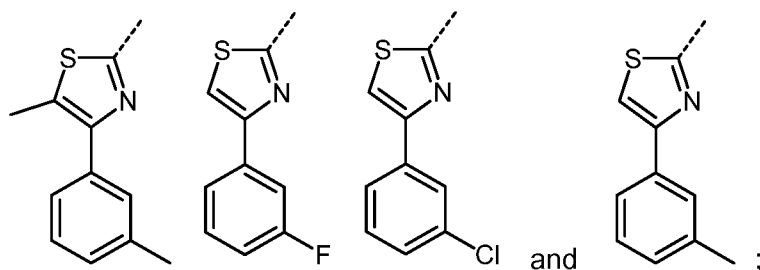
23) Another embodiment relates to compounds according to any one of embodiments 1) to 20), wherein, in case **Ar**² represents 8- to 10-membered bicyclic heteroaryl, said 8- to 10-membered bicyclic heteroaryl is a group selected from the group consisting of the following groups, alone or in any combination:

- a) benzoxazol-2-yl, 5-fluoro-benzoxazol-2-yl, 6-fluoro-benzoxazol-2-yl, 4-chloro-benzoxazol-2-yl, 5-chloro-benzoxazol-2-yl, and 6-chloro-benzoxazol-2-yl;
- b) 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;
- c) quinoxalin-2-yl;
- d) 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
- e) 5-fluoro-quinoxalin-2-yl, 8-fluoro-quinoxalin-2-yl, 7,8-difluoro-quinoxalin-2-yl, and 5,6-difluoro-quinoxalin-2-yl.

24) Another embodiment relates to compounds according to any one of embodiments 1) to 23), 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).

25) Another embodiment relates to compounds according to any one of embodiments 1) to 23), 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:

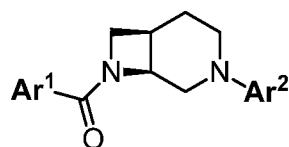




i.e. said **Ar²** is a group selected from the group consisting of 4-(3-methyl-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-thiazol-2-yl, 5-(3-fluoro-phenyl)-thiazol-2-yl, 4-(3-chloro-phenyl)-thiazol-2-yl, 5-(3-chloro-phenyl)-thiazol-2-yl, 4-(3-fluoro-phenyl)-oxazol-2-yl, 5-(3-fluoro-phenyl)-oxazol-2-yl, 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-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-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-(3-fluoro-phenyl)-4-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.

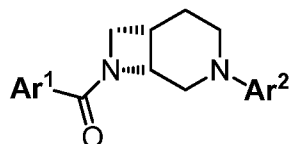
26) Another embodiment relates to compounds according to any one of embodiments 1) to 23), wherein, in case **Ar²** represents 5- or 6-membered heteroaryl (which is at least mono-substituted with phenyl or 5- or 6-membered heteroaryl as explicitly defined), said **Ar²** is a group selected from the group consisting of 5-(3-fluoro-phenyl)-4-methyl-thiazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-thiazol-2-yl, 4-(3-fluoro-phenyl)-5-methyl-oxazol-2-yl, 5-(3-fluoro-phenyl)-4-methyl-oxazol-2-yl, and 4-difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl.

27) A second embodiment relates to compounds according to any one of embodiments 1) to 26), which are also compounds of formula (I_{E1}) wherein the absolute configuration of the 3,8-diaza-bicyclo[4.2.0]octane moiety is (1S,6R):



Formula (I_{E1}).

28) Another embodiment relates to compounds according to any one of embodiments 1) to 26), which are also compounds of formula (I_{E2}) wherein the absolute configuration of the 3,8-diaza-bicyclo[4.2.0]octane moiety is (1R,6S):



5

Formula (I_{E2}).

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

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

10 [(1R*,6S*)-3-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

15 [(1R*,6S*)-3-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

20 [(1R*,6S*)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

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

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

30 {(1R*,6S*)-3-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

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

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

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

10 {(1R*,6S*)-3-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(4-methyl-biphenyl-2-yl)-methanone;

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

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

15 [(1R*,6S*)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;

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

20 {(1R*,6S*)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;

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

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

25 [(1R*,6S*)-3-(5-Fluoro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

30 [(1R*,6S*)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

35 {(1R*,6S*)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

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

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 (1S,6R), corresponding to the compounds of formula (I_{E1}) of
10 embodiment 27).

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

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

- 15 [(1S,6R)-3-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

- 20 [(1R*,6S*)-3-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

- 25 [(1S,6R)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

- 30 {(1S,6R)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

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

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

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

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

10 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;

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

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

15 {{(1R*,6S*)-3-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;

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

20 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;

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

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

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

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

30 [(1R*,6S*)-3-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

35 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

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

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

10 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

15 In a sub-embodiment of embodiment 30), the above listed compounds having the relative configuration (1R*,6S*) preferably are enantiomerically enriched, especially having the absolute configuration (1S,6R), corresponding to the compounds of formula (I_{E1}) of embodiment 27).

31) In addition to the compounds listed in any of embodiments 29) and 30), further
20 compounds of formula (I) according to any one of embodiments 1) to 3) are selected from the group consisting of:

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

25 [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

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

30 [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;

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

35 [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(4-methyl-biphenyl-2-yl)-methanone;

- [(1S,6R)-3-(8-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(4-methyl-biphenyl-2-yl)-methanone;
- [(1S,6R)-3-(5-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(4-methyl-biphenyl-2-yl)-methanone;
- 5 [(1S*,6R*)-3-(7-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(4-methyl-biphenyl-2-yl)-methanone;
- [(1R*,6S*)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-pyrazol-1-yl-phenyl)-methanone;
- [(1R*,6S*)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-
- 10 6-pyridin-2-yl-phenyl)-methanone;
- [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;
- (2-Fluoro-3-methyl-6-pyrazol-1-yl-phenyl)-[(1S,6R)-3-(6-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- 15 (2-Fluoro-3-methyl-6-pyridin-2-yl-phenyl)-[(1S,6R)-3-(6-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- (3-Fluoro-4-methyl-biphenyl-2-yl)-[(1S,6R)-3-(6-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-
- 20 [1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1R*,6S*)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-pyrazol-1-yl-phenyl)-methanone;
- [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-pyridin-2-yl-phenyl)-methanone;
- 25 [(1S,6R)-3-(5,6-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(3-fluoro-4-methyl-biphenyl-2-yl)-methanone;
- (2-Fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-[(1S,6R)-3-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- (2-Fluoro-3-methyl-6-pyrazol-1-yl-phenyl)-[(1R*,6S*)-3-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-
- 30 bicyclo[4.2.0]oct-8-yl]-methanone;
- (2-Fluoro-3-methyl-6-pyridin-2-yl-phenyl)-[(1S,6R)-3-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- (3-Fluoro-4-methyl-biphenyl-2-yl)-[(1S,6R)-3-(8-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;
- 35 (3-Fluoro-4-methyl-biphenyl-2-yl)-[(1S,6R)-3-(5-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone; and

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

In a sub-embodiment of embodiment 31), the above listed compounds having the relative configuration (1R*,6S*) preferably are enantiomerically enriched, especially having the absolute configuration (1S,6R), corresponding to the compounds of formula (I_{E1}) of embodiment 27).

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 (I) 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).

10 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).

15 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.

20 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.

25 Eating disorders may be defined as comprising metabolic dysfunction; dysregulated appetite control; compulsive obesities; emeto-bulimia 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_{E1}) and formula (I_{E2}).

Preparation of compounds of formula (I):

A further aspect of the invention is a process for the preparation of compounds of formula (I).

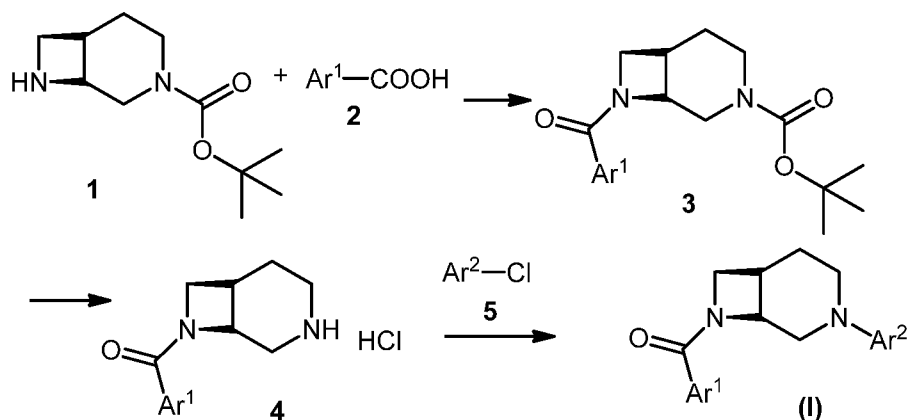
Compounds according to formula (I) of the present invention can be prepared according to the general sequence of reactions outlined in the schemes below wherein Ar¹, and Ar² are as defined for formula (I). In the schemes below, the generic substituent (R)_n refers to optional substituents that may be 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 enriched according to the same reference.

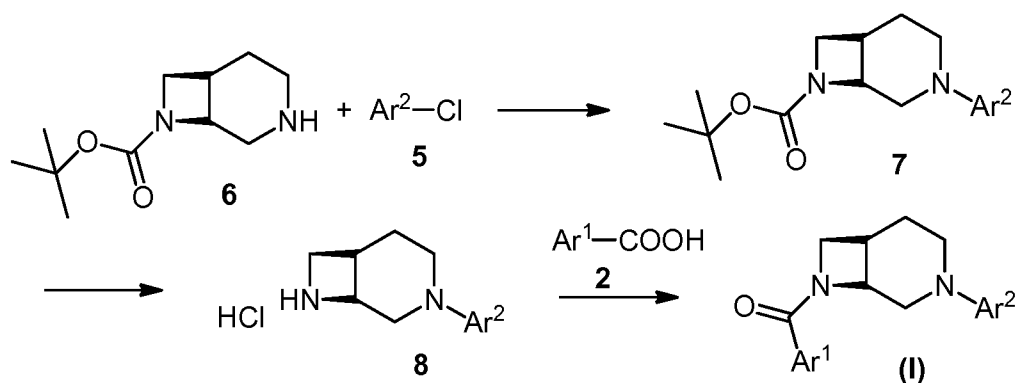
Compounds of formula (I) can be obtained according to Method **A** depicted in Scheme 1 or according to Method **B** depicted in Scheme 2.

Method A:



Scheme 1: Preparation of compounds of formula (I)

The starting material **1**, available in racemic or enantiomerically enriched form, can be coupled with a carboxylic acid derivative $\text{Ar}^1\text{-COOH}$ **2** via a peptidic coupling using TBTU as activating agent in the presence of a base such as DIPEA in CH_3CN 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_2O using Et_2O as solvent to give the amine's HCl salt **4**. Further nucleophilic substitution of a suitable $\text{Ar}^2\text{-Cl}$ **5**, by **4** in the presence of a base such as K_2CO_3 (or DBU) in DMF (or pyridine) at 60°C or 110°C give the final compounds of formula (I). Such nucleophilic substitution may in certain circumstances be carried out in presence of well known metal catalysts, see for example: L. Jiang, S. L. Buchwald "Palladium-Catalyzed Aromatic Carbon-Nitrogen Bond Formation". In: A. de Meijere, F. Diederich "*Metal-Catalyzed Cross-Couplings Reactions*", 2nd Edition 2004, Weinheim: Wiley-VCH; J. F. Hartwig *Acc. Chem. Res.* **1998**, 31, 852; J. F. Hartwig *Angew. Chem. Int. Ed.* **1998**, 37, 2046; and C. G. Frost, P. Mendonça *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615.

Method B:

Scheme 2: Preparation of compounds of formula (I)

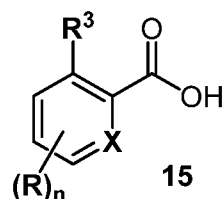
In analogy to the methods described above, the starting material **6**, available in racemic or enantiomerically enriched form, can be reacted with the suitable Ar^2 -halogenide or equivalent, e.g. $\text{Ar}^2\text{-Cl}$ **5**, via a nucleophilic substitution to afford intermediate **7**. Boc-deprotection is achieved as before to give the amine's HCl salt **8**. Ultimately **8** is coupled with the carboxylic acid derivative $\text{Ar}^1\text{-COOH}$ **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 $\text{Ar}^1\text{-CO-OH}$ and halogenides of formula Ar^2 -halogenide (such as $\text{Ar}^2\text{-Cl}$) 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 Ar^1 , Ar^2 , 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.) "Comprehensive Heterocyclic Chemistry II" 1996, Elsevier, ISBN 0-08-042072-9). Such heteroaryl moiety may replace a phenyl group in the schemes below as appropriate.

Preparation of building blocks of formula $\text{Ar}^1\text{-CO-OH}$:

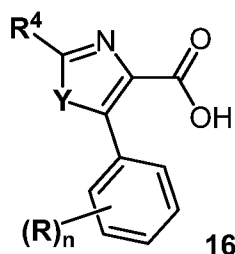
Carboxylic acid derivatives of formula $\text{Ar}^1\text{-CO-OH}$ are well known in the art and/or commercially available; or they may be synthesized according to methods described in the literature (see for example Schemes 5-11, wherein R^4 and R^5 correspond to the respective optional substituents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

Acids of structure **15** shown in Scheme 5 can especially be prepared following the procedures reported in WO2008/069997, WO2008/008517, WO2010/048012, WO2010/072722, WO2010/063662, and WO2010/063663.



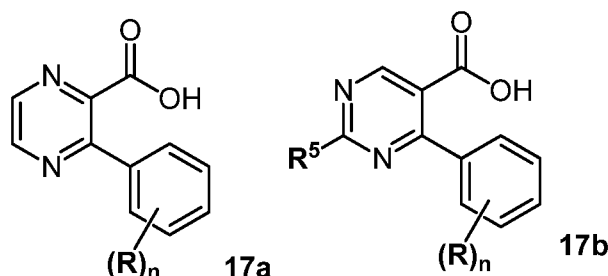
- 5 Scheme 5: Preparation of building blocks of formula Ar¹-CO-OH; wherein R³ is optionally substituted phenyl or 5- or 6-membered heteroaryl; X is CH or N

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



- 10 Scheme 6: Preparation of building blocks of formula Ar¹-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.

