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(54) **1-(Pyridin-2-yl)-3-(quinolin-4-yl)urea derivatives and related compounds as glycogen synthase kinase 3 (GSK-3) inhibitors for the treatment of neurodegenerative diseases**

1-(Pyridin-2-yl)-3-(Chinolin-4-yl)Harnstoff-Derivate und verwandte Verbindungen als Glykogen-Synthase Kinase 3 (GSK-3) Inhibitoren zur Behandlung von neurodegenerativen Erkrankungen

Dérivés d'urea 1-(pyridin-2-yl)-3-(quinolin-4-yl) et composés similaires en tant qu'inhibiteurs de la glycogène synthase kinase 3 (GSK-3) pour le traitement de maladies neurodégénératives

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(73) Proprietor: **Abbvie Deutschland GmbH & Co. KG**  
**65189 Wiesbaden (DE)**

(72) Inventors:  
• **TURNER, Sean, Colm**  
**67071 Ludwigshafen (DE)**

- **MACK, Helmut**  
**67061 Ludwigshafen (DE)**
- **BAKKER, Margaretha, Henrica, Maria**  
**67061 Ludwigshafen (DE)**
- **VAN GAALEN, Marcel**  
**67061 Ludwigshafen (DE)**
- **HOFT, Carolin**  
**67061 Ludwigshafen (DE)**
- **HORNBERGER, Wilfried**  
**67061 Ludwigshafen (DE)**

(74) Representative: **Reitstötter Kinzebach**  
**Patentanwälte**  
**Im Zollhof 1**  
**67061 Ludwigshafen (DE)**

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**WO-A1-2009/130317 WO-A2-2008/046919**

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**Description**

## Technical Field

5 **[0001]** The present invention relates to novel heterocyclic compounds which are useful for inhibiting glycogen synthase kinase 3 (GSK-3), methods of making the compounds, compositions containing the compounds, and the compounds for use in a treatment.

## Background of the Invention

10 **[0002]** Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase encoded by two isoforms, GSK-3 $\alpha$  and GSK-3 $\beta$ , with molecular weights of 51 and 47 kDa, respectively. These share 97% sequence similarity in their kinase catalytic domains. The GSK-3 $\alpha$  isoform has an extended glycine-rich N-terminal tail. A minor splice variant of GSK-3 $\beta$  has been identified (expressed at ~15% of total) with a 13 amino acid insert within the kinase domain. This variant had a reduced activity towards tau. GSK-3 is highly conserved throughout evolution, and found in all mammals thus far with high homology in the kinase domain. Both isoforms are ubiquitously expressed in mammalian tissues, including the brain. Pharmacological GSK-3 inhibitors are not able to selectively inhibit one of the isoforms.

15 **[0003]** GSK-3 $\beta$  plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. Subsequently, it was recognised that GSK-3 $\beta$  was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several tauopathies.

20 **[0004]** Interestingly, protein kinase B (AKT) phosphorylation of GSK-3 $\beta$  results in a loss of kinase activity, and it has been proposed that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation of  $\beta$ -catenin (a protein involved in cell survival) by GSK-3 $\beta$ , results in its degradation by an ubiquitination dependent proteasome pathway.

25 **[0005]** Therefore it appears that inhibition of GSK-3 $\beta$  activity may result in neurotrophic activity. There is evidence that lithium, an uncompetitive inhibitor of GSK-3 $\beta$ , enhances neuriteogenesis in some models and can also increase neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

30 **[0006]** Further studies have shown that  $\beta$ -amyloid increases GSK-3 $\beta$  activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of  $\beta$ -amyloid are blocked by lithium chloride and by a GSK-3 $\beta$  antisense mRNA. These observations taken together suggest that GSK-3 $\beta$  may be the link between the two major pathological processes in Alzheimer's disease: abnormal APP (Amyloid Precursor Protein) processing and tau protein hyperphosphorylation.

35 **[0007]** These experimental observations indicate that compounds which modulate the GSK-3 $\beta$  activity may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, but are not limited to: behavioural and psychiatric symptoms of dementia, Parkinson's disease, tauopathies (e.g. frontotemporal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy, argyophilic grain disease) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; bipolar disorders, retinopathies and glaucoma.

40 **[0008]** GSK-3 $\beta$  may also have utility in the treatment of pain.

45 **[0009]** GSK-3 $\beta$  may further have utility in the treatment of inflammatory diseases, such as rheumatoid arthritis and osteoarthritis.

**[0010]** GSK-3 $\beta$  may also have utility in the treatment of other diseases such as: Non-insulin dependent diabetes and obesity; osteoporosis; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

50 **[0011]** A review on GSK-3, its functions, its therapeutic potential and its possible inhibitors is given in "Glycogen Synthase Kinase 3 (GSK-3) and its inhibitors: Drug Discovery and Developments" by A. Martinez et al. (editors), John Wiley and Sons, 2006.

**[0012]** WO 03/053330 describes 2-oxindoles substituted in the 3-position with a bicyclic hetaryl group and their use for treating conditions related to glycogen synthase kinase-3. WO 03/082853 describes substituted 2-oxindoles substituted in the 3-position with a monocyclic hetaryl group and their use for treating conditions related to glycogen synthase kinase-3. WO 2005/123672 relates to 2-hydroxyindoles carrying in the 3-position an optionally fused pyrid-2-yl ring and their use for inhibiting kinases. WO 2005/061519 relates to 2-hydroxyindoles carrying in the 3-position a pyrid-2-yl ring fused to an aromatic or heteroaromatic ring and their use for inhibiting kinases.

55 **[0013]** WO 2008/046919 relates to quinolinyl or other fused systems which carry a urea or an acetamido group which

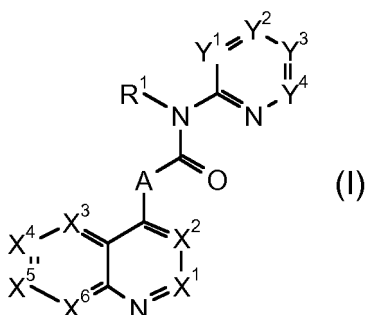
in turn is substituted by a nitrogen-containing heteroaromatic 5- or 6-membered ring bound in  $\alpha$ -position to its nitrogen ring atom, and the use of these compounds for inhibiting glycogen synthase kinase 3 (GSK-3).

[0014] WO 2009/130317 relates to quinolinyl or other fused systems which carry a urea or an acetamido group which in turn is substituted by a nitrogen-containing heteroaromatic 5- or 6-membered ring bound in  $\alpha$ -position to its nitrogen ring atom, where either the fused system or the heteroaromatic 5- or 6-membered ring carries a bicyclic or tricyclic saturated or unsaturated heterocyclic ring, and the use of these compounds for inhibiting glycogen synthase kinase 3 (GSK-3).

#### Summary of the Invention

[0015] The object of the present invention is to provide compounds which modulate the GSK-3 $\beta$  activity, in particular compounds which have an inhibitory activity on GSK-3 $\beta$  and which thus are useful as an active ingredient of a composition for preventive and/or therapeutic treatment of a disease caused by abnormal GSK-3 $\beta$  activity, especially of neurodegenerative and/or inflammatory diseases. More specifically, the goal is to provide novel compounds useful as an active ingredient of a composition that enables prevention and/or treatment of neurodegenerative diseases such as Alzheimer's disease.

[0016] It was surprisingly found that the problem is solved by providing a heterocyclic compound of the general formula I



the stereoisomers, prodrugs, N-oxides, tautomers and/or physiologically tolerated acid addition salts thereof, and the compounds of the general formula I, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, wherein

A is selected from the group consisting of  $\text{CRA}^1\text{RA}^2$  and  $\text{NR}^B$ ; where

$\text{RA}^1$  and  $\text{RA}^2$  are independently of each other selected from the group consisting of hydrogen,  $\text{C}_1$ - $\text{C}_2$ -alkyl,  $\text{C}_1$ - $\text{C}_2$ -haloalkyl,  $\text{NH}_2$  and OH; and

$\text{R}^B$  is selected from H,  $\text{C}_1$ - $\text{C}_4$ -alkyl and  $\text{C}_1$ - $\text{C}_4$ -haloalkyl;

$\text{X}^1$  and  $\text{X}^2$  are independently of each other selected from the group consisting of  $\text{CR}^2$  and N;

$\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$  and  $\text{X}^6$  are independently of each other selected from the group consisting of  $\text{CR}^3$ ,  $\text{CR}^4$  and N; with the proviso that no more than two of  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$  and  $\text{X}^6$  are  $\text{CR}^4$ ;

$\text{Y}^1$ ,  $\text{Y}^2$ ,  $\text{Y}^3$  and  $\text{Y}^4$  are independently of each other selected from the group consisting of  $\text{CR}^4$ ,  $\text{CR}^5$  and N; with the proviso that at most one of  $\text{Y}^1$ ,  $\text{Y}^2$ ,  $\text{Y}^3$  and  $\text{Y}^4$  is N and with the proviso that at most one of  $\text{Y}^1$ ,  $\text{Y}^2$ ,  $\text{Y}^3$  and  $\text{Y}^4$  is  $\text{CR}^4$ ; and with the proviso that one of  $\text{Y}^1$ ,  $\text{Y}^2$ ,  $\text{Y}^3$  and  $\text{Y}^4$  is  $\text{CR}^4$ , if none of  $\text{X}^3$ ,  $\text{X}^4$ ,  $\text{X}^5$  and  $\text{X}^6$  is  $\text{CR}^4$ ;

$\text{R}^1$  is selected from hydrogen,  $\text{C}_1$ - $\text{C}_4$ -alkyl and  $\text{C}_1$ - $\text{C}_4$ -haloalkyl;

each  $\text{R}^2$  is independently selected from the group consisting of hydrogen, OH, halogen (preferably F or Cl, more preferably F), CN,  $\text{C}_1$ - $\text{C}_6$ -alkyl,  $\text{C}_1$ - $\text{C}_6$ -haloalkyl,  $\text{C}_1$ - $\text{C}_6$ -alkoxy,  $\text{C}_1$ - $\text{C}_6$ -haloalkoxy and  $\text{NR}^a\text{R}^b$ ; or two radicals  $\text{R}^2$  bonded at the carbon atoms of groups  $\text{X}^1$  and  $\text{X}^2$ , together with the carbon atoms to which they are bonded, form a 5- or 6-membered saturated or unsaturated ring which may contain 1 or 2 heteroatoms as ring

members selected from the group consisting of N, O and S and which optionally carries 1, 2 or 3 substituents R<sup>6</sup>;

each R<sup>3</sup> is independently selected from the group consisting of hydrogen, CN, NR<sup>a</sup>R<sup>b</sup>, OH, halogen (preferably F or Cl, more preferably F), C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-haloalkenyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-NR<sup>a</sup>R<sup>b</sup> and an aromatic radical Ar, which is selected from the group consisting of phenyl and a 5- or 6-membered N- or C-bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein Ar is unsubstituted or carries one or two radicals R<sup>7</sup> and wherein Ar may also be bonded via a CH<sub>2</sub> group;

R<sup>4</sup> is a C-bound saturated or partially unsaturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from O, N, S, NO, SO and SO<sub>2</sub> as ring members, where the heterocyclic ring optionally carries 1, 2 or 3 C- or N-bound substituents R<sup>8</sup>;

R<sup>5</sup> is selected from the group consisting of hydrogen, CN, NR<sup>a</sup>R<sup>b</sup>, OH, halogen (preferably F or Cl, more preferably F), C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-haloalkenyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-NR<sup>a</sup>R<sup>b</sup> and an aromatic radical Ar, which is selected from the group consisting of phenyl and a 5- or 6-membered N- or C-bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein Ar is unsubstituted or carries one or two radicals R<sup>7</sup> and wherein Ar may also be bonded via a CH<sub>2</sub> group;

R<sup>6</sup> and R<sup>8</sup>, independently of each other and independently of each occurrence, are selected from the group consisting of CN, NR<sup>a</sup>R<sup>b</sup>, OH, halogen (preferably F or Cl, more preferably F), C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-haloalkenyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-NR<sup>a</sup>R<sup>b</sup> and an aromatic radical Ar, which is selected from the group consisting of phenyl and a 5- or 6-membered N- or C-bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein Ar is unsubstituted or carries one or two radicals R<sup>7</sup> and wherein Ar may also be bonded via a CH<sub>2</sub> group;

each R<sup>7</sup> is independently selected from the group consisting of halogen (preferably F or Cl, more preferably F), CN, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, NR<sup>a</sup>R<sup>b</sup>, a phenyl group and a 5- or 6-membered heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein phenyl and the heteroaromatic radical are, independently of each other, unsubstituted or substituted by 1, 2, 3 or 4 radicals selected from halogen, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy; and

R<sup>a</sup> and R<sup>b</sup> are independently of each other selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl and C<sub>1</sub>-C<sub>4</sub>-haloalkylcarbonyl; or R<sup>a</sup> and R<sup>b</sup> form, together with the nitrogen atom to which they are bonded, a 3-, 4-, 5-, 6- or 7-membered saturated or unsaturated aromatic or non-aromatic N-heterocyclic ring, which may contain 1 further heteroatom or heteroatom containing group selected from the group consisting of O, S, SO, SO<sub>2</sub> and N as a ring member;

where the prodrugs are selected from compounds of formula I, wherein a secondary nitrogen ring atom of the ring R<sup>4</sup> or a nitrogen atom of a primary or secondary amino group being a substituent R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and/or R<sup>8</sup> forms an amide/peptide bond in that this nitrogen atom is substituted by a C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl group, by benzoyl, or by glycine, alanine, serine or phenylalanine bonded via CO; or said nitrogen atom carries a group -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup>, wherein R<sup>x</sup> and R<sup>y</sup> independently of each other are C<sub>1</sub>-C<sub>4</sub>-alkyl.

**[0017]** Thus, the present invention relates to compounds of the formula I as defined herein and in the claims, to the stereoisomers, tautomers, prodrugs and/or physiologically tolerated acid addition salts thereof, and also to compounds of the general formula I, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope.

**[0018]** According to a further aspect, the present invention relates to a pharmaceutical composition comprising at least one compound of the formula I as defined herein, a stereoisomer, a tautomer, a prodrug and/or a physiologically tolerated acid addition salt thereof or comprising at least one heterocyclic compound as defined above, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, optionally together with at least one physiologically acceptable carrier and/or auxiliary substance.

**[0019]** According to a further aspect, the present invention relates to the use of at least one compound of the formula

I as defined herein, the stereoisomers, tautomers, prodrugs and/or physiologically tolerated acid addition salts thereof, for the preparation of a medicament for the treatment of a medical disorder susceptible to treatment with a compound that modulates glycogen synthase kinase 3 $\beta$  activity.

**[0020]** According to a further aspect, the present invention relates to the compounds of the formula I as defined herein for use in the treatment of a medical disorder susceptible to treatment with a compound that modulates glycogen synthase kinase 3 $\beta$  activity, said method comprising administering an effective amount of at least one compound of the formula I as defined herein, a stereoisomer, a tautomer, a prodrug and/or a physiologically tolerated acid addition salt thereof, to a subject in need thereof.

Detailed description of the invention

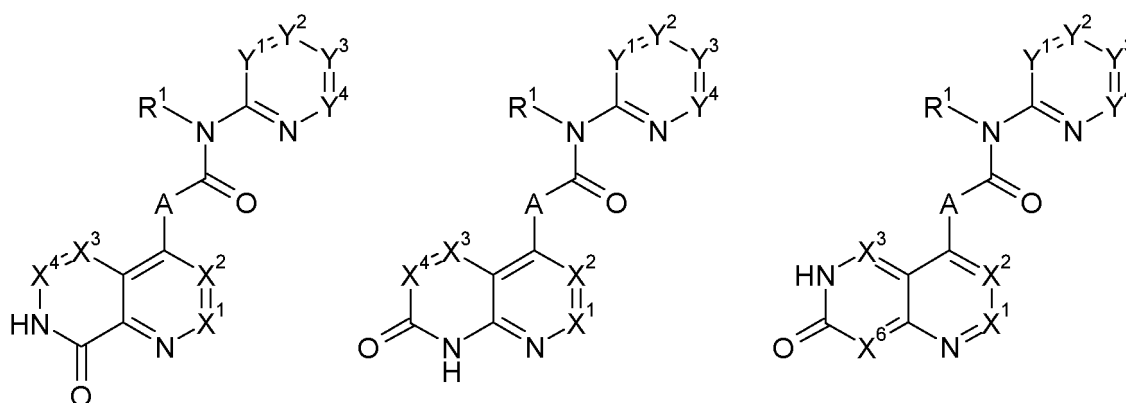
**[0021]** Provided the compounds of the formula I of a given constitution may exist in different spatial arrangements, for example if they possess one or more centers of asymmetry, polysubstituted rings or double bonds, or as different tautomers, it is also possible to use enantiomeric mixtures, in particular racemates, diastereomeric mixtures and tautomeric mixtures, preferably, however, the respective essentially pure enantiomers, diastereomers and tautomers of the compounds of formula I and/or of their salts.

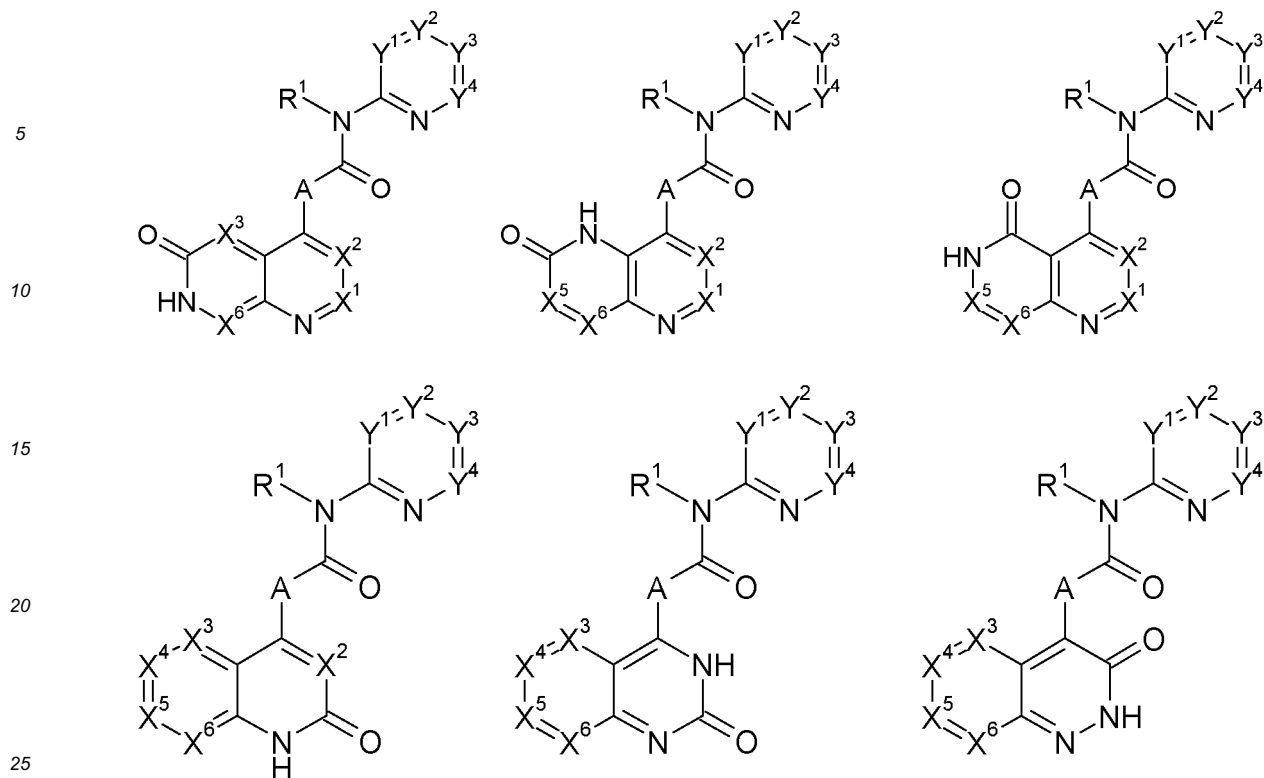
**[0022]** It is likewise possible to use physiologically tolerated salts of the compounds of the formula I, especially acid addition salts with physiologically tolerated acids. Examples of suitable physiologically tolerated organic and inorganic acids are hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, C<sub>1</sub>-C<sub>4</sub>-alkylsulfonic acids, such as methanesulfonic acid, aromatic sulfonic acids, such as benzenesulfonic acid and toluenesulfonic acid, oxalic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, adipic acid and benzoic acid. Other utilizable acids are described in Fortschritte der Arzneimittelforschung [Advances in drug research], Volume 10, pages 224 et seq., Birkhäuser Verlag, Basel and Stuttgart, 1966.

**[0023]** In the terms of the present invention, "prodrugs" are compounds which are metabolized in vivo to give the compounds of the invention of formula I. Typical examples for prodrugs are for example described in C.G. Wermeth (editor): The Practice of Medicinal Chemistry, Academic Press, San Diego, 1996, pages 671-715. Examples are phosphates, carbamates, aminoacids, esters, amides, peptides, urea and the like. In the present case, suitable prodrugs are compounds of formula I wherein an external nitrogen atom, to be more precise a secondary nitrogen ring atom of the ring R<sup>4</sup> or a nitrogen atom of a primary or secondary amino group being a substituent R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and/or R<sup>8</sup> (= at least one of R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is NR<sup>a</sup>R<sup>b</sup>, wherein at least one of R<sup>a</sup> and R<sup>b</sup> is H), forms an amide/peptide bond in that this nitrogen atom is substituted by a C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl group, e.g. by acetyl, propionyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl or tert-butylcarbonyl (pivaloyl), by benzoyl, or by an aminoacid group bonded via CO, to be more precise glycine, alanine, serine, phenylalanine and the like bonded via CO. Suitable prodrugs are furthermore alkylcarbonyloxyalkylcarbamates, wherein said nitrogen atom carries a group -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup>, wherein R<sup>x</sup> and R<sup>y</sup> independently of each other are C<sub>1</sub>-C<sub>4</sub>-alkyl. These carbamate compounds are for example described in J. Alexander, R. Cargill, S. R. Michelson, H. Schwam, J. Medicinal Chem. 1988, 31(2), 318-322. These groups can be removed under metabolic conditions and result in compounds I wherein said nitrogen atom carries a hydrogen atom instead. Also, R<sup>8</sup>, if bound to a nitrogen ring atom of R<sup>4</sup>, may be chosen so as to be hydrolysable under metabolic conditions and thus to be one of the above-listed

groups (i.a. a C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl group, an aminoacid group bonded via CO or a group -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup>).

**[0024]** The compounds of formula I may also be present in the form of the respective tautomers. Tautomerism may be present in compounds I wherein R<sup>2</sup> or R<sup>3</sup> is OH and this substituent is bonded to a carbon atom which is in  $\alpha$ -position to a nitrogen ring atom. This results for example in following tautomeric formulae:





**[0025]** The organic moieties mentioned in the above definitions of the variables are - like the term halogen - collective terms for individual listings of the individual group members. The prefix C<sub>n</sub>-C<sub>m</sub> indicates in each case the possible number of carbon atoms in the group.

**[0026]** The term halogen denotes in each case fluorine, bromine, chlorine or iodine, in particular fluorine, chlorine or bromine.

**[0027]** C<sub>1</sub>-C<sub>2</sub>-Alkyl is methyl or ethyl; C<sub>1</sub>-C<sub>3</sub>-alkyl is additionally n-propyl or isopropyl.

**[0028]** C<sub>1</sub>-C<sub>4</sub>-Alkyl is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms. Examples are methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl (sec-butyl), isobutyl and tert-butyl.

**[0029]** C<sub>1</sub>-C<sub>6</sub>-Alkyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms. Examples include the residues mentioned above for C<sub>1</sub>-C<sub>4</sub>-alkyl and also pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl.

**[0030]** C<sub>1</sub>-C<sub>2</sub>-Haloalkyl is an alkyl group having 1 or 2 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by halogen atoms as mentioned above, such as chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, bromomethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-chloroethyl, 2-bromoethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 2,2,2-trichloroethyl or pentafluoroethyl.

**[0031]** C<sub>1</sub>-C<sub>4</sub>-Haloalkyl is a straight-chain or branched alkyl group having 1 to 4 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by halogen atoms as mentioned above. Examples are, apart those listed above for C<sub>1</sub>-C<sub>2</sub>-haloalkyl, 1-chloropropyl, 1-bromopropyl, 1-fluoropropyl, 2-chloropropyl, 2-bromopropyl, 2-fluoropropyl, 3-chloropropyl, 3-bromopropyl, 3-fluoropropyl, 1,1-dichloropropyl, 1,1-difluoropropyl, 2,2-dichloropropyl, 2,2-difluoropropyl, 2,3-dichloropropyl, 2,3-difluoropropyl, 1,3-dichloropropyl, 1,3-difluoropropyl, 3,3-dichloropropyl, 3,3-difluoropropyl, 1,1,2-trichloropropyl, 1,1,2-trifluoropropyl, 1,2,2-trichloropropyl, 1,2,2-trifluoropropyl, 1,2,3-trichloropropyl, 1,2,3-trifluoropropyl, 2,2,3-trichloropropyl, 2,2,3-trifluoropropyl, 3,3,3-trichloropropyl, 3,3,3-trifluoropropyl, 1,1,1-trifluoroprop-2-yl, 1-chlorobutyl, 1-bromobutyl, 1-fluorobutyl, 2-chlorobutyl, 2-bromobutyl, 2-fluorobutyl, 3-chlorobutyl, 3-bromobutyl, 3-fluorobutyl, 4-chlorobutyl, 4-bromobutyl, 4-fluorobutyl, and the like.

**[0032]** C<sub>1</sub>-C<sub>6</sub>-Haloalkyl is a straight-chain or branched alkyl group having 1 to 6 carbon atoms (as mentioned above), where at least one of the hydrogen atoms in these groups is replaced by halogen atoms as mentioned above. Examples are, apart those listed above for C<sub>1</sub>-C<sub>4</sub>-haloalkyl, chloropentyl, bromopentyl, fluoropentyl, chlorohexyl, bromohexyl,

fluorohexyl, and the like.

**[0033]** C<sub>1</sub>-C<sub>2</sub>-Fluoroalkyl (= fluorinated C<sub>1</sub>-C<sub>2</sub>-alkyl) is an alkyl group having 1 or 2 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms, such as difluoromethyl, trifluoromethyl, 1-fluoroethyl, (R)-1-fluoroethyl, (S)-1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, or pentafluoroethyl.

**[0034]** C<sub>1</sub>-C<sub>4</sub>-Fluoroalkyl (= fluorinated C<sub>1</sub>-C<sub>4</sub>-alkyl) is a straight-chain or branched alkyl group having 1 to 4 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms. Examples are, apart those listed above for C<sub>1</sub>-C<sub>2</sub>-fluoroalkyl, 1-fluoropropyl, (R)-1-fluoropropyl, (S)-1-fluoropropyl, 2-fluoropropyl, (R)-2-fluoropropyl, (S)-2-fluoropropyl, 3-fluoropropyl, 1,1-difluoropropyl, 2,2-difluoropropyl, 1,2-difluoropropyl, 2,3-difluoropropyl, 1,3-difluoropropyl, 3,3-difluoropropyl, 1,1,2-trifluoropropyl, 1,2,2-trifluoropropyl, 1,2,3-trifluoropropyl, 2,2,3-trifluoropropyl, 3,3,3-trifluoropropyl, 1,1,1-trifluoroprop-2-yl, 2-fluoro-1-methylethyl, (R)-2-fluoro-1-methylethyl, (S)-2-fluoro-1-methylethyl, 2,2-difluoro-1-methylethyl, (R)-2,2-difluoro-1-methylethyl, (S)-2,2-difluoro-1-methylethyl, 1,2-difluoro-1-methylethyl, (R)-1,2-difluoro-1-methylethyl, (S)-1,2-difluoro-1-methylethyl, 2,2,2-trifluoro-1-methylethyl, (R)-2,2,2-trifluoro-1-methylethyl, (S)-2,2,2-trifluoro-1-methylethyl, 2-fluoro-1-(fluoromethyl)ethyl, 1-(difluoromethyl)-2,2-difluoroethyl, 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 1-(trifluoromethyl)-1,2,2,2-tetrafluoroethyl, 1-fluorobutyl, (R)-1-fluorobutyl, (S)-1-fluorobutyl, 2-fluorobutyl, (R)-2-fluorobutyl, (S)-2-fluorobutyl, 3-fluorobutyl, (R)-3-fluorobutyl, (S)-3-fluorobutyl, 4-fluorobutyl, 1,1-difluorobutyl, 2,2-difluorobutyl, 3,3-difluorobutyl, 4,4-difluorobutyl, 4,4,4-trifluorobutyl and the like.

**[0035]** C<sub>1</sub>-C<sub>6</sub>-Fluoroalkyl (= fluorinated C<sub>1</sub>-C<sub>6</sub>-alkyl) is a straight-chain or branched alkyl group having 1 to 6 carbon atoms (as mentioned above), where at least one of the hydrogen atoms, e.g. 1, 2, 3, 4 or 5 hydrogen atoms in these groups are replaced by fluorine atoms. Examples are, apart those listed above for C<sub>1</sub>-C<sub>4</sub>-fluoroalkyl, 1-fluoropentyl, (R)-1-fluoropentyl, (S)-1-fluoropentyl, 2-fluoropentyl, (R)-2-fluoropentyl, (S)-2-fluoropentyl, 3-fluoropentyl, (R)-3-fluoropentyl, (S)-3-fluoropentyl, 4-fluoropentyl, (R)-4-fluoropentyl, (S)-4-fluoropentyl, 5-fluoropentyl, (R)-5-fluoropentyl, (S)-5-fluoropentyl, 1-fluorohexyl, (R)-1-fluorohexyl, (S)-1-fluorohexyl, 2-fluorohexyl, (R)-2-fluorohexyl, (S)-2-fluorohexyl, 3-fluorohexyl, (R)-3-fluorohexyl, (S)-3-fluorohexyl, 4-fluorohexyl, (R)-4-fluorohexyl, (S)-4-fluorohexyl, 5-fluorohexyl, (R)-5-fluorohexyl, (S)-5-fluorohexyl, 6-fluorohexyl, (R)-6-fluorohexyl, (S)-6-fluorohexyl, and the like.

**[0036]** C<sub>1</sub>-C<sub>4</sub>-Alkoxy is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms, which is bound to the remainder of the molecule via an oxygen atom. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, 2-butoxy, isobutoxy and tert-butoxy.

**[0037]** C<sub>1</sub>-C<sub>6</sub>-Alkoxy is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms, which is bound to the remainder of the molecule via an oxygen atom. Examples include, apart those listed above for C<sub>1</sub>-C<sub>4</sub>-alkoxy, pentyloxy, 1-methylbutoxy, 2-methylbutoxy, 3-methylbutoxy, 2,2-dimethylpropoxy, 1-ethylpropoxy, hexyloxy, 1,1-dimethylpropoxy, 1,2-dimethylpropoxy, 1-methylpentyloxy, 2-methylpentyloxy, 3-methylpentyloxy, 4-methylpentyloxy, 1,1-dimethylbutyloxy, 1,2-dimethylbutyloxy, 1,3-dimethylbutyloxy, 2,2-dimethylbutyloxy, 2,3-dimethylbutyloxy, 3,3-dimethylbutyloxy, 1-ethylbutyloxy, 2-ethylbutyloxy, 1,1,2-trimethylpropoxy, 1,2,2-trimethylpropoxy, 1-ethyl-1-methylpropoxy and 1-ethyl-2-methylpropoxy.

**[0038]** Halogenated C<sub>1</sub>-C<sub>6</sub>-alkoxy (which is also termed C<sub>1</sub>-C<sub>6</sub>-haloalkoxy), in particular fluorinated C<sub>1</sub>-C<sub>6</sub>-alkoxy (also termed C<sub>1</sub>-C<sub>6</sub>-fluoroalkoxy) is a straight-chain or branched alkoxy group having from 1 to 6, in particular 1 to 4 carbon atoms (= fluorinated C<sub>1</sub>-C<sub>4</sub>-alkoxy), wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a halogen atoms, in particular fluorine atoms such as in fluoromethoxy, difluoro-methoxy, trifluoromethoxy, (R)-1-fluoroethoxy, (S)-1-fluoroethoxy, 2-fluoroethoxy, 1,1-difluoroethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, (R)-1-fluoropropoxy, (S)-1-fluoropropoxy, (R)-2-fluoropropoxy, (S)-2-fluoropropoxy, 3-fluoropropoxy, 1,1-difluoropropoxy, 2,2-difluoropropoxy, 3,3-difluoropropoxy, 3,3,3-trifluoropropoxy, (R)-2-fluoro-1-methylethoxy, (S)-2-fluoro-1-methylethoxy, (R)-2,2-difluoro-1-methylethoxy, (S)-2,2-difluoro-1-methylethoxy, (R)-1,2-difluoro-1-methylethoxy, (S)-1,2-difluoro-1-methylethoxy, (R)-2,2,2-trifluoro-1-methylethoxy, (S)-2,2,2-trifluoro-1-methylethoxy, 2-fluoro-1-(fluoromethyl)ethoxy, 1-(difluoromethyl)-2,2-difluoroethoxy, (R)-1-fluorobutoxy, (S)-1-fluorobutoxy, 2-fluorobutoxy, 3-fluorobutoxy, 4-fluorobutoxy, 1,1-difluorobutoxy, 2,2-difluorobutoxy, 3,3-difluorobutoxy, 4,4-difluorobutoxy, 4,4,4-trifluorobutoxy, and the like.

**[0039]** C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonyl is a straight-chain or branched alkyl group having from 1 to 4 carbon atoms, which is bound to the remainder of the molecule via a carbonyl group (CO), such as in acetyl, propionyl, isopropylcarbonyl, butylcarbonyl, sec-butylcarbonyl, isobutylcarbonyl, and tert-butylcarbonyl.

**[0040]** C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonyl is a straight-chain or branched alkyl group having from 1 to 6 carbon atoms, which is bound to the remainder of the molecule via a carbonyl group (CO). Examples include, apart those listed above for C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, pentylcarbonyl, hexylcarbonyl and the constitutional isomers thereof.

**[0041]** C<sub>1</sub>-C<sub>4</sub>-Haloalkylcarbonyl is a straight-chain or branched haloalkyl group having from 1 to 4 carbon atoms as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO)

**[0042]** C<sub>1</sub>-C<sub>6</sub>-Haloalkylcarbonyl is a straight-chain or branched haloalkyl group having from 1 to 6 carbon atoms as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO)

**[0043]** C<sub>1</sub>-C<sub>4</sub>-Fluoroalkylcarbonyl is a straight-chain or branched fluoroalkyl group having from 1 to 4 carbon atoms as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO)

**[0044]** C<sub>1</sub>-C<sub>6</sub>-fluoroalkylcarbonyl is a straight-chain or branched fluoroalkyl group having from 1 to 6 carbon atoms as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO)

**[0045]** C<sub>1</sub>-C<sub>6</sub>-Alkoxy carbonyl is a straight-chain or branched alkoxy group having from 1 to 6, especially 1 to 4 carbon atoms (= C<sub>1</sub>-C<sub>4</sub>-alkoxy carbonyl), in particular 1 to 3 carbon atoms (= C<sub>1</sub>-C<sub>3</sub>-alkoxy carbonyl), which is bound to the remainder of the molecule via a carbonyl group (CO), such as in methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, and isopropyloxycarbonyl.

