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(54) NEW SPIROTRICYCLIC DERIVATIVES AND THEIR USE AS PHOSPHODIESTERASE-7 INHIBITORS

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(56) References cited:
• WO-A-00/66560
• WO-A-97/14686
• TADASHI SASAKI ET AL.: "BRIDGEHEAD SUBSTITUTION REACTIONS OF 3-METHOXY-4-AZAHOMOADAMANTANE VIA N-ACYLIMINIUM IONS," JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., vol. 8, 1984, pages 1863-8, XP002206882 CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 1472-7781

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The file contains technical information submitted after the application was filed and not included in this specification

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Description

Field of the invention.

[0001] The invention relates to spirotricyclic derivatives, the process for their preparation, and their use as phosphodiesterase 7 (PDE7) inhibitors.

Background of the invention.

[0002] Phosphodiesterases (PDE) play an important role in various biological processes by hydrolysing the key second messengers adenosine and guanosine 3',5'-cyclic monophosphates (cAMP and cGMP respectively) into their corresponding 5'-monophosphate nucleotides. Therefore, inhibition of PDE activity produces an increase of cAMP and cGMP intracellular levels that activate specific protein phosphorylation pathways involved in a variety of functional responses.

[0003] At least eleven isoenzymes of mammalian cyclic nucleotide phosphodiesterases, numbered PDE 1 through PDE 11, have been identified on the basis of primary structure, substrate specificity or sensitivity to cofactors or inhibitory drugs.

[0004] Among these phosphodiesterases, PDE7 is a cAMP-specific PDE. The biochemical and pharmacological characterization showed a high-affinity cAMP-specific PDE (Km=0.2 μM), that was not affected by cGMP potent selective PDE isoenzyme inhibitors.

[0005] PDE7 activity or protein has been detected in T-cell lines, B-cell lines, airway epithelial (AE) cell lines and several foetal tissues.

[0006] Increasing cAMP levels by selective PDE7 inhibition appears to be a potentially promising approach to specifically block T-cell mediated immune responses. Further studies have demonstrated that elevation of intracellular cAMP levels can modulate inflammatory and immunological processes. This selective approach could presumably be devoid of the side effects associated with known selective PDE inhibitors (e.g. PDE3 or PDE4 selective inhibitors) and which limit their use.

[0007] A functional role of PDE7 in T-cell activation has also been disclosed; therefore selective PDE7 inhibitors would be candidates for the treatment of T-cell-related diseases.

[0008] AE cells actively participate in inflammatory airway diseases by liberating mediators such as arachidonate metabolites and cytokines. Selective inhibition of PDE7 may be a useful anti-inflammatory approach for treating AE cells related diseases.

[0009] Thus, there is a need for selective PDE7 inhibitors, which are active at very low concentrations, i.e. preferably nanomolar inhibitors.

[0010] WO 88/01508 discloses compounds of formula

![Chemical Structure](image)

where R is hydrogen, alkyl, alkoxyalkyl, hydroxyalkyl, halo, cyano, carbamoyl, alkyl carbamoyl, formyl, alkylamino or amino;

X is -(CR4R5)a-NR6-(CR4R5)b-;

R1, R2, R3, and R5 are hydrogen or alkyl;

R4 and R6 are hydrogen, alkyl or aralkyl; a and b are 0, 1 or 2 and a + b = 0, 1 or 2;

R4 and R5 groups on vicinal carbon atoms may together form a carbon-carbon double bond; and geminal R4 and R5 groups may together form a spiro substituent, -(CH2)d-, where d is 2 to 5; or a pharmaceutically acceptable salt thereof. These compounds are described as cardiotonics.

[0011] WO 97/14686 discloses compounds of formula
which are described as NO synthase inhibitors.

WO 00/66560 discloses compounds of formula

These compounds are described as progesterone receptor modulators.

The invention relates to compounds, which are PDE7 inhibitors, having the following formula (I):

in which:

- $X_1$, $X_2$ and $X_3$ are the same or different and are selected from C-$R^1$, in which $R^1$ is selected from:
  - $Q_1$, or
  - lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups $Q_2$;
  - the group $X^5$-$R^5$ in which,
    - $X^5$ is selected from a single bond or lower alkylene, optionally interrupted with 1 heteroatom chosen from O, S, or N; and
    - $R^5$ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with $C(=O)$ or with 1, 2, or 3 heteroatoms chosen from O, S, $S(=O)$, $SO_2$ or N, cycloalkenyl optionally interrupted with $C(=O)$ or with 1, 2, or 3 heteroatoms chosen from O, S, $S(=O)$, $SO_2$ or N, or a bicyclic group, these groups being unsubstituted or substituted with one or several groups selected from $Q_3$, heteroaryl or lower alkyl optionally substituted with $Q_3$;

in which $Q_1$, $Q_2$, $Q_3$ are the same or different and are selected from

- hydrogen, halogen, CN, $NO_2$, $SO_3$H.
- $OR^2$, $OC(=O)R^2$, $C(=O)OR^2$, $SR^2$, $S(=O)R^2$, $C(=O)-NH-SO_2$-$CH_3$, $NR^3R^4$, $Q-R^2$, $Q$-$NR^3R^4$, $NR^2$-$Q$-$NR^3R^4$ or $NR^3$-$Q$-$R^2$ in which $Q$ is selected from $C(=NR)$, $C(=O)$, $C(=S)$ or $SO_2$. $R$ is selected from hydrogen or lower alkyl
A is unsubstituted cyclohexyl or unsubstituted cycloheptyl; Z is O or N-