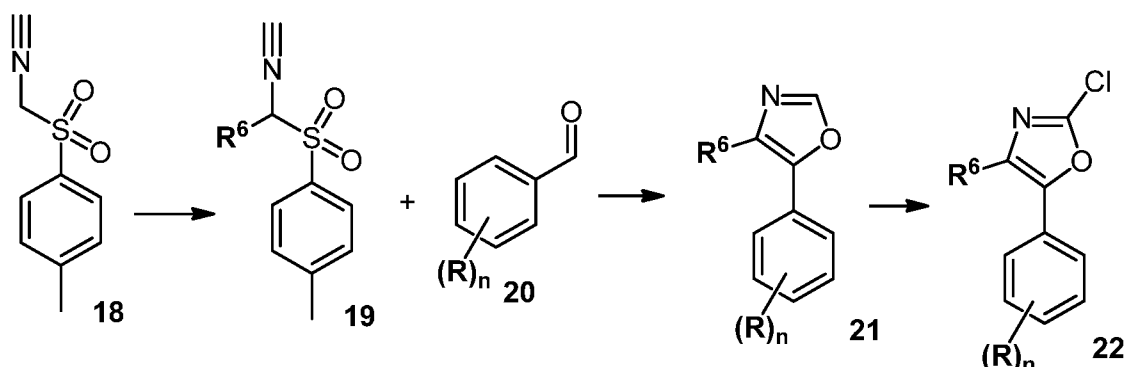


Scheme 7: Preparation of building blocks of formula Ar¹-CO-OH

- 15 **Preparation of building blocks of formula Ar²-Cl:**

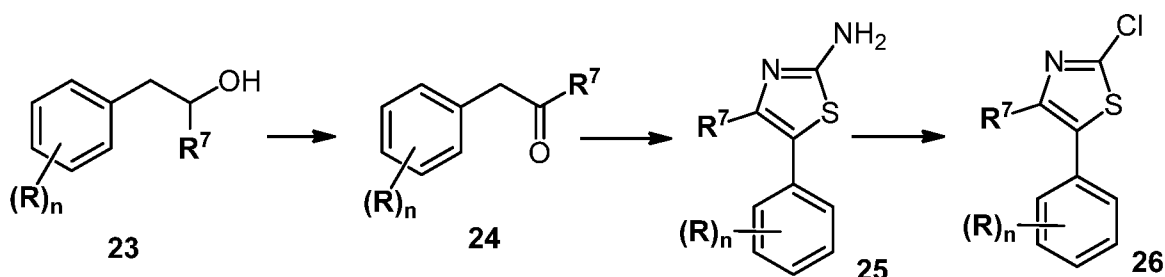
Building blocks of formula Ar²-Cl are well known in the art and/or commercially available, or they may be synthesized according to methods described in the literature. In addition, they may be synthesized in analogy to the methods given in the experimental part. General synthetic routes, which can be applied to several similar building blocks, are also shown in Schemes 8 through 11.

Ar²-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 Ar^2-Cl ; R^6 is H or alkyl

Optionally, in case $R^6 = CH_3$, commercially available TOSMIC **18** can be alkylated in a first step, e.g. to methyl-TOSMIC **19** with MeI, in the presence of benzyltriethylammonium chloride (TEBA) and NaOH 30% at $0^\circ C$ in DCM. Further condensation of **18** or **19** on commercially available aldehydes **20** in the presence of a base such as K_2CO_3 in MeOH at reflux affords the oxazoles **21**. Chlorination of **21** can be performed at $-78^\circ C$ in THF with a base such as LiHMDS (1.0 M in THF) and hexachloroethane to give final compounds of structure **22**.

Ar^2-Cl of structure **26** can be prepared according to general Method F depicted in Scheme 9.

Method F:Scheme 9: Preparation of building blocks of formula Ar^2-Cl ; 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 $-10^\circ C$ with 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 $80^\circ C$ in the presence of I_2 .

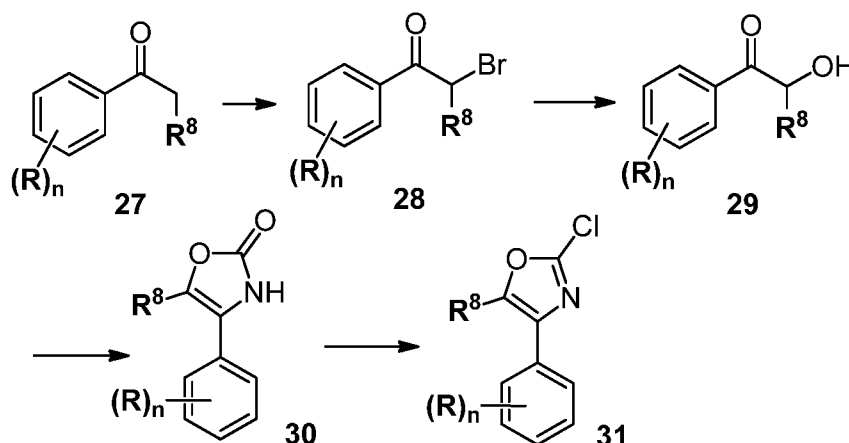
In case R^7 is alkyl, especially CH_3 , the respective commercially available ketone **24** can be directly used to give **25** in the same manner as described above. Chlorination of **25** can

finally be performed at RT in CH₃CN with CuCl₂ and tBuNO₂ 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 CsCO₃ (or TEA or DABCO), a ligand such as di-(1-adamantyl)-n-butylphosphine, and a catalyst such as 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 NaBH₄ (or Bu₃SnH) in MeOH at RT to the corresponding alcohols followed by bromination in the presence bromine, 1H-imidazole and PPh₃ in DCM at RT affords the corresponding substituted benzylbromides. Further nucleophilic substitution of the benzylbromides with KCN in EtOH/H₂O 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 H₂SO₄ in AcOH followed by reduction of the obtained acids to the alcohols with Borane-THF complex (or Borane-Me₂S 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,O-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.

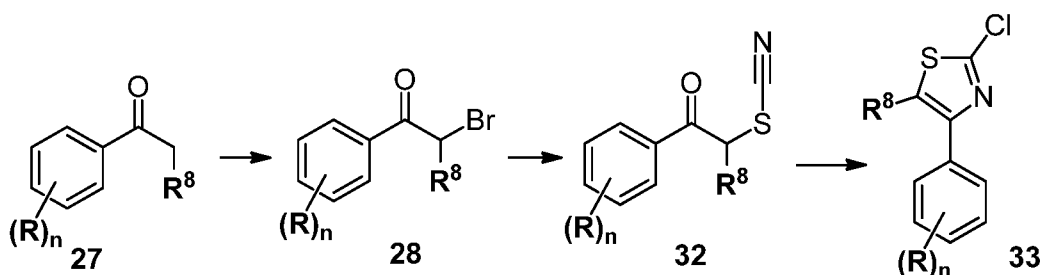
Ar²-Cl of general formula **31** can be prepared according to general Method **G** depicted in Scheme 10.

Method G:Scheme 10: Preparation of building blocks of formula $\text{Ar}^2\text{-Cl}$; $\text{R}^8 = \text{H}$ or alkyl

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**.

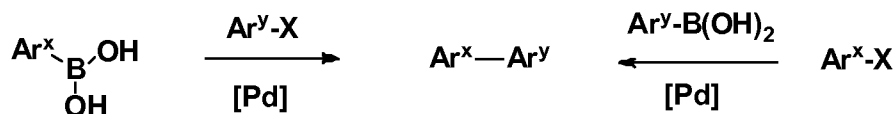
When not readily accessible, arylketones **27** wherein $\text{R}^8 = \text{H}$ can, for example, be synthesized starting from the corresponding commercially available substituted arylbromides, which are reacted with acetic anhydride in the presence of magnesium (or isopropylmagnesium chloride) in THF at reflux. For $\text{R}^8 = \text{CH}_3$: arylketones **27** can, for example, be synthesized starting from the corresponding commercially available substituted arylbromides, 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.

$\text{Ar}^2\text{-Cl}$ of structure **33** can be prepared according to general Method H in Scheme 11.

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

Similarly, phenylketone derivatives **27** can be brominated with Br₂ in AcOH at RT to give **28**, which can further be converted to **32** with NaSCN in acetone at RT. **32** can then be cyclized in 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.

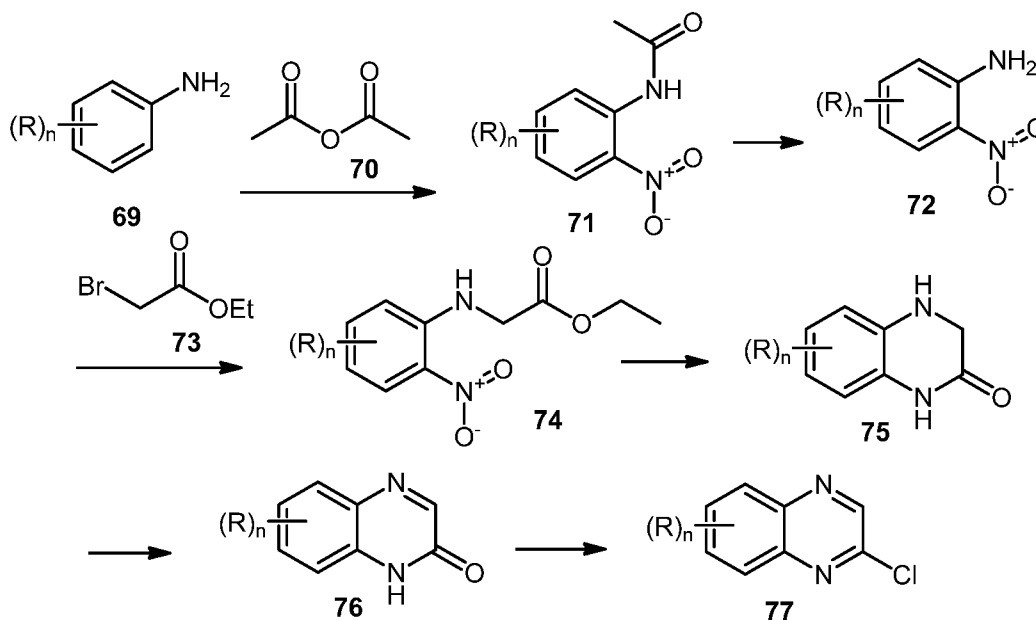


Scheme 12: Synthesis of bi-(hetero-)aryl like structures; X is Br, I

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 Pd(PPh₃)₄ or equivalent and a base such as Na₂CO₃ under heating in a solvent such as toluene, dioxane, THF provides the corresponding bi-(hetero-)aryl like structures.

Ar²-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 Ar²-Cl

The commercially available aniline derivative **69** ((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 K₂CO₃ 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 SnCl₂·2H₂O 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 H₂O₂ (3wt% in H₂O) in the presence of NaOH 50% at 100°C. Chlorination of **76** can finally be performed with neat POCl₃ 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 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 µm) column, a Daicel ChiralPak IC (5 µm) 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.

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	tert-Butoxycarbonyl
Boc ₂ O	di-tert-Butyl dicarbonate
BSA	Bovine serum albumine
Bu	Butyl such as tBu = tert-butyl = tertiary butyl
n-BuLi	n-Butyllithium
tBuNO ₂	tert-Butylnitrite

	CC	Column Chromatography on silica gel
	CH ₃ CN	Acetonitrile
	CHO	Chinese Hamster Ovary
	conc.	Concentrated
5	DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
	DABCO	1,4-Diazabicyclo[2.2.2]octane
	DCE	1,2-Dichloroethane
	DCM	Dichloromethane
	DEA	Diethylamine
10	Deoxo-Fluor	Bis(2-methoxyethyl)aminosulfur trifluoride
	DIBAL-H	Diisobutylaluminium hydride
	DIPEA	Diisopropylethylamine
	DMF	<i>N,N</i> -Dimethylformamide
	DMSO	Dimethyl sulfoxide
15	ELSD	Evaporative Light-Scattering Detection
	eq	Equivalent(s)
	ES	Electron spray
	Et	Ethyl
	Et ₂ O	Diethyl ether
20	EtOAc	Ethyl acetate
	EtOH	Ethanol
	FC	Flash Chromatography on silica gel
	FCS	Foatal calf serum
	FLIPR	Fluorescent imaging plate reader
25	h	Hour(s)
	HBSS	Hank's balanced salt solution
	HCl	Hydrogen chloride
	HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
	¹ H-NMR	Nuclear magnetic resonance of the proton
30	HPLC	High performance liquid chromatography
	H ₂ SO ₄	Sulfuric acid
	LC-MS	Liquid chromatography – Mass Spectroscopy
	LiHMDS	Lithium bis(trimethylsilyl)amide
	Lit.	Literature
35	M	Exact mass (as used for LC-MS)
	Me	Methyl

	MeCN	Acetonitrile
	<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
	MeOH	Methanol
	Mel	Methyl Iodide
5	MHz	Megahertz
	μl	microliter
	min	Minute(s)
	MS	Mass spectroscopy
	N	Normality
10	Pd(OAc) ₂	Palladium diacetate
	Pd(PPh ₃) ₄	Tetrakis(triphenylphosphine)palladium(0)
	Ph	Phenyl
	PPh ₃	Triphenylphosphine
	prep.	Preparative
15	2-PrOH	Isopropanol
	Rfx	reflux
	RT	Room temperature
	sat.	Saturated
	TBTU	O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
20	TEA	Triethylamine
	TEBA	Benzyltriethylammonium chloride
	TFA	trifluoroacetic acid
	Tf	Trifluoromethansulfonyl
	THF	Tetrahydrofuran
25	TLC	Thin Layer Chromatography
	TOSMIC	Toluenesulfonylmethyl isocyanide
	t _R	Retention time
	UV	Ultra violet

30 **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
 35 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 ^1H -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).

5 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 μm , 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.

10 LC-MS with basic conditions (conditions B)

Apparatus: Agilent 1100 series with mass spectroscopy detection (MS : Finnigan single quadrupole). Column: Waters XBridge C18 (5 μm , 4.6 x 50 mm). Conditions: MeCN [eluent A]; 13 mmol/l 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.

15 Preparative HPLC for purification of compounds (conditions C)

Column: Waters XBridge (10 μm , 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% NH_4OH (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)

20 Column: Waters Atlantis T3 OBD (10 μm , 75 x 30 mm). Conditions: MeCN [eluent A]; water + 0.5% HCOOH [eluent B]; Gradient: 90% B $\rightarrow$ 5% B over 6.4 min. (flow: 75 ml/min.). Detection: UV + ELSD.

LC-MS with basic conditions (conditions E)

25 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 NH_3 in water [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV + MS.