**[0046]** C<sub>1</sub>-C<sub>6</sub>-Haloalkoxy carbonyl is a straight-chain or branched haloalkoxy group having from 1 to 6, especially 1 to 4 carbon atoms (= C<sub>1</sub>-C<sub>4</sub>-haloalkoxy carbonyl), in particular 1 to 3 carbon atoms (= C<sub>1</sub>-C<sub>3</sub>-haloalkoxy carbonyl) as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO).

**[0047]** C<sub>1</sub>-C<sub>6</sub>-Fluoroalkoxy carbonyl is a straight-chain or branched fluoroalkoxy group having from 1 to 6, especially 1 to 4 carbon atoms (= C<sub>1</sub>-C<sub>4</sub>-fluoroalkoxy carbonyl), in particular 1 to 3 carbon atoms (= C<sub>1</sub>-C<sub>3</sub>-fluoroalkoxy carbonyl) as defined above, which is bound to the remainder of the molecule via a carbonyl group (CO).

**[0048]** C<sub>3</sub>-C<sub>6</sub>-Cycloalkyl is a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. C<sub>3</sub>-C<sub>4</sub>-cycloalkyl is a cycloaliphatic radical having from 3 to 4 C atoms, such as cyclopropyl and cyclobutyl.

**[0049]** C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl is a cycloaliphatic radical having from 3 to 7 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

**[0050]** C<sub>3</sub>-C<sub>6</sub>-Halocycloalkyl is a cycloaliphatic radical having from 3 to 6 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a halogen atoms, preferably by fluorine atoms such as in 1-fluorocyclopropyl, 2-fluorocyclopropyl, (S)- and (R)-2,2-difluorocyclopropyl, 1,2-difluorocyclopropyl, 2,3-difluorocyclopropyl, penta-fluorocyclopropyl, 1-fluorocyclobutyl, 2-fluorocyclobutyl, 3-fluorocyclobutyl, 2,2-difluorocyclobutyl, 3,3-difluorocyclobutyl, 1,2-difluorocyclobutyl, 1,3-difluorocyclobutyl, 2,3-difluorocyclobutyl, 2,4-difluorocyclobutyl, or 1,2,2-trifluorocyclobutyl.

**[0051]** C<sub>3</sub>-C<sub>7</sub>-Halocycloalkyl is a cycloaliphatic radical having from 3 to 7 C atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by a halogen atoms, preferably by fluorine atoms. Examples include, apart those listed above for C<sub>3</sub>-C<sub>6</sub>-fluorocycloalkyl, 1-fluorocycloheptyl, 2-fluorocycloheptyl, 3-fluorocycloheptyl, 4-fluorocycloheptyl, 1,2-difluorocycloheptyl, 1,3-difluorocycloheptyl, 1,4-difluorocycloheptyl, 2,2-difluorocycloheptyl, 2,3-difluorocycloheptyl, 2,4-difluorocycloheptyl, 2,5-difluorocycloheptyl, 2,6-difluorocycloheptyl, 2,7-difluorocycloheptyl, 3,3-difluorocycloheptyl, 3,4-difluorocycloheptyl, 3,5-difluorocycloheptyl, 3,6-difluorocycloheptyl, 4,4-difluorocycloheptyl, 4,5-difluorocycloheptyl, and the like.

**[0052]** C<sub>2</sub>-C<sub>4</sub>-Alkenyl is a singly unsaturated hydrocarbon radical having 2, 3 or 4 C-atoms and one C-C double bond, e.g. vinyl, allyl (2-propen-1-yl), 1-propen-1-yl, 2-propen-2-yl, buten-1-yl, buten-2-yl, buten-3-yl, methallyl (2-methylprop-2-en-1-yl) and the like. C<sub>2</sub>-C<sub>4</sub>-Haloalkenyl is a singly unsaturated hydrocarbon radical having 2, 3 or 4 C-atoms, wherein at least one, e.g. 1, 2, 3, 4 or all of the hydrogen atoms are replaced by halogen atoms, preferably by fluorine atoms such as in 1-fluorovinyl, 2-fluorovinyl, 2,2-fluorovinyl, 3,3,3-fluoropropenyl, 1,1-difluoro-2-propenyl, 1-fluoro-2-propenyl and the like.

**[0053]** Examples for 5- or 6-membered N- or C-bound heteroaromatic radicals comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members are pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]-1H-triazol-1-yl, [1,2,3]-1H-triazol-4-yl, [1,2,3]-1H-triazol-5-yl, [1,2,3]-2H-triazol-2-yl, [1,2,3]-2H-triazol-4-yl, [1,2,3]-2H-triazol-5-yl, [1,2,4]-1H-triazol-1-yl, [1,2,4]-1H-triazol-3-yl, [1,2,4]-1H-triazol-5-yl, [1,2,4]-4H-triazol-3-yl, [1,2,4]-4H-triazol-4-yl, oxadiazolyl, thiadiazolyl, [1,2,3,4]-1H-tetrazol-1-yl, [1,2,3,4]-1H-tetrazol-5-yl, [1,2,3,4]-2H-tetrazol-2-yl, [1,2,3,4]-2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl and triazin-2-yl.

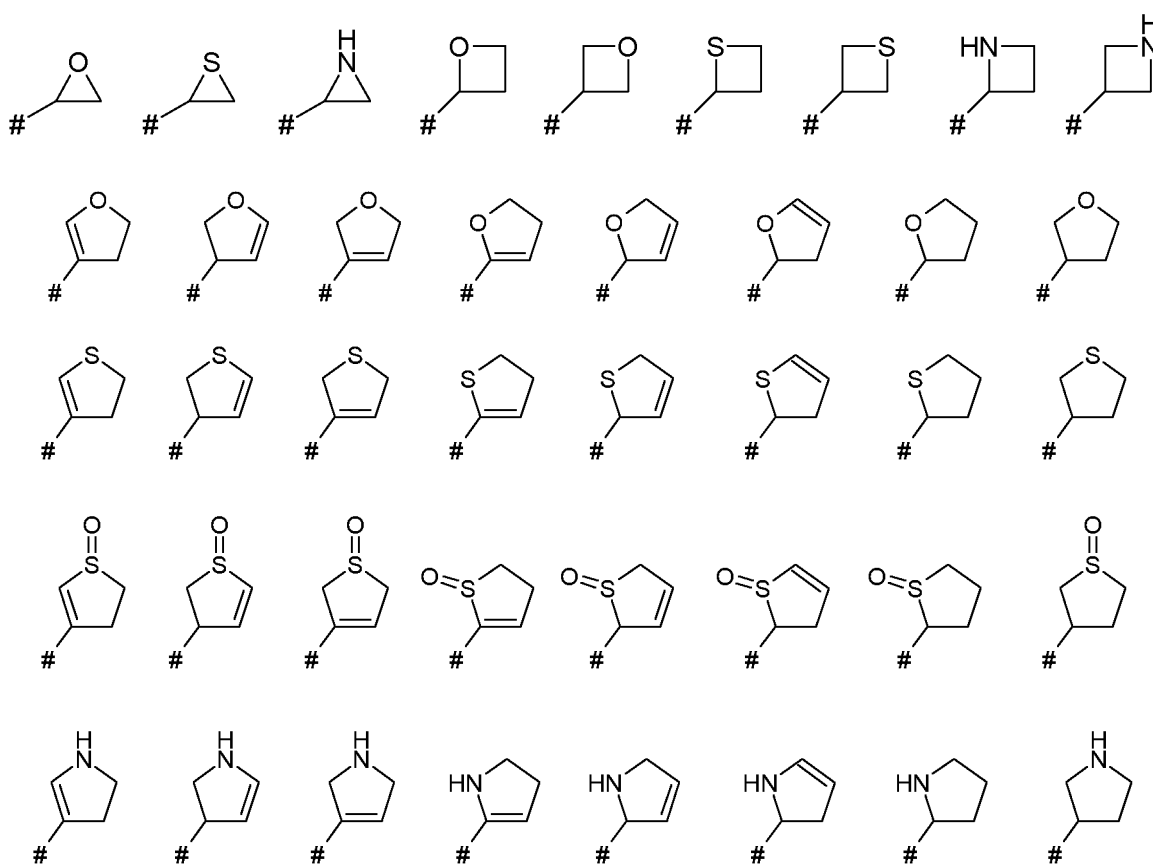
**[0054]** Examples for 5- or 6-membered N- or C-bound heteroaromatic radicals comprising 1, 2 or 3 heteroatoms independently selected from O, S and N as ring members are furan-2-yl, furan-3-yl, thien-2-yl, thien-3-yl, pyrrol-1-yl, pyrrol-2-yl, pyrrol-3-yl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, pyrazol-5-yl, imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, [1,2,3]-1H-triazol-1-yl, [1,2,3]-1H-triazol-4-yl, [1,2,3]-1H-triazol-5-yl, [1,2,3]-2H-triazol-2-yl, [1,2,3]-2H-triazol-4-yl, [1,2,3]-2H-triazol-5-yl, [1,2,4]-1H-triazol-1-yl, [1,2,4]-1H-triazol-3-yl, [1,2,4]-1H-triazol-5-yl, [1,2,4]-4H-triazol-3-yl, [1,2,4]-4H-triazol-4-yl, oxadiazolyl, thiadiazolyl, [1,2,3,4]-1H-tetrazol-1-yl, [1,2,3,4]-1H-tetrazol-5-yl, [1,2,3,4]-2H-tetrazol-2-yl, [1,2,3,4]-2H-tetrazol-5-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, pyridazin-3-yl, pyridazin-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyrazin-2-yl and triazin-2-yl.

**[0055]** Examples for N-bound 3-, 4-, 5-, 6- or 7-membered saturated or unsaturated aromatic or non-aromatic N-heterocyclic rings, which may contain 1 further heteroatom or heteroatom-containing group selected from the group

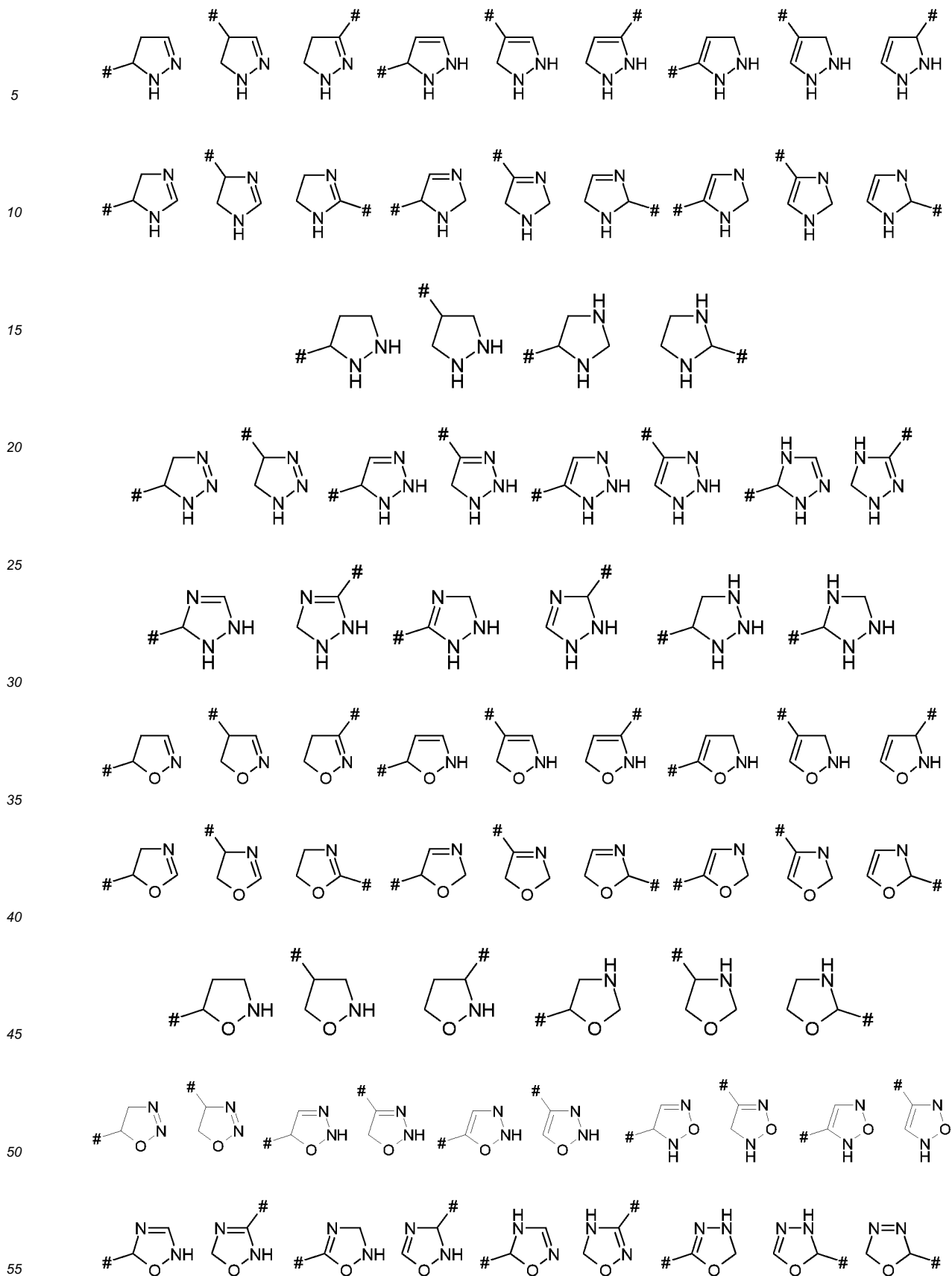
consisting of O, S, SO, SO<sub>2</sub> and N as a ring member (thus as rings formed by R<sup>a</sup> and R<sup>b</sup> together with the nitrogen atom to which they are bound), are aziridin-1-yl, azetidin-1-yl, pyrrolidin-1-yl, pyrazolidin-1-yl, imidazolidin-1-yl, oxazolidin-3-yl, isoxazolidin-2-yl, thiazolidin-3-yl, isothiazolidin-1-yl, [1,2,3]-triazolidin-1-yl, [1,2,3]-triazolidin-2-yl, [1,2,4]-triazolidin-1-yl, [1,2,4]-triazolidin-4-yl, piperidin-1-yl, piperazin-1-yl, morpholin-4-yl, thiomorpholin-1-yl, 1-oxohiomorpholin-1-yl, 1,1-dioxothiomorpholin-1-yl, azepan-1-yl, azirin-1-yl, azetin-1-yl, pyrrolin-1-yl, pyrazolin-1-yl, imidazolin-1-yl, oxazolin-3-yl, isoxazolin-2-yl, thiazolin-3-yl, isothiazolin-1-yl, 1,2-dihydropyridin-1-yl, 1,2,3,4-tetrahydropyridin-1-yl, 1,2,5,6-tetrahydropyridin-1-yl, 1,2-dihydropyridazin, 1,6-dihydropyridazin, 1,2,3,4-tetrahydropyridazin-1-yl, 1,2,5,6-tetrahydropyridazin-1-yl, 1,2-dihydropyrimidin, 1,6-dihydropyrimidin, 1,2,3,4-tetrahydropyrimidin-1-yl, 1,2,5,6-tetrahydropyrimidin-1-yl, 1,2-dihydropyrazin-1-yl, 1,2,3,4-tetrahydropyrazin-1-yl, 1,2,5,6-tetrahydropyrazin-1-yl, pyrrol-1-yl, pyrazol-1-yl, imidazol-1-yl, [1,2,3]-1H-triazol-1-yl, [1,2,3]-2H-triazol-2-yl, [1,2,4]-1H-triazol-1-yl and [1,2,4]-4H-triazol-4-yl.

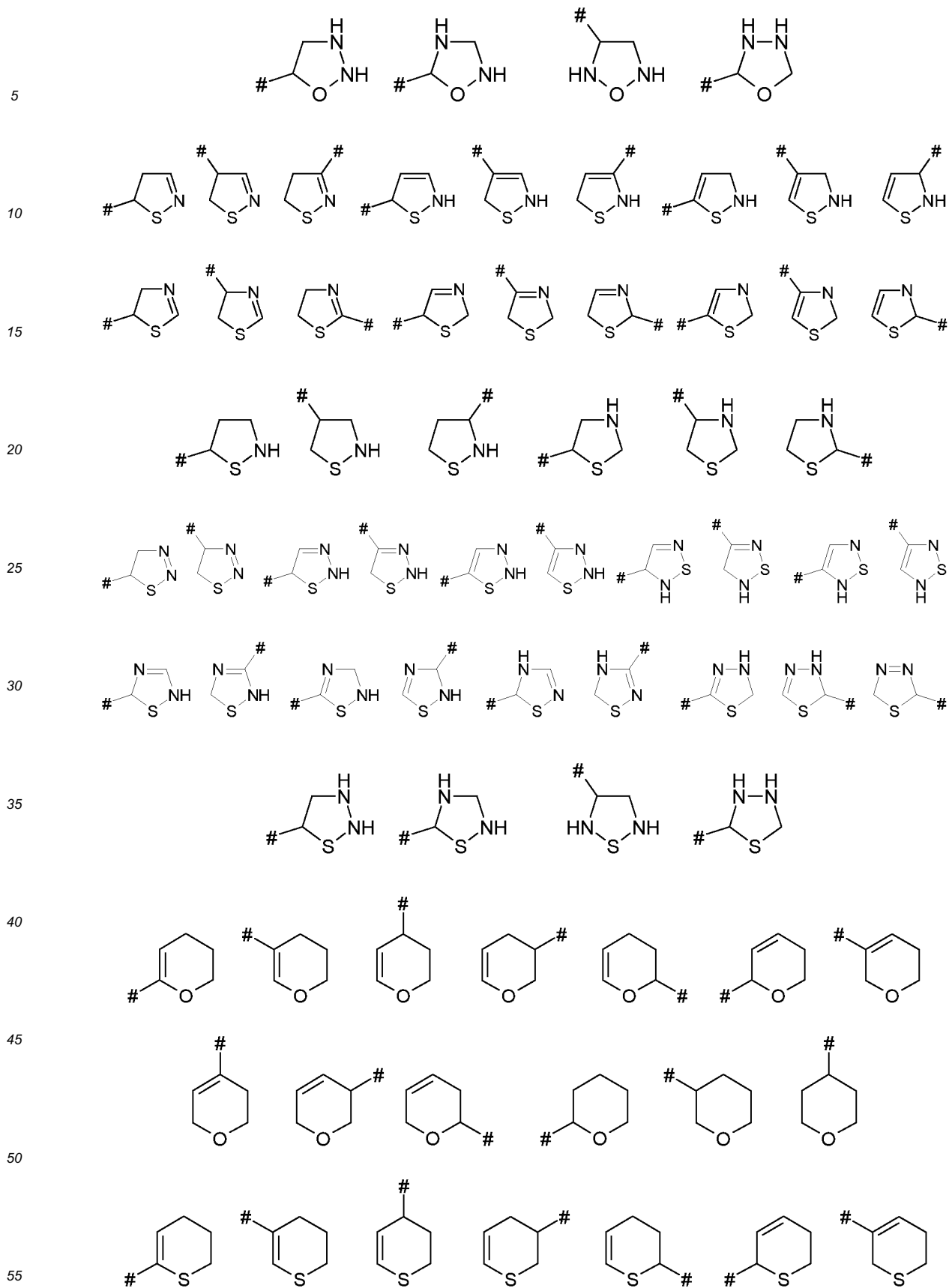
**[0056]** Examples for C-bound saturated or partially unsaturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from O, N, S, NO, SO and SO<sub>2</sub> as ring members (i.e. for rings R<sup>4</sup>) are C-bound oxiranyl, thiiranyl, aziridinyl, oxetanyl, azetidiny, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl, tetrahydrothienyl, dihydrothienyl-1-oxide, tetrahydrothienyl-1-oxide, pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazoliny, imidazolidinyl, triazoliny, triazolidinyl, oxazoliny, oxazolidinyl, isoxazoliny, isoxazolidinyl, oxadiazolinyl, oxadiazolidinyl, thiazolinyl, thiazolidinyl, isothiazolinyl, isothiazolidinyl, thiadiazolinyl, thiadiazolidinyl, dihydropyranyl, tetrahydropyranyl, dihydrothiopyranyl, tetrahydropyranyl, dihydropyridinyl, tetrahydropyridinyl, piperidinyl, dihydropyridazinyl, tetrahydropyridazinyl, hexahydropyridazinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, hexahydropyrimidinyl, dihydropyrazinyl, tetrahydropyrazinyl, piperazinyl, dihydro-[1,4]-oxazinyl, morpholinyl, dihydro-[1,4]-thiazinyl, thiomorpholinyl, thiomorpholinyl-1-oxide, thiomorpholinyl-1-dioxide, dihydroazepinyl, tetrahydroazepinyl, azepanyl, dihydrodi-azepinyl, tetrahydrodi-azepinyl, diazepanyl and the like.

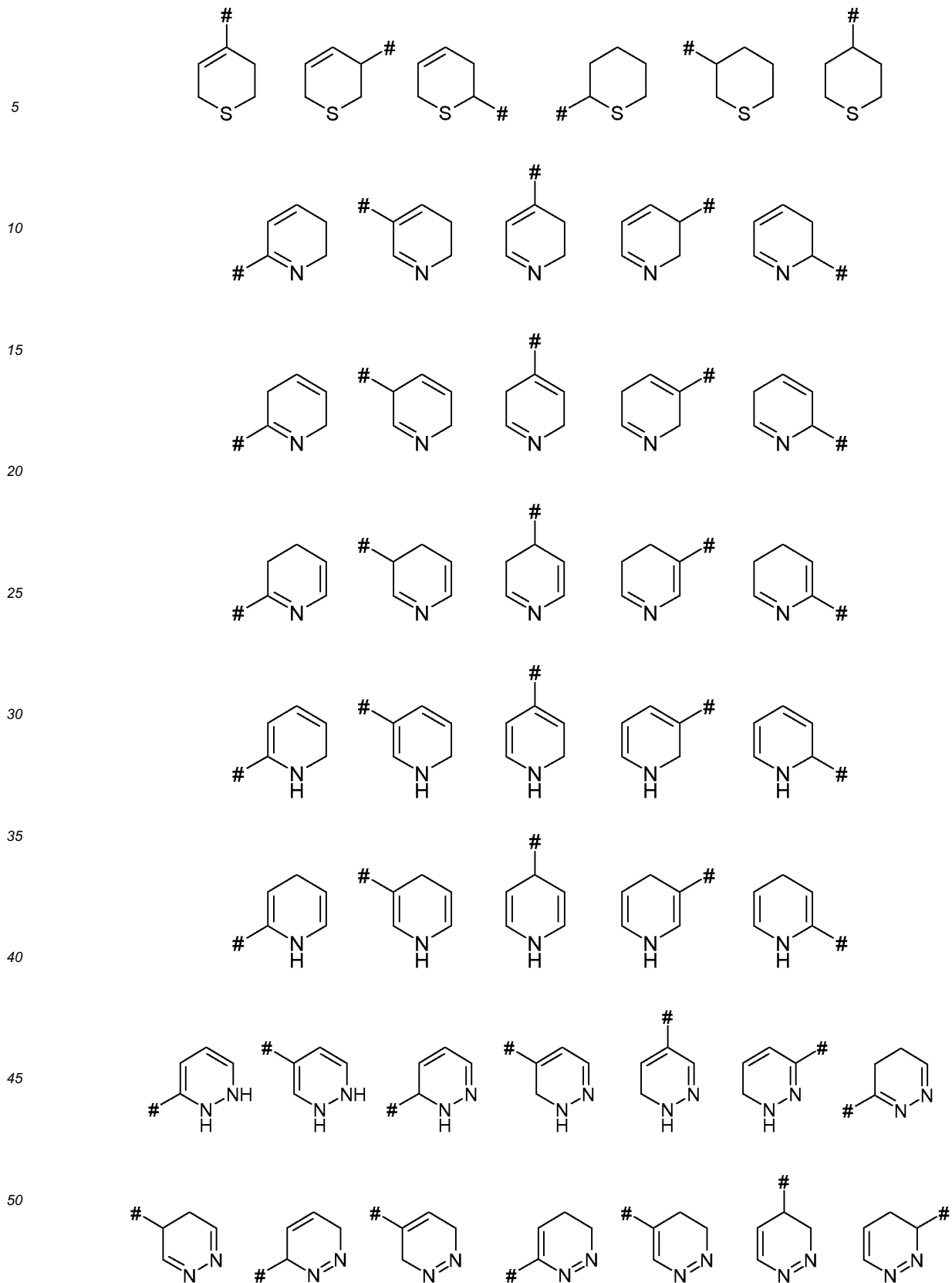
**[0057]** More precisely, examples for C-bound saturated or partially unsaturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from O, N, S, NO, SO and SO<sub>2</sub> as ring members (i.e. for rings R<sup>4</sup>) comprise the following structures:



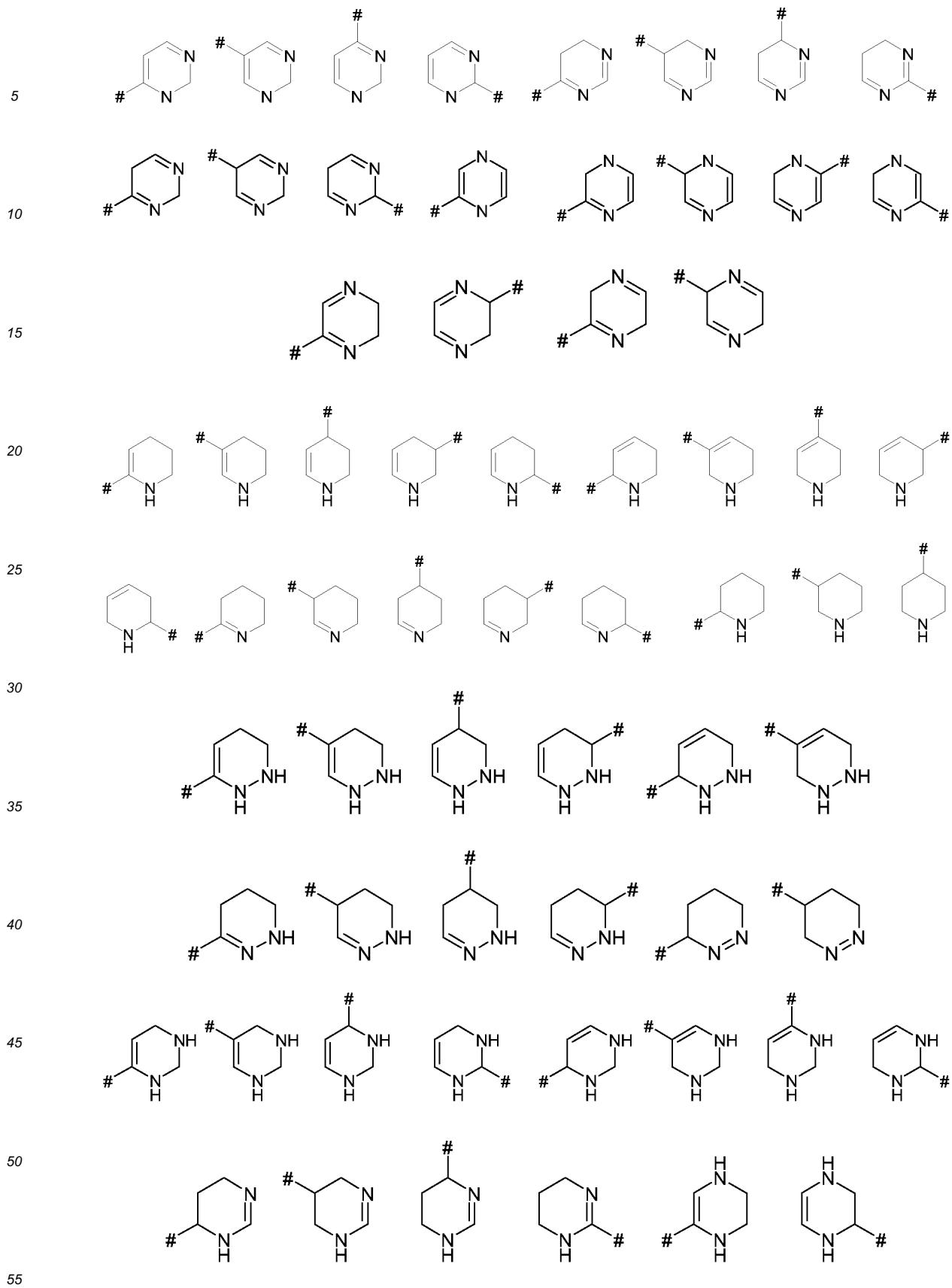
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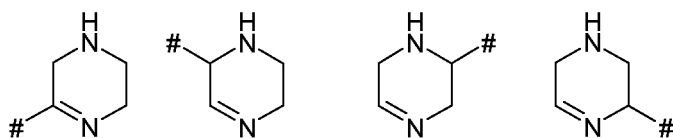




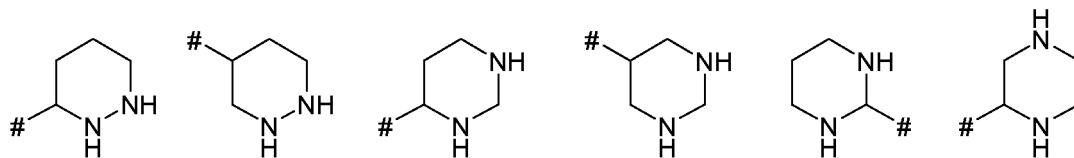
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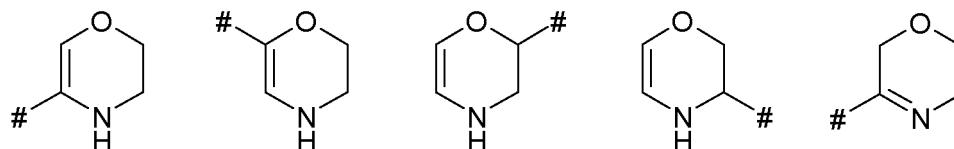
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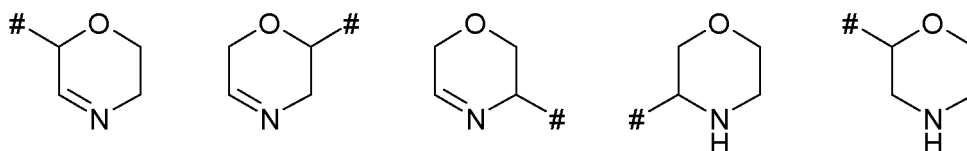
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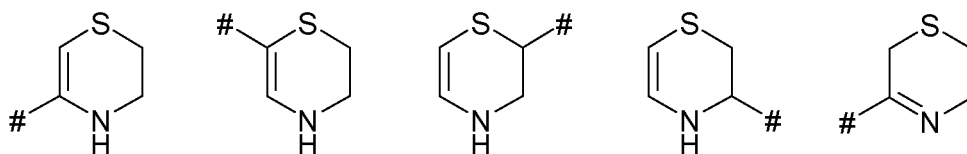
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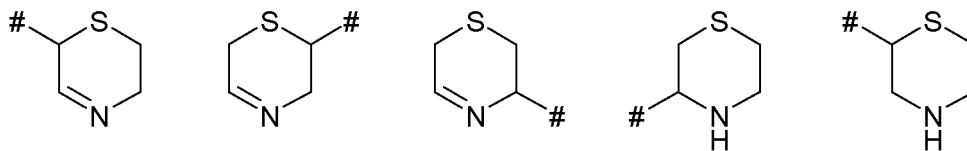
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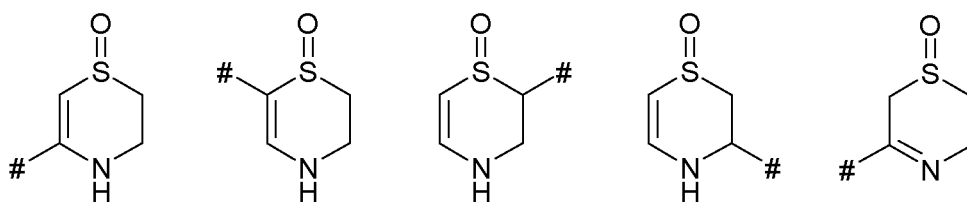
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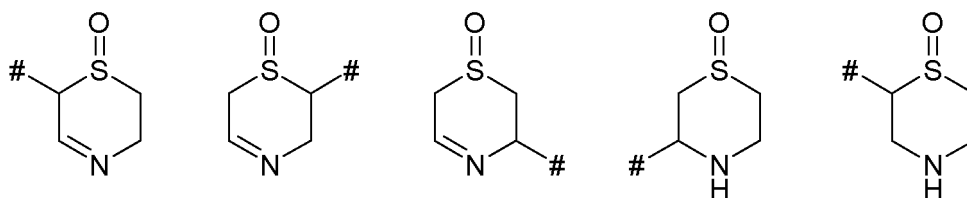
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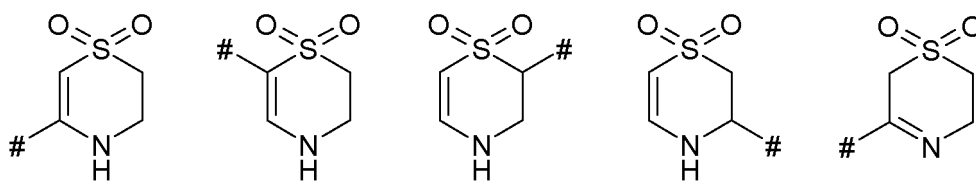