LC-MS with acidic conditions (conditions F)

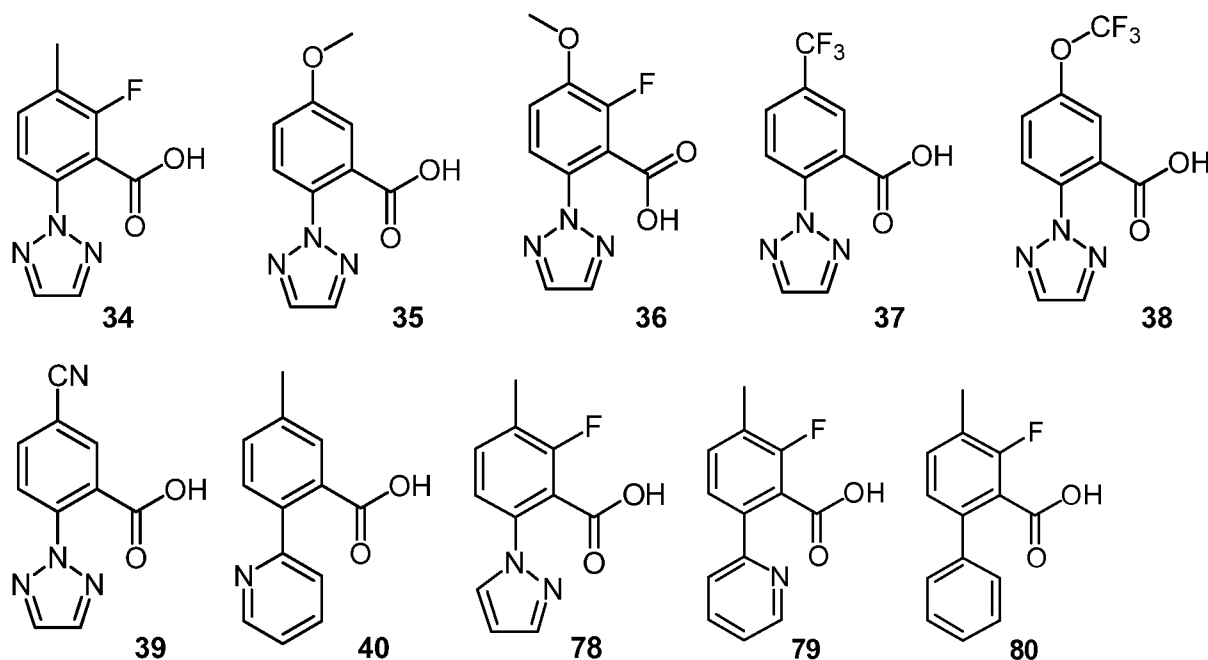
30 Apparatus: Agilent 1100 series with mass spectroscopy detection (MS : Finnigan single quadrupole). Column: Agilent Zorbax SB-Aq, (3.5 μm , 4.6 x 50mm). Conditions: MeCN [eluent A]; water + 0.04% TFA [eluent B]. Gradient: 95% B $\rightarrow$ 5% B over 1.5 min. (flow: 4.5 ml/min.). Detection: UV + MS.

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:

- 5 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**

- 10 2-Fluoro-3-methyl-6-(2H-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), CuI (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 aq. 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): t_R = 0.55 min, [M + 1]⁺ = 222.19.

20 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): t_R = 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): $t_R = 0.48$ min, $[M + 1]^+ = 238.18$.

5 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): $t_R = 0.64$ min, $[M + 1]^+ = 257.91$.

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

10 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): $t_R = 0.66$ min, $[M + 1]^+ = 273.69$.

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

15 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): $t_R = 0.46$ min, $[M + 1]^+ =$ not detectable. 1H NMR (D_6 -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

20 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), CuI (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
25 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): $t_R = 0.67$ min, $[M + 1]^+ = 228.07$.

30 b) To a solution of methyl 5-methyl-2-(pyridin-2-yl)benzoate (11.617 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): $t_R = 0.39$ 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): $t_R = 0.63$ 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), CuI (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): $t_R = 0.74$ 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

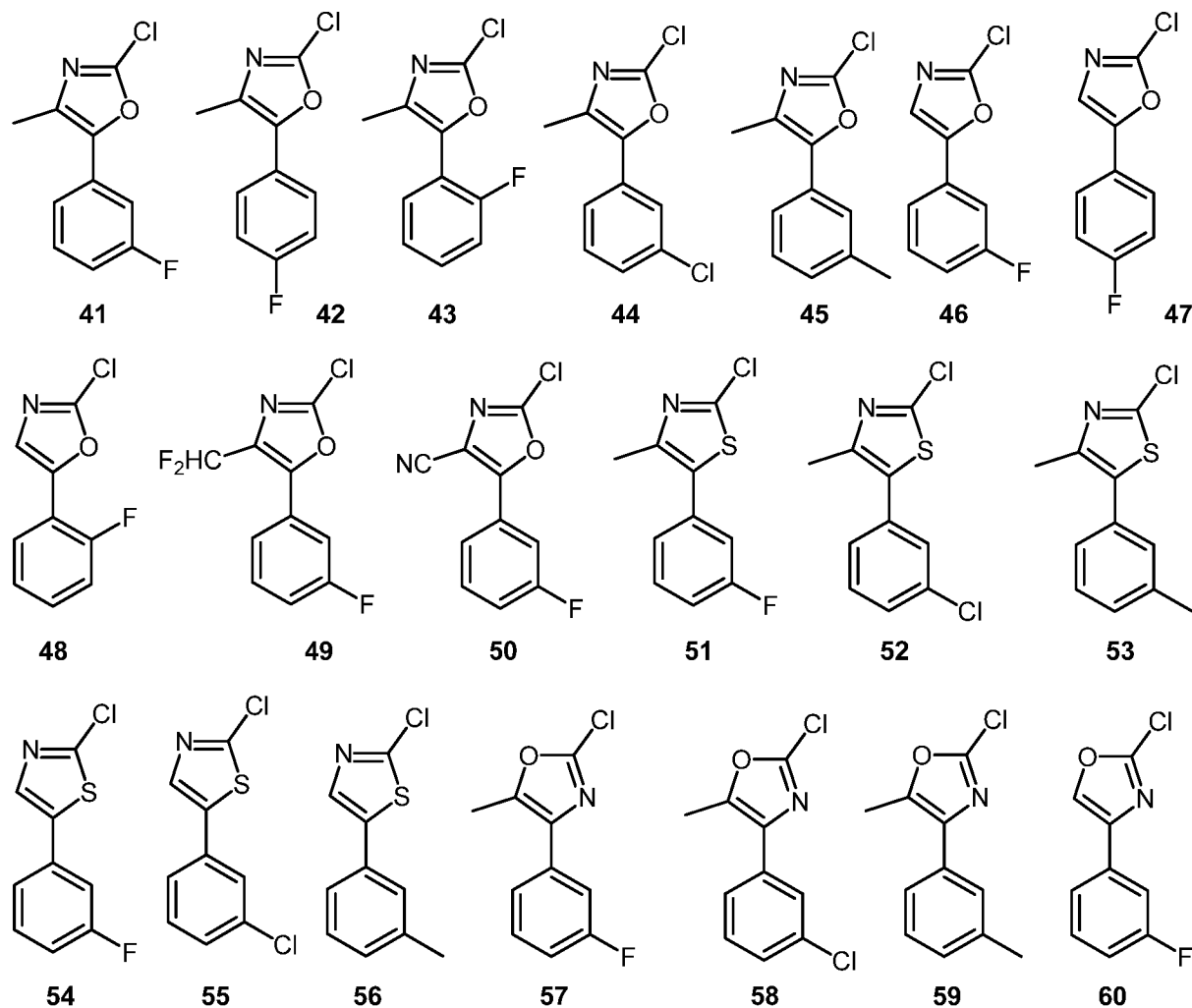
a) In a dry Schlenk Tube at RT under nitrogen are successively charged methyl 2-fluoro-6-iodo-3-methylbenzoate (23.5 mmol, 1 eq), Pd(PPh₃)₄ (1.17 mmol, 0.05 eq) and Toluene (60 mL). The resulting mixture is stirred at RT for 15 minutes before a solution of phenyloronic acid (25.8 mmol, 1.1 eq) in EtOH (26 mL) and 2 M Na₂CO₃ (54 mL) are successively added. The resulting mixture is stirred at reflux overnight. The obtained reaction mixture is diluted with Et₂O and the solvents are removed under reduced pressure. The residue is purified by FC (Teledyne Isco Combiflash Rf, SiO₂ 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, $[M + 1]^+ = 245.19$.

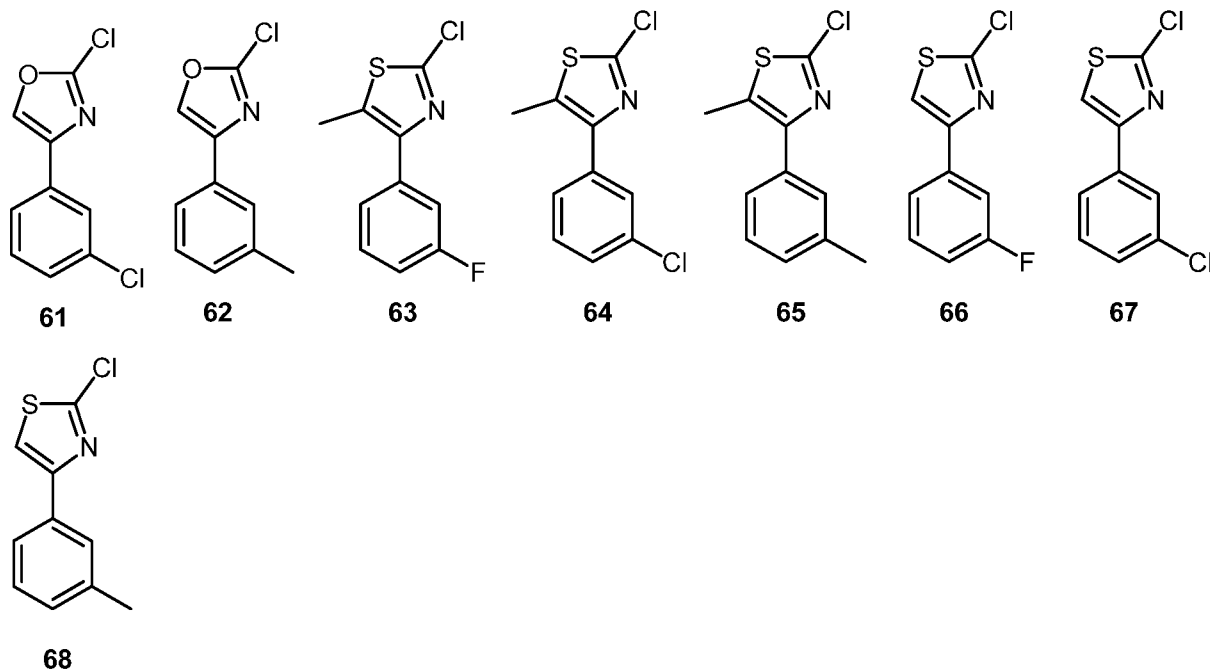
b) To a solution of methyl 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylate (23 mmol, 1 eq) in MeOH (42 mL) is added NaOH 32% (24 mL). The resulting mixture is stirred at 65°C for 2 hour. The volatiles are evaporated under reduced pressure and the remaining aq. phase is acidified with 7 M HCl to pH = 1-2. The resulting suspension is filtered under vacuum and the obtained solid dried under high 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 Ar^2-Cl :

In addition to commercially available building blocks, further particular building blocks of formula Ar^2-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 (9.11 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)

10 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 min, [M + 1]⁺ = 178.21.

15 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 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃): δ 7.53 (m, 2 H), 7.14 (m, 2 H), 2.37 (m, 3 H).

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

a) Identical to B.1 a)

20 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 min, [M + 1]⁺ = 178.26.

25 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 min, [M + 1]⁺ = 212.09.

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

a) Identical to B.1 a)

30 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): δ 8.36 (s, 1 H), 7.51 (m, 4 H), 2.37 (s, 3 H).

c) 2-Chloro-5-(3-chlorophenyl)-4-methyloxazole is prepared in analogy to 2-chloro-5-(3-fluorophenyl)-4-methyloxazole **41** starting from 5-(3-chlorophenyl)-4-methyloxazole (11.775 mmol, 1 eq). **44** (2.09 g) is obtained as an orange liquid. LC-MS (conditions A): $t_R = 1.26$ min, $[M + 1]^+ = 228.12$.

5 **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. ^1H NMR (CDCl_3): δ 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, $[M + 1]^+ = 208.13$.

B.6 2-Chloro-5-(3-fluorophenyl)oxazole 46

15 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
20 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. ^1H NMR (CDCl_3): δ 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
25 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
30 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. ^1H NMR (CDCl_3): δ 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).

B.7 2-Chloro-5-(4-fluorophenyl)oxazole 47

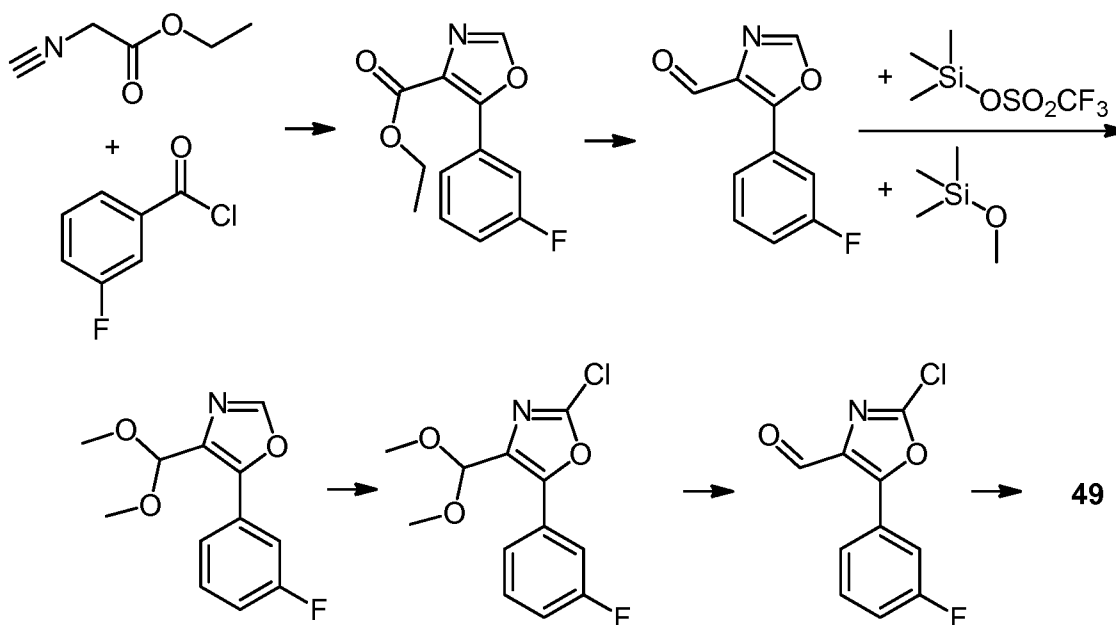
a) 5-(4-Fluorophenyl)oxazole is prepared in analogy to 5-(3-fluorophenyl)oxazole starting from 4-fluorobenzaldehyde (32.229 mmol, 1 eq). 5-(4-Fluorophenyl)oxazole (4.70 g) is obtained as a yellow solid. LC-MS (conditions A): $t_R = 0.66$ min, $[M + 1]^+$ = not detectable. 1H NMR ($CDCl_3$): δ 7.90 (s, 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, $[M + 1]^+$ = not detectable. 1H NMR ($CDCl_3$): δ 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, $[M + 1]^+$ = not detectable. 1H NMR ($CDCl_3$): δ 7.94 (s, 1 H), 7.77 (td, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, 1 H), 7.51 (d, $J = 3.9$ Hz, 1 H), 7.32 (m, 1 H), 7.20 (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, $[M + 1]^+$ = not detectable. 1H NMR ($CDCl_3$): δ 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

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 H₂O and extracted with EtOAc (3 times). The combined organic phases are washed with brine, dried over Na₂SO₄, 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 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 min, $[M + 1]^+ =$ not detectable. ¹H NMR (CDCl₃): δ 10.13 (s), 7.99 (m, 2 H), 7.95 (s, 1 H), 7.50 (td, $J_1 = 8.2$ Hz, $J_2 = 5.9$ Hz, 1 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 EtOAc (3 times). The combined organic layers are washed with H₂O 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 min, $[M + 1]^+ = 238.20$. ¹H NMR (CDCl₃): δ 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

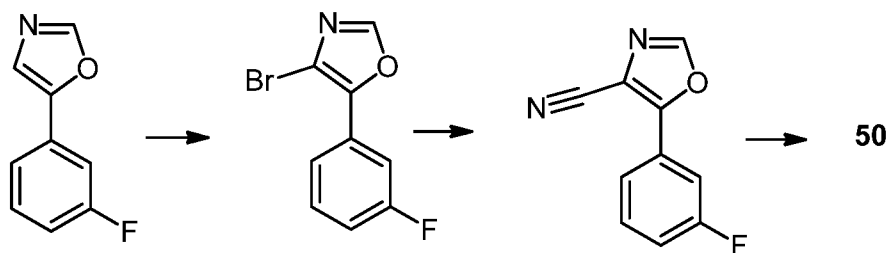
extrated with Et₂O (3 times). The combined organic layers are washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give 2-chloro-4-(dimethoxymethyl)-5-(3-fluorophenyl)oxazole (832 mg) as a brown oil. The compound is clean enough to be used in the next step without further purification. LC-MS (conditions A): *t_R* = 0.97 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃): δ 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) / H₂O (5 mL). The reaction mixture is stirred at RT for 16 h, quenched with a sat. aq. Sol. of Na₂CO₃.

The aq. layer is extracted with Et₂O (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 (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 (CDCl₃): δ 10.00 (m, 1 H), 7.93 (m, 2 H), 7.50 (m, 1 H), 7.23 (m, 1 H).

f) 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-Fluor (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 H₂O and 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 (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 (CDCl₃): δ 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*H*)-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 Br₂ (13.914 mmol, 1 eq). The reaction mixture is further stirred at this temperature for 1 h and poured onto a mixture of Et₂O / aq. 10 % Na₂SO₃ solution. The layers are separated and the organic phase is washed with brine, dried over Na₂SO₄, 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): δ 8.60 (m, 1 H), 7.65 (m, 4 H), 7.32 (m, 1 H).

- 5 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_2O 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. 1H NMR ($CDCl_3$): δ 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).

- 10 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_2O before heptane is added. The solid formed is filtered and the filtrate is diluted with EtOAc. The organic layer is washed with H_2O and brine, dried over Na_2SO_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. 1H NMR ($CDCl_3$): δ 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

- 25 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 re-dissolved in EtOAc, washed with a sat. aq. solution of $NaHCO_3$ (2 times) and brine, dried over Na_2SO_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.

- 30 b) To a suspension of $CuCl_2$ anhydrous (12.577 mmol, 1.2 eq) in dry CH_3CN (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 CH₃CN (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 H₂O and brine, dried over Na₂SO₄, 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 = 1.02 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃): δ 7.43 (m, 1 H), 7.20 (m, 1 H), 7.11 (m, 2 H), 2.48 (s, 3 H).

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 (3.06 g) is obtained as a red oil. LC-MS (conditions B): t_R = 0.84 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 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃): δ 7.42 (m, 3 H), 7.30 (m, 1 H), 2.48 (s, 3 H).

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-methylphenylacetone (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 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 min, [M + 1]⁺ = not detectable. ¹H NMR (CDCl₃): δ 7.30 (m, 1 H), 7.16 (m, 3 H), 2.43 (s, 3 H), 2.39 (s, 3 H).

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. ¹H NMR (CDCl₃): δ 9.77 (t, J = 3.0 Hz, 1 H), 7.33 (m, 1 H), 6.98 (m, 3 H), 3.69 (d, J = 3.0 Hz, 2 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. aq. solution of NaHCO₃ 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 9.75 (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 (CDCl_3): 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. ^1H NMR (CDCl_3): δ 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 **56** (730 mg) is obtained as a yellow liquid. LC-MS (conditions B): $t_R = 1.03$ min, $[M + 1]^+$ = not detectable. ^1H NMR (CDCl_3): δ 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 sat. NaHCO_3 and brine, dried over Na_2SO_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. ^1H NMR (D_6 -DMSO): δ 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_2O , dried over Na_2SO_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. ^1H NMR (D_6 -DMSO): δ 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 H₂O 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 (D₆-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 POCl₃ (45.968 mmol, 6 eq) is added pyridine (0.62 mL, 7.661 mmol, 1 eq.) at RT. The resulting 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 H₂O and the aq. phase is extracted with EtOAc (2 times). The combined organic layers are washed with brine, dried over Na₂SO₄, 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 (D₆-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 (D₆-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 (D₆-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-methyloxazol-2(3H)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one starting from 1-(3-chlorophenyl)-2-hydroxypropan-1-one (18.904 mmol, 1 eq). 4-(3-Chlorophenyl)-5-methyloxazol-2(3H)-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 (D₆-DMSO): δ 7.48 (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-methyloxazole **58** is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methyloxazole **57** starting from 4-(3-chlorophenyl)-5-methyloxazol-2(3H)-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

- 5 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. 1H NMR (D_6 -DMSO): δ 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).
- 10 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. 1H NMR (D_6 -DMSO): δ 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).
- 15 c) 5-Methyl-4-(m-tolyl)oxazol-2(3H)-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.
- 20 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(3H)-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. 1H NMR (D_6 -DMSO): δ 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).

25 **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. 1H NMR (D_6 -DMSO): δ 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).
- 30 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. ^1H NMR (D_6 -DMSO): δ 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(3*H*)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3*H*)-one starting from 1-(3-fluorophenyl)-2-hydroxyethanone (5.514 mmol, 1 eq). 4-(3-Fluorophenyl)oxazol-2(3*H*)-one (540 mg) is obtained as a light orange solid. LC-MS (conditions A): $t_R = 0.55$ min, $[M + 1]^+$ = not detectable. ^1H NMR (D_6 -DMSO): δ 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(3*H*)-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. ^1H NMR (D_6 -DMSO): δ 8.80 (s, 1 H), 7.53 (m, 3 H), 7.17 (m, 1 H).

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. ^1H NMR (D_6 -DMSO): δ 8.00 (m, 1 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. ^1H NMR (D_6 -DMSO): δ 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(3*H*)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3*H*)-one starting from 1-(3-chlorophenyl)-2-hydroxyethanone (8.50 mmol, 1 eq). 4-(3-Chlorophenyl)oxazol-2(3*H*)-one (922 mg) is obtained as a light red solid. LC-MS (conditions A): $t_R = 0.62$ min, $[M + 1]^+$ = not detectable. ^1H NMR (D_6 -DMSO): δ 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(3*H*)-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. ^1H NMR (D_6 -DMSO): δ 8.82 (s, 1 H), 7.79 (m, 1 H), 7.69 (m, 1 H), 7.45 (m, 2 H).

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. 1H NMR (D_6 -DMSO): δ 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 mmol, 1 eq). 2-Hydroxy-1-(m-tolyl)ethanone (1.22 g) is obtained as a pale yellow solid. LC-MS (conditions A): $t_R = 0.53$ min, $[M + 1]^+$ = not detectable. 1H NMR (D_6 -DMSO): δ 7.70 (m, 2 H), 7.41 (m, 2 H), 4.99 (t, $J = 6.0$ Hz, 1 H), 4.76 (d, $J = 6.0$ Hz, 2 H), 2.35 (s, 3 H).

c) 4-(m-Tolyl)oxazol-2(3H)-one is prepared in analogy to 4-(3-fluorophenyl)-5-methyloxazol-2(3H)-one starting from 2-hydroxy-1-(m-tolyl)ethanone (8.09 mmol, 1 eq). 4-(m-Tolyl)oxazol-2(3H)-one (740 mg) is obtained as a light red solid. LC-MS (conditions A): $t_R = 0.61$ min, $[2M + 1]^+ = 351.0$. 1H NMR (D_6 -DMSO): δ 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** is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methyloxazole **57** starting from 4-(m-tolyl)oxazol-2(3H)-one (4.196 mmol, 1 eq). **62** (255 mg) 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 8.72 (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).

B.23 2-Chloro-4-(3-fluorophenyl)-5-methylthiazole 63

a) To a solution of 2-bromo-1-(3-fluorophenyl)propan-1-one (B17.a, 6.167 mmol, 1 eq) in acetone (10 mL) at RT is added NaSCN (6.167 mmol, 1 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 (EtOAc/heptane, 5:95 to 3:7) to give 1-(3-fluorophenyl)-2-thiocyanatopropan-1-one (1.14 g) as a light yellow oil. LC-MS (conditions A): $t_R = 0.75$ min, $[M + 1]^+$ = not detectable. 1H NMR (D_6 -DMSO): δ 7.88 (m, 2 H), 7.59 (m, 2 H), 5.35 (q, $J = 6.0$ Hz, 1 H), 1.64 (d, $J = 6.0$ Hz, 3 H).

b) 1-(3-Fluorophenyl)-2-thiocyanatopropan-1-one (5.448 mmol, 1 eq) is dissolved in HCl (4 M in dioxane, 10 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 (EtOAc/heptane, 5:95) to give **63** (763 mg) as a colorless oil. LC-MS (conditions A): $t_R = 0.94$ min, $[M + 1]^+ = 228.06$. 1H NMR (D_6 -DMSO): δ 7.47 (m, 3 H), 7.21 (m, 1 H), 2.53 (s, 3 H).

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
5 obtained as a yellow solid. LC-MS (conditions A): $t_R = 0.81$ min, $[M + 1]^+$ = not detectable. 1H NMR (D_6 -DMSO): δ 8.09 (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).

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
10 (5.494 mmol, 1 eq). **64** (843 mg) is obtained as a white solid. LC-MS (conditions A): $t_R = 1.01$ min, $[M + 1]^+ = 243.95$. 1H NMR (D_6 -DMSO): δ 7.64 (m, 1 H), 7.59 (m, 1 H), 7.47 (m, 2 H), 2.52 (s, 3 H).

B.25 2-Chloro-5-methyl-4-(m-tolyl)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
15 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. 1H NMR (D_6 -DMSO): δ 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).

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**
20 (994 mg) is obtained as a light yellow oil. LC-MS (conditions A): $t_R = 0.99$ min, $[M + 1]^+ = 224.01$. 1H NMR (D_6 -DMSO): δ 7.38 (m, 3 H), 7.18 (m, 1 H), 2.50 (s, 3 H), 2.35 (s, 3 H).

B.26 2-chloro-4-(3-fluorophenyl)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
25 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. 1H NMR (D_6 -DMSO): δ 7.82 (m, 2 H), 7.60 (m, 2 H), 5.02 (s, 2 H).

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).
30 **66** (714 mg) is obtained as a white solid. LC-MS (conditions A): $t_R = 0.91$ min, $[M + 1]^+$ = not detectable. 1H NMR (D_6 -DMSO): δ 8.21 (s, 1 H), 7.74 (m, 2 H), 7.50 (m, 1 H), 7.21 (m, 1 H).

B.27 2-Chloro-4-(3-chlorophenyl)thiazole 67

a) 1-(3-Chlorophenyl)-2-thiocyanatoethanone is prepared in analogy to 1-(3-fluorophenyl)-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. 1H NMR (D_6 -DMSO): δ 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).

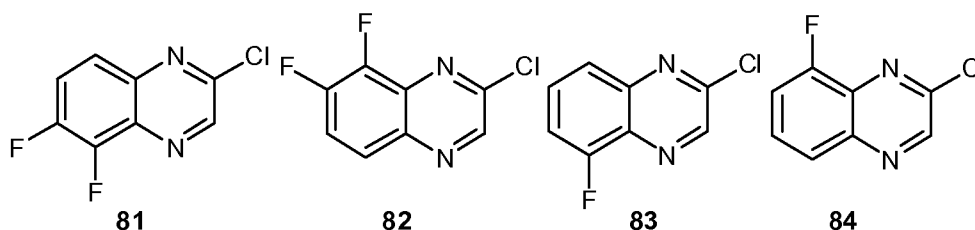
b) 2-Chloro-4-(3-chlorophenyl)thiazole is prepared in analogy to 2-chloro-4-(3-fluorophenyl)-5-methylthiazole starting from 1-(3-chlorophenyl)-2-thiocyanatoethanone (4.016 mmol, 1 eq). **67** (845 mg) is obtained as a white solid. LC-MS (conditions A): $t_R = 0.98$ min, $[M + 1]^+$ = not detectable. 1H NMR (D_6 -DMSO): δ 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. 1H NMR (D_6 -DMSO): δ 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, $[M + 1]^+ = 210.09$. 1H NMR (D_6 -DMSO): δ 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 non-commercially available quinoxalines of formula Ar^2-Cl :

**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_2CO_3 (254 mmol, 1.6 eq) is stirred at $137^\circ C$ 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_2SO_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, $[\text{M} + 1]^+ = 261.21$.