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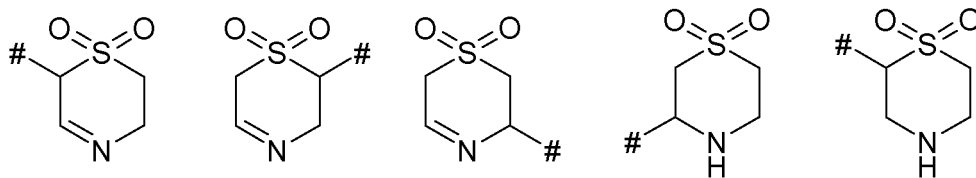
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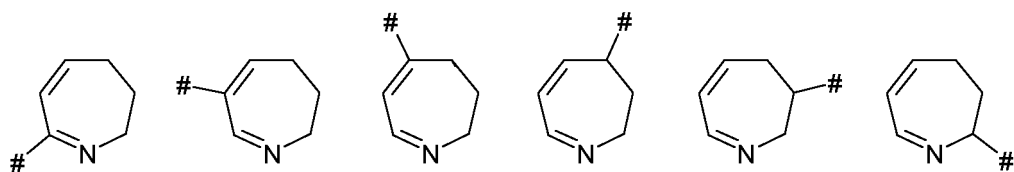
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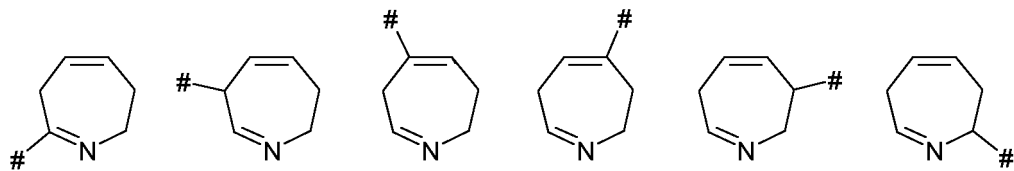
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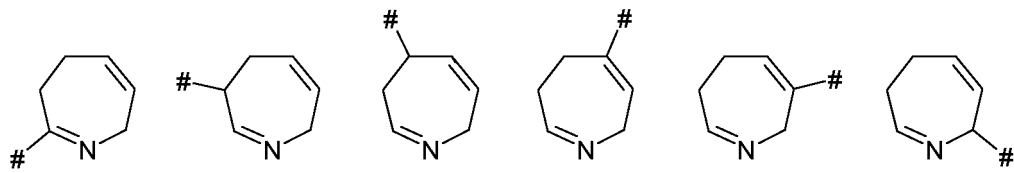
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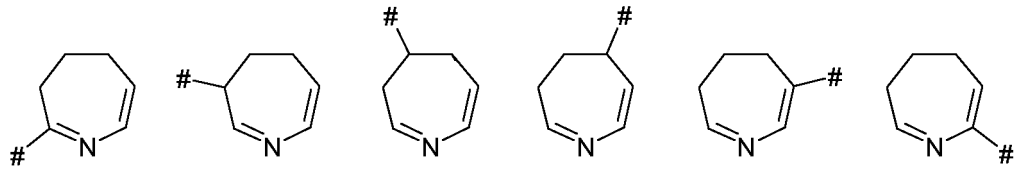
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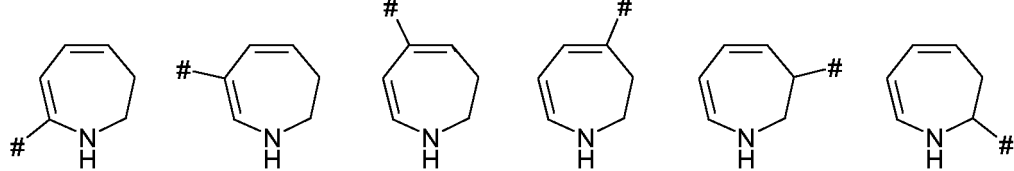
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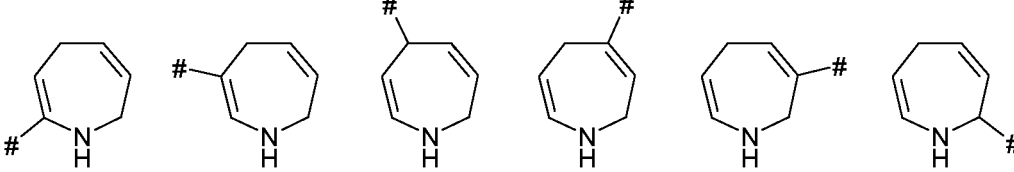
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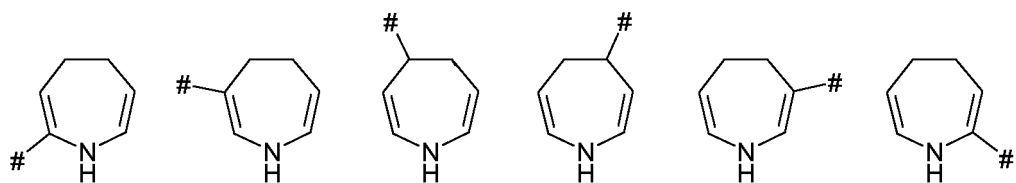


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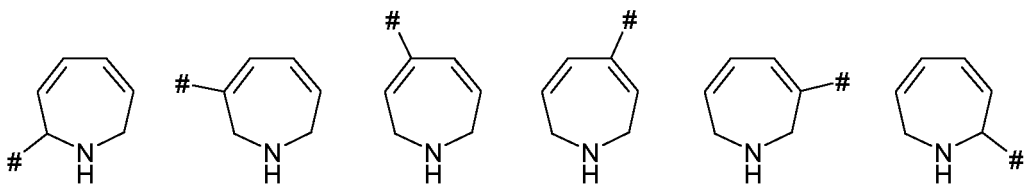
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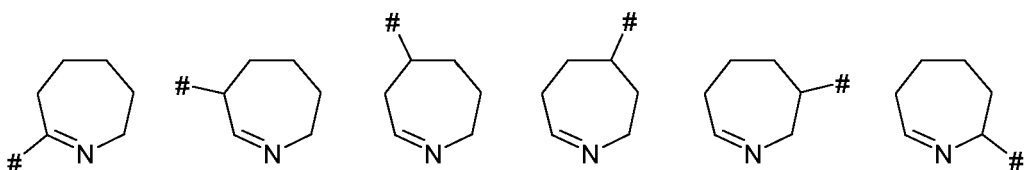
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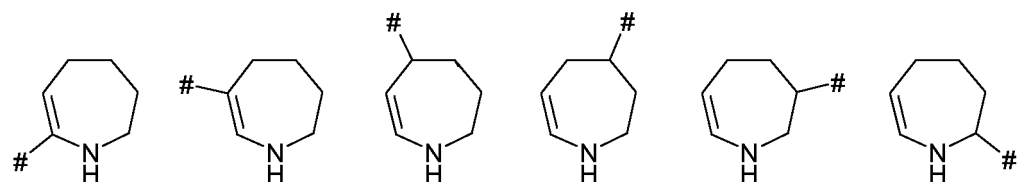
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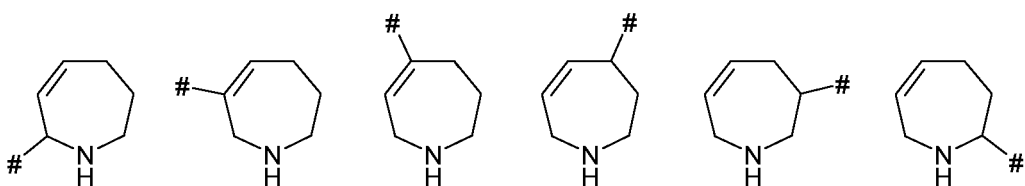
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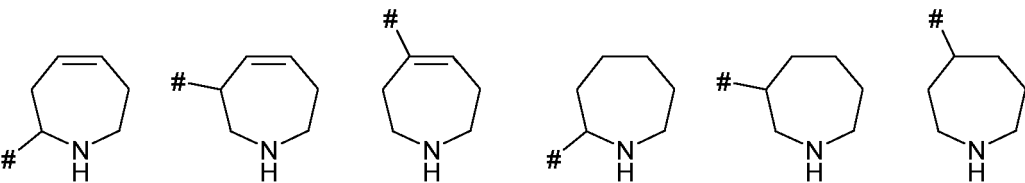
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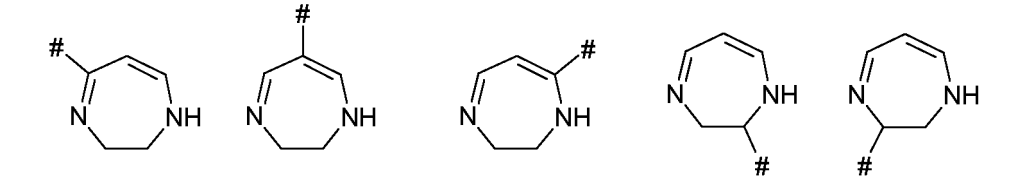
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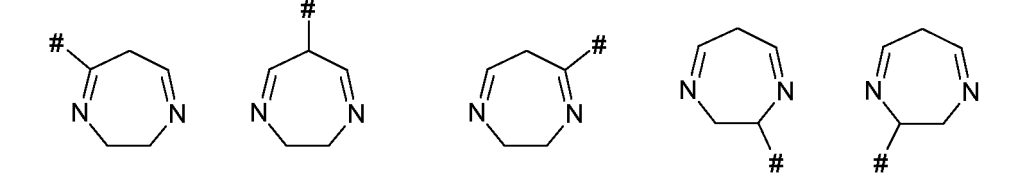
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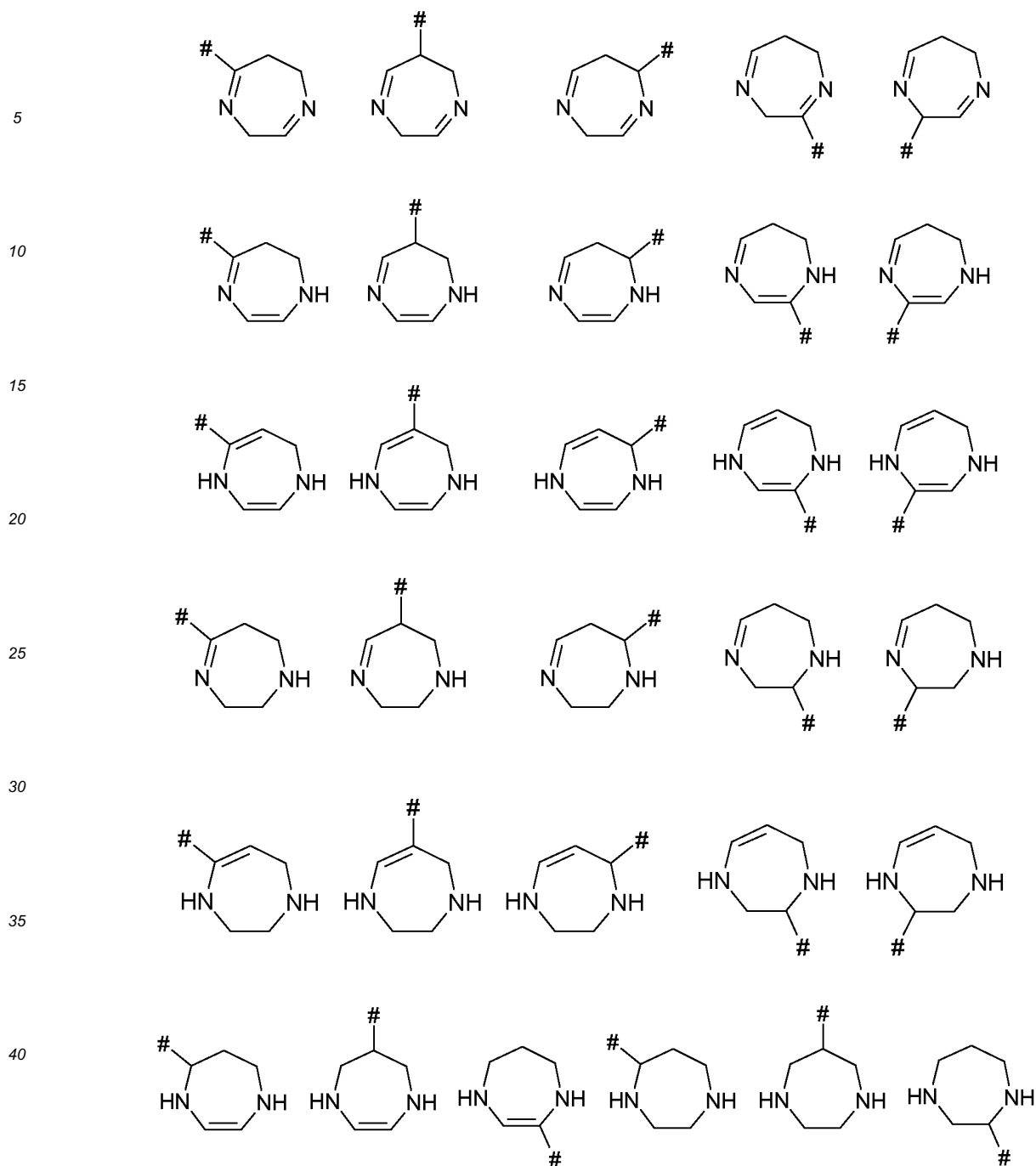


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where # is the attachment point to the remainder of the molecule.

**[0058]** The remarks made above and in the following with respect to preferred aspects of the invention, e.g. to preferred meanings of the variables  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$ ,  $X^6$ ,  $Y^1$ ,  $Y^2$ ,  $Y^3$ ,  $Y^4$ ,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ ,  $R^8$ ,  $R^a$ ,  $R^b$ ,  $R^{A1}$ ,  $R^{A2}$ ,  $R^B$  of compounds I, to preferred compounds I and to preferred embodiments of the use according to the invention, apply in each case on their own or in particular to combinations thereof.

**[0059]** In a preferred embodiment of the invention, either one of  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is  $CR^4$  and none of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $CR^4$ , or one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $CR^4$  and none of  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is  $CR^4$ . In other words, either the condensed ring system (with  $X^1$ - $X^6$  as ring members) carries one group  $R^4$  or the ring with  $Y^1$ - $Y^4$  as ring members carries one group  $R^4$ .

**[0060]** If the condensed ring system (with  $X^1$ - $X^6$  as ring members) carries one group  $R^4$ , this is preferably bound in the position of  $X^4$  or  $X^5$ .

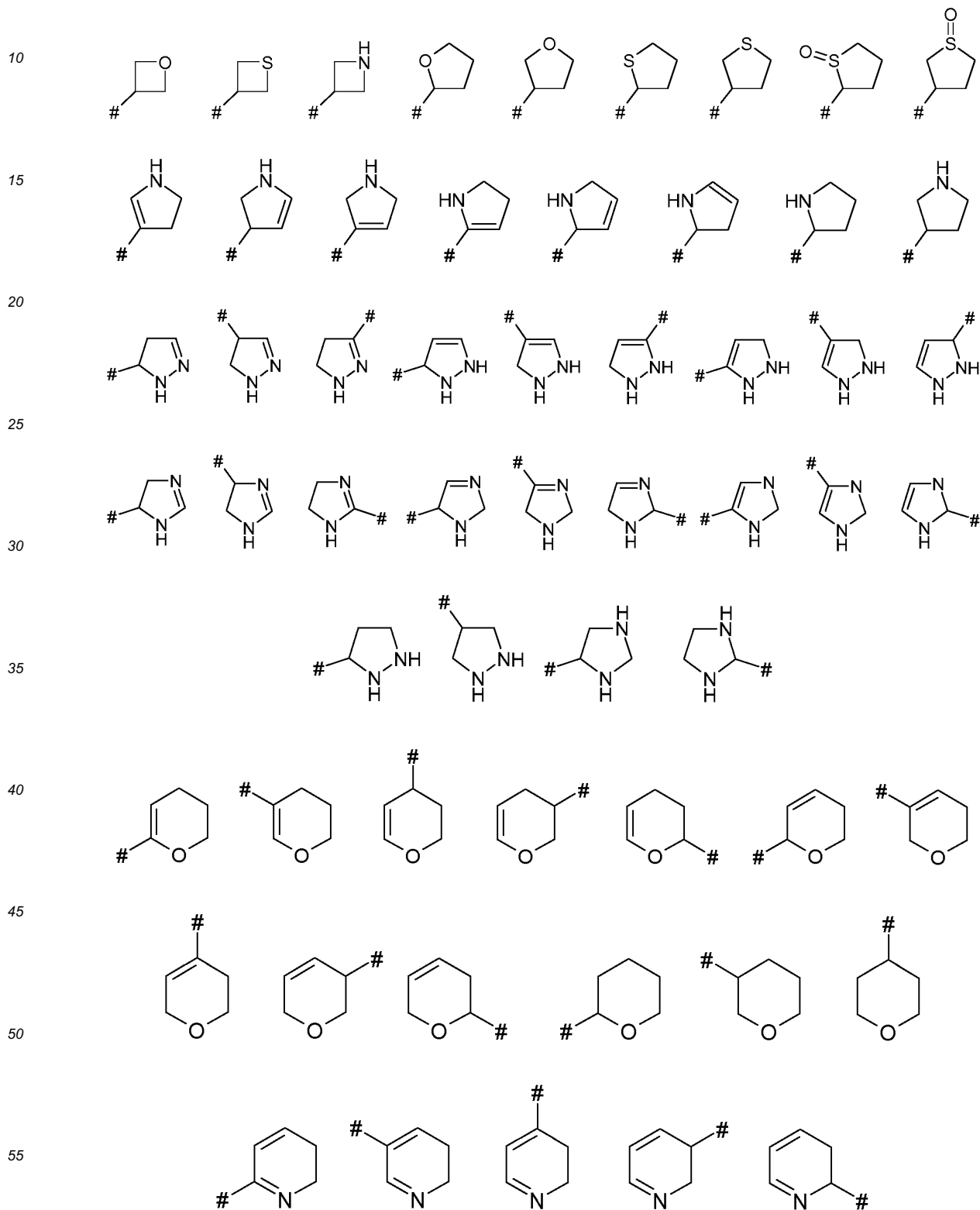
**[0061]** If the ring with  $Y^1$ - $Y^4$  as ring members carries one group  $R^4$ , this is preferably bound in the position of  $Y^4$ .

**[0062]**  $R^4$  is preferably selected from a C-bound saturated or partially unsaturated monocyclic 4-, 5- or 6-membered heterocyclic ring containing 1 or 2 or 3 heteroatoms selected from O, N, S and SO, as ring members, where the heterocyclic

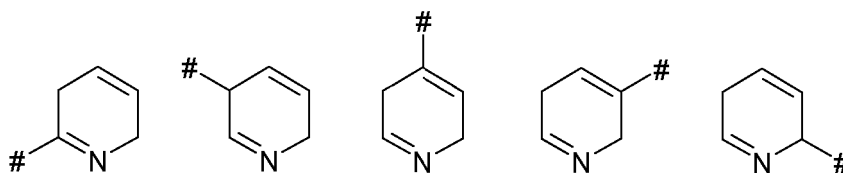
ring optionally carries 1, 2 or 3 substituents R<sup>8</sup>.

[0063] More preferably, R<sup>4</sup> is selected from C-bound oxetanyl, thietanyl, azetidiny, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl-1-oxide, pyrrolidiny, pyrrolinyl, pyrazolidinyl, pyrazolinyl, imidazolidinyl, imidazoliny, tetrahydropyranyl, dihydropyranyl, piperidiny, tetrahydropyridinyl, dihydropyridinyl, piperazinyl and morpholinyl, where the heterocyclic ring optionally carries 1, 2 or 3 substituents R<sup>8</sup>.

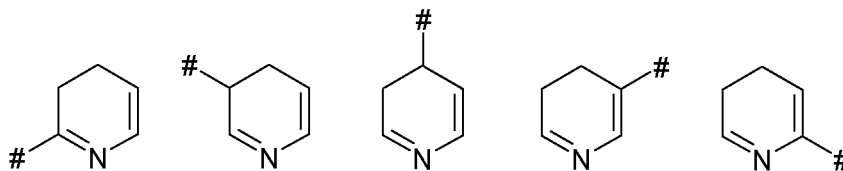
[0064] Preferably, these cyclic structures have the following formulae:



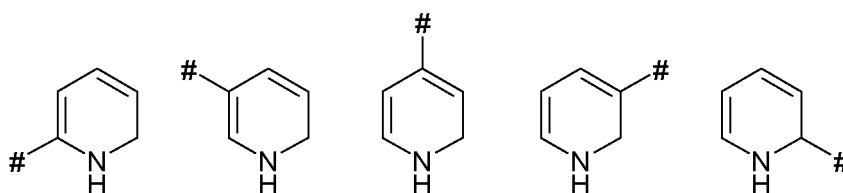
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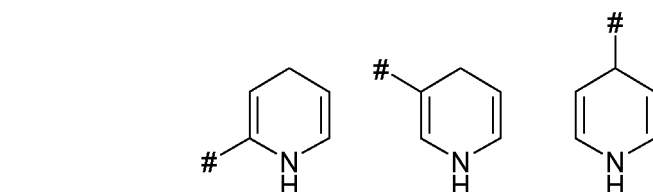


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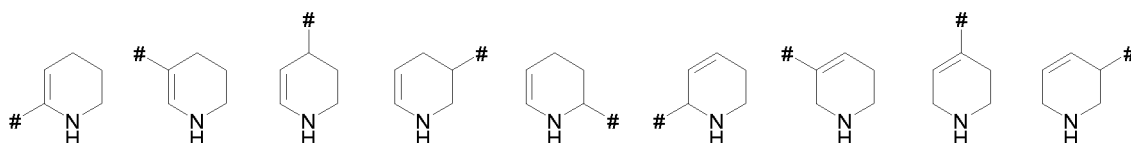
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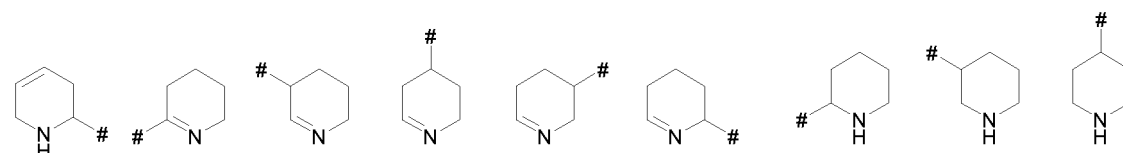


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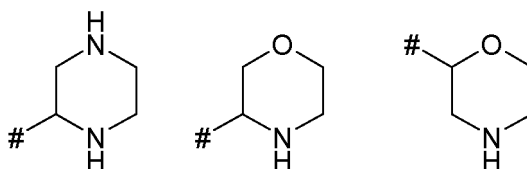
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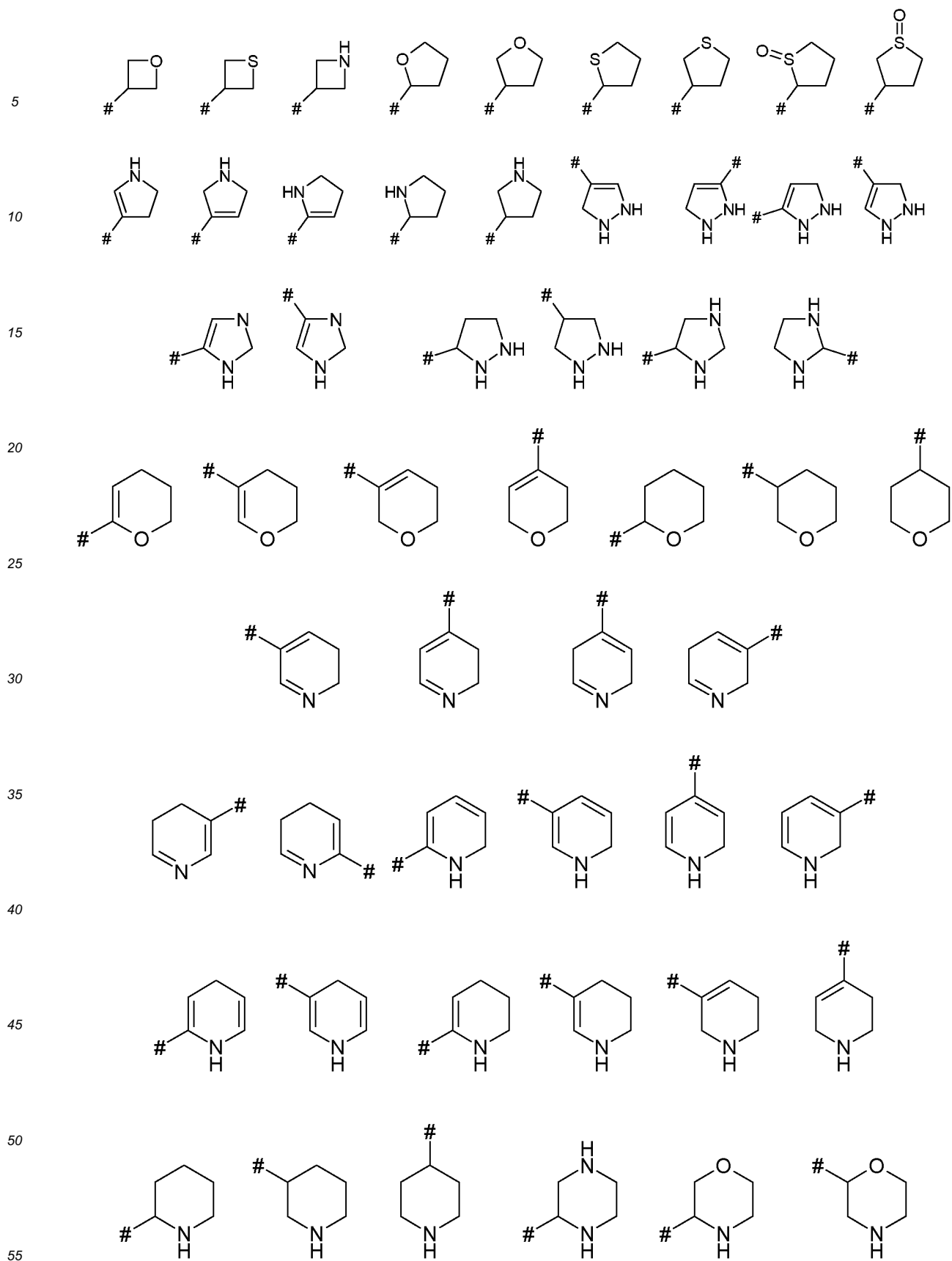
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where the above cyclic structures optionally carry 1, 2 or 3 substituents  $R^8$ , where  $R^8$  may be bound to a carbon ring atom or to a nitrogen ring atom, and where # is the attachment point to the remainder of the molecule.

**[0065]** Among the above partially saturated rings preference is given to those having one or more C=C bonds and where one carbon atom of such a C=C double bond forms the attachment point to the remainder of the molecule.

**[0066]** Thus, even more preferably  $R^4$  is selected from the following structures

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where the above cyclic structures optionally carry 1, 2 or 3 substituents  $R^8$ , where  $R^8$  may be bound to a carbon ring atom or to a nitrogen ring atom, and where # is the attachment point to the remainder of the molecule.

**[0067]** Particularly preferably,  $R^4$  is selected from azetidin-3-yl, tetrahydrofuran-3-yl, pyrrolidin-3-yl, pyrrolin-3-yl, tetrahydropyran-4-yl, tetrahydropyran-3-yl, dihydropyran-4-yl, dihydropyran-3-yl, piperidin-4-yl, 1,2,5,6-tetrahydropyridin-4-yl and 1,2-dihydropyridin-4-yl, where the heterocyclic ring optionally carries 1, 2 or 3 substituents  $R^8$ .

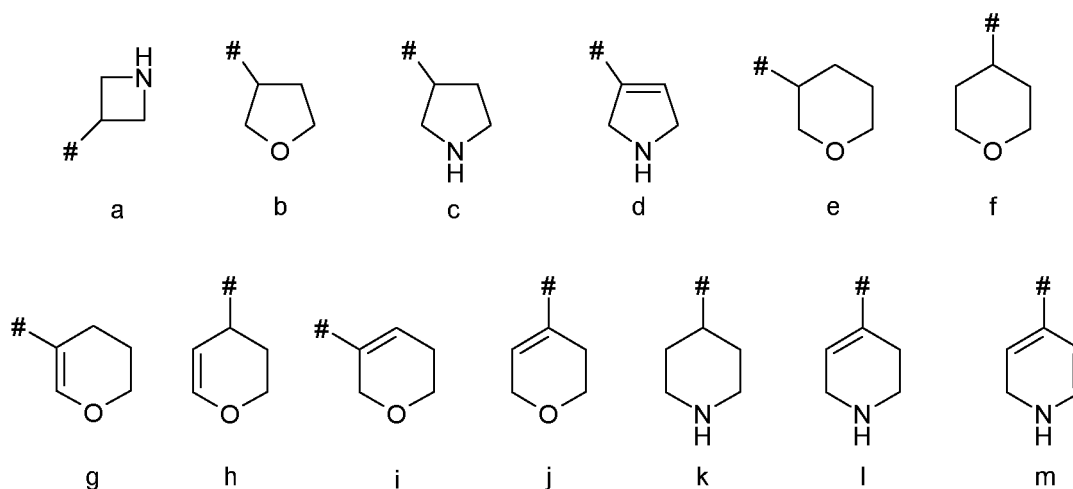
**[0068]** Preferably, these cyclic structures have the following formulae:

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where the above cyclic structures optionally carry 1, 2 or 3 substituents  $R^8$ , where  $R^8$  may be bound to a carbon ring atom or to a nitrogen ring atom, and where # is the attachment point to the remainder of the molecule.

**[0069]** Among these, more preference is given to structures c, d, e, f, g, j, k and l.

**[0070]**  $R^8$  is preferably selected from  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl,  $C_3$ - $C_7$ -cycloalkyl,  $C_3$ - $C_7$ -halocycloalkyl,  $C_2$ - $C_4$ -alkenyl,  $C_2$ - $C_4$ -haloalkenyl,  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -haloalkoxy, formyl,  $C_1$ - $C_6$ -alkylcarbonyl,  $C_1$ - $C_6$ -haloalkylcarbonyl,  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_1$ - $C_6$ -haloalkoxycarbonyl and benzyl and is more preferably  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl or  $C_1$ - $C_6$ -alkoxycarbonyl. Even more preferably,  $R^8$  is  $C_1$ - $C_4$ -alkyl,  $C_1$ - $C_4$ -haloalkyl, especially fluorinated  $C_1$ - $C_4$ -alkyl, or tert-butoxycarbonyl, and is in particular  $C_1$ - $C_2$ -alkyl,  $C_1$ - $C_2$ -haloalkyl, especially fluorinated  $C_1$ - $C_2$ -alkyl, or tert-butoxycarbonyl.

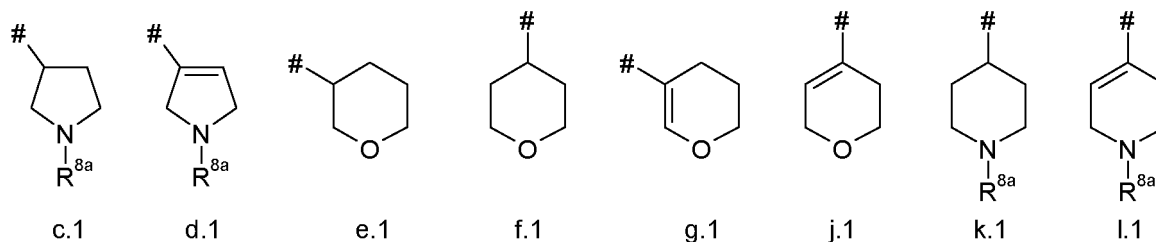
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**[0071]** Preferably,  $R^8$  is N-bound; i.e. it is bound to a nitrogen ring atom.

**[0072]** Specifically,  $R^4$  is selected from following structures:

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where

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$R^{8a}$  is hydrogen or has one of the general or, in particular, one of the preferred meanings given above for  $R^8$ ; and # is the attachment point to the remainder of the molecule.

**[0073]** Preferably, at most one of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is N. If one of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is N, this is preferably  $X^3$  or  $X^4$  and more preferably  $X^3$ .

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**[0074]** In one particular embodiment, none of  $X^1$ ,  $X^2$ ,  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is N. In other words, more preferably  $X^1$  and  $X^2$  are  $CR^2$  and  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  are  $CR^3$  or  $CR^4$ .

**[0075]** In another particular embodiment,  $X^1$  and  $X^2$  are  $CR^2$ ,  $X^3$  is N and  $X^4$ ,  $X^5$  and  $X^6$  are  $CR^3$  or  $CR^4$ .

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**[0076]** If one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is N, this is preferably  $Y^2$ . In other words, preferably  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  are  $CR^4$  or  $CR^5$ , or  $Y^2$  is N and  $Y^1$ ,  $Y^3$  and  $Y^4$  are  $CR^4$  or  $CR^5$ , of course with the proviso that at most one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $CR^4$ .

**[0077]** A is preferably  $NR^B$ .  $R^B$  is preferably hydrogen or  $C_1$ - $C_4$ -alkyl, more preferably hydrogen or methyl and specifically hydrogen. Thus, A is specifically NH.

**[0078]**  $R^1$  is preferably hydrogen or  $C_1$ - $C_4$ -alkyl, more preferably hydrogen or methyl and in particular hydrogen.

[0079] R<sup>2</sup> is preferably hydrogen.

[0080] R<sup>3</sup> is preferably selected from hydrogen, CN, halogen (preferably F or Cl, more preferably F), C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl and C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, more preferably from hydrogen, CN, F, Cl, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy and C<sub>1</sub>-C<sub>6</sub>-haloalkoxy and is in particular selected from hydrogen, CN, F, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy and C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, specifically hydrogen, F, C<sub>1</sub>-C<sub>2</sub>-alkyl, C<sub>1</sub>-C<sub>2</sub>-haloalkyl, C<sub>1</sub>-C<sub>2</sub>-alkoxy and C<sub>1</sub>-C<sub>2</sub>-haloalkoxy.

[0081] Preferably, 0, 1 or 2 of the radicals R<sup>3</sup> is different from hydrogen.

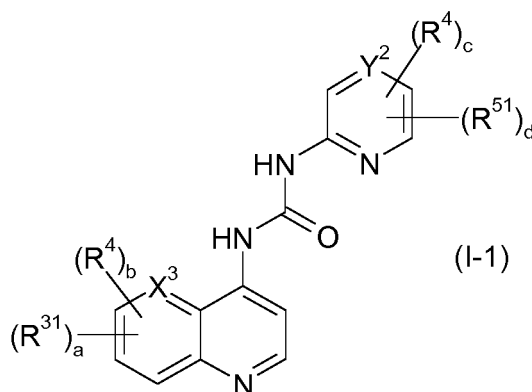
[0082] Specifically, R<sup>3</sup> is hydrogen if one or two of X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> and X<sup>6</sup> are CR<sup>4</sup>.

[0083] In particular, at most two of the radicals R<sup>3</sup> are different from hydrogen, if none of X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> and X<sup>6</sup> are CR<sup>4</sup>.

[0084] R<sup>5</sup> is preferably selected from hydrogen, CN, halogen (preferably F or Cl, more preferably F), C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl and C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, more preferably from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl and C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, even more preferably from hydrogen, F, Cl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl and C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, in particular from hydrogen, F, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl and C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl and specifically from hydrogen, fluorinated C<sub>1</sub>-C<sub>2</sub>-alkyl and C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

[0085] Preferably, at most one of the radicals R<sup>5</sup> is different from hydrogen.

[0086] In a particularly preferred embodiment of the invention the compounds of formula I are compounds of formula I-1



where

X<sup>3</sup> is N or CH;

Y<sup>2</sup> is N or CH;

R<sup>31</sup> has one of the general or, in particular, one of the preferred meanings given above for R<sup>3</sup> except for hydrogen, and is preferably halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy and more preferably F, C<sub>1</sub>-C<sub>4</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

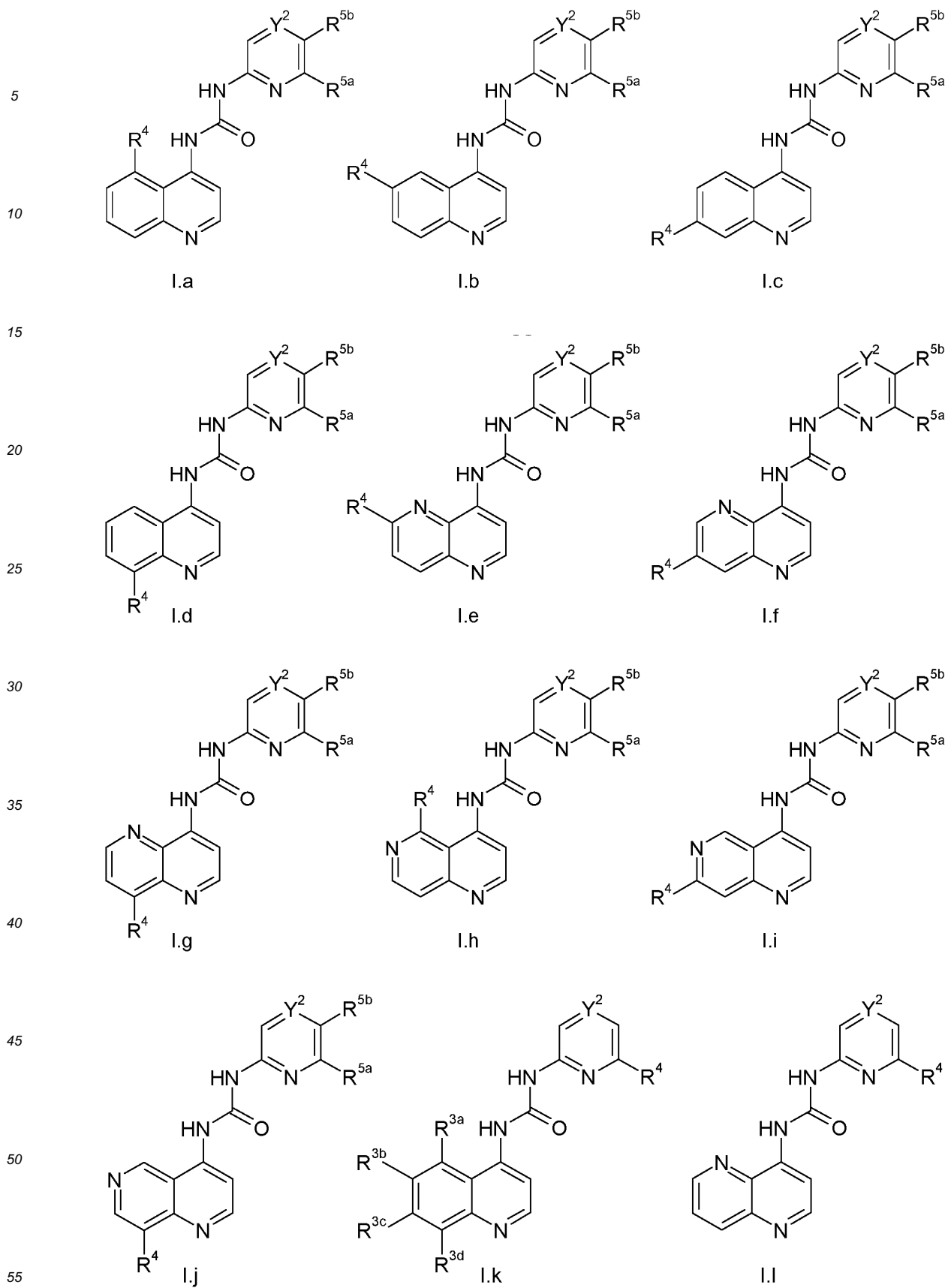
R<sup>4</sup> has one of the general or, in particular, one of the preferred meanings given above;

R<sup>51</sup> has one of the general or, in particular, one of the preferred meanings given above for R<sup>5</sup> except for hydrogen; and a is 0, 1 or 2; and

b, c and d are independently of each other 0 or 1, with the proviso that one of b and c is 1.

[0087] Preferably, a is 0 if b is 1.

[0088] Suitable compounds I are those of formulae I.a to I.l, the stereoisomers, N-oxides, prodrugs, tautomers and/or physiologically tolerated acid addition salts thereof, wherein Y<sup>2</sup> is N or CH, R<sup>4</sup> has the above-defined general or preferred meanings, R<sup>3a</sup>, R<sup>3b</sup>, R<sup>3c</sup> and R<sup>3d</sup> are hydrogen or have one of the above-defined general or preferred meanings given for R<sup>3</sup> and R<sup>5a</sup> and R<sup>5b</sup> are hydrogen or have one of the above-defined general or preferred meanings given for R<sup>5</sup>. Particularly preferred meanings of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>3c</sup>, R<sup>3d</sup>, R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup> and Y<sup>2</sup> specifically in compounds of formulae I.a to I.l are as defined below.



**[0089]** Examples of preferred compounds which are represented by the formulae I.a to I.l are the individual compounds compiled in the tables 1 to 418 below, where the variable R<sup>4</sup> has the meanings given in one row of Table A. Moreover,

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the meanings mentioned for the individual variables in the tables are per se, independently of the combination in which they are mentioned, a particularly preferred embodiment of the substituents in question.

Table 1

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**[0090]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  and  $R^{5b}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 2

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**[0091]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is F,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 3

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**[0092]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is Cl,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 4

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**[0093]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is Br,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 5

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**[0094]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is  $CH_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 6

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**[0095]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is  $CF_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 7

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**[0096]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is  $OCH_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 8

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**[0097]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is  $OCF_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 9

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**[0098]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is cyclopropyl,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 10

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**[0099]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is F and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 11

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**[0100]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is Cl and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 12

**[0101]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is Br and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 13

**[0102]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is  $CH_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 14

**[0103]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is  $CF_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 15

**[0104]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is  $OCH_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

20

Table 16

**[0105]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is  $OCF_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 17

**[0106]** Compounds of the formula I.a in which  $Y^2$  is CH,  $R^{5a}$  is H,  $R^{5b}$  is cyclopropyl and  $R^4$  for a compound corresponds in each case to one row of Table A.

30

Table 18

**[0107]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  and  $R^{5b}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

35

Table 19

**[0108]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is F,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

40

Table 20

**[0109]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is Cl,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 21

**[0110]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is Br,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 22

**[0111]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is  $CH_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 23

**[0112]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is  $CF_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in

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each case to one row of Table A.

Table 24

- 5 **[0113]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is  $OCH_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 25

- 10 **[0114]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is  $OCF_3$ ,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 26

- 15 **[0115]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is cyclopropyl,  $R^{5b}$  is H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 27

- 20 **[0116]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is F and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 28

- 25 **[0117]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is Cl and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 29

- 30 **[0118]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is Br and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 30

- 35 **[0119]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is  $CH_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 31

- 40 **[0120]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is  $CF_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 32

- 45 **[0121]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is  $OCH_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 33

- 50 **[0122]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is  $OCF_3$  and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 34

- 55 **[0123]** Compounds of the formula I.a in which  $Y^2$  is N,  $R^{5a}$  is H,  $R^{5b}$  is cyclopropyl and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 35 to 68

**[0124]** Compounds of the formula I.b in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 69 to 102

**[0125]** Compounds of the formula I.c in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 103 to 136

**[0126]** Compounds of the formula I.d in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 137 to 170

**[0127]** Compounds of the formula I.e in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 171 to 204

**[0128]** Compounds of the formula I.f in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 205 to 238

**[0129]** Compounds of the formula I.g in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 239 to 272

**[0130]** Compounds of the formula I.h in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 273 to 306

**[0131]** Compounds of the formula I.i in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Tables 307 to 340

**[0132]** Compounds of the formula I.j in which the combination of  $Y^2$ ,  $R^{5a}$  and  $R^{5b}$  is as defined in tables 1 to 34 and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 341

**[0133]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$ ,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 342

**[0134]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is F,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 343

**[0135]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is Cl,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound

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corresponds in each case to one row of Table A.

Table 344

- 5 **[0136]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is Br,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 345

- 10 **[0137]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is  $CH_3$ ,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 346

- 15 **[0138]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is  $CF_3$ ,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 347

- 20 **[0139]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is  $OCH_3$ ,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 348

- 25 **[0140]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is  $OCF_3$ ,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 349

- 30 **[0141]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3a}$  is cyclopropyl,  $R^{3b}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 350

- 35 **[0142]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is F,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 351

- 40 **[0143]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is Cl,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 352

- 45 **[0144]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is Br,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 353

- 50 **[0145]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $CH_3$ ,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 354

- 55 **[0146]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $CF_3$ ,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 355

**[0147]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $OCH_3$ ,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 356

**[0148]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $OCF_3$ ,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 357

**[0149]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is cyclopropyl,  $R^{3a}$ ,  $R^{3c}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 358

**[0150]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is F,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

20

Table 359

**[0151]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is Cl,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

25

Table 360

**[0152]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is Br,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 361

**[0153]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is  $CH_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

35

Table 362

**[0154]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is  $CF_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

40

Table 363

**[0155]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is  $OCH_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 364

**[0156]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is  $OCF_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 365

**[0157]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3c}$  is cyclopropyl,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3d}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

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Table 366

**[0158]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is F,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound

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corresponds in each case to one row of Table A.

Table 367

- 5 **[0159]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is Cl,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 368

- 10 **[0160]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is Br,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 369

- 15 **[0161]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is  $CH_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 370

- 20 **[0162]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is  $CF_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 371

- 25 **[0163]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is  $OCH_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 372

- 30 **[0164]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is  $OCF_3$ ,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 373

- 35 **[0165]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3d}$  is cyclopropyl,  $R^{3a}$ ,  $R^{3b}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 374

- 40 **[0166]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $CH_3$ ,  $R^{3d}$  is Cl,  $R^{3a}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 375

- 45 **[0167]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is Cl,  $R^{3d}$  is Cl,  $R^{3a}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 376

- 50 **[0168]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is F,  $R^{3d}$  is F,  $R^{3a}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 377

- 55 **[0169]** Compounds of the formula I.k in which  $Y^2$  is CH,  $R^{3b}$  is  $OCH_3$ ,  $R^{3d}$  is F,  $R^{3a}$  and  $R^{3c}$  are H and  $R^4$  for a compound corresponds in each case to one row of Table A.

Table 378

**[0170]** Compounds of the formula I.k in which Y<sup>2</sup> is CH, R<sup>3a</sup> is F, R<sup>3d</sup> is F, R<sup>3b</sup> and R<sup>3c</sup> are H and R<sup>4</sup> for a compound corresponds in each case to one row of Table A.

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Tables 379 to 416

**[0171]** Compounds of the formula I.k in which Y<sup>2</sup> is N, the combination of R<sup>3a</sup>, R<sup>3b</sup>, R<sup>3c</sup> and R<sup>3d</sup> is as defined in tables 341 to 378 and R<sup>4</sup> for a compound corresponds in each case to one row of Table A.

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Table 417

**[0172]** Compounds of the formula I.l in which Y<sup>2</sup> is CH and R<sup>4</sup> for a compound corresponds in each case to one row of Table A.

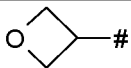

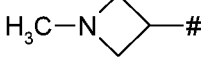
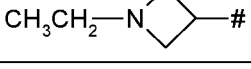
15

Table 418

**[0173]** Compounds of the formula I.l in which Y<sup>2</sup> is N and R<sup>4</sup> for a compound corresponds in each case to one row of Table A.

20

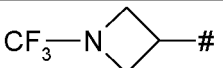
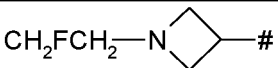
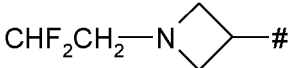
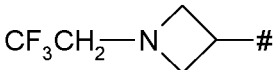
Table A

No.	R <sup>4</sup>
A-1	
A-2	
A-3	
A-4	

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No.	R <sup>4</sup>
A-5	
A-6	
A-7	
A-8	

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No.	R <sup>4</sup>
A-9	
A-10	
A-11	
A-12	
A-13	
A-14	
A-15	
A-16	
A-17	
A-18	
A-19	
A-20	
A-21	
A-22	
A-23	
A-24	
A-25	
A-26	

No.	R <sup>4</sup>
A-27	
A-28	
A-29	
A-30	
A-31	
A-32	
A-33	
A-34	
A-35	
A-36	
A-37	
A-38	
A-39	
A-40	
A-41	
A-42	
A-43	

No.	R <sup>4</sup>
A-44	
A-45	
A-46	
A-47	
A-48	
A-49	
A-50	
A-51	

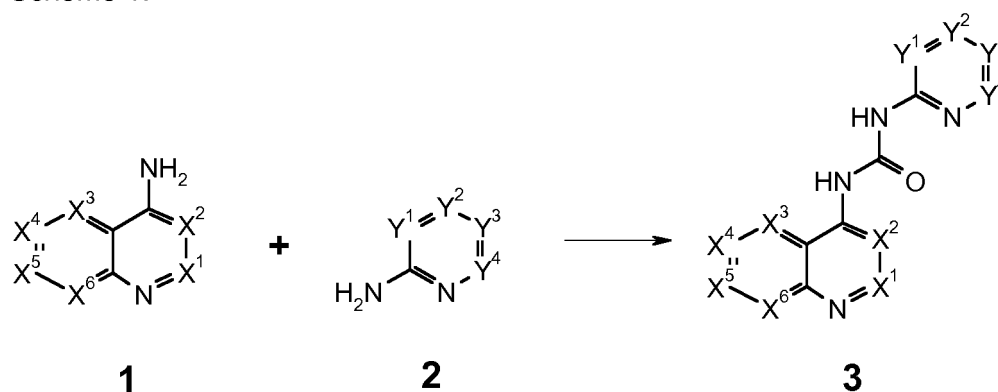
No.	R <sup>4</sup>
A-52	
A-53	
A-54	
A-55	
A-56	
A-57	

**[0174]** Among the above compounds, preference is given to compounds of formulae I.b, I.c, I.k and I.l.

**[0175]** The compounds of the present invention can be prepared by analogy to routine techniques a skilled person is familiar with. In particular, the compounds of the formula I can be prepared according to the following schemes, wherein the variables, if not stated otherwise, are as defined above and Z indicates a halogen atom, especially Br or I.

**[0176]** Compounds I wherein A is NR<sup>B</sup> can be prepared as described in schemes 1 to 4 and 6 to 8.

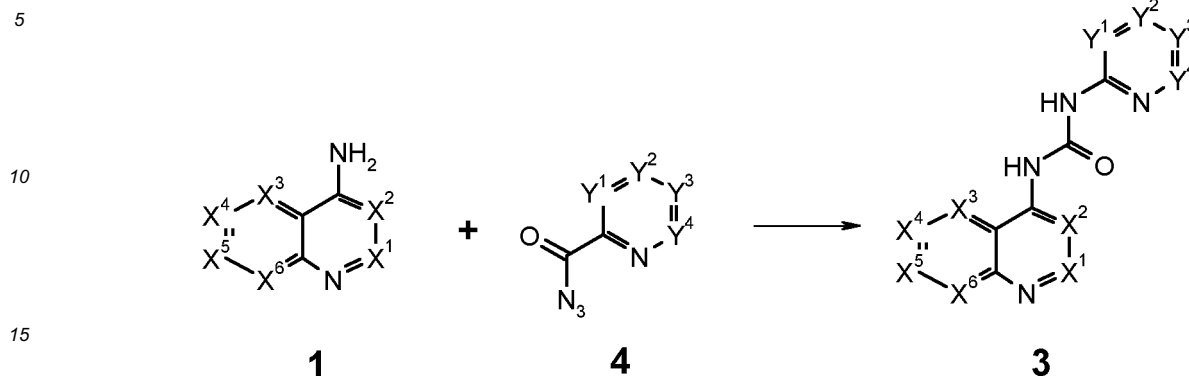
Scheme 1:



**[0177]** The bicyclic amine 1 can be reacted with amine 2 in the presence of triphosgene (or phosgene or other equivalent reagent), together with a non-alkylating base such as triethylamine. The reaction is carried out in the presence of a suitable solvent such as toluene or N,N-dimethylformamide. The reaction is usually carried out at temperatures of from -30 to 50°C to give substituted ureas of general formula 3.

**[0178]** Disubstituted urea compounds of the general formula 3 can also be prepared according to a route depicted in scheme 2.

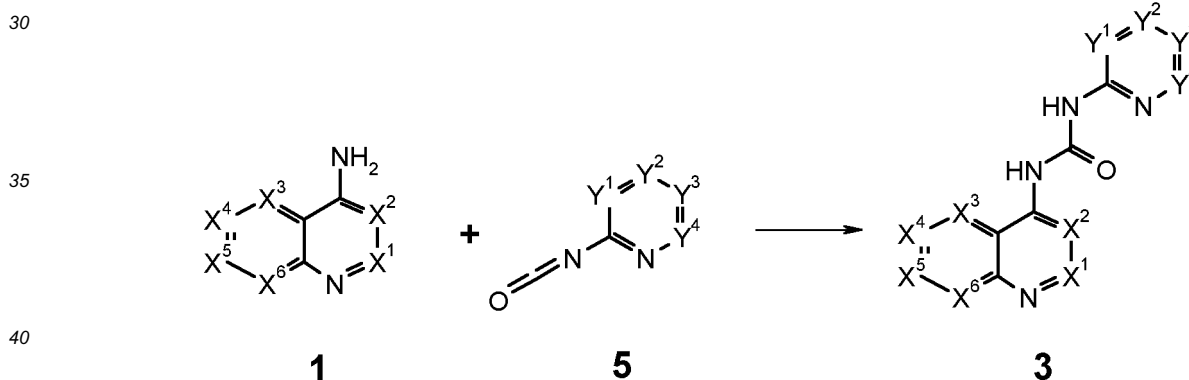
Scheme 2:



[0179] The amine 1 can be acylated by reaction with an acyl azide 4 (prepared by reaction of the corresponding acyl halide with a metal azide salt according to standard methods of organic chemistry) to give disubstituted ureas of general formula 3. The reaction is carried out in the presence of a suitable solvent such as toluene or N,N-dimethylformamide. The reaction is usually carried out at temperatures of from 20 - 120°C. Other conditions for this transformation (known as the Curtius rearrangement) are described in the following articles: Journal of Organic Chemistry, 1986, 51, 3007 & 5123; Journal of Organic Chemistry, 1987, 52, 4875; Tetrahedron Letters, 1984, 25, 3515; and Organic Reactions, 1947, 3, 337.

[0180] Disubstituted urea compounds of the general formula 3 can also be prepared according to a route depicted in scheme 3.

Scheme 3:

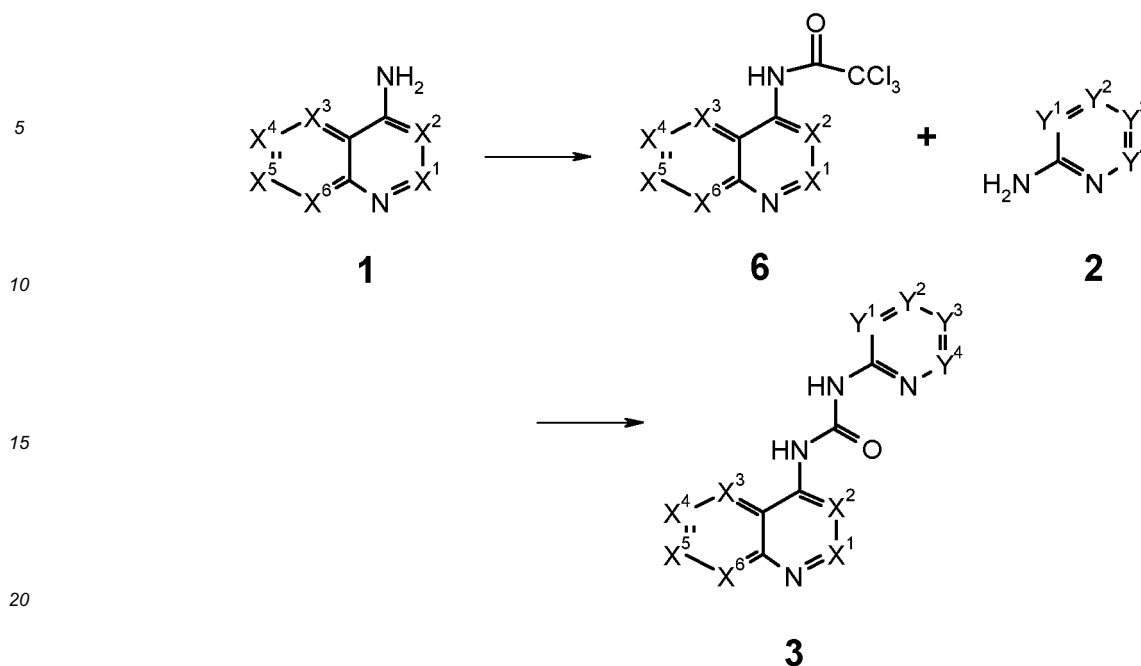


[0181] The amine 1 can be acylated by reaction with an isocyanate 5 to give disubstituted ureas of general formula 3. The reaction is carried out in the presence of a suitable solvent such as toluene or N,N-dimethylformamide. The reaction is usually carried out at temperatures of from 20 - 120°C.

Scheme 4:

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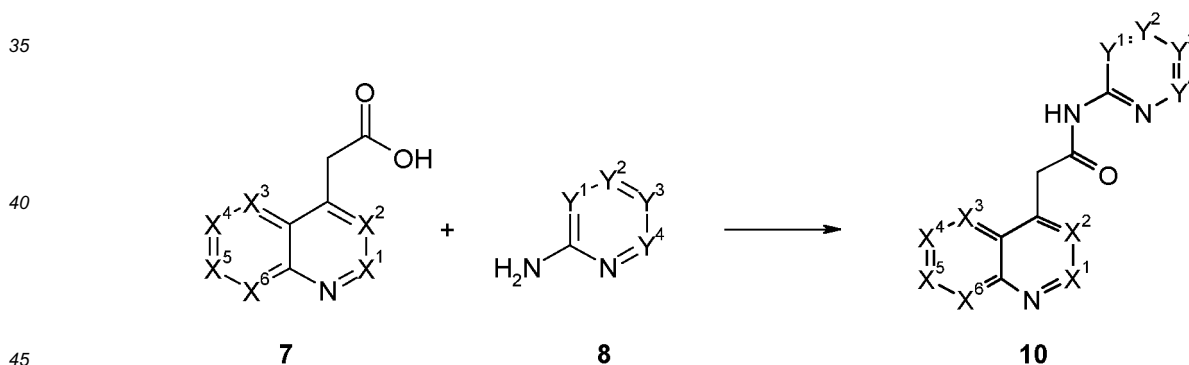


25 **[0182]** The bicyclic amine 1 can be converted to trichloroacetamide 6 by reaction with trichloroacetyl chloride. The reaction is carried out in the presence of a suitable solvent such as toluene or N,N-dimethylformamide. The reaction is usually carried out at temperatures of from 20 - 120°C. The trichloroacetamide 6 can be reacted with an amine 2 to give substituted ureas of general formula 3.

30 **[0183]** Compounds I wherein R<sup>B</sup> and/or R<sup>1</sup> are different from H can be prepared by N-alkylating compound 3.

**[0184]** Compounds I wherein A is CH<sub>2</sub> can be prepared as described in schemes 5 to 8.

Scheme 5:

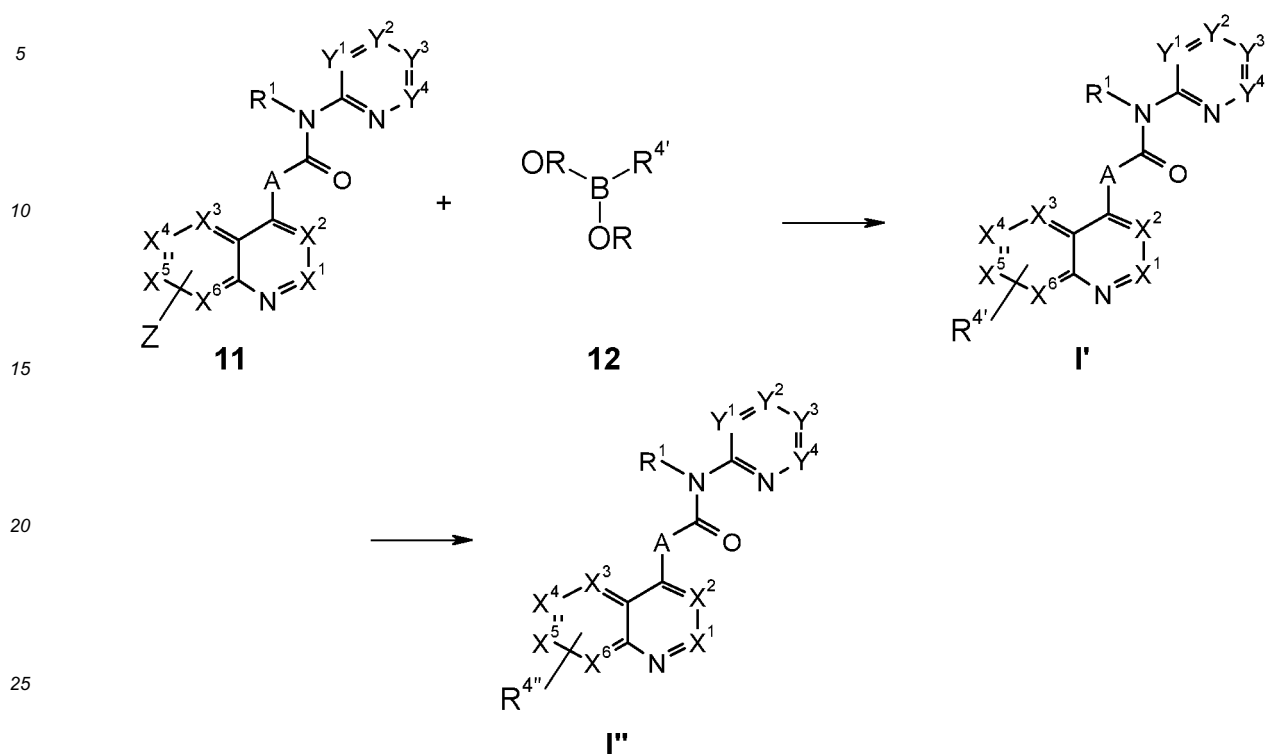


50 **[0185]** The carboxylic acid 7 can be converted into the amide 10 by reaction with an amine 8 using standard amide formation conditions familiar to those skilled in the art. The reaction is carried out in the presence of a suitable solvent such as dimethylacetamide, N,N-dimethylformamide or THF. The reaction is usually carried out at temperatures of from 20 to 120°C. Coupling reagents such as HOBT or carbonyl diimidazole are employed.

**[0186]** Compounds I, wherein A is CR<sup>A1</sup>R<sup>A2</sup> can be prepared analogously.

**[0187]** The introduction of the group R<sup>4</sup> can be accomplished as shown in the following schemes.

Scheme 6



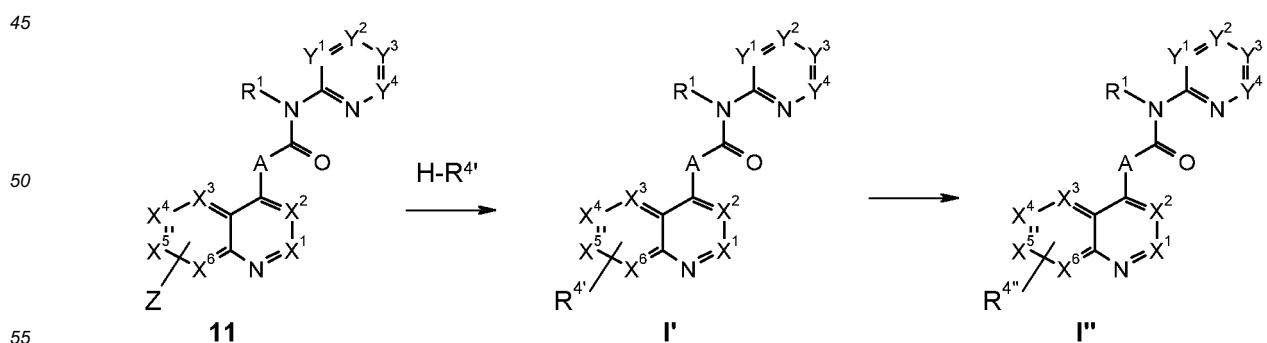
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**[0188]** Substitution of an appropriate placed halogen Z can be accomplished by Suzuki coupling of 11 with an appropriately substituted boronic acid (R = H) or ester (R ≠ H) 12, wherein R<sup>4'</sup> is a C-bound partially (C=C) unsaturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from O, N, S, NO, SO and SO<sub>2</sub> as ring members, where the heterocyclic ring optionally carries 1, 2 or 3 C- or N-bound substituents R<sup>8</sup>, where the ring has the C=C bond in α-position to the attachment point to the boron atom (so that the C=C double bond is a vinylic bond to B) to give substituted products of the general structure I'. The substitution may be conducted via a palladium-mediated coupling using a catalyst such as tetrakis(triphenylphosphine)palladium(0) in the presence of a base (e.g. Na<sub>2</sub>CO<sub>3</sub>) in a solvent such as DMF. The unsaturated compound I' may be reduced to the saturated product I'', wherein R<sup>4''</sup> is a C-bound saturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from O, N, S, NO, SO and SO<sub>2</sub> as ring members, where the heterocyclic ring optionally carries 1, 2 or 3 C- or N-bound substituents R<sup>8</sup>, by reduction of I' in the presence of a catalyst (e.g. Pd on carbon) in the presence of hydrogen.

Scheme 7:

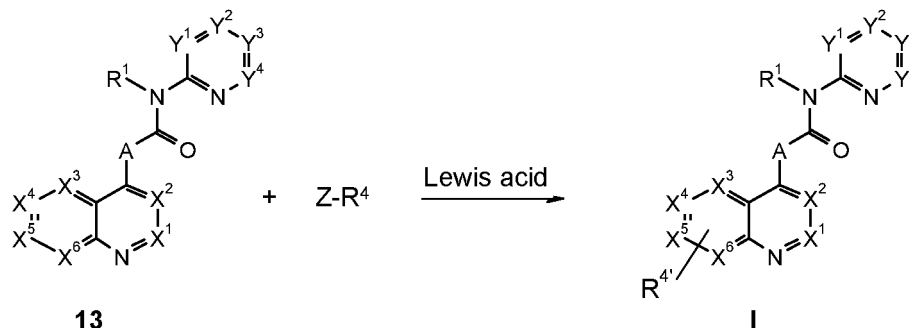


**[0189]** A similar sequence may be accomplished by reaction of 11 in a Heck coupling with a partially unsaturated ring H-R<sup>4'</sup> to give substituted products of general structure I' which can in turn be reduced to the saturated product I'' as

already described.

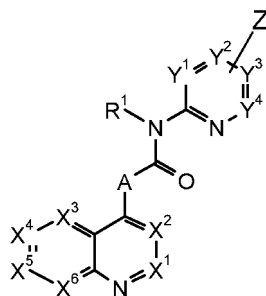
**[0190]** Starting compound 11 in schemes 6 and 7 can be obtained by using in the reactions of schemes 1 to 5 compounds 1 or 7 yet carrying a halogen atom Z in the desired position.

Scheme 8



**[0191]** Groups R<sup>4</sup> can moreover be introduced in an alkylation reaction, e.g. by reacting the compound 13 under the reaction conditions of a Friedel-Crafts alkylation with a compound Z-R<sup>4</sup>, where Z is a halogen atom, especially Cl or Br. Suitable Lewis acids are for example AlCl<sub>3</sub>, FeCl<sub>3</sub>, SbCl<sub>5</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>, TiCl<sub>4</sub> and ZnCl<sub>2</sub>.

**[0192]** Compounds I where R<sup>4</sup> is bound to the ring containing Y<sup>1</sup> to Y<sup>4</sup> as ring members can be prepared in analogy to the reactions shown in schemes 6 to 8 by starting from a compound 14, wherein Z is a halogen atom, especially Br or I.



**[0193]** Compound 14 can be prepared by using in the reactions of schemes 1 to 5 starting compounds 2, 4, 5 or 8 yet carrying a halogen atom Z in the desired position.

**[0194]** If not indicated otherwise, the above-described reactions are generally carried out in a solvent at temperatures between room temperature and the boiling temperature of the solvent employed. Alternatively, the activation energy which is required for the reaction can be introduced into the reaction mixture using microwaves, something which has proved to be of value, in particular, in the case of the reactions catalyzed by transition metals (with regard to reactions using microwaves, see Tetrahedron 2001, 57, p. 9199 ff. p. 9225 ff. and also, in a general manner, "Microwaves in Organic Synthesis", André Loupy (Ed.), Wiley-VCH 2002.

**[0195]** The acid addition salts of compounds I are prepared in a customary manner by mixing the free base with a corresponding acid, where appropriate in solution in an organic solvent, for example a lower alcohol, such as methanol, ethanol or propanol, an ether, such as methyl tert-butyl ether or diisopropyl ether, a ketone, such as acetone or methyl ethyl ketone, or an ester, such as ethyl acetate.

**[0196]** The present invention moreover relates to compounds of formula I as defined above, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope (e.g., hydrogen by deuterium, <sup>12</sup>C by <sup>13</sup>C, <sup>14</sup>N by <sup>15</sup>N, <sup>16</sup>O by <sup>18</sup>O) and preferably wherein at least one hydrogen atom has been replaced by a deuterium atom.

**[0197]** Of course, the compounds according to the invention contain more of the respective isotope than this naturally occurs and thus is anyway present in the compounds I.

**[0198]** Stable isotopes (e.g., deuterium, <sup>13</sup>C, <sup>15</sup>N, <sup>18</sup>O) are nonradioactive isotopes which contain one additional neutron than the normally abundant isotope of the respective atom. Deuterated compounds have been used in pharmaceutical research to investigate the in vivo metabolic fate of the compounds by evaluation of the mechanism of action

and metabolic pathway of the non deuterated parent compound (Blake et al. J. Pharm. Sci. 64, 3, 367-391 (1975)). Such metabolic studies are important in the design of safe, effective therapeutic drugs, either because the in vivo active compound administered to the patient or because the metabolites produced from the parent compound prove to be toxic or carcinogenic (Foster et al., Advances in Drug Research Vol. 14, pp. 2-36, Academic press, London, 1985; Kato et al., J. Labelled Comp. Radiopharmaceut., 36(10):927-932 (1995); Kushner et al., Can. J. Physiol. Pharmacol., 77, 79-88 (1999).

**[0199]** Incorporation of a heavy atom, particularly substitution of deuterium for hydrogen, can give rise to an isotope effect that could alter the pharmacokinetics of the drug. This effect is usually insignificant if the label is placed at a metabolically inert position of the molecule.

**[0200]** Stable isotope labeling of a drug can alter its physico-chemical properties such as  $pK_a$  and lipid solubility. These changes may influence the fate of the drug at different steps along its passage through the body. Absorption, distribution, metabolism or excretion can be changed. Absorption and distribution are processes that depend primarily on the molecular size and the lipophilicity of the substance. These effects and alterations can affect the pharmacodynamic response of the drug molecule if the isotopic substitution affects a region involved in a ligand-receptor interaction.