5 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 Na_2SO_4 , filtered, and concentrated under
10 reduced pressure. The residue is purified by FC (Teledyne Isco Combiflash Rf, SiO_2 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): $t_R = 0.60$ min, $[\text{M} + 1 + \text{CH}_3\text{CN}]^+ = 226.14$.

c) A suspension of 5,6-difluoro-3,4-dihydroquinoxalin-2(1H)-one (33.9 mmol, 1 eq), H_2O_2 (3 wt% in H_2O , 78.2 mmol, 2.3 eq) and NaOH 50% (4.29 mL) is heated at 100°C for 3 hours,
15 cooled down to 0°C and acidified with AcOH (81.3 mmol, 4.65 mL, 2.3 eq). The solid formed is filtrated, 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): $t_R = 0.55$ min, $[\text{M} + 1 + \text{CH}_3\text{CN}]^+ = 224.17$.

d) A mixture of 5,6-difluoroquinoxalin-2(1H)-one (23.1 mmol, 1 eq) and POCl_3 (461 mmol, 20 eq) is stirred at 100°C for 15 minutes. Upon completion, the reaction is cooled down to RT and excess POCl_3 removed under reduced pressure. The residual POCl_3 is carefully quenched with H_2O at RT and the aq. phase is extracted with DCM (3 times). The combined organic layers are washed with brine, dried over Na_2SO_4 , filtered, and concentrated under
20 reduced pressure. The residue is purified by FC (Teledyne Isco Combiflash Rf, SiO_2 cartridge 80 g; Heptane to EtOAc/Heptane 9:1) to give **81** (3.4 g) as a white solid. LC-MS (conditions F): $t_R = 0.79$ min, $[\text{M} + 1]^+ =$ not detectable. ^1H NMR (CDCl_3): 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): $t_R = 0.86$ min, $[\text{M} + 1]^+ = 261.10$.
30

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(1*H*)-one (0.85 g) is obtained as a beige solid. LC-MS (conditions F): $t_R = 0.56$ min, $[M + 1 + CH_3CN]^+ = 226.21$.

c) 7,8-difluoroquinoxalin-2(1*H*)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1*H*)-one starting from 7,8-difluoro-3,4-dihydroquinoxalin-2(1*H*)-one (4.62 mmol, 1 eq). 7,8-Difluoroquinoxalin-2(1*H*)-one (572 mg) is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.54$ min, $[M + 1 + CH_3CN]^+ = 224.02$.

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(1*H*)-one (3.09 mmol, 1 eq). **82** (300 mg) is obtained as a white solid. LC-MS (conditions F): $t_R = 0.79$ min, $[M + 1]^+ =$ not detectable. 1H NMR ($CDCl_3$): δ 8.79 (s, 1 H), 7.93 (dm, 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(1*H*)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2(1*H*)-one starting from ethyl 2-((2-fluoro-6-nitrophenyl)amino)acetate (5.57 mmol, 1 eq). 5-Fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (862 mg) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.53$ min, $[M + 1 + CH_3CN]^+ = 208.32$.

c) 5-Fluoroquinoxalin-2(1*H*)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1*H*)-one starting from 5-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (5.19 mmol, 1 eq). 5-Fluoroquinoxalin-2(1*H*)-one (572 mg) is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.50$ min, $[M + 1 + CH_3CN]^+ = 206.31$.

d) 2-Chloro-5-fluoroquinoxaline **83** is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline **81** starting from 5-fluoroquinoxalin-2(1*H*)-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. 1H NMR ($CDCl_3$): δ 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(1*H*)-one is prepared in analogy to 5,6-difluoro-3,4-dihydroquinoxalin-2(1*H*)-one starting from ethyl 2-((3-fluoro-2-nitrophenyl)amino)acetate (6.61 mmol, 1 eq). 8-Fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (1.05 g) is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.52$ min, $[M + 1 + CH_3CN]^+ = 208.22$.

5 c) 8-Fluoroquinoxalin-2(1*H*)-one is prepared in analogy to 5,6-difluoroquinoxalin-2(1*H*)-one starting from 8-fluoro-3,4-dihydroquinoxalin-2(1*H*)-one (41.5 mmol, 1 eq). 8-Fluoroquinoxalin-2(1*H*)-one (5.15 g) is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.50$ min, $[M + 1 + CH_3CN]^+ = 206.16$.

10 d) 2-Chloro-8-fluoroquinoxaline **84** is prepared in analogy to 2-chloro-5,6-difluoroquinoxaline **81** starting from 8-fluoroquinoxalin-2(1*H*)-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, $[M + 1 + CH_3CN]^+ = 224.1$.

All other groups Ar^2-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:

15 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 K_2CO_3 (2.5 mmol for the free amine; 3.5 mmol when HCl salt is present) and R^1-Cl or R^2-Cl (1.05 mmol). The resulting suspension is stirred at 60 °C overnight. Upon completion H_2O is added and the aq. phase is extracted with EtOAc (3
20 times). The combined organic phases are washed with brine, dried over Na_2SO_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
25 (5.5 mL) are successively added DBU (2.5 mmol for the free amine; 3.5 mmol when HCl salt is present) and R^1-Cl or R^2-Cl (1.2 mmol). The resulting suspension is stirred at 110 °C overnight. Upon completion H_2O is added and the aq. phase is extracted with EtOAc (3 times). The combined organic phases are washed with brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue is purified by column chromatography or
30 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

- 5 To a solution of 1 mmol of Boc-protected amine **3**, **7**, **10** or **13** (Schemes 1 + 2 + 3 + 4) in Et₂O (2.5 mL) at 0°C is added HCl 2 M in Et₂O (2.5 mL). The resulting white suspension is stirred at RT for 2 h, cooled down to 0°C diluted with Et₂O (1.25 mL) and treated again with HCl 2 M in Et₂O (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 R¹-OH or R²-OH (1 mmol) and TBTU (1.05 mmol) in CH₃CN (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 CH₃CN (2 mL). The resulting reaction mixture is stirred at RT overnight. Upon completion aq. Sat. NaHCO₃ is added and the aq. phase is extracted with EtOAc (3 times). The combined organic phases are washed with H₂O and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue is purified by FC or by preparative HPLC (conditions C).

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

- a) *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-3-carboxylate (**6**-) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (WO2008/069997) following *General Method E*. *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a off-white foam after CC (DCM/MeOH 99:1 to 96:4). LC-MS (conditions A): t_R = 0.74 min, [M + 1]⁺ = 398.16.
- 30 b) *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 8-(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following *General Method C*. *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-

1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a off-white foam. LC-MS (conditions A): $t_R = 0.43$ min, $[M + 1 - HCl]^+ = 298.23$.

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

- 5 a) *rac*-(1*R**,6*S**)-tert-Butyl 3-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1-) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A*. *rac*-(1*R**,6*S**)-tert-Butyl 3-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a light yellow foam after CC
10 (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): $t_R = 0.84$ min, $[M + 1]^+ = 364.12$.

- b) *rac*-2-((1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-chlorobenzo[d]oxazole hydrochloride is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3-(5-chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. *rac*-2-((1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-chlorobenzo[d]oxazole hydrochloride is
15 obtained as a beige solid. LC-MS (conditions A): $t_R = 0.48$ min, $[M + 1 - HCl]^+ = 264.21$.

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

- a) *rac*-(1*R**,6*R**)-tert-Butyl 8-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-3-carboxylate (6-) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid
20 (commercially available) following *General Method E*. *rac*-(1*R**,6*R**)-tert-Butyl 8-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a white foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): $t_R = 0.89$ min, $[M + 1]^+ = 407.27$.

- 25 b) *rac*-(1*R**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride is obtained by reacting *rac*-(1*R**,6*R**)-tert-butyl 8-(4-methyl-[1,1'-biphenyl]-2-carbonyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following *General Method D*. *rac*-(1*R**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions A): $t_R = 0.54$ min, $[M + 1 - HCl]^+ = 307.25$.
30

C.10 *rac*-(1*R,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride**

- a) *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(1*H*-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-

diazabicyclo[4.2.0]octane-3-carboxylate (**6-**) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(1*H*-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a light yellow foam after CC (DCM/MeOH 99:1 to 94:6). LC-MS (conditions A): $t_R = 0.74$ min, $[M + 1]^+ = 397.25$.

b) *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 8-(5-methyl-2-(1*H*-pyrazol-1-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following *General Method D*. *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride is obtained as white powder. LC-MS (conditions A): $t_R = 0.41$ min, $[M + 1 - HCl]^+ = 297.26$.

C.12 *rac*-(1*R,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride**

a) *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-3-carboxylate (**6-**) with 5-methyl-2-(pyridin-2-yl)benzoic acid (**40**, A.7) following *General Method E*. *rac*-(1*R**,6*S**)-tert-Butyl 8-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a light yellow foam after CC (DCM/MeOH 99:1 to 96:4). LC-MS (conditions A): $t_R = 0.63$ min, $[M + 1]^+ = 408.22$.

b) *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 8-(5-methyl-2-(pyridin-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following *General Method D*. *rac*-(1*R**,6*S**)-3,8-Diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions A): $t_R = 0.39$ min, $[M + 1 - HCl]^+ = 308.24$.

C.14 *rac*-(1*R,6*S**)-3,8-Diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride**

a) *rac*-(1*R**,6*S**)-tert-Butyl 8-(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-3-carboxylate (**6-**) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. *rac*-(1*R**,6*S**)-tert-Butyl 8-(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 99:1 to 98:2). LC-MS (conditions A): $t_R = 0.76$ min, $[M + 1]^+ = 416.21$.

b) *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained by reacting *rac*-(1*R**,6*S**)-tert-butyl 8-(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoyl)-3,8-diazabicyclo[4.2.0]octane-3-carboxylate with HCl following *General Method D*. *rac*-(1*R**,6*S**)-3,8-diazabicyclo [4.2.0]octan-8-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride is obtained as a white powder. LC-MS (conditions A): $t_R = 0.43$ min, $[M + 1 - HCl]^+ = 316.22$.

C.15 2-(*rac*-(1*S,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride**

a) *rac*-(1*S**,6*R**)-tert-Butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloroquinoxaline following *General Method A*. *rac*-(1*S**,6*R**)-tert-Butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.77$ min, $[M + 1]^+ = 341.39$.

b) 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride is obtained as a yellow foam. LC-MS (conditions F): $t_R = 0.50$ min, $[M + 1 - HCl]^+ = 241.3$.

C.16 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride

a) (1*S*,6*R*)-tert-Butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloroquinoxaline following *General Method A*. (1*S*,6*R*)-tert-Butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.77$ min, $[M + 1]^+ = 341.35$.

b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride is obtained by reacting (1*S*,6*R*)-tert-butyl 3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.50$ min, $[M + 1 - HCl]^+ = 241.08$.

C.17 2-(*rac*-(1*S,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7-fluoroquinoxaline hydrochloride**

a) *rac*-(1*S**,6*R**)-tert-Butyl 3-(7-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloro-7-fluoroquinoxaline following *General*

Method A. *rac*-(1*S**,6*R**)-tert-Butyl 3-(7-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a light yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.87$ min, $[M + 1]^+ = 359.12$.

b) 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7-fluoroquinoxaline hydrochloride is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3-(7-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.54$ min, $[M + 1 - HCl]^+ = 259.17$.

C.18 2-(*rac*-(1*S,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline**

hydrochloride

a) *rac*-(1*S**,6*R**)-tert-Butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloro-6-fluoroquinoxaline following *General Method A*. *rac*-(1*S**,6*R**)-tert-Butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.87$ min, $[M + 1]^+ = 359.21$.

b) 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.54$ min, $[M + 1 - HCl]^+ = 259.32$.

C.19 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride

a) (1*S*,6*R*)-tert-Butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloro-6-fluoroquinoxaline following *General Method A*. (1*S*,6*R*)-tert-Butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.86$ min, $[M + 1]^+ = 359.15$.

b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride is obtained by reacting (1*S*,6*R*)-tert-butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.53$ min, $[M + 1 - HCl]^+ = 259.18$.

C.20 2-(rac-(1S*,6R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride

a) *rac*-(1S*,6R*)-tert-Butyl 3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1S*,6R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with 2-chloro-8-fluoroquinoxaline (**84**, B.32) following *General Method A*. *rac*-(1S*,6R*)-tert-Butyl 3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a light yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.89$ min, $[M + 1]^+ = 359.24$.

b) 2-(*rac*-(1S*,6R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride is obtained by reacting *rac*-(1S*,6R*)-tert-butyl 3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1S*,6R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.54$ min, $[M + 1 - HCl]^+ = 259.25$.

C.21 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride

a) (1S,6R)-tert-Butyl 3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1S,6R)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with 2-chloro-8-fluoroquinoxaline (**84**, B.32) following *General Method A*. (1S,6R)-tert-Butyl 3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.88$ min, $[M + 1]^+ = 359.13$.

b) 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride is obtained by reacting (1S,6R)-tert-butyl 3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.53$ min, $[M + 1 - HCl]^+ = 259.20$.

C.22 2-(rac-(1S*,6R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride

a) *rac*-(1S*,6R*)-tert-Butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1S*,6R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with 2-chloro-5-fluoroquinoxaline (**83**, B.31) following *General Method A*. *rac*-(1S*,6R*)-tert-Butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a light yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.86$ min, $[M + 1]^+ = 359.24$.

b) 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride is obtained as
5 a yellow solid. LC-MS (conditions F): $t_R = 0.52$ min, $[M + 1 - HCl]^+ = 259.25$.

C.23 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride

a) (1*S*,6*R*)-tert-Butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with 2-chloro-5-fluoroquinoxaline (**83**, B.31) following *General Method A*.
10 (1*S*,6*R*)-tert-Butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.85$ min, $[M + 1]^+ = 359.14$.

b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride is obtained by reacting (1*S*,6*R*)-tert-butyl 3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.52$ min, $[M + 1 - HCl]^+ = 259.19$.
15

C.24 2-(*rac*-(1*S,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride**

a) *rac*-(1*S**,6*R**)-tert-Butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloro-6,7-difluoroquinoxaline following *General Method A*. *rac*-(1*S**,6*R**)-tert-Butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH
20 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.92$ min, $[M + 1]^+ = 377.19$.
25

b) 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride is obtained by reacting *rac*-(1*S**,6*R**)-tert-butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride is obtained
30 as a brown solid. LC-MS (conditions F): $t_R = 0.57$ min, $[M + 1 - HCl]^+ = 277.10$.

C.25 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride

a) (1*S*,6*R*)-tert-Butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-

carboxylate (1) with commercially available 2-chloro-6,7-difluoroquinoxaline following *General Method A*. (1*S*,6*R*)-tert-Butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a pale yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.92$ min, $[M + 1]^+ = 377.34$.

- 5 b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride is obtained by reacting (1*S*,6*R*)-tert-Butyl 3-(6,7-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride is obtained as a brown solid. LC-MS (conditions F): $t_R = 0.57$ min, $[M + 1 - HCl]^+ = 277.11$.

10 **C.26 2-(rac-(1*S*^{*},6*R*^{*})-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7,8-difluoroquinoxaline hydrochloride**

a) rac-(1*S*^{*},6*R*^{*})-tert-Butyl 3-(7,8-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1*S*^{*},6*R*^{*})-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 2-chloro-7,8-difluoroquinoxaline (82, B.30) following *General Method A*.

- 15 rac-(1*S*^{*},6*R*^{*})-tert-Butyl 3-(7,8-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a light yellow solid after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.93$ min, $[M + 1]^+ = 377.24$.