**[0201]** Drug metabolism can give rise to large isotopic effect if the breaking of a chemical bond to a deuterium atom is the rate limiting step in the process. While some of the physical properties of a stable isotope-labeled molecule are different from those of the unlabeled one, the chemical and biological properties are the same, with one important exception: because of the increased mass of the heavy isotope, any bond involving the heavy isotope and another atom will be stronger than the same bond between the light isotope and that atom. In any reaction in which the breaking of this bond is the rate limiting step, the reaction will proceed slower for the molecule with the heavy isotope due to "kinetic isotope effect". A reaction involving breaking a C--D bond can be up to 700 percent slower than a similar reaction involving breaking a C--H bond. If the C--D bond is not involved in any of the steps leading to the metabolite, there may not be any effect to alter the behavior of the drug. If a deuterium is placed at a site involved in the metabolism of a drug, an isotope effect will be observed only if breaking of the C--D bond is the rate limiting step. There is evidence to suggest that whenever cleavage of an aliphatic C--H bond occurs, usually by oxidation catalyzed by a mixed-function oxidase, replacement of the hydrogen by deuterium will lead to observable isotope effect. It is also important to understand that the incorporation of deuterium at the site of metabolism slows its rate to the point where another metabolite produced by attack at a carbon atom not substituted by deuterium becomes the major pathway a process called "metabolic switching".

**[0202]** Deuterium tracers, such as deuterium-labeled drugs and doses, in some cases repeatedly, of thousands of milligrams of deuterated water, are also used in healthy humans of all ages, including neonates and pregnant women, without reported incident (e.g. Pons G and Rey E, Pediatrics 1999 104: 633; Coward W A et al., Lancet 1979 7: 13; Schwarcz H P, Control. Clin. Trials 1984 5(4 Suppl): 573; Rodewald L E et al., J. Pedi-atr. 1989 114: 885; Butte N F et al. Br. J. Nutr. 1991 65: 3; MacLennan A H et al. Am. J. Obstet Gynecol. 1981 139: 948). Thus, it is clear that any deuterium released, for instance, during the metabolism of compounds of this invention poses no health risk.

**[0203]** The weight percentage of hydrogen in a mammal (approximately 9%) and natural abundance of deuterium (approximately 0.015%) indicates that a 70 kg human normally contains nearly a gram of deuterium. Furthermore, replacement of up to about 15% of normal hydrogen with deuterium has been effected and maintained for a period of days to weeks in mammals, including rodents and dogs, with minimal observed adverse effects (Czajka D M and Finkel A J, Ann. N.Y. Acad. Sci. 1960 84: 770; Thomson J F, Ann. New York Acad. Sci 1960 84: 736; Czajka D M et al., Am. J. Physiol. 1961 201: 357). Higher deuterium concentrations, usually in excess of 20%, can be toxic in animals. However, acute replacement of as high as 15%-23% of the hydrogen in humans' fluids with deuterium was found not to cause toxicity (Blagojevic N et al. in "Dosimetry & Treatment Planning for Neutron Capture Therapy", Zamenhof R, Solares G and Harling O Eds. 1994. Advanced Medical Publishing, Madison Wis. pp.125-134; Diabetes Metab. 23: 251 (1997)).

**[0204]** Increasing the amount of deuterium present in a compound above its natural abundance is called enrichment or deuterium-enrichment. Examples of the amount of enrichment include from about 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 21, 25, 29, 33, 37, 42, 46, 50, 54, 58, 63, 67, 71, 75, 79, 84, 88, 92, 96, to about 100 mol %.

**[0205]** The hydrogens present on a particular organic compound have different capacities for exchange with deuterium. Certain hydrogen atoms are easily exchangeable under physiological conditions and, if replaced by deuterium atoms, it is expected that they will readily exchange for protons after administration to a patient. Certain hydrogen atoms may be exchanged for deuterium atoms by the action of a deuterium acid such as  $D_2SO_4/D_2O$ . Alternatively, deuterium atoms may be incorporated in various combinations during the synthesis of compounds of the invention. Certain hydrogen atoms are not easily exchangeable for deuterium atoms. However, deuterium atoms at the remaining positions may be incorporated by the use of deuterated starting materials or intermediates during the construction of compounds of the invention.

**[0206]** Deuterated and deuterium-enriched compounds of the invention can be prepared by using known methods described in the literature. Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard

synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Relevant procedures and intermediates are disclosed, for instance in Lizondo, J et al., *Drugs Fut*, 21(11), 1116 (1996); Brickner, S J et al., *J Med Chem*, 39(3), 673 (1996); Mallesham, B et al., *Org Lett*, 5(7), 963 (2003); PCT publications WO1997010223 WO2005099353, WO1995007271, WO2006008754; US Patent Nos. 7538189; 7534814; 7531685; 7528131; 7521421; 7514068; 7511013; and US Patent Application Publication Nos. 20090137457; 20090131485; 20090131363; 20090118238; 20090111840; 20090105338; 20090105307; 20090105147; 20090093422; 20090088416; 20090082471.

**[0207]** The present invention further relates to a pharmaceutical composition comprising at least one compound of formula I, a stereoisomer, prodrug, tautomer and/or physiologically tolerated acid addition salt thereof and optionally at least one physiologically acceptable carrier and/or auxiliary substance.

**[0208]** The invention also relates to compounds of formula I or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof for use as a medicament, and to compounds of formula I or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof for use in the treatment of a medical disorder susceptible to the treatment with a compound that modulates, preferably inhibits, the activity of glycogen synthase kinase 3 $\beta$ .

**[0209]** The invention also relates to the use of the compounds of formula I or of a stereoisomer, prodrug, tautomer or physiologically tolerated acid addition salt thereof for the preparation of a medicament for the treatment of a disorder susceptible to the treatment with a compound that modulates, preferably inhibits, the activity of glycogen synthase kinase 3 $\beta$ .

**[0210]** The compounds of the of formula I according to the present invention, as well as the stereoisomers, the tautomers, the prodrugs and physiologically tolerated acid addition salts thereof, are capable of modulating the activity on glycogen synthase kinase 3 $\beta$ . In particular, the compounds of the of formula I, as well as the stereoisomers, the tautomers, the prodrugs and physiologically tolerated acid addition salts thereof, have an inhibitory activity on glycogen synthase kinase 3 $\beta$ . Amongst the compounds of formula I those are preferred which achieve effective inhibition at low concentrations. In particular, compounds of the formula I are preferred which inhibit glycogen synthase kinase 3 $\beta$  at a level of  $IC_{50} < 1 \mu\text{Mol}$ , more preferably at a level of  $IC_{50} < 0.5 \mu\text{Mol}$ , particularly preferably at a level of  $IC_{50} < 0.2 \mu\text{Mol}$  and most preferably at a level of  $IC_{50} < 0.1 \mu\text{Mol}$ .

**[0211]** Therefore the compounds of the of formula I according to the present invention, their stereoisomers, tautomers, their prodrugs and their physiologically tolerated acid addition salts are useful for the treatment of a medical disorder susceptible to treatment with a compound that modulates glycogen synthase kinase 3 $\beta$  activity. As mentioned above, diseases caused by abnormal GSK-3 $\beta$  activity and which thus can be treated by supplying the compound of the formula I, a stereoisomer, tautomer, prodrug and/or a physiologically tolerated acid addition salt thereof, include in particular neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful for treatment of other neurodegenerative diseases such as behavioural psychiatric symptoms of dementia, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy, argyophilic brain disease) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; bipolar disorders, retinopathies and glaucoma. In addition, the compounds of the present invention are also useful for treatment of schizophrenia. The compounds of the present invention are also useful for treatment of pain.

**[0212]** Diseases which can be treated by supplying the compound of the of formula I, a stereoisomer, tautomer, prodrug and/or a physiologically tolerated acid addition salt thereof, include furthermore inflammatory diseases, such as rheumatoid arthritis and osteoarthritis.

**[0213]** Within the meaning of the invention, a treatment also includes a preventive treatment (prophylaxis), in particular as relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example as the suppression of symptoms. It can be effected over a short period, be orientated over the medium term or can be a long-term treatment, for example within the context of a maintenance therapy.

**[0214]** Within the context of the treatment, in the use according to the invention of the compounds of the formula I an effective quantity of one or more compounds I, a stereoisomer, tautomer, prodrug or physiologically tolerable acid addition salt thereof, as a rule formulated in accordance with pharmaceutical and veterinary practice, is administered to the individual to be treated, preferably a mammal, in particular a human being, productive animal or domestic animal. Whether such a treatment is indicated, and in which form it is to take place, depends on the individual case and is subject to medical assessment (diagnosis) which takes into consideration signs, symptoms and/or malfunctions which are present, the risks of developing particular signs, symptoms and/or malfunctions, and other factors.

**[0215]** As a rule, the treatment is effected by means of single or repeated daily administration, where appropriate together, or alternating, with other active compounds or active compound-containing preparations such that a daily dose of preferably from about 0.1 to 1000 mg/kg of bodyweight, in the case of oral administration, or of from about 0.1 to 100

mg/kg of bodyweight, in the case of parenteral administration, is supplied to an individual to be treated.

**[0216]** The invention also relates to pharmaceutical compositions for treating an individual, preferably a mammal, in particular a human being, productive animal or domestic animal. Thus, the compounds according to the invention are customarily administered in the form of pharmaceutical compositions which comprise a pharmaceutically acceptable excipient together with at least one compound according to the invention and, where appropriate, other active compounds. These compositions can, for example, be administered orally, rectally, transdermally, subcutaneously, intravenously, intramuscularly or intranasally.

**[0217]** Examples of suitable pharmaceutical formulations are solid medicinal forms, such as powders, granules, tablets, in particular film tablets, lozenges, sachets, cachets, sugar-coated tablets, capsules, such as hard gelatin capsules and soft gelatin capsules, suppositories or vaginal medicinal forms, semisolid medicinal forms, such as ointments, creams, hydrogels, pastes or plasters, and also liquid medicinal forms, such as solutions, emulsions, in particular oil-in-water emulsions, suspensions, for example lotions, injection preparations and infusion preparations, and eyedrops and ear-drops. Implanted release devices can also be used for administering inhibitors according to the invention. In addition, it is also possible to use liposomes or microspheres.

**[0218]** When producing the pharmaceutical compositions, the compounds according to the invention are optionally mixed or diluted with one or more excipients. Excipients can be solid, semisolid or liquid materials which serve as vehicles, carriers or medium for the active compound.

**[0219]** Suitable excipients are listed in the specialist medicinal monographs. In addition, the formulations can comprise pharmaceutically acceptable carriers or customary auxiliary substances, such as glidants; wetting agents; emulsifying and suspending agents; preservatives; antioxidants; antiirritants; chelating agents; coating auxiliaries; emulsion stabilizers; film formers; gel formers; odor masking agents; taste corrigents; resin; hydrocolloids; solvents; solubilizers; neutralizing agents; diffusion accelerators; pigments; quaternary ammonium compounds; refatting and overfatting agents; raw materials for ointments, creams or oils; silicone derivatives; spreading auxiliaries; stabilizers; sterilants; suppository bases; tablet auxiliaries, such as binders, fillers, glidants, disintegrants or coatings; propellants; drying agents; opacifiers; thickeners; waxes; plasticizers and white mineral oils. A formulation in this regard is based on specialist knowledge as described, for example, in Fiedler, H.P., *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete* [Encyclopedia of auxiliary substances for pharmacy, cosmetics and related fields], 4th edition, Aulendorf: ECV-Editio-Kantor-Verlag, 1996.

**[0220]** The following examples serve to explain the invention without limiting it.

#### Examples

**[0221]** The compounds were either characterized via proton-NMR in  $d_6$ -dimethylsulfoxide or d-chloroform on a 400 MHz or 500 MHz NMR instrument (Bruker AVANCE), or by mass spectrometry, generally recorded via HPLC-MS in a fast gradient on C18-material (electrospray-ionisation (ESI) mode), or melting point.

**[0222]** The magnetic nuclear resonance spectral properties (NMR) refer to the chemical shifts ( $\delta$ ) expressed in parts per million (ppm). The relative area of the shifts in the  $^1\text{H}$ -NMR spectrum corresponds to the number of hydrogen atoms for a particular functional type in the molecule. The nature of the shift, as regards multiplicity, is indicated as singlet (s), broad singlet (s. br.), doublet (d), broad doublet (d br.), triplet (t), broad triplet (t br.), quartet (q), quintet (quint.) and multiplet (m).

#### Abbreviations:

##### **[0223]**

DCM	dichloromethane
DMSO	dimethylsulfoxide
DMF	dimethylformamide
MeOH	methanol
AcOH	acetic acid
TFA	trifluoroacetic acid
RT	room temperature
quant.	quantitative

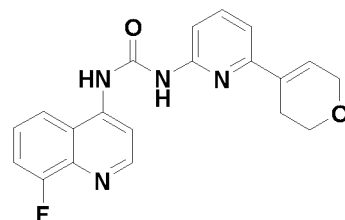
## I. Preparation Examples

## Example 1

5 1-(6-(3,6-Dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea

[0224]

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[0225] 1-(8-Fluoroquinolin-4-yl)-3-(6-iodopyridin-2-yl)urea (250 mg, 0.582 mmol), 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (187 mg, 0.873 mmol), sodium carbonate solution (2M, 1.31 mL, 2.62 mmol) and tetrakis(triphenylphosphine)-palladium(0) (68 mg, 0.058 mmol) were dissolved in 5 ml of DMF under an argon atmosphere and the mixture was stirred at 80°C, in a microwave oven, for one hour. After the solvent had been evaporated down to dryness, the resulting residue was treated with water and the mixture was then extracted with ethyl acetate. After the combined organic phases had been dried over sodium sulfate and the solvent had been filtered and evaporated down to dryness, the resulting residue was purified by column chromatography to give the title product (50 mg, 19%).

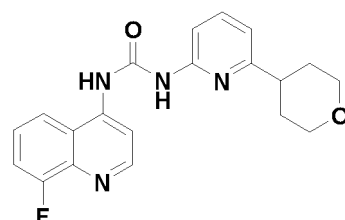
20 [0226] <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO, 400 MHz) δ 3.32 (m, 5H), 3.95 (s, 2H), 4.21 (s, 2H), 6.65 (s, 1H), 7.19 (m, 1H), 7.60 (m, 4H), 7.78 (m, 1H), 8.01 (m, 1H), 8.32 (s, 1H), 8.80 (m, 1H), 9.98 (s, 1H), 10.70 (s, 1H); MS (APCI+) m/z 365.1 (M+H<sup>+</sup>, 100%).

30 Example 2

1-(8-Fluoroquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)urea

[0227]

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[0228] A solution of (1-(6-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea (21 mg, 0.058 mmol) and 12.3 mg of palladium on charcoal in 20 mL of methanol together with 1 mL of DMF and 1 drop of AcOH was stirred under 1 atm of hydrogen for 18h. Filtration and evaporation to dryness afforded 21 mg (99%) of the desired title product.

45 [0229] <sup>1</sup>H-NMR (d<sub>6</sub>-DMSO, 400 MHz) δ 1.15 (m, 2H), 1.78 (m, 4H), 2.95 (m, 1H), 3.95 (d, 2H), 6.97 (d, 1H), 7.48 (br s, 1H), 7.65 (m, 2H), 7.75 (t, 1H), 8.08 (m, 1H), 8.35 (d, 1H), 9.82 (m, 1H), 10.11 (s, 1H); MS (APCI+) m/z 367.1 (M+H<sup>+</sup>, 100%).

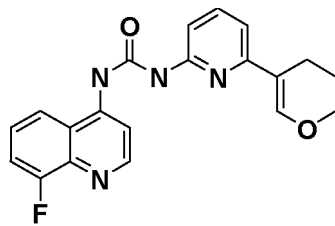
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Example 3

1-(6-(3,4-Dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea

55 [0230]

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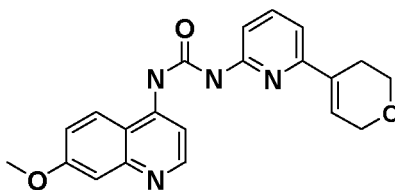
10 **[0231]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 365.1 (M+H+, 100%).

Example 4

15 1-(6-(3,6-Dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(7-methoxyquinolin-4-yl)urea

**[0232]**

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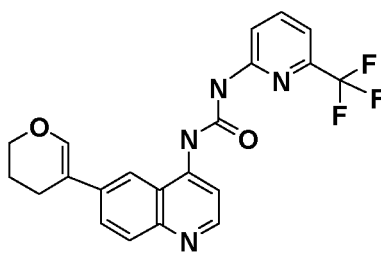
**[0233]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 377.1 (M+H+, 100%).

30 Example 5

1-(6-(3,4-Dihydro-2H-pyran-5-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

**[0234]**

35



40

45 **[0235]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 415.1 (M+H+, 100%).

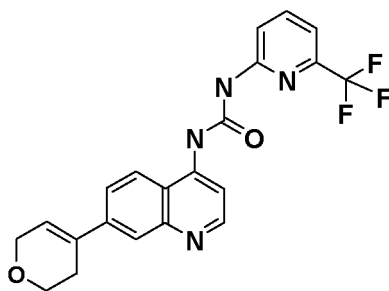
Example 6

50 1-(7-(3,6-Dihydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

**[0236]**

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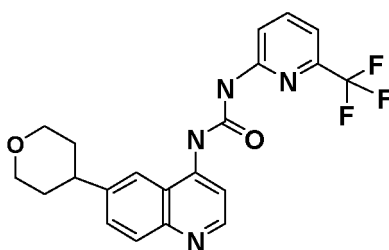
10

**[0237]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 415.1 (M+H<sup>+</sup>, 100%).

15 Example 7

1-(6-(Tetrahydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

20 **[0238]**



25

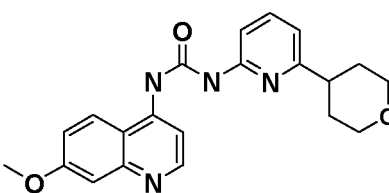
30 **[0239]** Prepared by the method described for Example 2.  
MS (APCI+) m/z 417.1 (M+H<sup>+</sup>, 100%).

Example 8

35 1-(7-Methoxyquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)urea

**[0240]**

40



45

**[0241]** Prepared by the method described for Example 2.  
MS (APCI+) m/z 379.1 (M+H<sup>+</sup>, 100%).

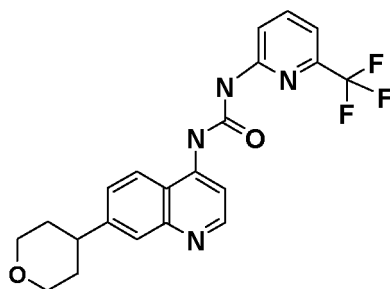
50 Example 9

1-(7-(Tetrahydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

**[0242]**

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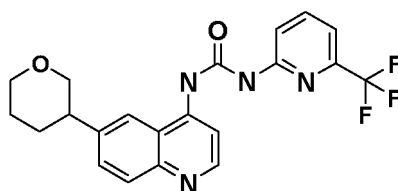
**[0243]** Prepared by the method described for Example 2.  
MS (APCI+) m/z 417.1 (M+H+, 100%).

15 Example 10

1-(6-(Tetrahydro-2H-pyran-3-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

**[0244]**

20



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**[0245]** Prepared by the method described for Example 2.  
MS (APCI+) m/z 417.1 (M+H+, 100%).

30

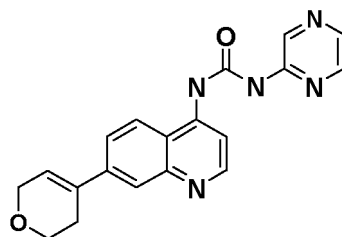
Example 11

1-(7-(3,6-Dihydro-2H-pyran-4-yl)quinolin-4-yl)-3-(pyrazin-2-yl)urea

35

**[0246]**

40



45

**[0247]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 348.1 (M+H+, 100%).

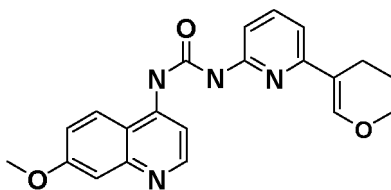
50 Example 12

1-(6-(3,4-Dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(7-methoxyquinolin-4-yl)urea

**[0248]**

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**[0249]** Prepared by the method described for Example 1.

MS (APCI+) m/z 377.1 (M+H<sup>+</sup>, 100%).

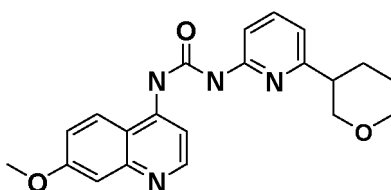
Example 13

15

1-(7-Methoxyquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-3-yl)pyridin-2-yl)urea

**[0250]**

20



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**[0251]** Prepared by the method described for Example 2.

MS (APCI+) m/z 379.2 (M+H<sup>+</sup>, 100%).

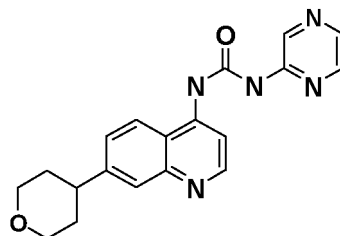
Example 14

30

1-(Pyrazin-2-yl)-3-(7-(tetrahydro-2H-pyran-4-yl)quinolin-4-yl)urea

**[0252]**

35



40

**[0253]** Prepared by the method described for Example 2.

45 MS (APCI+) m/z 350.2 (M+H<sup>+</sup>, 100%).

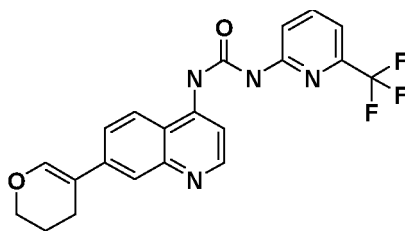
Example 15

50

1-(7-(3,4-Dihydro-2H-pyran-5-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

**[0254]**

55

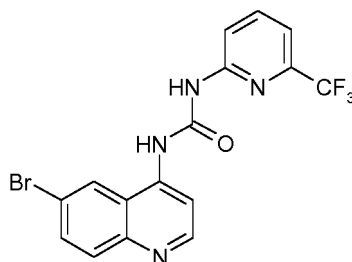


5

10 **[0255]** Prepared by the method described for Example 1.  
MS (APCI+) m/z 415.1 (M+H<sup>+</sup>, 100%).

Example 16: 1-(6-Bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

15 **[0256]**



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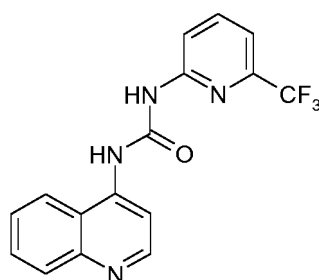
25

30 **[0257]** 366 mg of bis(trichloromethyl)carbonate (1.234mmol) were dissolved in 7 ml of dichloromethane (DCM) and cooled to 0°C. To this mixture a solution of 400 mg 6-(trifluoromethyl)pyridin-2-amine (2.467mmol) and 379  $\mu$ l triethylamine (5.43 mmol) in 9.7 ml DCM was slowly added over 60 minutes at 0°C and stirring was then continued for additional 60 minutes at 23°C. 550 mg 6-bromoquinolin-4-amine (2.467mmol) and 379  $\mu$ l triethylamine (5.43 mmol) were suspended in 9.7 ml DCM and the suspension was slowly added to the reaction mixture at 23°C, which became a clear solution after 45 minutes. After stirring over night the reaction mixture was poured into ice water and stirred for 2 h. The precipitate formed was filtered off and dried in vacuo for 24 h. 810 mg of the desired product were obtained as off white powder (yield: 80%). The already quite pure raw material was used without further purification.

35 **[0258]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz):  $\delta$  [ppm]: 10.26 (s, 1 H), 9.70 (s, 1 H), 8.79 (d, 1 H), 8.44 (d, 1 H), 8.28 (d, 1 H), 8.19 (d, 1 H), 8.09 (dd, 1 H), 7.88 (dd, 1H), 7.93 (d, 1H), 7.57 (d, 1H) ESI-MS [M+H<sup>+</sup>]: 413.0

Example 17: 1-(6-(Trifluoromethyl)pyridin-2-yl)-3-quinolin-4-yl-urea (not according to the invention)

40 **[0259]**



45

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**[0260]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by quinolin-4-ylamine.

ESI-MS [M+H<sup>+</sup>]: 333.1

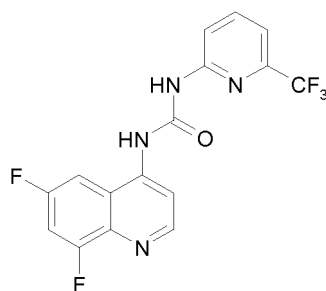
55

Example 18: 1-(6,8-Difluoroquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

**[0261]**

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[0262] The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 6,8-difluoro-quinolin-4-ylamine.

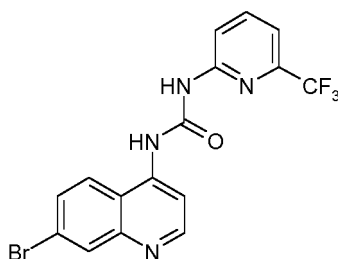
ESI-MS [M+H<sup>+</sup>]: 369.0

15

Example 19: 1-(7-Bromoquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

[0263]

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[0264] The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 7-bromoquinolin-4-amine.

ESI-MS [M+H<sup>+</sup>]: 410.9/412.9

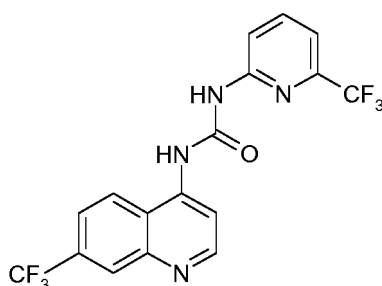
30

Example 20: 1-(7-Trifluoromethylquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

35

[0265]

40



45

[0266] The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 7-trifluoromethyl-quinolin-4-ylamine.

ESI-MS [M+H<sup>+</sup>]: 401.1

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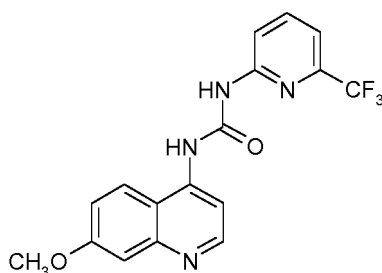
Example 21: 1-(7-Methoxyquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

55

[0267]

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**[0268]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 7-methoxy-quinolin-4-ylamine.

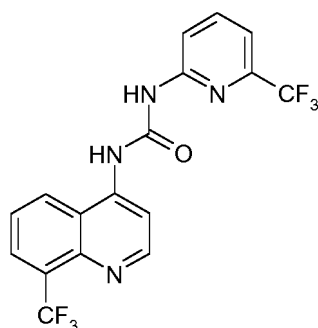
ESI-MS [M+H<sup>+</sup>]: 363.1

15

Example 22: 1-(8-Trifluoromethylquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

**[0269]**

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**[0270]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 8-trifluoromethyl-quinolin-4-ylamine.

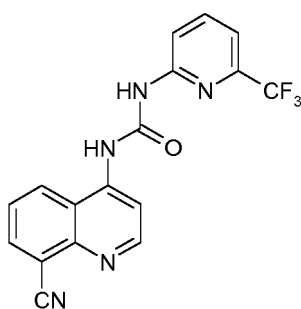
ESI-MS [M+H<sup>+</sup>]: 401.1

35

Example 23: 1-(8-Cyanoquinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea (not according to the invention)

**[0271]**

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**[0272]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 8-cyano-quinolin-4-ylamine.

ESI-MS [M+H<sup>+</sup>]: 358.1

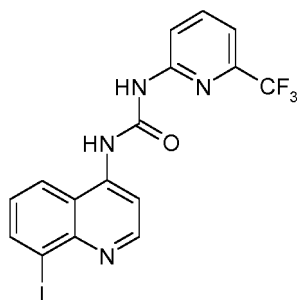
55

Example 24: 1-(8-Iodoquinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (not according to the invention)

**[0273]**

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10

**[0274]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 8-iodoquinolin-4-ylamine.

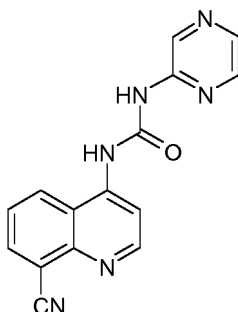
ESI-MS [M+H<sup>+</sup>]: 459.0/459.9

15

Example 25: 1-(8-Cyanoquinolin-4-yl)-3-pyrazin-2-yl-urea (not according to the invention)

**[0275]**

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**[0276]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 8-cyano-quinolin-4-ylamine and 6-trifluoromethylpyridine-2-amine by pyrazine-2-ylamine.

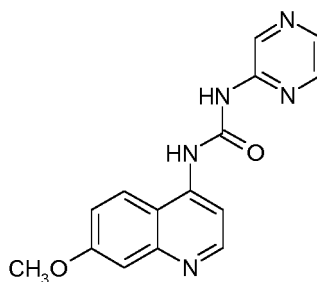
ESI-MS [M+H<sup>+</sup>]: 291.1

35

Example 26: 1-(7-Methoxyquinolin-4-yl)-3-pyrazin-2-yl-urea (not according to the invention)

**[0277]**

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50

**[0278]** The title compound was prepared as described in example 16, substituting 6-bromoquinolin-4-amine by 7-methoxy-quinolin-4-ylamine and 6-trifluoromethylpyridine-2-amine by pyrazine-2-ylamine..

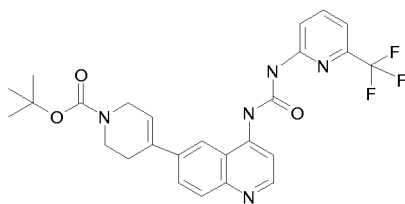
ESI-MS [M+H<sup>+</sup>]: 296.1

55

Example 27: tert-Butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate

**[0279]**

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Step 1: 1-(6-Bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea

**[0280]** 366 mg of bis(trichloromethyl)carbonate (1,234 mmol) were dissolved in 7 ml of DCM and cooled to 0°C. To this mixture the solution of 400 mg of 6-(trifluoromethyl)pyridin-2-amine (2.467 mmol) and 379 µl of triethylamine (5.43 mmol) in 9.7ml DCM was slowly added over 60 minutes at 0°C, and stirring was continued for an additional 60 minutes at room temperature. 550 mg of 6-bromoquinolin-4-amine (2.467 mmol) and 379 µl of triethylamine (5.43 mmol) were suspended in 9.7 ml and subsequently slowly added to the reaction mixture at RT, which became a clear solution after 45 minutes. After stirring over night the reaction mixture was poured into ice water and stirred for 2h. The precipitation formed was filtered off and dried in vacuum for 24h. 810 mg of the desired product were obtained as an off white powder (yield: 80%). The quite pure raw material was used without further purification in the next step.

**[0281]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400MHz): δ [ppm]: 10.26 (s, 1 H), 9.70 (s, 1 H), 8.79 (d, 1 H), 8.44 (d, 1 H), 8.28 (d, 1 H), 8.19 (d, 1 H), 8.09 (dd, 1 H), 7.88 (dd, 1H), 7.93 (d, 1H), 7.57 (d, 1 H)

ESI-MS [M+H<sup>+</sup>]: 413.0

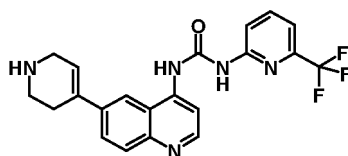
Step 2: tert-Butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate

**[0282]** 1.500g of 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea (3.65 mmol), 1.692 g of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (5.47 mmol), 0.422g of tetrakis(triphenylphosphine)palladium(0) (0.365 mmol) and 8.21 ml of a 2M sodium carbonate solution (16.42 mmol) were dissolved/suspended in 32ml DMF in a microwave vessel, flushed with vacuum/argon, and subsequently heated in the microwave for 1h at 80°C. HPLC/MSD indicated almost complete formation of the desired product. The reaction mixture was poured on ice, stirred for 1h, and the precipitation formed was filtered off and dried in vacuum for 24h. 2 g of the desired product were obtained as an off white powder (yield: quant.). The quite pure raw material was used without further purification in the next step.

ESI-MS [M+H<sup>+</sup>]: 514.2

Example 28: 1-[6-(1,2,3,6-Tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

**[0283]**



**[0284]** 0.2 g of tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate (0.389 mmol) were dissolved in 0.6 ml DCM (yellow solution). 0.300 ml of TFA (3.89 mmol) were added and the reaction mixture was stirred for 2h at RT. After evaporation of the solvent and excess TFA in vacuum, water was added to the residue, the acidic mixture extracted with ethyl acetate, the water phase adjusted to pH 9 with 1M NaOH and subsequently extracted three times with DCM. The combined DCM solutions were washed with a small amount of brine, dried over sodium sulphate and the solvent was removed in vacuum. 130 mg of the desired product were obtained as light yellow powder (yield: 81%).

**[0285]** <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500MHz): δ [ppm]: 10.81 (broad s, 1 H), 10.11 (broad s, 1 H), 8.67 (d, 1 H), 8.28 (d, 1 H), 8.23 (s, 1 H), 8.20 (d, 1 H), 8.06 (dd, 1 H), 7.88 and 7.91 (2d, 2H), 7.53 (d, 1H), 6.47 (broad s, 1H), 3.45 (broad s, 2H), 3.3 (very broad s), 3.00 (t, 2H), 2.56 (broad s, 2H)

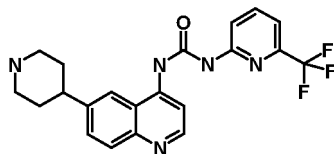
ESI-MS [M+H<sup>+</sup>]: 414.1

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Example 29: 1-(6-(Piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea

[0286]

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[0287] 0.59 g of 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea (0.427 mmol) were dissolved in a mixture of 143 ml of dioxane and 10 ml of ethanol. After addition of 0.152 g of Pd/C (1.427 mmol) and 0.082 ml of acetic acid (1.427 mmol), hydrogenation was performed for 7h at 60°C and over night at room temperature, which led to complete double bond hydrogenation according to HPLC/MSD analysis. The catalyst was filtered off, the solvent removed under reduced pressure and the residue extracted three times with ethyl acetate after adding water and a small amount of NaOH (pH 9). The combined organic phases were washed with a small amount of brine, dried over sodium sulfate and the solvent was removed under reduced pressure. 593 mg of the desired product were obtained as light yellow powder (yield: 64%).

15

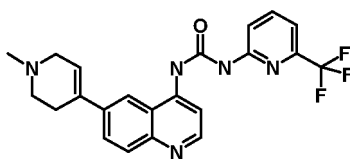
[0288] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 500MHz): δ [ppm]: 10.64 (broad s, 1 H), 9.79 (broad s, 1 H), 8.70 (d, 1 H), 8.21-8.24 (m, 2H), 8.05-8.09 (m, 2H), 7.93 (d, 1H), 7.66 (d, 1H), 7.54 (d, 1H), 3.74 (very broad s), 3.16 (broad d, 2H), 2.82-2.89 (m, 1H), 2.69-2.77 (m, 2H), 1.75-1.89 (m, 4H),  
ESI-MS [M+H<sup>+</sup>]: 416.2

20

Example 30: 1-[6-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

[0289]

30



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[0290] To 0.12 g of 1-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea (0.290 mmol) were added subsequently 2 ml of methanol, 0.366 ml of formaldehyde (4.64 mmol) and a solution of 0.055 g of sodium borohydride (1.451 mmol) in 0.8 ml of water. The reaction was slightly exotherm. A small amount of 2M HCl was added to the reaction mixture up to a pH of 3 to destroy the excess of sodium borohydride. After neutralization with sodium bicarbonate, methanol was evaporated under reduced pressure, water added to the residue, the reaction mixture extracted three times with ethylacetate, the organic phases combined and dried over sodium sulfate and the solvent evaporated under reduced pressure. 120 mg of the desired product were obtained as an off white powder (yield: 97%).

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[0291] <sup>1</sup>H NMR (DMSO-d<sub>6</sub>,500MHz): δ [ppm]: 10.45 (broad s, 1 H), 9.47 (broad s, 1 H), 8.67 (d, 1 H), 8.28 (d, 1 H), 8.22 (d, 1 H), 8.10 (s, 1 H), 8.06 (dd, 1 H), 7.89 (dd, 2 H), 7.53 (d, 1 H), 6.39 (broad s, 1 H), 3.40 (s, 3H), 3.09 (s, 2H), 2.68 (broad s, 2H), 2.64-2.66 (m, 2H).

45

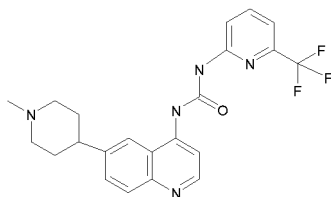
ESI-MS [M+H<sup>+</sup>]: 428.2

Example 31: 1-[6-(1-Methyl-piperidin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

[0292]

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**[0293]** The title compound was prepared as described in example 29, substituting 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-[6-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea.

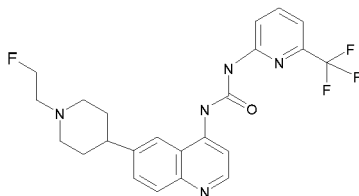
ESI-MS [M+H<sup>+</sup>]: 430.1

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Example 32: 1-[6-[1-(2-Fluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

**[0294]**

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**[0295]** The reaction mixture containing 0.27 g of 1-(6-(piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea (0.650 mmol), 0.073 ml of 1-bromo-2-fluoroethane (0.975 mmol), 1.059g of cesium carbonate (3.25 mmol) and 6.5 of dioxane was shaken in a flask at 60°C for 4h. Due to non complete reaction, additional 0.049 ml of 1-bromo-2-fluoroethane (0.650 mmol) were added and the reaction mixture was shaken at 60°C for 18h. Saturated sodium bicarbonate solution was added and the mixture extracted three times with ethyl acetate. The combined organic phases were washed once with brine, dried over sodiumsulfat and the solvent removed under reduced pressure. After purifying of the raw material (190 mg) by column chromatography (silica gel, DCM/MeOH 95:5) 90mg of the desired product were obtained as beige powder (yield: 30%).

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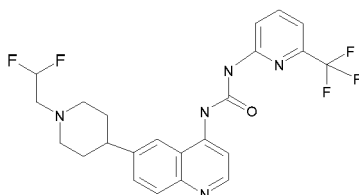
25

**[0296]** ESI-MS [M+H<sup>+</sup>]: 462.2

Example 33: 1-[6-[1-(2,2-Difluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

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**[0297]**



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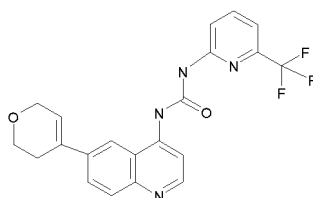
**[0298]** The title compound was prepared as described in example 32, substituting 1-bromo-2-fluoroethane by 1,1-difluoro-2-iodoethane.

**[0299]** ESI-MS [M+H<sup>+</sup>]: 480.2

Example 34: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

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**[0300]**



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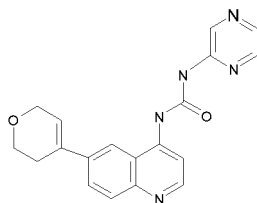
**[0301]** The title compound was prepared as described in example 27 step 2, substituting tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

[0302] ESI-MS [M+H<sup>+</sup>]: 415.1

Example 35: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-quinolin-4-yl]-3-pyrazin-2-yl-urea

5 [0303]

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15 Step 1: 1-(6-Bromoquinolin-4-yl)-3-(pyrazin-2-yl)urea

[0304] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-bromoquinolin-4-amine and 6-bromoquinolin-4-amine by pyrazin-2-amine.

[0305] ESI-MS [M+H<sup>+</sup>]: 345.9

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Step 2: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-quinolin-4-yl]-3-pyrazin-2-yl-urea

[0306] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-bromoquinolin-4-yl)-3-(pyrazin-2-yl)urea and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

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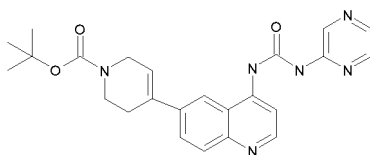
[0307] ESI-MS [M+H<sup>+</sup>]: 348.1

Example 36: tert-Butyl 4-[4-(3-pyrazin-2-ylureido)quinolin-6-yl]-5,6-dihydropyridine-1(2H)-carboxylate

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[0308]

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[0309] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-bromoquinolin-4-yl)-3-(pyrazin-2-yl)urea (example 35 step 1).

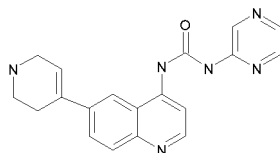
40

[0310] ESI-MS [M+H<sup>+</sup>]: 447.2

Example 37: 1-Pyrazin-2-yl-3-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-urea

45 [0311]

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[0312] The title compound was prepared as described in example 28, substituting tert-butyl 4-[4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate by tert-butyl 4-[4-(3-pyrazin-2-ylureido)quinolin-6-yl]-5,6-dihydropyridine-1(2H)-carboxylate (example 36).

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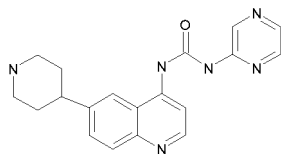
[0313] ESI-MS [M+H<sup>+</sup>]: 347.1

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Example 38: 1-(6-Piperidin-4-yl-quinolin-4-yl)-3-pyrazin-2-yl-urea

[0314]

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[0315] The title compound was prepared as described in example 29, substituting 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-pyrazin-2-yl-3-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-urea (example 37).

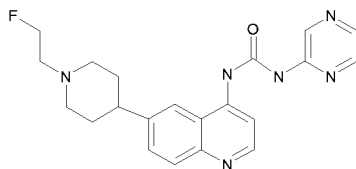
[0316] ESI-MS [M+H<sup>+</sup>]: 349.2

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Example 39: 1-{6-[1-(2-Fluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl}-3-pyrazin-2-yl-urea

[0317]

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[0318] The title compound was prepared as described in example 32, substituting 1-(6-(piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-(6-piperidin-4-yl-quinolin-4-yl)-3-pyrazin-2-yl-urea (example 38).

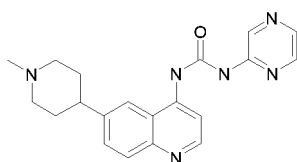
[0319] ESI-MS [M+H<sup>+</sup>]: 395.2

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Example 40: 1-[6-(1-Methyl-piperidin-4-yl)-quinolin-4-yl]-3-pyrazin-2-yl-urea

[0320]

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[0321] The title compound was prepared as described in example 30, substituting 1-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-piperidin-4-yl-quinolin-4-yl)-3-pyrazin-2-yl-urea (example 38).

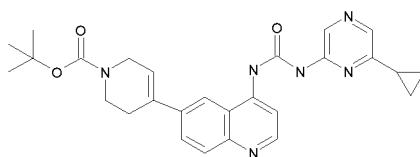
[0322] ESI-MS [M+H<sup>+</sup>]: 363.2

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Example 41: tert-Butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate

[0323]

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Step 1: 1-(6-Bromoquinolin-4-yl)-3-(6-cyclopropylpyrazin-2-yl)urea

[0324] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-bromoquinolin-4-amine and 6-bromoquinolin-4-amine by 6-cyclopropylpyrazin-2-amine.

[0325] ESI-MS [M+H<sup>+</sup>]: 386.0

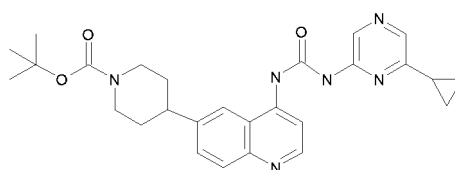
Step 2: Tert-butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate

[0326] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-bromoquinolin-4-yl)-3-(6-cyclopropylpyrazin-2-yl)urea (example 15 step 1).

[0327] ESI-MS [M+H<sup>+</sup>]: 487.2

Example 42: tert-Butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-piperidine-1-carboxylate

[0328]

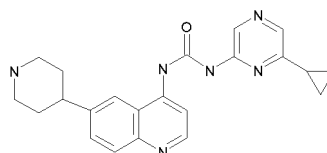


[0329] The title compound was prepared as described in example 29, substituting 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by tert-butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate (example 41).

[0330] ESI-MS [M+H<sup>+</sup>]: 489.2

Example 43: 1-(6-Cyclopropyl-pyrazin-2-yl)-3-(6-piperidin-4-yl-quinolin-4-yl)-urea

[0331]

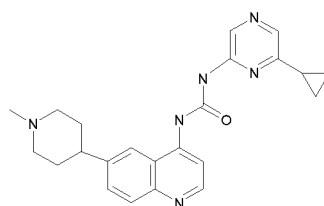


[0332] The title compound was prepared as described in example 28, substituting tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate by tert-butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-piperidine-1-carboxylate (example 42).

[0333] ESI-MS [M+H<sup>+</sup>]: 389.2

Example 44: 1-(6-Cyclopropyl-pyrazin-2-yl)-3-[6-(1-methyl-piperidin-4-yl)-quinolin-4-yl]-urea

[0334]



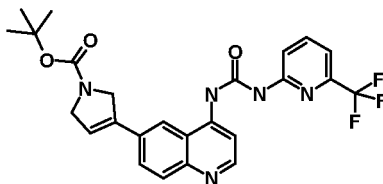
[0335] The title compound was prepared as described in example 30, substituting 1-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-cyclopropyl-pyrazin-2-yl)-3-(6-piperidin-4-yl-quinolin-4-yl)-urea

yl)-urea (example 43).

**[0336]** ESI-MS  $[M+H]^+$ : 403.1

Example 45: tert-Butyl 3-{4-[3-(6-Trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-2,5-dihydro-pyrrole-1-carboxylate

**[0337]**

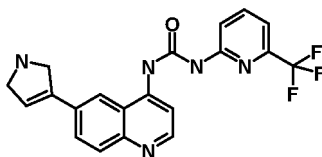


**[0338]** The title compound was prepared as described in example 27 step 2, substituting tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate.

**[0339]** ESI-MS  $[M+H]^+$ : 500.2

Example 46: 1-[6-(2,5-Dihydro-1H-pyrrol-3-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea

**[0340]**

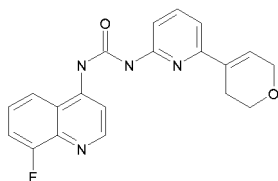


**[0341]** The title compound was prepared as described in example 28, substituting tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate by tert-butyl 3-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-2,5-dihydro-pyrrole-1-carboxylate (example 45).

**[0342]** ESI-MS  $[M+H]^+$ : 400.1

Example 47: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea

**[0343]**



Step 1: 1-(8-Fluoroquinolin-4-yl)-3-(6-iodopyridin-2-yl)urea

**[0344]** The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 4-amino-8-fluoroquinoline and 6-bromoquinolin-4-amine by 6-iodopyridin-2-amine.

**[0345]** ESI-MS  $[M+H]^+$ : 409.0

Step 2: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea

**[0346]** The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(8-fluoroquinolin-4-yl)-3-(6-iodopyridin-2-yl)urea (example 47, step 1) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by 2-(3,6-dihydro-2H-

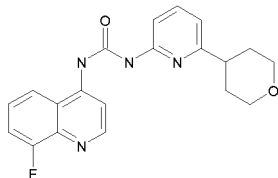
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pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

**[0347]** ESI-MS  $[M+H]^+$ : 365.1

Example 48: 1-(8-Fluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

**[0348]**

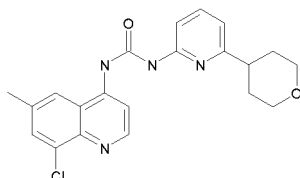


**[0349]** The title compound was prepared as described in example 29, substituting 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-[6-(3,6-dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea (example 47) and by performing the hydrogenation at room temperature for at least 24h .

**[0350]** ESI-MS  $[M+H]^+$ : 367.15

Example 49: 1-(8-Chloro-6-methyl-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

**[0351]**

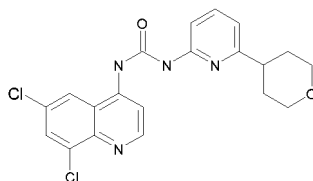


**[0352]** The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 4-amino-8-chloro-6-methylquinoline and 6-bromoquinolin-4-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine .

**[0353]** ESI-MS  $[M+H]^+$ : 397.1

Example 50: 1-(6,8-Dichloro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

**[0354]**



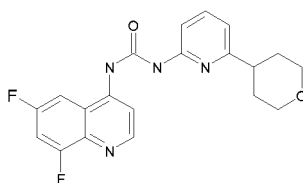
**[0355]** The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine and 6-bromoquinolin-4-amine by 4-amino-6,8-dichloroquinoline.

**[0356]** ESI-MS  $[M+H]^+$ : 418.1

Example 51: 1-(6,8-Difluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

**[0357]**

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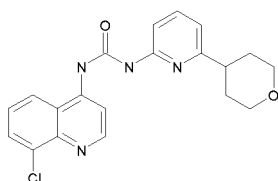
[0358] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 4-amino-6,8-difluoroquinoline and 6-bromoquinolin-4-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine.

10 [0359] ESI-MS [M+H<sup>+</sup>]: 385.1

Example 52: 1-(8-Chloro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

[0360]

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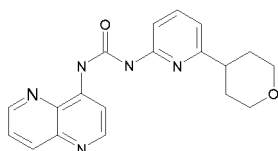
[0361] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine and 6-bromoquinolin-4-amine by 8-chloroquinolin-4-amine.

25 [0362] ESI-MS [M+H<sup>+</sup>]: 383.2

Example 53: 1-[1,5]Naphthyridin-4-yl-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

[0363]

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[0364] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine and 6-bromoquinolin-4-amine by 1,5-naphthyridin-4-amine.

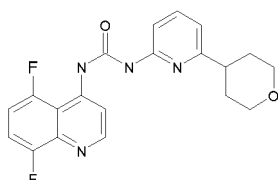
40 [0365] ESI-MS [M+H<sup>+</sup>]: 350.2

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Example 54: 1-(5,8-Difluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

[0366]

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[0367] The title compound was prepared as described in example 1 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 5,8-difluoroquinolin-4-amine and 6-bromoquinolin-4-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine.

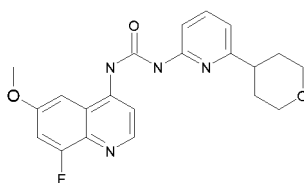
55 [0368] ESI-MS [M+H<sup>+</sup>]: 385.1

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Example 55: 1-(8-Fluoro-6-methoxy-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

[0369]

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**[0370]** The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 8-fluoro-6-methoxyquinolin-4-amine and 6-bromoquinolin-4-amine by 6-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine .

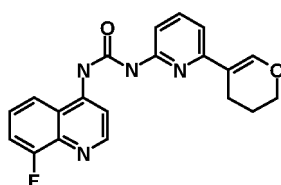
10

**[0371]** ESI-MS [M+H<sup>+</sup>]: 397.2

Example 56: 1-[6-(5,6-Dihydro-4H-pyran-3-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea

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**[0372]**



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**[0373]** The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(8-fluoroquinolin-4-yl)-3-(6-iodopyridin-2-yl)urea (example 47, step 1) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by 2-(3,4-dihydro-2H-pyran-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

25

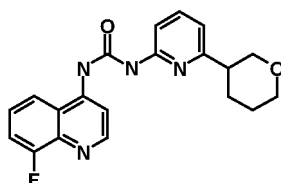
**[0374]** ESI-MS [M+H<sup>+</sup>]: 365.1

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Example 57: 1-(8-Fluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-3-yl)-pyridin-2-yl]-urea

**[0375]**

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**[0376]** The title compound was prepared as described in example 29, substituting 1-(6-(1,2,3,6-tetrahydropyridin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-[6-(5,6-dihydro-4H-pyran-3-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea (example 56) and by performing the hydrogenation at room temperature for at least 24h .

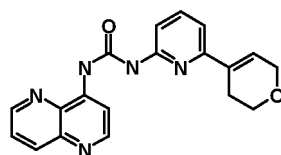
45

**[0377]** ESI-MS [M+H<sup>+</sup>]: 367.15

Example 58: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-[1,5]naphthyridin-4-yl-urea

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**[0378]**



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Step 1: 1-(6-iodopyridin-2-yl)-3-(1,5-naphthyridin-4-yl)urea

[0379] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 6-iodopyridin-2-amine and 6-bromoquinolin-4-amine by 1,5-naphthyridin-4-ylamine.

[0380] ESI-MS [M+H<sup>+</sup>]: 392.0

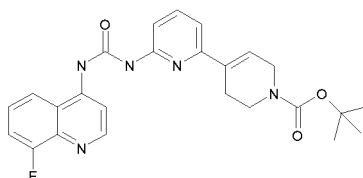
Step 2: 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-[1,5]naphthyridin-4-yl-urea

[0381] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-iodopyridin-2-yl)-3-(1,5-naphthyridin-4-yl)urea (example 58, step 1) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

[0382] ESI-MS [M+H<sup>+</sup>]: 348.1

Example 59: tert-Butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate

[0383]

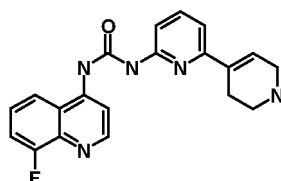


[0384] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(8-fluoroquinolin-4-yl)-3-(6-iodopyridin-2-yl)urea (example 47 step 1).

[0385] ESI-MS [M+H<sup>+</sup>]: 464.0

Example 60: 1-(8-Fluoro-quinolin-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea

[0386]

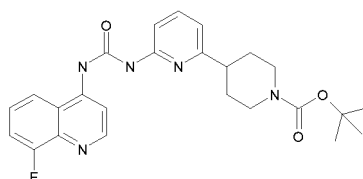


[0387] The title compound was prepared as described in example 28, substituting tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate by tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate (example 59).

[0388] ESI-MS [M+H<sup>+</sup>]: 364.0

Example 61: tert-Butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylate

[0389]



[0390] 0.340 g of tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate (0.734 mmol) were dissolved in a mixture of 220 ml of DMF and 125 ml of methanol. After addition of 0.078 g of Pd/C (0.734

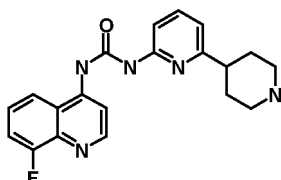
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mmol) and 0.5 ml of acetic acid (8.73 mmol) hydrogenation was performed for 24h at room temperature, which led to complete double bond hydrogenation according to HPLC/MSD analysis. The catalyst was filtered off, the solvent removed under reduced pressure and the residue extracted three times with ethyl acetate after adding water and a small amount of NaOH (pH 9). The combined organic phases were washed with a small amount of brine, dried over sodium sulfate and the solvent was removed under reduced pressure. 300 mg of the desired product were obtained as a powder (yield: 88%).

**[0391]** ESI-MS  $[M+H]^+$ : 466.2

Example 62: 1-(8-Fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea

**[0392]**

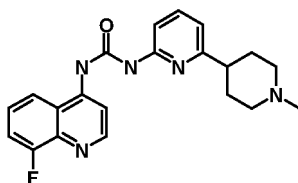


**[0393]** The title compound was prepared as described in example 28, substituting tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate by tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylate (example 61).

ESI-MS  $[M+H]^+$ : 366.2

Example 63: 1-(8-Fluoro-quinolin-4-yl)-3-(1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea

**[0394]**

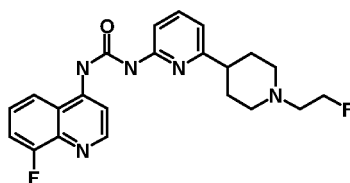


**[0395]** The title compound was prepared as described in example 30, substituting 1-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea (example 62).

**[0396]** ESI-MS  $[M+H]^+$ : 380.2

Example 64: 1-[1'-(2-Fluoro-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluoro-quinolin-4-yl)-urea

**[0397]**



**[0398]** The title compound was prepared as described in example 32, substituting 1-(6-(piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea (example 62).

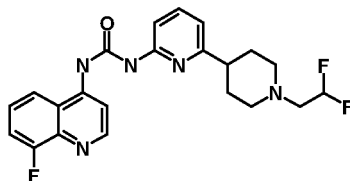
**[0399]** ESI-MS  $[M+H]^+$ : 412.2

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Example 65: 1-[1'-(2,2-Difluoro-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluoro-quinolin-4-yl)-urea

[0400]

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[0401] The title compound was prepared as described in example 32, substituting 1-(6-(piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea by 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea (example 62) and 1-bromo-2-fluoroethane by 1,1-difluoro-2-iodoethane.

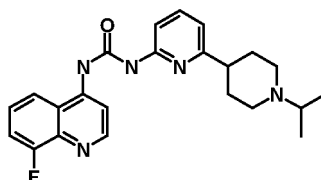
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[0402] ESI-MS [M+H<sup>+</sup>]: 430.2

Example 66: 1-(8-Fluoro-quinolin-4-yl)-3-(1'-isopropyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea

[0403]

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[0404] To a solution of 50 mg of 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea (example 62) (0.137 mmol) in 50 ml of acetone were added 26 mg of sodium borohydride (0.684 mmol) in small portions. The reaction was slightly exotherm. After stirring the reaction mixture over night a small amount of 2M HCl was added to the reaction mixture up to a pH of 3 to destroy the excess of sodium borohydride. After neutralization with sodium bicarbonate, acetone was evaporated under reduced pressure, water added to the residue, the reaction mixture extracted three times with DCM, the organic phases combined and dried over sodium sulfate and the solvent evaporated under reduced pressure. 45 mg of the desired product were obtained as off white powder (yield: 81 %) after column chromatography (silica gel, DCM/MeOH 98/2).

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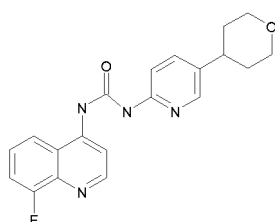
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[0405] ESI-MS [M+H<sup>+</sup>]: 408.2

Example 67: 1-(8-Fluoro-quinolin-4-yl)-3-[5-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

[0406]

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Step 1: 5-(3,6-Dihydro-2H-pyran-4-yl)pyridin-2-amine

[0407] 0.220 g of 5-iodopyridin-2-amine (1.0 mmol), 0.315 g of 2-(3,6-dihydro-2H-pyran-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.50 mmol), 0.116 g of tetrakis(triphenylphosphine)palladium(0) (0.100 mmol) and 2.25 ml of a 2M sodium carbonate solution (4.50 mmol) were dissolved/suspended in 8.6 ml of DMF in a microwave vessel, flushed with vacuum/argon, and subsequently heated in the microwave for 20 min at 120°C. HPLC/MSD indicated almost complete formation of the desired product. The solvent was evaporated under reduced pressure, 2M HCl was added to the residue and the mixture extracted three times with DCM. To the acidic water phase 2M NaOH was added up to pH 9 and the

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mixture was extracted three times with ethyl acetate. The combined ethyl acetate solutions were washed once with brine, dried over sodium sulfate and the solvent removed under reduced pressure. 195 mg of the desired product were obtained as yellow powder (yield: quant.). The quite pure raw material (about 90%) was used without further purification in the next step.

5 [0408] ESI-MS [M+H<sup>+</sup>]: 177.1

Step 2: 5-(Tetrahydro-2H-pyran-4-yl)pyridin-2-amine

10 [0409] The title compound was prepared as described in example 61, substituting tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate by 5-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-amine and by using ethanol as solvent.

[0410] ESI-MS [M+H<sup>+</sup>]: 179.1

Step 3: 1-(8-Fluoro-quinolin-4-yl)-3-[5-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea

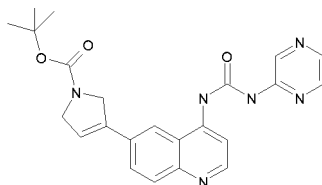
15 [0411] The title compound was prepared as described in example 27 step 1, substituting 6-(trifluoromethyl)pyridin-2-amine by 8-fluoroquinolin-4-amine and 6-bromoquinolin-4-amine by 5-(tetrahydro-2H-pyran-4-yl)pyridin-2-amine (example 67, step 2).

20 [0412] ESI-MS [M+H<sup>+</sup>]: 367.1

Example 68: tert-Butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-2,5-dihydro-pyrrole-1-carboxylate

[0413]

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[0414] The title compound was prepared as described in example 27 step 2, substituting 1-(6-bromo-quinolin-4-yl)-3-(6-trifluoromethyl-pyridin-2-yl)-urea by 1-(6-bromoquinolin-4-yl)-3-(pyrazin-2-yl)urea (example 9, step 1) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate by tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate.

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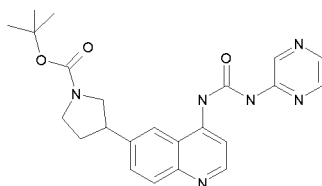
[0415] ESI-MS [M+H<sup>+</sup>]: 433.2

Example 69: tert-Butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-pyrrolidine-1-carboxylate

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[0416]

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[0417] The title compound was prepared as described in example 61, substituting tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate by tert-butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-2,5-dihydro-pyrrole-1-carboxylate (example 68).

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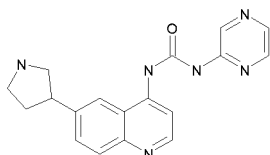
[0418] ESI-MS [M+H<sup>+</sup>]: 435.2

Example 70: 1-Pyrazin-2-yl-3-(6-pyrrolidin-3-yl-quinolin-4-yl)-urea

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[0419]

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**[0420]** To a solution of 50 mg of tert-butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-pyrrolidine-1-carboxylate (example 43) (0,120 mmol) in 5 ml of DCM was added 1 ml of 6M HCl solution in propanol-2 with stirring at room temperature. After reaction over night the solvent and excess HCl was removed in vacuum, and the residue was co-distilled at least three times with propanol-2. 50 mg of the desired product were obtained as powder as the di-hydrochloride salt (yield: quant.).

**[0421]** ESI-MS [M+H<sup>+</sup>]: 335.1

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II. Biological tests

**[0422]** The compounds according to the invention exhibit very good affinities for GSK-3 (< 1 μM, frequently < 100 nM) and exhibited good selectivity against multiple kinase targets.

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Methods - biochemical hGSK-3beta assay

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**[0423]** Compounds were tested for their ability to inhibit human Glycogen Synthase Kinase-3 beta (hGSK-3β) to phosphorylate biotin-YRRAVPPSPSLSRHSSPHQ(pS)EDEEE. Compounds were incubated with 0.5 μCi 33P-ATP, 10 μM ATP, 0.0125U hGSK-3β (Upstate cell signaling solutions) and 1 μM substrate (biotin-YRRAVPPSPSLSRHSSPHQ(pS)EDEEE) in 50 mM HEPES, 10 mM MgCl<sub>2</sub>, 100 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM DTT, 0.0075% Triton, 2% DMSO (total volume 50 μL) for 30 minutes at room temperature. The incubation was stopped by addition of an equal volume of 100 mM EDTA, 4M NaCl. 80 μL of this mixture was added to streptavidin-coated Flash-plates (PerkinElmer). Following a wash step, 33P incorporation was quantified on a MicroBeta microplate liquid scintillation counter (PerkinElmer). IC<sub>50</sub>'s were determined by fitting a sigmoidal dose-response curve to the counts obtained at the different concentrations in GraphPad Prism.

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**[0424]** The results of the binding tests are given in the table below.

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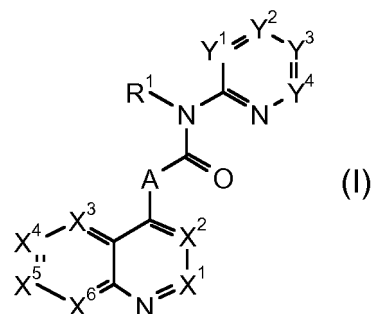
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Example #	GSK-3β IC <sub>50</sub>
1	+++
2	+++
3	+++
16	+++
17	+++
18	+++
19	+++
20	+++
21	+++
22	+++
23	+++
24	+++
n.d. not determined GSK-3β IC <sub>50</sub> : + > 10 μM ++ from 100nM to 10 μM +++ < 100 nM	

## Claims

1. A heterocyclic compound of the formula (I)



the stereoisomers, N-oxides, prodrugs, tautomers and/or physiologically tolerated acid addition salts thereof, and the compounds of the general formula I, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, wherein

20 A is selected from the group consisting of  $CR^{A1}R^{A2}$  and  $NR^B$ ; where

$R^{A1}$  and  $R^{A2}$  are independently of each other selected from the group consisting of hydrogen,  $C_1$ - $C_2$ -alkyl,  $C_1$ - $C_2$ -haloalkyl,  $NH_2$  and  $OH$ ; and

25  $R^B$  is selected from hydrogen,  $C_1$ - $C_4$ -alkyl and  $C_1$ - $C_4$ -haloalkyl;

$X^1$  and  $X^2$  are independently of each other selected from the group consisting of  $CR^2$  and  $N$ ;

$X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  are independently of each other selected from the group consisting of  $CR^3$ ,  $CR^4$  and  $N$ ; with the proviso that no more than two of  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  are  $CR^4$ ;

30  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  are independently of each other selected from the group consisting of  $CR^4$ ,  $CR^5$  and  $N$ ; with the proviso that at most one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $N$  and with the proviso that at most one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $CR^4$ ; and

with the proviso that one of  $Y^1$ ,  $Y^2$ ,  $Y^3$  and  $Y^4$  is  $CR^4$  if none of  $X^3$ ,  $X^4$ ,  $X^5$  and  $X^6$  is  $CR^4$ ;

$R^1$  is selected from hydrogen,  $C_1$ - $C_4$ -alkyl and  $C_1$ - $C_4$ -haloalkyl;

35 each  $R^2$  is independently selected from the group consisting of hydrogen,  $OH$ , halogen,  $CN$ ,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl,  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -haloalkoxy and  $NR^aR^b$ ;

or two radicals  $R^2$  bonded at the carbon atoms of groups  $X^1$  and  $X^2$ , together with the carbon atoms to which they are bonded, form a 5- or 6-membered saturated or unsaturated ring which may contain 1 or 2 heteroatoms as ring members selected from the group consisting of  $N$ ,  $O$  and  $S$  and which optionally carries 1, 2 or 3 substituents  $R^6$ ;

40 each  $R^3$  is independently selected from the group consisting of hydrogen,  $CN$ ,  $NR^aR^b$ ,  $OH$ , halogen,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl,  $C_3$ - $C_7$ -cycloalkyl,  $C_3$ - $C_7$ -halocycloalkyl,  $C_2$ - $C_4$ -alkenyl,  $C_2$ - $C_4$ -haloalkenyl,  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -haloalkoxy, formyl,  $C_1$ - $C_6$ -alkylcarbonyl,  $C_1$ - $C_6$ -haloalkylcarbonyl,  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_1$ - $C_6$ -haloalkoxycarbonyl,  $C_1$ - $C_6$ -alkyl- $NR^aR^b$  and an aromatic radical  $Ar$ , which is selected from the group consisting of phenyl and a 5- or 6-membered  $N$ - or  $C$ -bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from  $O$ ,  $S$  and  $N$  as ring members, wherein  $Ar$  is unsubstituted or carries one or two radicals  $R^7$  and wherein  $Ar$  may also be bonded via a  $CH_2$  group;

45  $R^4$  is a  $C$ -bound saturated or partially unsaturated monocyclic 3-, 4-, 5-, 6- or 7-membered heterocyclic ring containing 1, 2 or 3 heteroatoms or heteroatom-containing groups selected from  $O$ ,  $N$ ,  $S$ ,  $NO$ ,  $SO$  and  $SO_2$  as ring members, where the heterocyclic ring optionally carries 1, 2 or 3  $C$ - or  $N$ -bound substituents  $R^8$ ;

50  $R^5$  is selected from the group consisting of hydrogen,  $CN$ ,  $NR^aR^b$ ,  $OH$ , halogen,  $C_1$ - $C_6$ -alkyl,  $C_1$ - $C_6$ -haloalkyl,  $C_3$ - $C_7$ -cycloalkyl,  $C_3$ - $C_7$ -halocycloalkyl,  $C_2$ - $C_4$ -alkenyl,  $C_2$ - $C_4$ -haloalkenyl,  $C_1$ - $C_6$ -alkoxy,  $C_1$ - $C_6$ -haloalkoxy, formyl,  $C_1$ - $C_6$ -alkylcarbonyl,  $C_1$ - $C_6$ -haloalkylcarbonyl,  $C_1$ - $C_6$ -alkoxycarbonyl,  $C_1$ - $C_6$ -haloalkoxycarbonyl,  $C_1$ - $C_6$ -alkyl- $NR^aR^b$  and an aromatic radical  $Ar$ , which is selected from the group consisting of phenyl and a 5- or 6-membered  $N$ - or  $C$ -bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from  $O$ ,  $S$  and  $N$  as ring members, wherein  $Ar$  is unsubstituted or carries one or two radicals  $R^7$  and wherein  $Ar$  may also be bonded via a  $CH_2$  group;

55  $R^6$  and  $R^8$ , independently of each other and independently of each occurrence, are selected from the group

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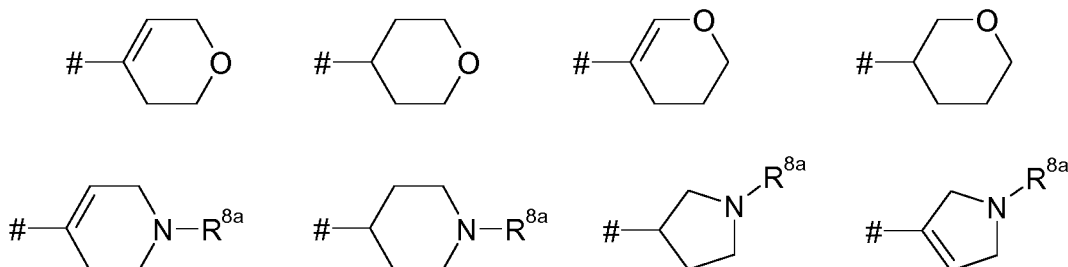
consisting of CN, NR<sup>a</sup>R<sup>b</sup>, OH, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-haloalkenyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkyl-NR<sup>a</sup>R<sup>b</sup> and an aromatic radical Ar, which is selected from the group consisting of phenyl and a 5- or 6-membered N- or C-bound heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein Ar is unsubstituted or carries one or two radicals R<sup>7</sup> and wherein Ar may also be bonded via a CH<sub>2</sub> group;

each R<sup>7</sup> is independently selected from the group consisting of halogen, CN, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, NR<sup>a</sup>R<sup>b</sup>, a phenyl group and a 5- or 6-membered heteroaromatic radical comprising one nitrogen atom and optionally 1, 2 or 3 further heteroatoms independently selected from O, S and N as ring members, wherein phenyl and the heteroaromatic radical are, independently of each other, unsubstituted or substituted by 1, 2, 3 or 4 radicals selected from halogen, cyano, C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>1</sub>-C<sub>4</sub>-haloalkoxy; and

R<sup>a</sup> and R<sup>b</sup> are independently of each other selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl and C<sub>1</sub>-C<sub>4</sub>-haloalkylcarbonyl; or R<sup>a</sup> and R<sup>b</sup> form, together with the nitrogen atom to which they are bonded, a 3-, 4-, 5-, 6- or 7-membered saturated or unsaturated aromatic or non-aromatic N-heterocyclic ring, which may contain 1 further heteroatom or heteroatom containing group selected from the group consisting of O, S, SO, SO<sub>2</sub> and N as a ring member;

where the prodrugs are selected from compounds of formula I, wherein a secondary nitrogen ring atom of the ring R<sup>4</sup> or a nitrogen atom of a primary or secondary amino group being a substituent R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and/or R<sup>8</sup> forms an amide/peptide bond in that this nitrogen atom is substituted by a C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl group, by benzoyl, or by glycine, alanine, serine or phenylalanine bonded via CO; or said nitrogen atom carries a group -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup>, wherein R<sup>x</sup> and R<sup>y</sup> independently of each other are C<sub>1</sub>-C<sub>4</sub>-alkyl.