- b) 2-(rac-(1*S*^{*},6*R*^{*})-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7,8-difluoroquinoxaline hydrochloride is obtained by reacting rac-(1*S*^{*},6*R*^{*})-tert-butyl 3-(7,8-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(rac-(1*S*^{*},6*R*^{*})-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7,8-difluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.57$ min, $[M + 1 - HCl]^+ = 277.20$.

C.27 2-(rac-(1*S*^{*},6*R*^{*})-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride

- 25 a) rac-(1*S*^{*},6*R*^{*})-tert-Butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting rac-(1*S*^{*},6*R*^{*})-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (1) with 2-chloro-5,6-difluoroquinoxaline (81, B.29) following *General Method A*. rac-(1*S*^{*},6*R*^{*})-tert-Butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R = 0.91$ min, $[M + 1]^+ = 377.22$.

b) 2-(rac-(1*S*^{*},6*R*^{*})-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride is obtained by reacting rac-(1*S*^{*},6*R*^{*})-tert-butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-(rac-

(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride is obtained as a yellow solid. LC-MS (conditions F): $t_R = 0.56$ min, $[M + 1 - HCl]^+ = 277.14$.

C.28 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride

5 a) (1*S*,6*R*)-tert-Butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with 2-chloro-5,6-difluoroquinoxaline (**81**, B.29) following *General Method A*. (1*S*,6*R*)-tert-Butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a yellow foam after CC (DCM/MeOH 100:0 to 96:4). LC-MS (conditions F): $t_R =$
10 0.90 min, $[M + 1]^+ = 377.08$.

b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride is obtained by reacting (1*S*,6*R*)-tert-butyl 3-(5,6-difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride is obtained as a pale
15 yellow solid. LC-MS (conditions F): $t_R = 0.56$ min, $[M + 1 - HCl]^+ = 277.13$.

C.29 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluorobenzo[d]oxazole hydrochloride

a) (1*S*,6*R*)-tert-Butyl 3-(5-fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained by reacting (1*S*,6*R*)-tert-butyl 3,8-diazabicyclo[4.2.0]octane-8-carboxylate (**1**) with commercially available 2-chloro-5-fluorobenzo[d]oxazole following
20 *General Method A*. (1*S*,6*R*)-tert-Butyl 3-(5-fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate is obtained as a brown foam after FC (Teledyne Isco Combiflash Rf, SiO₂ cartridge 4 g; DCM/MeOH 100:0 to 96:4). LC-MS (conditions A): $t_R = 0.77$ min, $[M + 1]^+ = 349.29$.

25 b) 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluorobenzo[d]oxazole hydrochloride is obtained by reacting (1*S*,6*R*)-tert-butyl 3-(5-fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octane-8-carboxylate with HCl following *General Method C*. 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5-fluorobenzo[d]oxazole hydrochloride is obtained as a light yellow solid. LC-MS (conditions A): $t_R = 0.43$ min, $[M + 1 - HCl]^+ = 248.04$.

30 **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*-((1*R,6*S**)-3-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A* or by reacting
5 *rac*-2-((1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-chlorobenzo[d]oxazole hydrochloride (C.3) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (WO2008/069997) following *General Method E*. LC-MS (conditions A): rotamers $t_R = 0.76$ min, $[M + 1]^+ = 449.15$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m;
10 30*250 mm) column, CH₃CN/MeOH + 0.1% DEA 95:5, flow rate = 34 mL/min.

Reference Example 1a (enantiomer 1)

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

15 $t_R = 8.62$ min.

Reference Example 1b (enantiomer 2)

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

20 $t_R = 11.90$ min.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS
25 (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 433.18$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2,6-dichlorobenzo[d]thiazole (commercially available) following *General Method A*. LC-MS
30 (conditions B): $t_R = 0.92$ min, $[M + 1]^+ = 465.09$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-6-fluorobenzo[*d*]thiazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 449.23$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m; 30*250 mm) column, CH₃CN/EtOH + 0.1% DEA 95:5, flow rate = 34 mL/min.

Example 4a (enantiomer 1)

((1*S*,6*R*)-3-(6-Fluorobenzo[*d*]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone $t_R = 8.17$ min.

Example 4b (enantiomer 2)

((1*R*,6*S*)-3-(6-Fluorobenzo[*d*]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone. $t_R = 9.89$ min.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2,6,7-trichloroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.98$ min, $[M + 1]^+ = 494.07$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2,7-dichloroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.90$ min, $[M + 1]^+ = 460.08$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2,6-dichloroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.90$ min, $[M + 1]^+ = 460.08$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 462.13$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m; 30*250 mm) column, THF/tBME + 0.1% DEA 70:30, flow rate = 34 mL/min.

Example 8a (enantiomer 1)

((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 5.82$ min.

Example 8b (enantiomer 2)

((1*R*,6*S*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 7.26$ min.

Example 9: *rac*-((1*R,6*S**)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-6-fluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.84$ min, $[M + 1]^+ = 444.22$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m; 30*250 mm) column, EtOH/tBME (1:1) + 0.1% DEA/CH₃CN 20:80, flow rate = 34 mL/min.

Example 9a (enantiomer 1)

((1*S*,6*R*)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 7.09$ min.

Example 9b (enantiomer 2)

((1*R*,6*S*)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 9.18$ min.

Example 10: *rac*-((1*R,6*S**)-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

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

fluorophenyl)-4-methyloxazole (B.1 - **41**) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 473.25$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m; 30*250 mm) column, EtOH + 0.1% DEA/CH₃CN 5:95, flow rate = 34 mL/min.

5 **Example 10a (enantiomer 1)**

((1*S*,6*R*)-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 6.81$ min.

Example 10b (enantiomer 2)

10 ((1*R*,6*S*)-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 9.57$ min.

Example 11: *rac*-((1*R,6*S**)-3-(5-(3-Fluorophenyl)-4-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

15 The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-5-(3-fluorophenyl)-4-methylthiazole (B.11 - **51**) following *General Method A*. LC-MS (conditions B): $t_R = 0.95$ min, $[M + 1]^+ = 489.00$.

Example 12: *rac*-((1*R,6*S**)-3-(4-(3-Fluorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

20 The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-4-(3-fluorophenyl)-5-methyloxazole (B.17 - **57**) following *General Method A*. LC-MS (conditions B): $t_R = 0.92$ min, $[M + 1]^+ = 473.27$.

The two enantiomers are separated by chiral preparative HPLC: Daicel ChiralPak IA (5 μ m; 30*250 mm) column, EtOH + 0.1% DEA/CH₃CN 5:95, flow rate = 34 mL/min.

25 **Example 12a (enantiomer 1)**

((1*S*,6*R*)-3-(4-(3-Fluorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 6.67$ min.

Example 12b (enantiomer 2)

30 ((1*R*,6*S*)-3-(4-(3-Fluorophenyl)-5-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone: $t_R = 8.95$ min.

Example 13: *rac*-((1*R,6*S**)-3-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following *General Method A*. LC-MS (conditions B): $t_R = 0.99$ min, $[M + 1]^+ = 489.89$.

Example 14: *rac*-((1*R,6*S**)-3-(4-(Difluoromethyl)-5-(3-fluorophenyl)oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 2-chloro-4-(difluoromethyl)-5-(3-fluorophenyl)oxazole (B.9 - 49) following *General Method A*. LC-MS (conditions B): $t_R = 0.91$ min, $[M + 1]^+ = 509.18$.

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

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.2) with 3,5-dichlorobenzo[d]isoxazole (commercially available) following *General Method B*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 449.09$.

Reference Example 16: *rac*-((1*R,6*S**)-3-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.97$ min, $[M + 1]^+ = 457.86$.

Reference Example 17: *rac*-((1*R,6*S**)-3-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.93$ min, $[M + 1]^+ = 442.15$.

Reference Example 17a: ((1*S*,6*R*)-3-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluorobenzo[d]oxazole hydrochloride (C.29) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid

(commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.91$ min, $[M + 1]^+ = 442.32$.

Example 18: *rac*-((1*R,6*S**)-3-(6-Fluorobenzo[d]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

- 5 The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-6-fluorobenzo[d]thiazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.96$ min, $[M + 1]^+ = 457.83$.

Example 19: *rac*-((1*R,6*S**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

- 10 The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.98$ min, $[M + 1]^+ = 471.19$.

Example 19a: ((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

- 15 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.25) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.97$ min, $[M + 1]^+ = 471.16$.

Example 20: *rac*-((1*R,6*S**)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

- 20 The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-6-fluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.95$ min, $[M + 1]^+ = 453.13$.

Example 20a: ((1*S*,6*R*)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

- 25 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.92$ min, $[M + 1]^+ = 453.36$.

Example 21: *rac*-((1*R,6*S**)-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following *General Method A*. LC-MS (conditions B): $t_R = 0.98$ min, $[M + 1]^+ = 482.15$.

Example 22: *rac*-((1*R,6*S**)-3-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*R**)-3,8-diazabicyclo[4.2.0]octan-8-yl(4-methyl-[1,1'-biphenyl]-2-yl)methanone hydrochloride (C.8) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following *General Method A*. LC-MS (conditions B): $t_R = 1.07$ min, $[M + 1]^+ = 498.13$.

Reference Example 23: *rac*-((1*R,6*S**)-3-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.86$ min, $[M + 1]^+ = 449.23$.

Reference Example 24: *rac*-((1*R,6*S**)-3-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.82$ min, $[M + 1]^+ = 432.16$.

Example 25: *rac*-((1*R,6*S**)-3-(6-Fluorobenzo[d]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-6-fluorobenzo[d]thiazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.85$ min, $[M + 1]^+ = 448.09$.

Example 26: *rac*-((1*R,6*S**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-6,7-

difluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 461.14$.

Example 26a: ((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

- 5 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.25) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.87$ min, $[M + 1]^+ = 461.18$.

Example 27: *rac*-((1*R*^{*},6*S*^{*})-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

- 10 The title compound is prepared by reacting *rac*-(1*R*^{*},6*S*^{*})-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-6-fluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 443.09$.

Example 27a: ((1*S*,6*R*)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

- 15 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.81$ min, $[M + 1]^+ = 443.33$.

Example 28: *rac*-((1*R*^{*},6*S*^{*})-3-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

- 25 The title compound is prepared by reacting *rac*-(1*R*^{*},6*S*^{*})-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2,7-dichloroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.89$ min, $[M + 1]^+ = 460.23$.

Example 29: *rac*-((1*R*^{*},6*S*^{*})-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

- 30 The title compound is prepared by reacting *rac*-(1*R*^{*},6*S*^{*})-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - 41) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 472.16$.

Example 30: *rac*-((1*R,6*S**)-3-(4-(3-Fluorophenyl)-5-methylthiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone hydrochloride (C.10) with 2-chloro-4-(3-fluorophenyl)-5-methylthiazole (B.23 - 63) following *General Method A*. LC-MS (conditions B): $t_R = 0.97$ min, $[M + 1]^+ = 488.21$.

Example 31: *rac*-((1*R,6*S**)-3-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 459.07$.

Example 32: *rac*-((1*R,6*S**)-3-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 443.14$.

Example 32a: (1*S*,6*R*)-3-(5-Fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluorobenzo[d]oxazole hydrochloride (C.29) with 5-methyl-2-(pyridin-2-yl)benzoic acid (40, A.7) following *General Method E*. LC-MS (conditions F): $t_R = 0.72$ min, $[M + 1]^+ = 443.31$.

Example 33: *rac*-((1*R,6*S**)-3-(6-Fluorobenzo[d]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2-chloro-6-fluorobenzo[d]thiazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 459.02$.

Example 34: *rac*-((1*R,6*S**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2-chloro-6,7-

difluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 472.21$.

Example 34a: ((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

- 5 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.25) with 5-methyl-2-(pyridin-2-yl)benzoic acid (**40**, A.7) following *General Method E*. LC-MS (conditions F): $t_R = 0.78$ min, $[M + 1]^+ = 472.16$.

Example 35: *rac*-((1*R,6*S**)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

- 10 The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2-chloro-6-fluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.81$ min, $[M + 1]^+ = 454.31$.

Example 35a: ((1*S*,6*R*)-3-(6-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

- 15 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 5-methyl-2-(pyridin-2-yl)benzoic acid (**40**, A.7) following *General Method E*. LC-MS (conditions F): $t_R = 0.73$ min, $[M + 1]^+ = 454.34$.

Example 36: *rac*-((1*R,6*S**)-3-(7-Chloroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

- 20 The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2,7-dichloroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.90$ min, $[M + 1]^+ = 470.14$.

Example 37: *rac*-((1*R,6*S**)-3-(5-(3-Fluorophenyl)-4-methyloxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

- 25 The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-8-yl(5-methyl-2-(pyridin-2-yl)phenyl)methanone hydrochloride (C.12) with 2-chloro-5-(3-fluorophenyl)-4-methyloxazole (B.1 - **41**) following *General Method A*. LC-MS (conditions B):
30 $t_R = 0.89$ min, $[M + 1]^+ = 483.13$.

Reference Example 38: *rac*-((1*R,6*S**)-3-(5-Chlorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.14) with 2,5-dichlorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.88$ min, $[M + 1]^+ = 468.11$.

Reference Example 39: *rac*-(2-Fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*R,6*S**)-3-(5-fluorobenzo[d]oxazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.14) with 2-chloro-5-fluorobenzo[d]oxazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.83$ min, $[M + 1]^+ = 452.13$.

Example 40: *rac*-(2-Fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*R,6*S**)-3-(6-fluorobenzo[d]thiazol-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.14) with 2-chloro-6-fluorobenzo[d]thiazole (commercially available) following *General Method A*. LC-MS (conditions B): $t_R = 0.87$ min, $[M + 1]^+ = 467.10$.

Example 41: *rac*-((1*R,6*S**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.14) with 2-chloro-6,7-difluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): rotamers $t_{R1} = 0.88$ min / $t_{R2} = 0.91$ min, $[M + 1]^+ = 480.13$.

Example 41a: ((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.25) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.88$ min, $[M + 1]^+ = 479.96$.

Example 42: *rac*-(2-Fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*R,6*S**)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting *rac*-(1*R**,6*S**)-3,8-diazabicyclo[4.2.0]octan-3-yl(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone hydrochloride (C.14) with 2-chloro-6-fluoroquinoxaline (commercially available) following *General Method A*. LC-MS (conditions B): rotamers $t_{R1} = 0.84$ min / $t_{R2} = 0.87$ min, $[M + 1]^+ = 462.07$.

Example 42a: (2-Fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*S*,6*R*)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.83$ min, $[M + 1]^+ = 461.94$.

Reference Example 43: *rac*-[1,1'-Biphenyl]-2-yl((1*S,6*R**)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.15) with [1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 421.05$.