2. The heterocyclic compound according to claim 1, wherein either one of X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> and X<sup>6</sup> is CR<sup>4</sup> and none of Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> and Y<sup>4</sup> is CR<sup>4</sup>, or one of Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> and Y<sup>4</sup> is CR<sup>4</sup> and none of X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> and X<sup>6</sup> is CR<sup>4</sup>.
3. The heterocyclic compound according to any of the preceding claims, where R<sup>4</sup> is selected from C-bound oxetanyl, azetidiny, tetrahydrofuranyl, tetrahydrothienyl, tetrahydrothienyl-1-oxide, pyrrolidinyl, pyrrolinyl, tetrahydropyranyl, dihydropyranyl, piperidinyl, tetrahydropyridinyl, dihydropyridinyl, piperazinyl and morpholinyl, where the heterocyclic ring optionally carries 1, 2 or 3 substituents R<sup>8</sup>.
4. The heterocyclic compound according to any of the preceding claims, where R<sup>8</sup> is selected from C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>2</sub>-C<sub>4</sub>-alkenyl, C<sub>2</sub>-C<sub>4</sub>-haloalkenyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy-carbonyl and benzyl and is preferably C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl or C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl.
5. The heterocyclic compound according to any of the preceding claims, where R<sup>8</sup> is N-bound.
6. The heterocyclic compound according to any of the preceding claims, where R<sup>4</sup> is selected from following structures:



where

R<sup>8a</sup> is hydrogen or has one of the meanings given in claims 1 or 4 for R<sup>8</sup>; and # is the attachment point to the remainder of the molecule.

7. The heterocyclic compound according to any of the preceding claims, where X<sup>1</sup> and X<sup>2</sup> are CR<sup>2</sup> and X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> and

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X<sup>6</sup> are CR<sup>3</sup> or CR<sup>4</sup>, or where X<sup>1</sup> and X<sup>2</sup> are CR<sup>2</sup>, X<sup>3</sup> is N and X<sup>4</sup>, X<sup>5</sup> and X<sup>6</sup> are CR<sup>3</sup> or CR<sup>4</sup>.

8. The heterocyclic compound according to any of the preceding claims, where Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> and Y<sup>4</sup> are CR<sup>4</sup> or CR<sup>5</sup> or Y<sup>2</sup> is N and Y<sup>1</sup>, Y<sup>3</sup> and Y<sup>4</sup> are CR<sup>4</sup> or CR<sup>5</sup>.

9. The heterocyclic compound according to any of the preceding claims, where A is NR<sup>B</sup>, preferably NH.

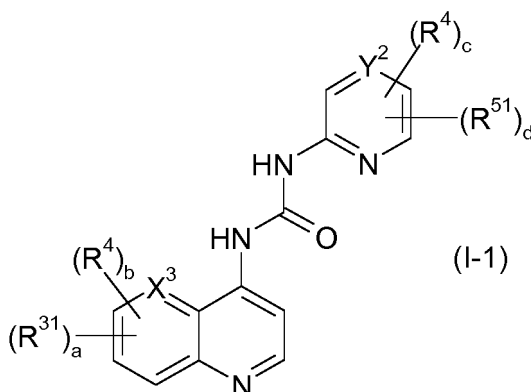
10. The heterocyclic compound according to any of the preceding claims, where R<sup>1</sup> is hydrogen or methyl, preferably hydrogen.

11. The heterocyclic compound according to any of the preceding claims, where R<sup>2</sup> is hydrogen.

12. The heterocyclic compound according to any of the preceding claims, where R<sup>3</sup> is selected from hydrogen, CN, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl and C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl and is preferably selected from hydrogen, CN, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy and C<sub>1</sub>-C<sub>6</sub>-haloalkoxy.

13. The heterocyclic compound according to any of the preceding claims, where R<sup>5</sup> is selected from hydrogen, CN, halogen, C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-haloalkoxy, formyl, C<sub>1</sub>-C<sub>6</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-haloalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl and C<sub>1</sub>-C<sub>6</sub>-haloalkoxycarbonyl and is preferably selected from hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>3</sub>-C<sub>7</sub>-cycloalkyl and C<sub>3</sub>-C<sub>7</sub>-halocycloalkyl and in particular from hydrogen, fluorinated C<sub>1</sub>-C<sub>2</sub>-alkyl and C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

14. The heterocyclic compound according to any of the preceding claims, of formula I-1



where

X<sup>3</sup> is N or CH;

Y<sup>2</sup> is N or CH;

R<sup>31</sup> has one of the meanings given in claims 1 or 12 for R<sup>3</sup> except for hydrogen, and is preferably halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

R<sup>4</sup> has one of the meanings given in claims 1 or 3 to 6;

R<sup>51</sup> has one of the meanings given in claims 1 or 13 for R<sup>5</sup> except for hydrogen;

a is 0, 1 or 2; and

b, c and d are independently of each other 0 or 1, with the proviso that one of b and c is 1.

15. The heterocyclic compound according to claim 1, which is selected from the group consisting of

1-(6-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea,

1-(8-fluoroquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)urea,

1-(6-(3,4-dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(8-fluoroquinolin-4-yl)urea,

1-(6-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(7-methoxyquinolin-4-yl)urea,

1-(6-(3,4-dihydro-2H-pyran-5-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,

1-(7-(3,6-dihydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,

1-(6-(tetrahydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,  
 1-(7-methoxyquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)urea,  
 1-(7-(tetrahydro-2H-pyran-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,  
 1-(6-(tetrahydro-2H-pyran-3-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,  
 5 1-(7-(3,6-dihydro-2H-pyran-4-yl)quinolin-4-yl)-3-(pyrazin-2-yl)urea,  
 1-(6-(3,4-dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(7-methoxyquinolin-4-yl)urea,  
 1-(7-methoxyquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-3-yl)pyridin-2-yl)urea,  
 1-(pyrazin-2-yl)-3-(7-(tetrahydro-2H-pyran-4-yl)quinolin-4-yl)urea,  
 1-(7-(3,4-dihydro-2H-pyran-5-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)-urea,  
 10 tert-butyl 4-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate,  
 1-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 1-(6-(piperidin-4-yl)quinolin-4-yl)-3-(6-(trifluoromethyl)pyridin-2-yl)urea,  
 1-[6-(1-methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 1-[6-(1-methyl-piperidin-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 15 1-[6-[1-(2-fluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 1-[6-[1-(2,2-difluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 1-[6-(3,6-dihydro-2H-pyran-4-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 1-[6-(3,6-dihydro-2H-pyran-4-yl)-quinolin-4-yl]-3-pyrazin-2-yl-urea,  
 tert-butyl 4-[4-(3-pyrazin-2-ylureido)quinolin-6-yl]-5,6-dihydropyridine-1(2H)-carboxylate,  
 20 1-pyrazin-2-yl-3-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-quinolin-4-yl]-urea,  
 1-(6-piperidin-4-yl-quinolin-4-yl)-3-pyrazin-2-yl-urea,  
 1-[6-[1-(2-fluoro-ethyl)-piperidin-4-yl]-quinolin-4-yl]-3-pyrazin-2-yl-urea,  
 1-[6-(1-methyl-piperidin-4-yl)-quinolin-4-yl]-3-pyrazin-2-yl-urea,  
 tert-butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate,  
 25 tert-butyl 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-quinolin-6-yl}-piperidine-1-carboxylate,  
 1-(6-cyclopropyl-pyrazin-2-yl)-3-(6-piperidin-4-yl-quinolin-4-yl)-urea,  
 1-(6-cyclopropyl-pyrazin-2-yl)-3-[6-(1-methyl-piperidin-4-yl)-quinolin-4-yl]-urea,  
 tert-butyl 3-{4-[3-(6-trifluoromethyl-pyridin-2-yl)-ureido]-quinolin-6-yl}-2,5-dihydro-pyrrole-1-carboxylate,  
 1-[6-(2,5-dihydro-1H-pyrrol-3-yl)-quinolin-4-yl]-3-(6-trifluoromethyl-pyridin-2-yl)-urea,  
 30 1-[6-(3,6-dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea,  
 1-(8-fluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-(8-chloro-6-methyl-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-(6,8-dichloro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-(6,8-difluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 35 1-(8-chloro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-[1,5]naphthyridin-4-yl-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-(5,8-difluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-(8-fluoro-6-methoxy-quinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 1-[6-(5,6-dihydro-4H-pyran-3-yl)-pyridin-2-yl]-3-(8-fluoro-quinolin-4-yl)-urea,  
 40 1-(8-fluoro-quinolin-4-yl)-3-[6-(tetrahydro-pyran-3-yl)-pyridin-2-yl]-urea,  
 1-[6-(3,6-dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-[1,5]naphthyridin-4-yl-urea,  
 tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylate,  
 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea,  
 tert-butyl-6-[3-(8-fluoro-quinolin-4-yl)-ureido]-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylate,  
 45 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea,  
 1-(8-fluoro-quinolin-4-yl)-3-(1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea,  
 1-[1'-(2-fluoro-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluoro-quinolin-4-yl)-urea,  
 1-[1'-(2,2-difluoro-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluoro-quinolin-4-yl)-urea,  
 1-(8-fluoro-quinolin-4-yl)-3-(1'-isopropyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-urea,  
 50 1-(8-fluoro-quinolin-4-yl)-3-[5-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-urea,  
 tert-butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-2,5-dihydro-pyrrole-1-carboxylate,  
 tert-butyl-3-[4-(3-pyrazin-2-yl-ureido)-quinolin-6-yl]-pyrrolidine-1-carboxylate,  
 1-pyrazin-2-yl-3-(6-pyrrolidin-3-yl-quinolin-4-yl)-urea,  
 the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof.

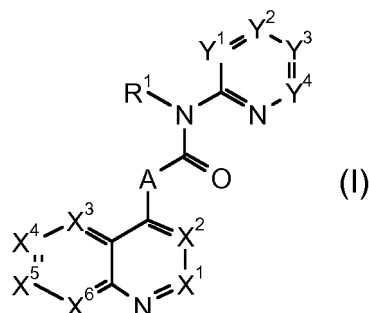
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16. The heterocyclic compound according to claim 15, which is selected from 1-(8-fluoroquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)urea, the stereoisomers, N-oxides, prodrugs, tautomers and physiologically tolerated acid addition salts thereof.

17. The heterocyclic compound according to claim 15, which is selected from 1-[1'-(2-fluoro-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluoro-quinolin-4-yl)-urea, the stereoisomers, N-oxides, prodrugs, tautomers and physiologically tolerated acid addition salts thereof.
18. The heterocyclic compound according to claim 15, which is selected from 1-(7-methoxyquinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-3-yl)pyridin-2-yl)urea, the stereoisomers, tautomers and physiologically tolerated acid addition salts thereof.
19. The heterocyclic compound according to claim 15, which is selected from 1-(8-fluoro-quinolin-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-urea, the stereoisomers, tautomers and physiologically tolerated acid addition salts thereof.
20. The heterocyclic compound according to any of the preceding claims, wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, and preferably wherein at least one hydrogen atom has been replaced by a deuterium atom.
21. A pharmaceutical composition comprising at least one heterocyclic compound as defined in any of the preceding claims, a stereoisomer, N-oxide, prodrug, tautomer and/or physiologically tolerated acid addition salt thereof or comprising at least one heterocyclic compound as defined in any of the preceding claims wherein at least one of the atoms has been replaced by its stable, non-radioactive isotope, preferably wherein at least one hydrogen atom has been replaced by a deuterium atom, and at least one physiologically acceptable carrier and/or auxiliary substance.
22. The heterocyclic compounds as defined in any of claims 1 to 20 or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof for use as a medicament.
23. The heterocyclic compounds as defined in any of claims 1 to 20 or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof for use in the treatment of a medical disorder susceptible to the treatment with a compound that modulates, preferably inhibits, the activity of glycogen synthase kinase 3 $\beta$ .
24. The heterocyclic compounds or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof according to claim 23, where the medical disorder is a neurodegenerative disorder or an inflammatory disorder.
25. The heterocyclic compounds or the stereoisomers, N-oxides, prodrugs, tautomers or physiologically tolerated acid addition salts thereof according to claim 24, where the medical disorder is selected from schizophrenia, Alzheimer's disease, behavioural and psychiatric symptoms of dementia, Parkinson's disease, tauopathies, vascular dementia, acute stroke and other traumatic injuries, cerebrovascular accidents, brain and spinal cord trauma, peripheral neuropathies, bipolar disorders, retinopathies, glaucoma, pain, rheumatoid arthritis and osteoarthritis.

## Patentansprüche

1. Heterocyclische Verbindung der allgemeinen Formel (I)



die Stereoisomere, die N-oxide, die Prodrugs, die Tautomere und/oder die physiologisch verträglichen Säureaddi-

tionssalze davon, und die Verbindungen der allgemeinen Formel I, worin wenigstens eines der Atome durch sein stabiles nicht-radioaktives Isotop ersetzt wurde, worin

A ausgewählt ist aus der Gruppe bestehend aus  $CR^{A1}RA^2$  und  $NR^B$ ; wobei

$RA^1$  und  $RA^2$  unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus Wasserstoff,  $C_1$ - $C_2$ -Alkyl,  $C_1$ - $C_2$ -Halogenalkyl,  $NH_2$  und  $OH$ ; und  
 $R^B$  ausgewählt ist unter Wasserstoff,  $C_1$ - $C_4$ -Alkyl und  $C_1$ - $C_4$ -Halogenalkyl;

$X^1$  und  $X^2$  unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus  $CR^2$  und  $N$ ;  
 $X^3$ ,  $X^4$ ,  $X^5$  und  $X^6$  unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus  $CR^3$ ,  $CR^4$  und  $N$ ;  
mit der Maßgabe, dass nicht mehr als zwei Reste  $X^3$ ,  $X^4$ ,  $X^5$  und  $X^6$  für  $CR^4$  stehen;  
 $Y^1$ ,  $Y^2$ ,  $Y^3$  und  $Y^4$  unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus  $CR^4$ ,  $CR^5$  und  $N$ ;  
mit der Maßgabe, dass höchstens einer der Reste  $Y^1$ ,  $Y^2$ ,  $Y^3$  und  $Y^4$  für  $N$  steht und mit der Maßgabe, dass  
höchstens einer der Reste  $Y^1$ ,  $Y^2$ ,  $Y^3$  und  $Y^4$  für  $CR^4$  steht; und  
mit der Maßgabe, dass einer der Reste  $Y^1$ ,  $Y^2$ ,  $Y^3$  und  $Y^4$  für  $CR^4$  steht, falls keiner der Reste  $X^3$ ,  $X^4$ ,  $X^5$  und  $X^6$  für  $CR^4$  steht;

$R^1$  ausgewählt ist unter Wasserstoff,  $C_1$ - $C_4$ -Alkyl und  $C_1$ - $C_4$ -Halogenalkyl;

jedes  $R^2$  jeweils unabhängig ausgewählt ist aus der Gruppe bestehend aus Wasserstoff,  $OH$ , Halogen,  $CN$ ,  $C_1$ - $C_6$ -Alkyl,  $C_1$ - $C_6$ -Halogenalkyl,  $C_1$ - $C_6$ -Alkoxy,  $C_1$ - $C_6$ -Halogenalkoxy und  $NR^aR^b$ ;  
oder zwei Reste  $R^2$ , die an die Kohlenstoffatome der Reste  $X^1$  und  $X^2$  gebunden sind, zusammen mit den Kohlenstoffatomen, an die sie gebunden sind, einen 5- oder 6-gliedrigen gesättigten oder ungesättigten Ring bilden, der 1 oder 2 Heteroatome, die ausgewählt sind aus der Gruppe bestehend aus  $N$ ,  $O$  und  $S$ , als Ringlieder enthalten kann, und der gegebenenfalls 1, 2 oder 3 Substituenten  $R^6$  trägt;

jedes  $R^3$  jeweils unabhängig ausgewählt ist aus der Gruppe bestehend aus Wasserstoff,  $CN$ ,  $NR^aR^b$ ,  $OH$ , Halogen,  $C_1$ - $C_6$ -Alkyl,  $C_1$ - $C_6$ -Halogenalkyl,  $C_3$ - $C_7$ -Cycloalkyl,  $C_3$ - $C_7$ -Halogencycloalkyl,  $C_2$ - $C_4$ -Alkenyl,  $C_2$ - $C_4$ -Halogenalkenyl,  $C_1$ - $C_6$ -Alkoxy,  $C_1$ - $C_6$ -Halogenalkoxy, Formyl,  $C_1$ - $C_6$ -Alkylcarbonyl,  $C_1$ - $C_6$ -Halogenalkylcarbonyl,  $C_1$ - $C_6$ -Alkoxycarbonyl,  $C_1$ - $C_6$ -Halogenalkoxycarbonyl,  $C_1$ - $C_6$ -Alkyl- $NR^aR^b$  und einem aromatischen Rest  $Ar$ , der ausgewählt ist aus der Gruppe bestehend aus Phenyl und einem 5- oder 6-gliedrigen  $N$ - oder  $C$ -gebundenen heteroaromatischen Rest, der ein Stickstoffatom und gegebenenfalls 1, 2 oder 3 weitere Heteroatome, die unabhängig voneinander ausgewählt sind unter  $O$ ,  $S$  und  $N$ , als Ringlieder enthält, wobei  $Ar$  unsubstituiert ist oder ein oder zwei Reste  $R^7$  trägt und wobei  $Ar$  auch über eine  $CH_2$ -Gruppe gebunden sein kann;  
 $R^4$  für einen  $C$ -gebundenen gesättigten oder partiell ungesättigten monocyclischen 3-, 4-, 5-, 6- oder 7-gliedrigen heterocyclischen Ring steht, der 1, 2 oder 3 Heteroatome oder Heteroatom-haltige Gruppen, die ausgewählt sind unter  $O$ ,  $N$ ,  $S$ ,  $NO$ ,  $SO$  und  $SO_2$ , als Ringlieder enthält, wobei der heterocyclische Ring gegebenenfalls 1, 2 oder 3  $C$ - oder  $N$ -gebundene Substituenten  $R^8$  trägt;

$R^5$  ausgewählt ist aus der Gruppe bestehend aus Wasserstoff,  $CN$ ,  $NR^aR^b$ ,  $OH$ , Halogen,  $C_1$ - $C_6$ -Alkyl,  $C_1$ - $C_6$ -Halogenalkyl,  $C_3$ - $C_7$ -Cycloalkyl,  $C_3$ - $C_7$ -Halogencycloalkyl,  $C_2$ - $C_4$ -Alkenyl,  $C_2$ - $C_4$ -Halogenalkenyl,  $C_1$ - $C_6$ -Alkoxy,  $C_1$ - $C_6$ -Halogenalkoxy, Formyl,  $C_1$ - $C_6$ -Alkylcarbonyl,  $C_1$ - $C_6$ -Halogenalkylcarbonyl,  $C_1$ - $C_6$ -Alkoxycarbonyl,  $C_1$ - $C_6$ -Halogenalkoxycarbonyl,  $C_1$ - $C_6$ -Alkyl- $NR^aR^b$  und einem aromatischen Rest  $Ar$ , welcher ausgewählt ist aus der Gruppe bestehend aus Phenyl und einem 5- oder 6-gliedrigen  $N$ - oder  $C$ -gebundenen heteroaromatischen Rest, der ein Stickstoffatom und gegebenenfalls 1, 2 oder 3 weitere Heteroatome, die unabhängig voneinander ausgewählt sind unter  $O$ ,  $S$  und  $N$ , als Ringlieder enthält, wobei  $Ar$  unsubstituiert ist oder ein oder zwei Reste  $R^7$  trägt und wobei  $Ar$  auch über eine  $CH_2$ -Gruppe gebunden sein kann;

$R^6$  und  $R^8$  unabhängig voneinander und unabhängig von ihrem jeweiligen Auftreten ausgewählt sind aus der Gruppe bestehend aus  $CN$ ,  $NR^aR^b$ ,  $OH$ , Halogen,  $C_1$ - $C_6$ -Alkyl,  $C_1$ - $C_6$ -Halogenalkyl,  $C_3$ - $C_7$ -Cycloalkyl,  $C_3$ - $C_7$ -Halogencycloalkyl,  $C_2$ - $C_4$ -Alkenyl,  $C_2$ - $C_4$ -Halogenalkenyl,  $C_1$ - $C_6$ -Alkoxy,  $C_1$ - $C_6$ -Halogenalkoxy, Formyl,  $C_1$ - $C_6$ -Alkylcarbonyl,  $C_1$ - $C_6$ -Halogenalkylcarbonyl,  $C_1$ - $C_6$ -Alkoxycarbonyl,  $C_1$ - $C_6$ -Halogenalkoxycarbonyl,  $C_1$ - $C_6$ -Alkyl- $NR^aR^b$  und einem aromatischen Rest  $Ar$ , welcher ausgewählt ist aus der Gruppe bestehend aus Phenyl und einem 5- oder 6-gliedrigen  $N$ - oder  $C$ -gebundenen heteroaromatischen Rest, der ein Stickstoffatom und gegebenenfalls 1, 2 oder 3 weitere Heteroatome, die unabhängig voneinander ausgewählt sind unter  $O$ ,  $S$  und  $N$ , als Ringlieder enthält, wobei  $Ar$  unsubstituiert ist oder ein oder zwei Reste  $R^7$  trägt und wobei  $Ar$  auch über eine  $CH_2$ -Gruppe gebunden sein kann;

jedes  $R^7$  jeweils unabhängig ausgewählt ist aus der Gruppe bestehend aus Halogen,  $CN$ ,  $C_1$ - $C_6$ -Alkyl,  $C_1$ - $C_6$ -Halogenalkyl,  $C_3$ - $C_6$ -Cycloalkyl,  $C_3$ - $C_6$ -Halogencycloalkyl,  $C_1$ - $C_6$ -Alkoxy,  $C_1$ - $C_6$ -Halogenalkoxy,  $NR^aR^b$ , einer Phenylgruppe und einem 5- oder 6-gliedrigen heteroaromatischen Rest, der ein Stickstoffatom und gegebenenfalls 1, 2 oder 3 weitere Heteroatome, die unabhängig voneinander ausgewählt sind unter  $O$ ,  $S$  und  $N$ , als Ringlieder enthält, wobei Phenyl und der heteroaromatische Rest, unabhängig voneinander, unsubstituiert sind

oder mit 1, 2, 3 oder 4 Resten, ausgewählt unter Halogen, Cyano, C<sub>1</sub>-C<sub>4</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy und C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, substituiert sind; und

R<sup>a</sup> und R<sup>b</sup> unabhängig voneinander ausgewählt sind aus der Gruppe bestehend aus Wasserstoff, C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>4</sub>-Alkoxy, C<sub>1</sub>-C<sub>4</sub>-Halogenalkoxy, C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonyl und C<sub>1</sub>-C<sub>4</sub>-Halogenalkylcarbonyl; oder R<sup>a</sup> und R<sup>b</sup>, zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 3-, 4-, 5-, 6- oder 7-gliedrigen gesättigten oder ungesättigten aromatischen oder nicht-aromatischen N-heterocyclischen Ring bilden, welcher 1 weiteres Heteroatom oder Heteroatom-haltige Gruppe, ausgewählt aus der Gruppe bestehend aus O, S, SO, SO<sub>2</sub> und N, als Ringglied enthalten kann;

wobei die Prodrugs ausgewählt sind unter Verbindungen der Formel (I), worin ein sekundäres Stickstoffringatom des Rings R<sup>4</sup> oder ein Stickstoffatom einer primären oder sekundären Aminogruppe, die ein Substituent R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> und/oder R<sup>8</sup> ist, eine Amid-/Peptid-Bindung bildet, indem dieses Stickstoffatom mit einer C<sub>1</sub>-C<sub>4</sub>-Alkylcarbonylgruppe, mit Benzoyl, oder mit über CO-gebundenem Glycin, Alanin, Serin oder Phenylalanin substituiert ist; oder das besagte Stickstoffatom eine Gruppe -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup> trägt, worin R<sup>x</sup> und R<sup>y</sup> unabhängig voneinander für C<sub>1</sub>-C<sub>4</sub>-Alkyl stehen.

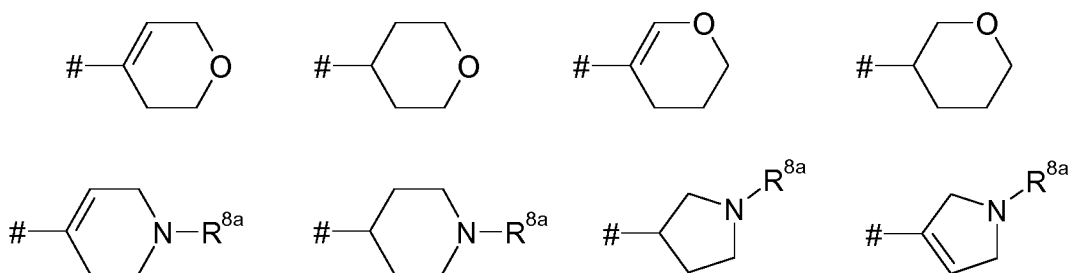
2. Heterocyclische Verbindung nach Anspruch 1, worin entweder einer der Reste X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> und X<sup>6</sup> für CR<sup>4</sup> steht und keiner der Reste Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> und Y<sup>4</sup> für CR<sup>4</sup> steht, oder einer der Reste Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> und Y<sup>4</sup> für CR<sup>4</sup> steht und keiner der Reste X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> und X<sup>6</sup> für CR<sup>4</sup> steht.

3. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>4</sup> ausgewählt ist unter C-gebundenem Oxetanyl, Azetidiny, Tetrahydrofuranyl, Tetrahydrothienyl, Tetrahydrothienyl-1-oxid, Pyrrolidiny, Pyrroliny, Tetrahydropyranyl, Dihydropyranyl, Piperidiny, Tetrahydropyridiny, Dihydropyridiny, Piperazinyl und Morpholinyl, wobei der heterocyclische Ring gegebenenfalls 1, 2 oder 3 Substituenten R<sup>8</sup> trägt.

4. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>8</sup> ausgewählt ist unter C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Halogenycloalkyl, C<sub>2</sub>-C<sub>4</sub>-Alkenyl, C<sub>2</sub>-C<sub>4</sub>-Halogenalkenyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxy, Formyl, C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxycarbonyl und Benzyl und bevorzugt für C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkyl oder C<sub>1</sub>-C<sub>6</sub>-Alkoxy-carbonyl steht.

5. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>8</sup> N-gebunden ist.

6. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>4</sup> ausgewählt ist unter den folgenden Strukturen:



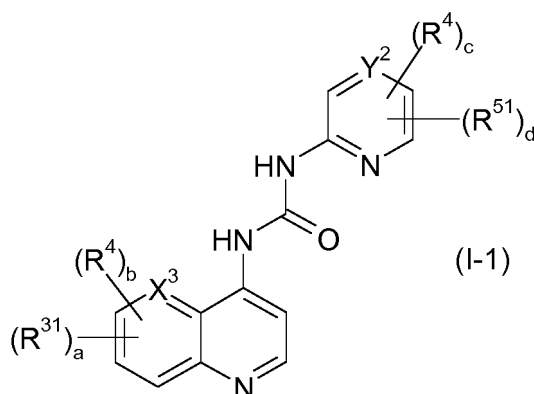
wobei

R<sup>8a</sup> für Wasserstoff steht oder eine der in den Ansprüchen 1 oder 4 für R<sup>8</sup> genannten Bedeutungen hat; und # den Verknüpfungspunkt zum Rest des Moleküls kennzeichnet.

7. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei X<sup>1</sup> und X<sup>2</sup> für CR<sup>2</sup> stehen und X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> und X<sup>6</sup> für CR<sup>3</sup> oder CR<sup>4</sup> stehen, oder wobei X<sup>1</sup> und X<sup>2</sup> für CR<sup>2</sup> stehen, X<sup>3</sup> für N steht und X<sup>4</sup>, X<sup>5</sup> und X<sup>6</sup> für CR<sup>3</sup> oder CR<sup>4</sup> stehen.

8. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> und Y<sup>4</sup> für CR<sup>4</sup> oder CR<sup>5</sup> stehen oder Y<sup>2</sup> für N steht und Y<sup>1</sup>, Y<sup>3</sup> und Y<sup>4</sup> für CR<sup>4</sup> oder CR<sup>5</sup> stehen.

9. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei A für NR<sup>B</sup>, bevorzugt für NH, steht.
10. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>1</sup> für Wasserstoff oder Methyl, bevorzugt für Wasserstoff, steht.
11. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>2</sup> für Wasserstoff steht.
12. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>3</sup> ausgewählt ist unter Wasserstoff, CN, Halogen, C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Halogencycloalkyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxy, Formyl, C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl und C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxycarbonyl und bevorzugt ausgewählt ist unter Wasserstoff, CN, Halogen, C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy und C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxy.
13. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, wobei R<sup>5</sup> ausgewählt ist unter Wasserstoff, CN, Halogen, C<sub>1</sub>-C<sub>6</sub>-Alkyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl, C<sub>3</sub>-C<sub>7</sub>-Halogencycloalkyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxy, C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxy, Formyl, C<sub>1</sub>-C<sub>6</sub>-Alkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Halogenalkylcarbonyl, C<sub>1</sub>-C<sub>6</sub>-Alkoxycarbonyl und C<sub>1</sub>-C<sub>6</sub>-Halogenalkoxycarbonyl und bevorzugt ausgewählt ist unter Wasserstoff, Halogen, C<sub>1</sub>-C<sub>4</sub>-Halogenalkyl, C<sub>3</sub>-C<sub>7</sub>-Cycloalkyl und C<sub>3</sub>-C<sub>7</sub>-Halogencycloalkyl und insbesondere unter Wasserstoff, fluoriertem C<sub>1</sub>-C<sub>2</sub>-Alkyl und C<sub>3</sub>-C<sub>6</sub>-Cycloalkyl.
14. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, die der Formel I-1 entspricht



worin

X<sup>3</sup> für N oder CH steht;

Y<sup>2</sup> für N oder CH steht;

R<sup>31</sup> eine der in den Ansprüchen 1 oder 12 genannten Bedeutungen für R<sup>3</sup> hat, ausgenommen Wasserstoff, und bevorzugt für Halogen, C<sub>1</sub>-C<sub>4</sub>-Alkyl oder C<sub>1</sub>-C<sub>4</sub>-Alkoxy steht;

R<sup>4</sup> eine der in den Ansprüchen 1 oder 3 bis 6 genannten Bedeutungen hat; R<sup>5</sup>

1 eine der in den Ansprüchen 1 oder 13 für R<sup>5</sup> genannten Bedeutungen hat, ausgenommen Wasserstoff;

a für 0, 1 oder 2 steht; und

b, c und d unabhängig voneinander für 0 oder 1 steht, mit der Maßgabe, dass einer der Indizes b und c für 1 steht.

15. Heterocyclische Verbindung nach Anspruch 1, die ausgewählt ist aus der Gruppe bestehend aus

1-(6-(3,6-Dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(8-fluorchinolin-4-yl)harnstoff,  
 1-(8-Fluorchinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)harnstoff,  
 1-(6-(3,4-Dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(8-fluorchinolin-4-yl)harnstoff,  
 1-(6-(3,6-Dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(7-methoxychinolin-4-yl)harnstoff,  
 1-(6-(3,4-Dihydro-2H-pyran-5-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,  
 1-(7-(3,6-Dihydro-2H-pyran-4-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,  
 1-(6-(Tetrahydro-2H-pyran-4-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,  
 1-(7-Methoxychinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)harnstoff,  
 1-(7-(Tetrahydro-2H-pyran-4-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,

- 1-(6-(Tetrahydro-2H-pyran-3-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,  
 1-(7-(3,6-Dihydro-2H-pyran-4-yl)chinolin-4-yl)-3-(pyrazin-2-yl)harnstoff,  
 1-(6-(3,4-Dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(7-methoxychinolin-4-yl)harnstoff,  
 1-(7-Methoxychinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-3-yl)pyridin-2-yl)harnstoff,  
 5 1-(Pyrazin-2-yl)-3-(7-(tetrahydro-2H-pyran-4-yl)chinolin-4-yl)harnstoff,  
 1-(7-(3,4-Dihydro-2H-pyran-5-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)-harnstoff,  
 tert-Butyl-4-{4-[3-(6-trifluormethyl-pyridin-2-yl)-ureido]-chinolin-6-yl}-3,6-dihydro-2H-pyridin-1-carboxylat,  
 1-[6-(1,2,3,6-Tetrahydro-pyridin-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-(6-(Piperidin-4-yl)chinolin-4-yl)-3-(6-(trifluormethyl)pyridin-2-yl)harnstoff,  
 10 1-[6-(1-Methyl-1,2,3,6-tetrahydro-pyridin-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-[6-(1-Methyl-piperidin-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-[6-(1-(2-Fluor-ethyl)-piperidin-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-[6-(1-(2,2-Difluor-ethyl)-piperidin-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 15 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-chinolin-4-yl]-3-pyrazin-2-yl-harnstoff,  
 tert-Butyl-4-[4-(3-pyrazin-2-ylureido)chinolin-6-yl]-5,6-dihydropyridin-1(2H)-carboxylat,  
 1-Pyrazin-2-yl-3-[6-(1,2,3,6-tetrahydro-pyridin-4-yl)-chinolin-4-yl]-harnstoff,  
 1-(6-Piperidin-4-yl-chinolin-4-yl)-3-pyrazin-2-yl-harnstoff,  
 1-[6-(1-(2-Fluor-ethyl)-piperidin-4-yl)-chinolin-4-yl]-3-pyrazin-2-yl-harnstoff,  
 20 1-[6-(1-Methylpiperidin-4-yl)-chinolin-4-yl]-3-pyrazin-2-yl-harnstoff,  
 tert-Butyl-4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-chinolin-6-yl}-3,6-dihydro-2H-pyridin-1-carboxylat,  
 tert-Butyl-4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-ureido]-chinolin-6-yl}-piperidin-1-carboxylat,  
 1-(6-Cyclopropyl-pyrazin-2-yl)-3-(6-piperidin-4-yl-chinolin-4-yl)-harnstoff,  
 1-(6-Cyclopropyl-pyrazin-2-yl)-3-[6-(1-methyl-piperidin-4-yl)-chinolin-4-yl]-harnstoff,  
 25 tert-Butyl-3-{4-[3-(6-trifluormethyl-pyridin-2-yl)-ureido]-chinolin-6-yl}-2,5-dihydro-pyrrole-1-carboxylat,  
 1-[6-(2,5-Dihydro-1H-pyrrol-3-yl)-chinolin-4-yl]-3-(6-trifluormethyl-pyridin-2-yl)-harnstoff,  
 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluor-chinolin-4-yl)-harnstoff,  
 1-(8-Fluor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-(8-Chlor-6-methyl-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 30 1-(6,8-Dichlor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-(6,8-Difluor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-(8-Chlor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-[1,5]Naphthyridin-4-yl-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-(5,8-Difluor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 35 1-(8-Fluor-6-methoxy-chinolin-4-yl)-3-[6-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 1-[6-(5,6-Dihydro-4H-pyran-3-yl)-pyridin-2-yl]-3-(8-fluor-chinolin-4-yl)-harnstoff,  
 1-(8-Fluor-chinolin-4-yl)-3-[6-(tetrahydro-pyran-3-yl)-pyridin-2-yl]-harnstoff,  
 1-[6-(3,6-Dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-[1,5]naphthyridin-4-yl-harnstoff,  
 tert-Butyl-6-[3-(8-fluor-chinolin-4-yl)-ureido]-3',6'-dihydro-2'H-[2,4']bipyridinyl-1'-carboxylat,  
 40 1-(8-Fluor-chinolin-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-harnstoff, tert-Butyl-6-[3-(8-fluor-chinolin-4-yl)-ureido]-3',4',5',6'-tetrahydro-2'H-[2,4']bipyridinyl-1'-carboxylat,  
 1-(8-Fluor-chinolin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-harnstoff,  
 1-(8-Fluor-chinolin-4-yl)-3-(1'-methyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-harnstoff,  
 1-[1'-(2-Fluor-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluor-chinolin-4-yl)-harnstoff,  
 45 1-[1'-(2,2-Difluor-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluor-chinolin-4-yl)-harnstoff,  
 1-(8-Fluor-chinolin-4-yl)-3-(1'-isopropyl-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl)-harnstoff,  
 1-(8-Fluor-chinolin-4-yl)-3-[5-(tetrahydro-pyran-4-yl)-pyridin-2-yl]-harnstoff,  
 tert-Butyl-3-[4-(3-pyrazin-2-yl-ureido)-chinolin-6-yl]-2,5-dihydro-pyrrole-1-carboxylat,  
 tert-Butyl-3-[4-(3-pyrazin-2-yl-ureido)-chinolin-6-yl]-pyrrolidine-1-carboxylat,  
 50 1-pyrazin-2-yl-3-(6-pyrrolidin-3-yl-chinolin-4-yl)-harnstoff,

die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere oder die physiologisch verträglichen Säureadditionssalze davon.

- 55 **16.** Heterocyclische Verbindung nach Anspruch 15, die ausgewählt ist unter 1-(8-Fluorchinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-4-yl)pyridin-2-yl)harnstoff, die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere und die physiologisch verträglichen Säureadditionssalze davon.

17. Heterocyclische Verbindung nach Anspruch 15, die ausgewählt ist unter 1-[1'-(2-Fluor-ethyl)-1',2',3',4',5',6'-hexahydro-[2,4']bipyridinyl-6-yl]-3-(8-fluor-chinolin-4-yl)-harnstoff, die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere und die physiologisch verträglichen Säureadditionssalze davon.
- 5 18. Heterocyclische Verbindung nach Anspruch 15, die ausgewählt ist unter 1-(7-Methoxychinolin-4-yl)-3-(6-(tetrahydro-2H-pyran-3-yl)pyridin-2-yl)harnstoff, die Stereoisomere, die Tautomere und die physiologisch verträglichen Säureadditionssalze davon.
- 10 19. Heterocyclische Verbindung nach Anspruch 15, die ausgewählt ist unter 1-(8-Fluor-chinolin-4-yl)-3-(1',2',3',6'-tetrahydro-[2,4']bipyridinyl-6-yl)-harnstoff, die Stereoisomere, die Tautomere und die physiologisch verträglichen Säureadditionssalze davon.
- 15 20. Heterocyclische Verbindung nach einem der vorhergehenden Ansprüche, worin wenigstens eines der Atome durch sein stabiles, nicht-radioaktives Isotop ersetzt wurde, und worin bevorzugt wenigstens ein Wasserstoffatom durch ein Deuteriumatom ersetzt wurde.
- 20 21. Pharmazeutische Zusammensetzung, enthaltend wenigstens eine heterocyclische Verbindung, wie in einem der vorhergehenden Ansprüche definiert, ein Stereoisomer, ein N-Oxid, ein Prodrug, ein Tautomer und/oder ein physiologisch tolerierbares Säureadditionssalz davon, oder enthaltend wenigstens eine heterocyclische Verbindung, wie in einem der vorhergehenden Ansprüche definiert, worin wenigstens eines der Atome durch sein stabiles, nicht-radioaktives Isotop ersetzt wurde, worin bevorzugt wenigstens ein Wasserstoffatom durch ein Deuteriumatom ersetzt wurde, und wenigstens ein physiologisch verträglicher Träger und/oder Hilfsstoff.
- 25 22. Heterocyclische Verbindungen, wie in einem der Ansprüche 1 bis 20 definiert, oder die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere oder die physiologisch verträglichen Säureadditionssalze davon zur Verwendung als Medikament.
- 30 23. Heterocyclische Verbindungen, wie in einem der Ansprüche 1 bis 20 definiert, oder die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere oder die physiologisch verträglichen Säureadditionssalze davon zur Verwendung in der Behandlung einer medizinischen Erkrankung, die auf die Behandlung mit einer Verbindung, welche die Aktivität von Glykogen Synthase Kinase 3 $\beta$  moduliert, bevorzugt inhibiert, anspricht.
- 35 24. Heterocyclische Verbindungen oder die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere oder die physiologisch verträglichen Säureadditionssalze davon nach Anspruch 23, wobei die medizinische Erkrankung eine neurodegenerative Erkrankung oder eine entzündliche Erkrankung ist.
- 40 25. Heterocyclische Verbindungen oder die Stereoisomere, die N-Oxide, die Prodrugs, die Tautomere oder die physiologisch verträglichen Säureadditionssalze davon nach Anspruch 24, wobei die medizinische Erkrankung ausgewählt ist unter Schizophrenie, Alzheimer-Krankheit, Verhaltens- und psychiatrischen Symptomen der Demenz, Parkinson-Krankheit, Tauopathien, vaskulärer Demenz, akutem Schlaganfall und anderen traumatischen Verletzungen, zerebrovaskulären Unfällen, Hirn- und Rückenmarkstrauma, peripheren Neuropathien, bipolaren Störungen, Retinopathien, Glaukom, Schmerz, rheumatoider Arthritis und Osteoarthritis.

45 **Revendications**

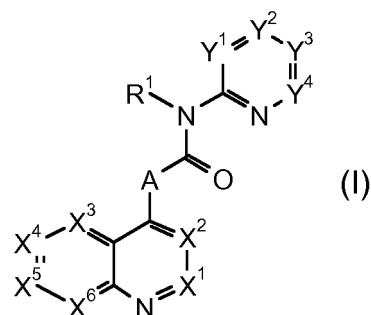
1. Composé hétérocyclique de formule (I)

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stéréoisomères, N-oxydes, promédicaments, tautomères et/ou sels d'addition acide physiologiquement tolérés de celui-ci, et composés de formule générale I où au moins l'un des atomes a été remplacé par son isotope stable non radioactif, où

A est choisi dans le groupe constitué par  $CR^{A1}RA^2$  et  $NR^B$  ; où

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chacun des radicaux  $RA^1$  et  $RA^2$  est choisi indépendamment de l'autre dans le groupe constitué par l'atome d'hydrogène et les groupements alkyle en  $C_1-C_2$ , halogénoalkyle en  $C_1-C_2$ ,  $NH_2$  et OH; et

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$R^B$  est choisi parmi l'atome d'hydrogène et les groupements alkyle en  $C_1-C_4$  et halogénoalkyle en  $C_1-C_4$ ; chacun des chaînons  $X^1$  et  $X^2$  est choisi indépendamment des autres dans le groupe constitué par  $CR^2$  et N; chacun des chaînons  $X^3$ ,  $X^4$ ,  $X^5$  et  $X^6$  est choisi indépendamment des autres dans le groupe constitué par  $CR^3$ ,  $CR^4$  et N;

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à la condition que pas plus de deux des chaînons  $X^3$ ,  $X^4$ ,  $X^5$  et  $X^6$  ne représentent  $CR^4$ ; chacun des chaînons  $Y^1$ ,  $Y^2$ ,  $Y^3$  et  $Y^4$  est choisi indépendamment des autres dans le groupe constitué par  $CR^4$ ,  $CR^5$  et N; à la condition qu'au maximum un des chaînons  $Y^1$ ,  $Y^2$ ,  $Y^3$  et  $Y^4$  représente N et à la condition qu'au maximum un des chaînons  $Y^1$ ,  $Y^2$ ,  $Y^3$  et  $Y^4$  représente  $CR^4$ ; et à la condition que l'un des chaînons  $Y^1$ ,  $Y^2$ ,  $Y^3$  et  $Y^4$  représente  $CR^4$  si aucun des chaînons  $X^3$ ,  $X^4$ ,  $X^5$  et  $X^6$  ne représente  $CR^4$ ;

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$R^1$  est choisi parmi l'atome d'hydrogène et les groupements alkyle en  $C_1-C_4$  et halogénoalkyle en  $C_1-C_4$ ; chacun des radicaux  $R^2$  est indépendamment choisi dans le groupe constitué par l'atome d'hydrogène et les groupements OH, halogène, CN, alkyle en  $C_1-C_6$ , halogénoalkyle en  $C_1-C_6$ , alkoxy en  $C_1-C_6$ , halogénoalkoxy en  $C_1-C_6$  et  $NR^aR^b$ ;

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ou deux radicaux  $R^2$  liés au niveau des atomes de carbone des groupements  $X^1$  et  $X^2$  forment avec les atomes de carbone auxquels ils sont liés un cycle saturé ou insaturé comportant 5 ou 6 chaînons ainsi qu'éventuellement 1 ou 2 hétéroatomes en tant que chaînons choisis dans le groupe constitué par N, O et S et portant éventuellement 1, 2 ou 3 substituants  $R^6$ ;

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chacun des radicaux  $R^3$  est indépendamment choisi dans le groupe constitué par l'atome d'hydrogène et les groupements CN,  $NR^aR^b$ , OH, halogène, alkyle en  $C_1-C_6$ , halogénoalkyle en  $C_1-C_6$ , cycloalkyle en  $C_3-C_7$ , halogénocycloalkyle en  $C_3-C_7$ , alcényle en  $C_2-C_4$ , halogénoalcényle en  $C_2-C_4$ , alkoxy en  $C_1-C_6$ , halogénoalkoxy en  $C_1-C_6$ , formyle, (alkyle en  $C_1-C_6$ )-carbonyle, (halogénoalkyle en  $C_1-C_6$ )-carbonyle, (alkoxy en  $C_1-C_6$ )-carbonyle, (halogénoalkoxy en  $C_1-C_6$ )-carbonyle, (alkyle en  $C_1-C_6$ )- $NR^aR^b$  et un radical aromatique Ar, qui est choisi dans le groupe constitué par les groupements phényle et un radical hétéroaromatique à 5 ou 6 chaînons lié par N ou C comportant un atome d'azote et éventuellement 1, 2 ou 3 hétéroatomes supplémentaires indépendamment choisis parmi O, S et N en tant que chaînons, où Ar est non substitué ou porte un ou deux radicaux  $R^7$  et où Ar peut également être lié via un groupement  $CH_2$ ;

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$R^4$  représente un cycle hétérocyclique monocyclique lié par C saturé ou partiellement insaturé comportant 3, 4, 5, 6 ou 7 chaînons ainsi que 1, 2 ou 3 hétéroatomes ou groupements contenant des hétéroatomes choisis parmi O, N, S, NO, SO et  $SO_2$  en tant que chaînons, où le cycle hétérocyclique porte éventuellement 1, 2 ou 3 substituants  $R^8$  liés par C ou N;

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$R^5$  est choisi dans le groupe constitué par l'atome d'hydrogène et les groupements CN,  $NR^aR^b$ , OH, halogène, alkyle en  $C_1-C_6$ , halogénoalkyle en  $C_1-C_6$ , cycloalkyle en  $C_3-C_7$ , halogénocycloalkyle en  $C_3-C_7$ , alcényle en  $C_2-C_4$ , halogénoalcényle en  $C_2-C_4$ , alkoxy en  $C_1-C_6$ , halogénoalkoxy en  $C_1-C_6$ , formyle, (alkyle en  $C_1-C_6$ )-carbonyle, (halogénoalkyle en  $C_1-C_6$ )-carbonyle, (alkoxy en  $C_1-C_6$ )-carbonyle, (halogénoalkoxy en  $C_1-C_6$ )-carbonyle, (alkyle en  $C_1-C_6$ )- $NR^aR^b$  et un radical aromatique Ar, qui est choisi dans le groupe constitué par les

groupements phényle et un radical hétéroaromatique à 5 ou 6 chaînons lié par N ou C comportant un atome d'azote et éventuellement 1, 2 ou 3 hétéroatomes supplémentaires indépendamment choisis parmi O, S et N en tant que chaînons, où Ar est non substitué ou porte un ou deux radicaux R<sup>7</sup> et où Ar peut également être lié via un groupement CH<sub>2</sub>;

chacun des radicaux R<sup>6</sup> et R<sup>8</sup>, indépendamment de l'autre et indépendamment dans chaque occurrence, est choisi dans le groupe constitué par les groupements CN, NR<sup>a</sup>R<sup>b</sup>, OH, halogène, alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, halogénocycloalkyle en C<sub>3</sub>-C<sub>7</sub>, alcényle en C<sub>2</sub>-C<sub>4</sub>, halogénoalcényle en C<sub>2</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>, formyle, (alkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (alkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (alkyle en C<sub>1</sub>-C<sub>6</sub>)-NR<sup>a</sup>R<sup>b</sup> et un radical aromatique Ar, qui est choisi dans le groupe constitué par les groupements phényle et un radical hétéroaromatique à 5 ou 6 chaînons lié par N ou C comportant un atome d'azote et éventuellement 1, 2 ou 3 hétéroatomes supplémentaires indépendamment choisis parmi O, S et N en tant que chaînons, où Ar est non substitué ou porte un ou deux radicaux R<sup>7</sup> et où Ar peut également être lié via un groupement CH<sub>2</sub>;

chacun des radicaux R<sup>7</sup> est indépendamment choisi dans le groupe constitué par les atomes d'halogène et les groupements CN, alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, cycloalkyle en C<sub>3</sub>-C<sub>6</sub>, halogénocycloalkyle en C<sub>3</sub>-C<sub>6</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>, NR<sup>a</sup>R<sup>b</sup>, un groupement phényle et un radical hétéroaromatique comportant 5 ou 6 chaînons ainsi qu'un atome d'azote est éventuellement 1, 2 ou 3 hétéroatomes supplémentaires indépendamment choisis parmi O, S et N en tant que chaînons, où le groupement phényle et le radical hétéroaromatique sont non substitués ou substitués indépendamment l'un de l'autre par 1, 2, 3 ou 4 radicaux choisis parmi les atomes d'halogène et les groupements cyano, alkyle en C<sub>1</sub>-C<sub>4</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>4</sub> et halogénoalkoxy en C<sub>1</sub>-C<sub>4</sub>; et

chacun des radicaux R<sup>a</sup> et R<sup>b</sup> est choisi indépendamment de l'autre dans le groupe constitué par l'atome d'hydrogène et les groupements alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>4</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>4</sub>, (alkyle en C<sub>1</sub>-C<sub>4</sub>)-carbonyle et (halogénoalkyle en C<sub>1</sub>-C<sub>4</sub>)-carbonyle; ou

R<sup>a</sup> et R<sup>b</sup> forment, avec l'atome d'azote auquel ils sont liés, un cycle N-hétérocyclique aromatique ou non aromatique, saturé ou insaturé, comportant 3, 4, 5, 6 ou 7 chaînons, qui peut comporter 1 hétéroatome ou groupement contenant un hétéroatome supplémentaire choisi dans le groupe constitué par O, S, SO, SO<sub>2</sub> et N en tant que chaînon;

où les promédicaments sont choisis parmi les composés de formule I, où un atome d'azote de cycle secondaire du cycle R<sup>4</sup> ou un atome d'azote d'un groupement amino primaire ou secondaire qui est un substituant R<sup>2</sup>, R<sup>3</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> et/ou R<sup>8</sup> forme une liaison amide/peptide en ce que cet atome d'azote est substitué par un groupement (alkyle en C<sub>1</sub>-C<sub>4</sub>), par benzoyle, ou par glycine, alanine, sérine ou phénylalanine liée via CO; ou ledit atome d'azote porte un groupement -C(=O)-O-CHR<sup>x</sup>-O-C(=O)-R<sup>y</sup>, où chacun des radicaux R<sup>x</sup> et R<sup>y</sup> représente indépendamment de l'autre un groupement alkyle en C<sub>1</sub>-C<sub>4</sub>.

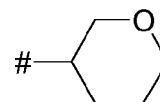
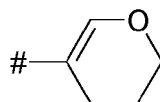
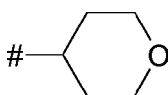
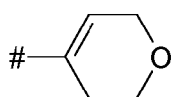
2. Composé hétérocyclique selon la revendication 1, où l'un des chaînons X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> et X<sup>6</sup> représente CR<sup>4</sup> et aucun des chaînons Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> et Y<sup>4</sup> ne représente CR<sup>4</sup>, ou l'un des chaînons Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> et Y<sup>4</sup> représente CR<sup>4</sup> et aucun des chaînons X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> et X<sup>6</sup> ne représente CR<sup>4</sup>.

3. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>4</sup> est choisi parmi les groupements liés à C oxétanyle, azétidinyle, tétrahydrofuranyle, tétrahydrothiényne, tétrahydrothiényl-1-oxyde, pyrrolidinyle, pyrrolinyle, tétrahydropyranyle, dihydropyranyle, pipéridinyle, tétrahydropyridinyle, dihydropyridinyle, pipérazinyle et morpholinyle, où le cycle hétérocyclique porte éventuellement 1, 2 ou 3 substituants R<sup>8</sup>.

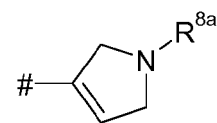
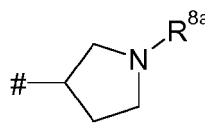
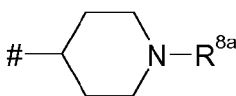
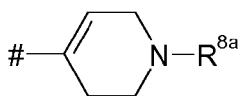
4. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>8</sup> est choisi parmi les groupements alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, halogénocycloalkyle en C<sub>3</sub>-C<sub>7</sub>, alcényle en C<sub>2</sub>-C<sub>4</sub>, halogénoalcényle en C<sub>2</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>, formyle, (alkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (alkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle et benzyle et représente préférentiellement un groupement alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub> ou (alkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle.

5. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>8</sup> est lié par N.

6. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>4</sup> est choisi parmi les structures suivantes:



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où

R<sup>8a</sup> représente un atome d'hydrogène ou prend l'une des valeurs données pour R<sup>8</sup> dans les revendications 1 ou 4 ; et

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# est le point de liaison au reste de la molécule.

7. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où X<sup>1</sup> et X<sup>2</sup> représentent CR<sup>2</sup> et X<sup>3</sup>, X<sup>4</sup>, X<sup>5</sup> et X<sup>6</sup> représentent CR<sup>3</sup> ou CR<sup>4</sup>, ou où X<sup>1</sup> et X<sup>2</sup> représentent CR<sup>2</sup>, X<sup>3</sup> représente N et X<sup>4</sup>, X<sup>5</sup> et X<sup>6</sup> représentent CR<sup>3</sup> ou CR<sup>4</sup>.

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8. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où Y<sup>1</sup>, Y<sup>2</sup>, Y<sup>3</sup> et Y<sup>4</sup> représentent CR<sup>4</sup> ou CR<sup>5</sup> ou Y<sup>2</sup> représente N et Y<sup>1</sup>, Y<sup>3</sup> et Y<sup>4</sup> représentent CR<sup>4</sup> ou CR<sup>5</sup>.

9. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où A représente NR<sup>B</sup>, préférentiellement NH.

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10. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>1</sup> représente un atome d'hydrogène ou un groupement méthyle, préférentiellement un atome d'hydrogène.

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11. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>2</sup> représente un atome d'hydrogène.

12. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>3</sup> est choisi parmi l'atome d'hydrogène et les groupements CN, halogène, alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, halogénocycloalkyle en C<sub>3</sub>-C<sub>7</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>, formyle, (alkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (alkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle et (halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle et est préférentiellement choisi parmi l'atome d'hydrogène et les groupements CN, halogène, alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub> et halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>.

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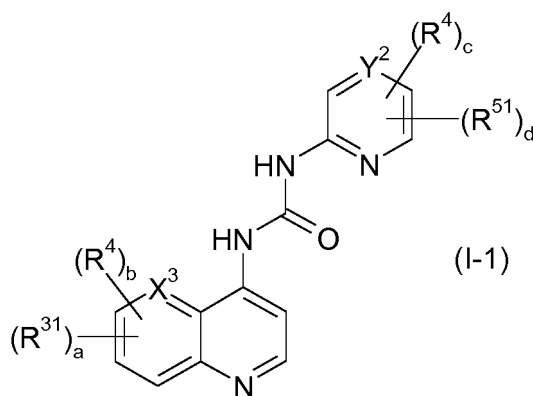
13. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où R<sup>5</sup> est choisi parmi l'atome d'hydrogène et les groupements CN, halogène, alkyle en C<sub>1</sub>-C<sub>6</sub>, halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub>, halogénocycloalkyle en C<sub>3</sub>-C<sub>7</sub>, alkoxy en C<sub>1</sub>-C<sub>6</sub>, halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>, formyle, (alkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (halogénoalkyle en C<sub>1</sub>-C<sub>6</sub>)-carbonyle, (alkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle et (halogénoalkoxy en C<sub>1</sub>-C<sub>6</sub>)-carbonyle et est préférentiellement choisi parmi l'atome d'hydrogène et les groupements halogène, halogénoalkyle en C<sub>1</sub>-C<sub>4</sub>, cycloalkyle en C<sub>3</sub>-C<sub>7</sub> et halogénocycloalkyle en C<sub>3</sub>-C<sub>7</sub> et en particulier parmi l'atome d'hydrogène et les groupements fluoroalkyle en C<sub>1</sub>-C<sub>2</sub> et cycloalkyle en C<sub>3</sub>-C<sub>6</sub>.

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14. Composé hétérocyclique selon l'une quelconque des revendications précédentes, répondant à la formule I-1

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où

X<sup>3</sup> représente N ou CH ;

Y<sup>2</sup> représente N ou CH ;

R<sup>31</sup> prend l'une des valeurs données dans les revendications 1 ou 12 pour R<sup>3</sup>, à l'exception de l'hydrogène, et représente préférentiellement un atome d'halogène ou un groupement alkyle en C<sub>1</sub>-C<sub>4</sub> ou alkoxy en C<sub>1</sub>-C<sub>4</sub>;

R<sup>4</sup> prend l'une des valeurs données dans les revendications 1 ou 3 à 6;

R<sup>51</sup> prend l'une des valeurs données dans les revendications 1 ou 13 pour R<sub>5</sub>, à l'exception de l'hydrogène; a est égal à 0, 1 ou 2; et

chacun des nombres b, c et d est égal indépendamment des autres à 0 ou 1, à la condition que l'un des nombres b et c soit égal à 1.

15. Composé hétérocyclique selon la revendication 1, qui est choisi dans le groupe constitué par les suivants:

1-(6-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(8-fluoroquinoléin-4-yl)urée,

1-(8-fluoroquinoléin-4-yl)-3-(6-(tétrahydro-2H-pyran-4-yl)pyridin-2-yl)urée,

1-(6-(3,4-dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(8-fluoroquinoléin-4-yl)urée,

1-(6-(3,6-dihydro-2H-pyran-4-yl)pyridin-2-yl)-3-(7-méthoxyquinoléin-4-yl)-urée,

1-(6-(3,4-dihydro-2H-pyran-5-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

1-(7-(3,6-dihydro-2H-pyran-4-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

1-(6-(tétrahydro-2H-pyran-4-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

1-(7-méthoxyquinoléin-4-yl)-3-(6-(tétrahydro-2H-pyran-4-yl)pyridin-2-yl)urée,

1-(7-(tétrahydro-2H-pyran-4-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

1-(6-(tétrahydro-2H-pyran-3-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

1-(7-(3,6-dihydro-2H-pyran-4-yl)quinoléin-4-yl)-3-(pyrazin-2-yl)urée,

1-(6-(3,4-dihydro-2H-pyran-5-yl)pyridin-2-yl)-3-(7-méthoxyquinoléin-4-yl)-urée,

1-(7-méthoxyquinoléin-4-yl)-3-(6-(tétrahydro-2H-pyran-3-yl)pyridin-2-yl)urée,

1-(pyrazin-2-yl)-3-(7-(tétrahydro-2H-pyran-4-yl)quinoléin-4-yl)urée,

1-(7-(3,4-dihydro-2H-pyran-5-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)-urée,

4-[4-[3-(6-trifluorométhyl-pyridin-2-yl)-uréido]-quinoléin-6-yl]-3,6-dihydro-2H-pyridine-1-carboxylate de tert-butyle,

1-[6-(1,2,3,6-tétrahydro-pyridin-4-yl)-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,

1-(6-(pipéridin-4-yl)quinoléin-4-yl)-3-(6-(trifluorométhyl)pyridin-2-yl)urée,

1-[6-(1-méthyl-1,2,3,6-tétrahydro-pyridin-4-yl)-quinoléin-4-yl]-3-(6-trifluoro-méthyl-pyridin-2-yl)-urée,

1-[6-(1-méthyl-pipéridin-4-yl)-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,

1-[6-[1-(2-fluoro-éthyl)-pipéridin-4-yl]-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,

1-[6-[1-(2,2-difluoro-éthyl)-pipéridin-4-yl]-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,

1-[6-(3,6-dihydro-2H-pyran-4-yl)-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,

1-[6-(3,6-dihydro-2H-pyran-4-yl)-quinoléin-4-yl]-3-pyrazin-2-yl-urée,

4-[4-(3-pyrazin-2-yluréido)quinoléin-6-yl]-5,6-dihydropyridine-1(2H)-carboxylate de tert-butyle,

1-pyrazin-2-yl-3-[6-(1,2,3,6-tétrahydro-pyridin-4-yl)-quinoléin-4-yl]-urée,

1-(6-pipéridin-4-yl-quinoléin-4-yl)-3-pyrazin-2-yl-urée,

1-[6-[1-(2-fluoro-éthyl)-pipéridin-4-yl]-quinoléin-4-yl]-3-pyrazin-2-yl-urée,

1-[6-(1-méthyl-pipéridin-4-yl)-quinoléin-4-yl]-3-pyrazin-2-yl-urée,

- 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-uréido]-quinoléin-6-yl}-3,6-dihydro-2H-pyridine-1-carboxylate de tert-butyle,  
 4-{4-[3-(6-cyclopropyl-pyrazin-2-yl)-uréido]-quinoléin-6-yl}-pipéridine-1-carboxylate de tert-butyle,  
 1-(6-cyclopropyl-pyrazin-2-yl)-3-(6-piperidin-4-yl)-quinoléin-4-yl-urée,  
 1-(6-cyclopropyl-pyrazin-2-yl)-3-[6-(1-méthyl-pipéridin-4-yl)-quinoléin-4-yl]-urée,  
 3-{4-[3-(6-trifluorométhyl-pyridin-2-yl)-uréido]-quinoléin-6-yl}-2,5-dihydro-pyrrole-1-carboxylate de tert-butyle,  
 1-[6-(2,5-dihydro-1H-pyrrol-3-yl)-quinoléin-4-yl]-3-(6-trifluorométhyl-pyridin-2-yl)-urée,  
 1-[6-(3,6-dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-(8-fluoro-quinoléin-4-yl)-urée,  
 1-(8-fluoro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(8-chloro-6-méthyl-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(6,8-dichloro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(6,8-difluoro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(8-chloro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-[1,5]naphtyridin-4-yl-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(5,8-difluoro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-(8-fluoro-6-méthoxy-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 1-[6-(5,6-dihydro-4H-pyran-3-yl)-pyridin-2-yl]-3-(8-fluoro-quinoléin-4-yl)-urée,  
 1-(8-fluoro-quinoléin-4-yl)-3-[6-(tétrahydro-pyran-3-yl)-pyridin-2-yl]-urée,  
 1-[6-(3,6-dihydro-2H-pyran-4-yl)-pyridin-2-yl]-3-[1,5]naphtyridin-4-yl-urée,  
 6-[3-(8-fluoro-quinoléin-4-yl)-uréido]-3',6'-dihydro-2'H-[2,4]bipyridinyl-1'-carboxylate de tert-butyle,  
 1-(8-fluoro-quinoléin-4-yl)-3-(1',2',3',6'-tétrahydro-[2,4]bipyridinyl-6-yl)-urée,  
 6-[3-(8-fluoro-quinoléin-4-yl)-uréido]-3',4',5',6'-tétrahydro-2'H-[2,4]bipyridinyl-1'-carboxylate de tert-butyle,  
 1-(8-fluoro-quinoléin-4-yl)-3-(1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl)-urée,  
 1-(8-fluoro-quinoléin-4-yl)-3-(1'-méthyl-1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl)-urée,  
 1-[1'-(2-fluoro-éthyl)-1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl]-3-(8-fluoro-quinoléin-4-yl)-urée,  
 1-[1'-(2,2-difluoro-éthyl)-1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl]-3-(8-fluoro-quinoléin-4-yl)-urée,  
 1-(8-fluoro-quinoléin-4-yl)-3-(1'-isopropyl-1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl)-urée,  
 1-(8-fluoro-quinoléin-4-yl)-3-[5-(tétrahydro-pyran-4-yl)-pyridin-2-yl]-urée,  
 3-[4-(3-pyrazin-2-yl-uréido)-quinoléin-6-yl]-2,5-dihydro-pyrrole-1-carboxylate de tert-butyle,  
 3-[4-(3-pyrazin-2-yl-uréido)-quinoléin-6-yl]-pyrrolidine-1-carboxylate de tert-butyle,  
 1-pyrazin-2-yl-3-(6-pyrrolidin-3-yl-quinoléin-4-yl)-urée,  
 les stéréoisomères, N-oxydes, promédicaments, tautomères ou sels d'addition acide physiologiquement tolérés de ceux-ci.
16. Composé hétérocyclique selon la revendication 15, qui est choisi parmi la 1-(8-fluoroquinoléin-4-yl)-3-(6-(tétrahydro-2H-pyran-4-yl)pyridin-2-yl)urée, et les stéréoisomères, N-oxydes, promédicaments, tautomères et sels d'addition acide physiologiquement tolérés de celle-ci.
17. Composé hétérocyclique selon la revendication 15, qui est choisi parmi la 1-[1'-(2-fluoro-éthyl)-1',2',3',4',5',6'-hexahydro-[2,4]bipyridinyl-6-yl]-3-(8-fluoro-quinoléin-4-yl)-urée, et les stéréoisomères, N-oxydes, promédicaments, tautomères et sels d'addition acide physiologiquement tolérés de celle-ci.
18. Composé hétérocyclique selon la revendication 15, qui est choisi parmi la 1-(7-méthoxyquinoléin-4-yl)-3-(6-(tétrahydro-2H-pyran-3-yl)pyridin-2-yl)urée, et les stéréoisomères, tautomères et sels d'addition acide physiologiquement tolérés de celle-ci.
19. Composé hétérocyclique selon la revendication 15, qui est choisi parmi la 1-(8-fluoro-quinoléin-4-yl)-3-(1',2',3',6'-tétrahydro-[2,4]bipyridinyl-6-yl)-urée, et les stéréoisomères, tautomères et sels d'addition acide physiologiquement tolérés de celle-ci.
20. Composé hétérocyclique selon l'une quelconque des revendications précédentes, où au moins l'un des atomes a été remplacé par son isotope stable non radioactif, et préférentiellement où au moins un atome d'hydrogène a été remplacé par un atome de deutérium.
21. Composition pharmaceutique comprenant au moins un composé hétérocyclique selon l'une quelconque des revendications précédentes, un stéréoisomère, N-oxyde, promédicament, tautomère et/ou sel d'addition acide physiologiquement toléré de celui-ci ou comprenant au moins un composé hétérocyclique selon l'une quelconque des revendications précédentes, où au moins l'un des atomes a été remplacé par son isotope stable non radioactif,

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préférentiellement où au moins un atome d'hydrogène a été remplacé par un atome de deutérium, et au moins un vecteur physiologiquement acceptable et/ou substance auxiliaire.

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- 22.** Composés hétérocycliques selon l'une quelconque des revendications 1 à 20 ou stéréoisomères, N-oxydes, promédicaments, tautomères ou sels d'addition acide physiologiquement tolérés de ceux-ci pour utilisation en tant que médicament.
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- 23.** Composés hétérocycliques selon l'une quelconque des revendications 1 à 20 ou stéréoisomères, N-oxydes, promédicaments, tautomères ou sels d'addition acide physiologiquement tolérés de ceux-ci pour utilisation dans le traitement d'un trouble médical sensible au traitement par un composé qui module, préférentiellement inhibe, l'activité de la glycogène synthase kinase 3 $\beta$ .
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- 24.** Composés hétérocycliques ou stéréoisomères, N-oxydes, promédicaments, tautomères ou sels d'addition acide physiologiquement tolérés de ceux-ci selon la revendication 23, où le trouble médical est un trouble neurodégénératif ou un trouble inflammatoire.
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- 25.** Composés hétérocycliques ou stéréoisomères, N-oxydes, promédicaments, tautomères ou sels d'addition acide physiologiquement tolérés de ceux-ci selon la revendication 24, où le trouble médical est choisi parmi les suivants: schizophrénie, maladie d'Alzheimer, symptômes comportementaux et psychiatriques de démence, maladie de Parkinson, tauopathies, démence vasculaire, accident vasculaire cérébral aigu et autres lésions traumatiques, accidents vasculaires cérébraux, traumatismes du cerveau et de la moelle épinière, neuropathies périphériques, troubles bipolaires, rétinopathies, glaucome, douleur, polyarthrite rhumatoïde et arthrose.
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