Reference Example 43a: [1,1'-Biphenyl]-2-yl((1*S*,6*R*)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.16) with [1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 421.08$.

Reference Example 44: *rac*-(5-Methyl-2-(1*H*-pyrazol-1-yl)phenyl)((1*S,6*R**)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.15) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.73$, $[M + 1]^+ = 425.32$.

Reference Example 44a: (5-Methyl-2-(1*H*-pyrazol-1-yl)phenyl)((1*S*,6*R*)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.16) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.73$, $[M + 1]^+ = 425.33$.

Reference Example 45: *rac*-(4-Methyl-[1,1'-biphenyl]-2-yl)((1*S*^{*},6*R*^{*})-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.15) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.85$, $[M + 1]^+ = 435.33$.

Reference Example 45a: (4-Methyl-[1,1'-biphenyl]-2-yl)((1*S*,6*R*)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.16) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.86$, $[M + 1]^+ = 435.23$.

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

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.15) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.73$, $[M + 1]^+ = 426.32$.

Reference Example 46a: (5-Methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*S*,6*R*)-3-(quinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)quinoxaline hydrochloride (C.16) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.74$, $[M + 1]^+ = 426.31$.

Example 47: *rac*-((1*S*^{*},6*R*^{*})-3-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-7,8-difluoroquinoxaline hydrochloride (C.26) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.86$, $[M + 1]^+ = 462.29$.

Example 48: *rac*-((1*S*^{*},6*R*^{*})-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic

acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.85$, $[M + 1]^+ = 462.16$.

Example 48a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

- 5 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.85$, $[M + 1]^+ = 462.29$.

Example 49: *rac*-((1*S*^{*},6*R*^{*})-3-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

- 10 The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.83$, $[M + 1]^+ = 444.15$.

Example 49a: ((1*S*,6*R*)-3-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

- 15 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.21) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 444.08$.

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

- 25 The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.22) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.81$, $[M + 1]^+ = 444.14$.

Example 50a: ((1*S*,6*R*)-3-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

- 30 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.23) with 5-methyl-2-(2*H*-1,2,3-triazol-2-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.80$, $[M + 1]^+ = 444.09$.

Example 51: *rac*-((1*S,6*R**)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.84$, $[M + 1]^+ = 461.29$.

Example 51a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(1*H*-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 5-methyl-2-(1*H*-pyrazol-1-yl)benzoic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.84$, $[M + 1]^+ = 461.29$.

Example 52: *rac*-((1*S,6*R**)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 5-methyl-2-(pyridin-2-yl)benzoic acid (**40**, A.7) following *General Method E*. LC-MS (conditions F): $t_R = 0.76$, $[M + 1]^+ = 472.29$.

Example 52a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(5-methyl-2-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 5-methyl-2-(pyridin-2-yl)benzoic acid (**40**, A.7) following *General Method E*. LC-MS (conditions F): $t_R = 0.76$, $[M + 1]^+ = 472.27$.

Example 53: *rac*-((1*S,6*R**)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.95$, $[M + 1]^+ = 471.28$.

Example 53a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.95$, $[M + 1]^+ = 471.29$.

Example 54: *rac*-((1*S,6*R**)-3-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.93$, $[M + 1]^+ = 453.29$.

Example 54a: ((1*S*,6*R*)-3-(8-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.21) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.93$, $[M + 1]^+ = 453.29$.

Example 55: *rac*-((1*S,6*R**)-3-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.22) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.91$, $[M + 1]^+ = 453.30$.

Example 55a: ((1*S*,6*R*)-3-(5-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.23) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.91$, $[M + 1]^+ = 453.11$.

Example 56: *rac*-((1*S,6*R**)-3-(7-Fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(4-methyl-[1,1'-biphenyl]-2-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-7-fluoroquinoxaline hydrochloride (C.17) with 4-methyl-[1,1'-biphenyl]-2-carboxylic acid (commercially available) following *General Method E*. LC-MS (conditions F): $t_R = 0.93$, $[M + 1]^+ = 453.13$.

Example 57: *rac*-((1*S,6*R**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)phenyl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.24) with 2-fluoro-3-methyl-6-(1*H*-pyrazol-1-

yl)benzoic acid (**78**, A.8) following *General Method E*. LC-MS (conditions F): $t_R = 0.87$, $[M + 1]^+ = 479.13$.

Example 58: *rac*-((1*S,6*R**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone**

- 5 The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.24) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.84$, $[M + 1]^+ = 490.15$.

Example 59: *rac*-((1*S,6*R**)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone**

- 10 The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.24) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.97$, $[M + 1]^+ = 489.14$.

Example 59a: ((1*S*,6*R*)-3-(6,7-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

- 15 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6,7-difluoroquinoxaline hydrochloride (C.25) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.97$, $[M + 1]^+ = 488.96$.

Example 60: *rac*-(2-Fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)phenyl)((1*S,6*R**)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

- 20 The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.18) with 2-fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)benzoic acid (**78**, A.8) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 461.06$.

Example 60a: (2-Fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)phenyl)((1*S*,6*R*)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 30 The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 2-fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)benzoic acid (**78**, A.8) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 460.97$.

Example 61: *rac*- (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1*S,6*R**)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.18) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.79$, $[M + 1]^+ = 472.18$.

Example 61a: (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1*S*,6*R*)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.78$, $[M + 1]^+ = 471.98$.

Example 62: *rac*- (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1*S,6*R**)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.18) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.93$, $[M + 1]^+ = 471.17$.

Example 62a: (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1*S*,6*R*)-3-(6-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-6-fluoroquinoxaline hydrochloride (C.19) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.93$, $[M + 1]^+ = 470.99$.

Example 63: *rac*- ((1*S,6*R**)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone**

The title compound is prepared by reacting 2-(*rac*-(1*S**,6*R**)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.86$, $[M + 1]^+ = 480.16$.

Example 63a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.86$, $[M + 1]^+ = 479.96$.

Example 64: *rac*-((1*S*^{*},6*R*^{*})-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)phenyl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 2-fluoro-3-methyl-6-(1*H*-pyrazol-1-yl)benzoic acid (**78**, A.8) following *General Method E*. LC-MS (conditions F): $t_R = 0.86$, $[M + 1]^+ = 479.17$.

Example 65: *rac*-((1*S*^{*},6*R*^{*})-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.83$, $[M + 1]^+ = 490.14$.

Example 65a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(2-fluoro-3-methyl-6-(pyridin-2-yl)phenyl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.82$, $[M + 1]^+ = 489.96$.

Example 66: *rac*-((1*S*^{*},6*R*^{*})-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.27) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.96$, $[M + 1]^+ = 489.16$.

Example 66a: ((1*S*,6*R*)-3-(5,6-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-((1*S*,6*R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5,6-difluoroquinoxaline hydrochloride (C.28) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.96$, $[M + 1]^+ = 488.97$.

Example 67: *rac*- (2-Fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-yl)phenyl)((1*S*^{*},6*R*^{*})-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-(*rac*-(1*S*^{*},6*R*^{*})-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 2-fluoro-3-methyl-6-(2*H*-1,2,3-triazol-2-

yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.83$, $[M + 1]^+ = 462.04$.

Example 67a: (2-Fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)phenyl)((1S,6R)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 5 The title compound is prepared by reacting 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.21) with 2-fluoro-3-methyl-6-(2H-1,2,3-triazol-2-yl)benzoic acid (**34**, A.1) following *General Method E*. LC-MS (conditions F): $t_R = 0.84$, $[M + 1]^+ = 461.96$.

Example 68: rac- (2-Fluoro-3-methyl-6-(1H-pyrazol-1-yl)phenyl)((1S*,6R*)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 10 The title compound is prepared by reacting 2-(rac-(1S*,6R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 2-fluoro-3-methyl-6-(1H-pyrazol-1-yl)benzoic acid (**78**, A.8) following *General Method E*. LC-MS (conditions F): $t_R = 0.84$, $[M + 1]^+ = 461.01$.

Example 69: rac- (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1S*,6R*)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 15 The title compound is prepared by reacting 2-(rac-(1S*,6R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.80$, $[M + 1]^+ = 472.17$.

Example 69a: (2-Fluoro-3-methyl-6-(pyridin-2-yl)phenyl)((1S,6R)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 25 The title compound is prepared by reacting 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.21) with 2-fluoro-3-methyl-6-(pyridin-2-yl)benzoic acid (**79**, A.9) following *General Method E*. LC-MS (conditions F): $t_R = 0.79$, $[M + 1]^+ = 471.98$.

Example 70: rac- (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1S*,6R*)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

- 30 The title compound is prepared by reacting 2-(rac-(1S*,6R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.20) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (**80**, A.10) following *General Method E*. LC-MS (conditions F): rotamers $t_{R1} = 0.91$ min / $t_{R2} = 0.95$ min, $[M + 1]^+ = 471.18$.

Example 70a: (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1S,6R)-3-(8-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1S,6R)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-8-fluoroquinoxaline hydrochloride (C.21) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (80, A.10) following *General Method E*. LC-MS (conditions F): rotamers $t_{R1} = 0.92$ min / $t_{R2} = 0.95$ min, $[M + 1]^+ = 470.97$.

Example 71: *rac*-(3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1S*,6R*)-3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-(*rac*-(1S*,6R*)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.22) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (80, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.92$ min, $[M + 1]^+ = 471.19$.

Example 71a: (3-Fluoro-4-methyl-[1,1'-biphenyl]-2-yl)((1S,6R)-3-(5-fluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)methanone

The title compound is prepared by reacting 2-((1S,6R)-3,8-diazabicyclo[4.2.0]octan-3-yl)-5-fluoroquinoxaline hydrochloride (C.23) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (80, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.92$ min, $[M + 1]^+ = 470.97$.

Example 72: *rac*-(1S*,6R*)-3-(7,8-Difluoroquinoxalin-2-yl)-3,8-diazabicyclo[4.2.0]octan-8-yl)(3-fluoro-4-methyl-[1,1'-biphenyl]-2-yl)methanone

The title compound is prepared by reacting 2-(*rac*-(1S*,6R*)-3,8-Diazabicyclo[4.2.0]octan-3-yl)-7,8-difluoroquinoxaline hydrochloride (C.26) with 3-fluoro-4-methyl-[1,1'-biphenyl]-2-carboxylic acid (80, A.10) following *General Method E*. LC-MS (conditions F): $t_R = 0.97$ min, $[M + 1]^+ = 489.18$.

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 μ g/ml G418, 100 U/ml penicillin, 100 μ g/ml streptomycin and 10 % heat inactivated fetal calf serum (FCS). The cells are seeded at 20'000 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. Average IC₅₀ values from several measurements are given as geometric mean values.

Table 1

Example	IC₅₀ OX1 [nM]	IC₅₀ OX2 [nM]	Example	IC₅₀ OX1 [nM]	IC₅₀ OX2 [nM]	Example	IC₅₀ OX1 [nM]	IC₅₀ OX2 [nM]
1	22	31	25	30	67	51	34	10
1a	13	26	26	28	9	51a	36	12
1b	594	2187	26a	16	4	52	36	11
2	26	40	27	15	12	52a	20	9
3	66	29	27a	11	5	53	8	2

4	11	17	28	38	264	53a	4	1
4a	22	16	29	5	34	54	10	8
4b	936	469	30	7	70	54a	3	4
5	5	45	31	25	154	55	7	8
6	31	151	32	5	30	55a	3	5
7	23	13	32a	17	35	56	34	13
8	10	3	33	34	137	57	79	30
8a	6	2	34	24	13	58	85	20
8b	366	149	34a	14	6	59	10	3
9	5	4	35	4	10	59a	6	3
9a	2	1	35a	11	7	60	27	18
9b	425	271	36	38	157	60a	17	12
10	5	14	37	5	17	61	30	18
10a	2	5	38	62	48	61a	13	13
10b	202	996	39	65	131	62	5	3
11	58	38	40	9	25	62a	3	2
12	32	4	41	18	7	63	32	16
12a	58	8	41a	12	6	63a	7	12
12b	939	961	42	10	7	64	90	17
13	7	15	42a	7	5	65	43	19
14	35	99	43	120	53	65a	29	13
15	625	259	43a	73	28	66	10	5
16	9	26	44	27	39	66a	6	3
17	4	15	44a	9	26	67	18	25
17a	4	7	45	4	6	67a	6	25
18	7	15	45a	2	3	68	20	34
19	5	3	46	10	14	69	22	27
19a	6	2	46a	6	8	69a	13	28
20	4	3	47	90	79	70	4	7
20a	2	1	48	10	5	70a	3	6
21	4	22	48a	9	4	71	9	10
22	5	41	49	11	26	71a	6	10
23	53	132	50	16	39	72	57	8
24	31	152	50a	9	20			

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 measurments [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 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 μ M 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 6 β -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 μ L, 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 μ M (1 μ L 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 μ M (2 μ L of a 15 mM stock solution in acetonitrile) is added and the reaction is initiated by addition of 10 μ L of the NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase and terminated after 10 min with a 50 μ L-aliquot of ice-cold methanol containing 1.4 μ M of cortisone. After sealing the PCR plate with aluminum foil and centrifugation at 465 g at 4 °C for 20 min, a 20 μ L-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 μ L, a 1.0 μ L-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 μ M 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 μ L of the NADPH-regenerating system containing the glucose-6-phosphate dehydrogenase. At the end of the 30 min pre-incubation period, 2 μ L of the 15 mM testosterone stock solution in acetonitrile are added to yield a final concentration of 300 μ M. The reaction is terminated after 10 min with a 50 μ L-aliquot of ice-cold methanol containing 1.4 μ M 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 μ L-aliquot of the supernatant is submitted to LC-MS/MS analysis according to the analytical method described below.

Mibefradil 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 μ M according to the protocol above.

The chromatographic analysis of 6 β -hydroxytestosterone is achieved on a Phenomenex Luna C18 column (5 μ m, 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, 6 β -hydroxytestosterone and cortisone exhibit retention times of 0.95 min and 0.98 min, respectively.

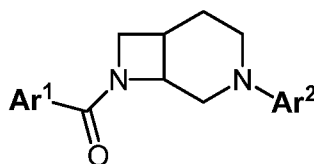
Gradient for the analysis of 6 β -hydroxytestosterone:

time [min]	0.00	0.5	1	1.2	1.25	1.5
phase B [%]	30	65	100	100	30	30

The quantification of 6 β -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 6 β -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)



Formula (I)

5 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 *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-, di-, or tri-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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

and

- **Ar²** represents 5- or 6-membered heteroaryl, wherein the 5- or 6-membered heteroaryl independently is mono-, di-, or tri-substituted; wherein

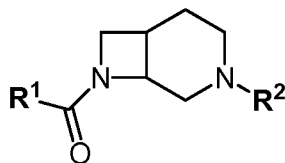
- one of said substituents is phenyl or 5- or 6-membered heteroaryl; wherein said phenyl or 5- or 6-membered heteroaryl is independently unsubstituted, or mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen,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

- or **Ar²** 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

with the exception of the compounds of Formula X:



Formula X

wherein

R¹ is a member selected from the group consisting of:

A) phenyl substituted or unsubstituted with R^a, and substituted in the *ortho* position with R^b;

R^a is a member independently selected from the group consisting of: halo, -C₁₋₄alkyl, and -C₁₋₄alkoxy;

R^b is a member selected from the group consisting of:

a) halo or -C₁₋₄alkoxy,

b) thiophen-2-yl, 2H-1,2,3-triazole, 1H-1,2,3-triazol-1-yl, 1H-pyrazol-1-yl, 1H-pyrazol-5-yl, pyrimidin-2-yl, or 3-methyl-1,2,4-oxadiazol-5-yl, and

c) phenyl;

B) pyridine substituted or unsubstituted with one or two members independently selected from the group consisting of: C₁₋₄alkyl and 1H-1,2,3-triazol-1-yl, wherein the substituents are positioned adjacent to the point of attachment by R¹; and

C) methylthiazole substituted with 2-fluorophenyl;

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 selected from the group consisting of: -C₁₋₄alkyl, -C₁₋₄alkoxy, -CF₃, halo, -N(C₁₋₄alkyl)₂, -NH₂, and phenyl;

B) pyridine substituted or unsubstituted with one or more members independently selected from the group consisting of: -CF₃ and -C₁₋₄alkyl;

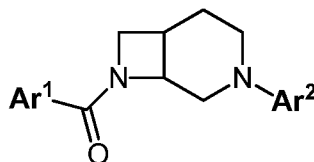
C) quinoxalin-2-yl or quinoline substituted or unsubstituted with -C₁₋₄alkyl;

D) benzoxazol-2-yl substituted or unsubstituted with halo; and

E) 4-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidine;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I) according to claim 1



Formula (I)

wherein the relative configuration of the diazabicyclooctane moiety is *cis*;

5 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-, 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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

and **Ar²** 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 (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy; and
 - ii.) phenyl; wherein said phenyl is mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- d) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, naphthyridinyl, cinnolynyl, and quinazolinyl; which group 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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)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 (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- f) 8- to 10-membered bicyclic heteroaryl which is benzoxazolyl which is mono-, di-, or tri-substituted; wherein
- the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- g) and 8- to 10-membered bicyclic heteroaryl which is quinolynyl which is mono-, di-, or tri-substituted; wherein
- the substituents are independently selected from the group consisting of (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claims 1 or 2; 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-,
5 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,
10 (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, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

b) 8- to 10-membered bicyclic heteroaryl which is selected from the group consisting of
15 indolyl, benzofuranyl, benzothiophenyl, indazolyl, benzisoxazolyl, benzothiazolyl,
benzothiazolyl, naphthyridinyl, cinnolinyl, and quinazolinyl; which group 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, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and
20 (C₁₋₃)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
(C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and
25 (C₁₋₃)fluoroalkoxy;

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

➤ the substituents are independently selected from the group consisting of
(C₁₋₄)alkyl, (C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, cyano, (C₁₋₃)fluoroalkyl, and
30 (C₁₋₃)fluoroalkoxy;

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

➤ the substituents are independently selected from the group consisting of
(C₁₋₄)alkoxy, (C₃₋₆)cycloalkyl, halogen, cyano, (C₁₋₃)fluoroalkyl, and
35 (C₁₋₃)fluoroalkoxy;

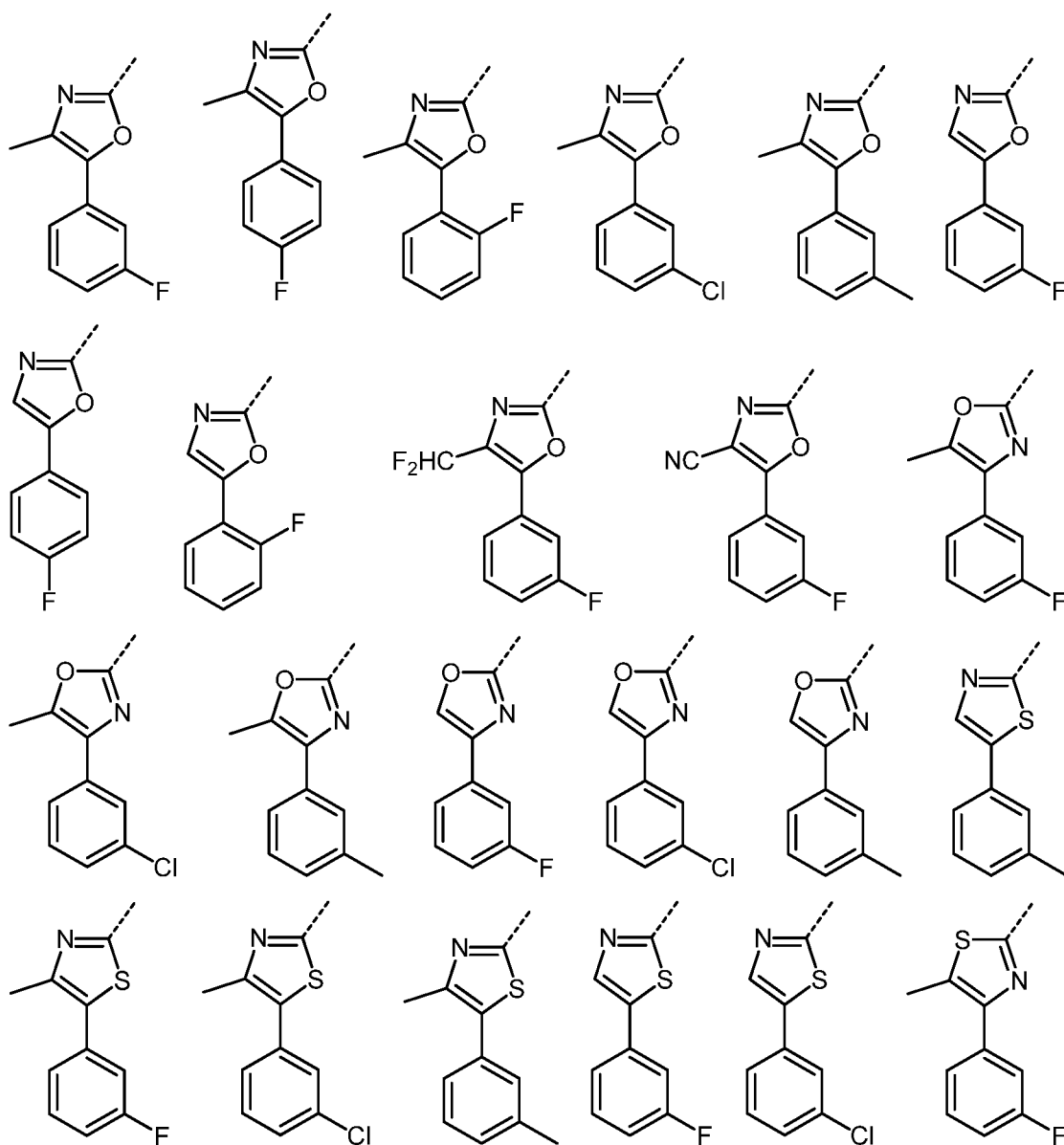
or a pharmaceutically acceptable salt thereof.

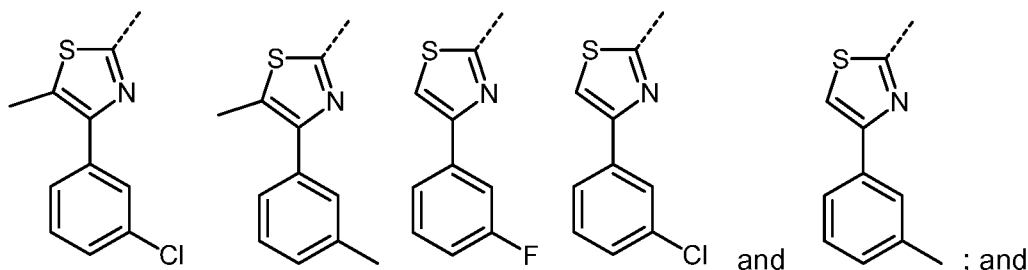
4. A compound according to any one of claims 1 to 3; wherein, in case Ar^2 represents 5- or 6-membered heteroaryl which is at least mono-substituted with phenyl or 5- or 6-membered heteroaryl, said phenyl or 5- or 6-membered heteroaryl substituent is attached in *meta*-position to the point of attachment of Ar^2 to the rest of the molecule;

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 1 to 3; wherein 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.) 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; and
- ii.) 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

- **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, which is independently unsubstituted, or mono-, or di-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, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- or **Ar¹** 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 **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, 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, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy.

or a pharmaceutically acceptable salt thereof.

7. A compound according to any one of claims 1 to 5; wherein **Ar**¹ is a group selected from the group consisting of any of the following groups:

a) phenyl, which is mono-, or di-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 a group selected from the group consisting of any of the following groups:

i.) phenyl which is independently mono-, or di-substituted (notably 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);

ii.) pyridinyl; which is 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

iii.) pyrazolyl, triazolyl, or pyrimidinyl which is independently mono-, or di-substituted (notably 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, and halogen;

b) phenyl, which is di-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);

- 5 ➤ and the other of said substituents is independently selected from the group consisting of cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

c) phenyl, which is tri-substituted; wherein

- 10 ➤ 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, 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;

- 15 ➤ and the other of said substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

d) 5- or 6-membered heteroaryl selected from the group consisting of oxazolyl, isoxazolyl, pyrimidinyl and pyrazinyl; which group is independently mono-, di-, or tri-substituted; wherein

- 20 ➤ 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;

- 25 ➤ 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;

30 e) 5-membered heteroaryl which is thiazolyl which is mono-substituted; wherein

- 35 ➤ said substituent 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, 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;

f) 5-membered heteroaryl which is thiazolyl which is di-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, 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 is independently selected from the group consisting of (C₁₋₄)alkoxy, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

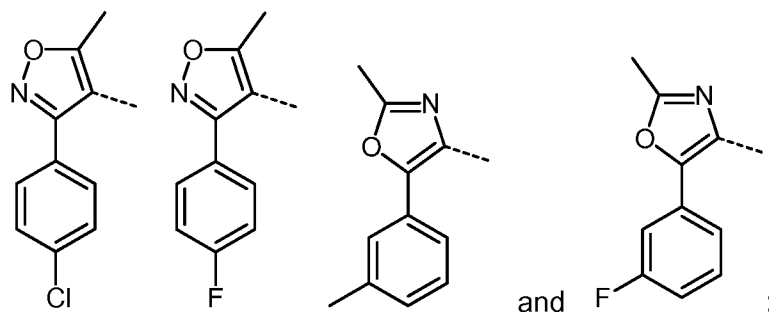
g) 5-membered heteroaryl which is thiazolyl which is di-substituted; wherein

- 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, wherein the substituents are independently selected from the group consisting of (C₁₋₄)alkyl, (C₁₋₄)alkoxy, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;
- and the other of said substituents is (C₁₋₄)alkyl;

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

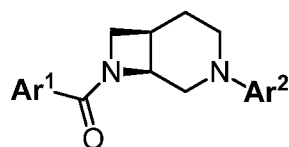
- one of said substituents is attached in *ortho*-position to the point of attachment of Ar¹ to the rest of the molecule, wherein said substituent is a group selected from the group consisting of
 - i.) phenyl,
 - ii.) oxadiazolyl, pyrazolyl, pyridinyl, or pyrimidinyl; and
 - iii.) [1,2,3]-triazole-2-yl;which group is independently unsubstituted, or mono-, or di-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, halogen, cyano, (C₁₋₃)fluoroalkyl, and (C₁₋₃)fluoroalkoxy;

or a pharmaceutically acceptable salt thereof.



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 (1S,6R):



Formula (I_{E1});

or a pharmaceutically acceptable salt thereof.

10. A compound according to claims 1 or 2 selected from the group consisting of:

- 10 [(1R*,6S*)-3-(6-Chloro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1S,6R)-3-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- 15 [(1R*,6S*)-3-(6,7-Dichloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1R*,6S*)-3-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1R*,6S*)-3-(6-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- 20 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1S,6R)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
- [(1R,6S)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-
- 25 [1,2,3]triazol-2-yl-phenyl)-methanone;

- {{(1S,6R)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{{(1R*,6S*)-3-[5-(3-Fluoro-phenyl)-4-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
5 {{(1S,6R)-3-[4-(3-Fluoro-phenyl)-5-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{{(1R*,6S*)-3-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
{{(1R*,6S*)-3-[4-Difluoromethyl-5-(3-fluoro-phenyl)-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
10 [(1R*,6S*)-3-(5-Chloro-benzo[d]isoxazol-3-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-[1,2,3]triazol-2-yl-phenyl)-methanone;
[(1R*,6S*)-3-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;
15 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1S,6R)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;
{{(1R*,6S*)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;
20 {{(1R*,6S*)-3-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(4-methyl-biphenyl-2-yl)-methanone;
[(1R*,6S*)-3-(6-Fluoro-benzothiazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
25 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
[(1S,6R)-3-(6-Fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
[(1R*,6S*)-3-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
30 {{(1R*,6S*)-3-[5-(3-Fluoro-phenyl)-4-methyl-oxazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
{{(1R*,6S*)-3-[4-(3-Fluoro-phenyl)-5-methyl-thiazol-2-yl]-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyrazol-1-yl-phenyl)-methanone;
35 [(1R*,6S*)-3-(5-Chloro-benzooxazol-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl}-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

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

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

10 [(1R*,6S*)-3-(7-Chloro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(5-methyl-2-pyridin-2-yl-phenyl)-methanone;

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

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

15 [(1S,6R)-3-(6,7-Difluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-(2-fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-methanone;

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

20 (2-Fluoro-3-methyl-6-[1,2,3]triazol-2-yl-phenyl)-[(1S,6R)-3-(6-fluoro-quinoxalin-2-yl)-3,8-diaza-bicyclo[4.2.0]oct-8-yl]-methanone;

or a pharmaceutically acceptable salt thereof.

11. 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.

25 **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
30 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/055840

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/008517 A2 (MERCK & CO INC [US]; COLEMAN PAUL J [US]; COX CHRISTOPHER D [US]; MCGA) 17 January 2008 (2008-01-17) cited in the application page 1, line 26 - page 2, line 3 -----	1-14
A	COLEMAN P J ET AL: "Design and synthesis of conformationally constrained N,N-disubstituted 1,4-diazepanes as potent orexin receptor antagonists", BIOORGANIC & 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 ----- -/--	1-14

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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