A preferred group of compounds are compounds of formula (I) in which: X

Detailed description of the invention.

The invention also concerns a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

The invention also provides the use of a compound of formula (I) in the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

These compounds are selective PDE7 inhibitors. They can be used in the treatment of various diseases, such as T-cell-related diseases, autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS), allergy or inflammatory bowel disease (IBD).

The invention also relates to a process for preparing the above compounds.

The invention further concerns the use of a compound of formula (I) for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.

The invention also provides the use of a compound of formula (I) in the preparation of a medicament for the treatment of T-cell-related diseases, autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease (COPD), asthma, cancer, acquired immune deficiency syndrome (AIDS), allergy or inflammatory bowel disease (IBD).

The invention also concerns a pharmaceutical composition comprising a compound of formula (I) together with a pharmaceutically acceptable carrier, excipient, diluent or delivery system.

Detailed description of the invention.

The invention comprises compounds of formula (I), as defined above.

A preferred group of compounds are compounds of formula (I) in which: X1, X2 and X3 are the same or different and are selected from C-R1, in which R1 is selected from:

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X⁵-R⁵ in which:

- X⁵ is selected from a single bond or lower alkylene optionally interrupted with 1 or 2 heteroatoms chosen from O, S, or N;

- R⁵ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, or N.

- X is selected from a single bond or lower alkylene optionally interrupted with 1 or 2 heteroatoms chosen from O, S, or N; and

- R⁵ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, or N. These groups, when substituted, may be substituted with 1, 2, or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

in which Q₁, Q₂, Q₃ are the same or different and are selected from:

- hydrogen, halogen, CN, NO₂, SO₃H,

- OR², OC(=O)R², C(=O)OR², SR², S(=O)R², NR³R⁴, Q-R², Q-Q-R², Q-OR², N=S-R², NR²-S-R², NR²-Q-R², NR²-Q-Q-R² in which Q is selected from C(=NR), C(=S) or SO₂, R is selected from hydrogen or lower alkyl and R², R³ and R⁴ are the same or different and are selected from:

- hydrogen,

- lower alkyl optionally interrupted with C(=O), (CH₂)ₙ-aryl, (CH₂)ₙ-heteroaryl, (CH₂)ₙ-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N.

- these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, SO₂H, CH₃, CH₂OH, CF₃, C(=O)-NH-SO₂CH₃, OR₆, COOR₆, NR₆R⁷, C(=O)NR₆R⁷ or SO₂NR₆R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR² in which R and R² are hydrogen or lower alkyl, and,

- R⁶ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, or N, and which may be substituted with:

- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR³, OR², or COOR in which R³ and R² are the same or different and are selected from:

- hydrogen,

- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R* together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

- X₄ is C-R¹, in which R¹ is selected from F, Cl, Br, CH₃ and CF₃;

- Z is O or N-CN; and

- A is unsubstituted cyclohexyl or unsubstituted cycloheptyl.

[0022] A preferred group of compounds of formula (I) is a group in which X₁, X₂, X₃, X₄, Z and A are as disclosed hereabove wherein when X₂ is C-R¹ and R¹ is X⁵-R⁵, then X⁵ is not a single bond.

[0023] Preferred compounds of formula (I) are those in which:

- X₁, X₂ and X₃ are the same or different and are selected from C-R¹, in which R¹ is selected from:

- Q₁, or

- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q₂;

- the group X⁵-R⁵ in which:

- X⁵ is selected from a single bond or lower alkylene, optionally interrupted with 1 or 2 heteroatoms chosen from O, S or N; and

- R⁵ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N.

- cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃, heteroaryl or lower alkyl optionally substituted with Q₃;
in which Q1, Q2, Q3 are the same or different and are selected from:

- hydrogen, halogen, CN, NO₂, SO₃H,
- OR₂, OC(=O)R₂, C(=O)OR₂, SR₂, SR(=O)R₂, NR₃R₄, Q- R², Q- NR₃R₄, NR²-Q- NR³R₄ or NR³-Q- R² in which Q is selected from C(=NR), C(=O), C(=S) or SO₂. R is selected from hydrogen or lower alkyl and R², R³ and R⁴ are the same or different and are selected from:

- hydrogen,
- lower alkyl optionally interrupted with C(=O), (CH₃)₂-aryl, (CH₃)₂-heteroaryl, (CH₃)₂-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S or N or (CH₂)ₙ-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S or N, in which n is an integer selected from 0, 1, 2 or 3; these groups being unsubstituted or substituted with 1 or 2 groups selected from halogen, CN, NO₂H, CH₃, SO₂CH₃, CF₃, OR₆, COOR₆, NR₆R₇, C(=O)NR₆R₇ or SO₂NR₆R₇, in which R₆ and R₇ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NR₆R₇ in which R and R₆ are hydrogen or lower alkyl, and,
- R⁶ and R⁷, and/or, R₃ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO₂ or N, and which may be substituted with

- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR, NR₆R₇, C(=O)NR₆R₇ or COOR in which R’ and R” are the same or different and are selected from

- H, or,
- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R’ and R” together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

X₄ is C-R¹, in which R¹ is selected from F, Cl, Br, CF₃ and CH₃;
Z is O or N-CN; and
A is unsubstituted cyclohexyl or unsubstituted cycloheptyl.

[0024] A preferred group of compounds of formula (I) is a group in which X₁, X₂, X₃, X₄, Z and A are as disclosed hereabove wherein when X₂ is C-R¹ and R¹ is X₅-R⁵, then X₅ is not a single bond.

[0025] More preferred compounds of formula (I) are those in which:

X₁, X₂ and X₃ are the same or different and are C-R¹, in which R¹ is selected from:

- hydrogen, halogen, CN, SO₃H, NO₂, CF₃, OR₂, SR₂, NR²R³, COR², COOR², CONR²R³, SO₂CH₃, SO₂NR²R³ in which R² and R³ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR₆, COOR₆, NR₆R₇, SO₂NR₆R₇ or C(=O)NR₆R₇ in which R₆ and R₇ are the same or different and are selected from hydrogen or lower alkyl, and, R⁶ and R⁷, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, NO₂H, OR₂, COOR₂, NR₃R₄, SO₂NR₃R₄ or C(=O)NR₃R₄ in which R₃ and R₄ are the same or different and are selected from hydrogen or lower alkyl, and, R₃ and R₄, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X₅-R⁵ in which,

- X₅ is selected from a lower alkyne or a single bond, and,
- R⁵ is selected from phenyl, pyridyl or indolyl,

these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃, heteroaryloxy or lower alkynyl optionally substituted with Q₃ in which Q₃ is selected from:

- halogen, CN, SO₃H, NO₂, CF₃, OR₂, OC(=O)R₂, C(=O)R₂, C(=O)OR₂, NH-C(=O)R², NR³R₄, SO₂NR₃R₄ or C(=O)NR₃R₄ in which R², R₃ and R⁴ are the same or different and are selected from:
EP 1 373 224 B1

- hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR, COOR or NR\(_2\)R\(_7\) in which R\(_6\) and R\(_7\) are the same or different and are selected from hydrogen or lower alkyl and,
- R\(_6\) and R\(_7\), and/or, R\(_3\) and R\(_4\), together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR, NR\(_2\)R, C(=O)NR\(_2\)R\(_4\) or COOR in which R\(_1\) and R\(_2\) are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R\(_1\) and R\(_2\) together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N;

X\(_4\) is C-R\(_1\) in which R\(_1\) is selected from F, Cl, Br, CH\(_3\) or CF\(_3\);
Z is O or N-CN; and
A is unsubstituted cyclohexyl or unsubstituted cycloheptyl.

[0026] A preferred group of compounds of formula (I) is a group in which X\(_1\), X\(_2\), X\(_3\), X\(_4\), Z and A are as disclosed hereabove wherein when X\(_2\) is C-R\(_1\) and R\(_1\) is X\(_5\)-R\(_5\), then X\(_5\) is not a single bond.

[0027] Most preferred compounds of formula (I) are those in which:

X\(_1\), X\(_2\) and X\(_3\) are the same or different and are C-R\(_1\), in which R\(_1\) is selected from:
- hydrogen, halogen, CN, OR, in which R\(_2\) is selected from hydrogen or lower alkyl;
- lower alkyl, lower alketyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, SO\(_2\)H, OR, COOR, NR\(_3\)R\(_4\), SO\(_2\)NR\(_3\)R\(_4\) or C(=O)NR\(_3\)R\(_4\) in which R\(_2\), R\(_3\) and R\(_4\) are the same or different and are selected from hydrogen or lower alkyl and,
- R\(_3\) and R\(_4\), together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;

X\(_4\) is C-R\(_1\) in which R\(_1\) is selected from F, Cl, Br or CH\(_3\);
Z is O or N-CN; and
A is unsubstituted cyclohexyl or unsubstituted cycloheptyl.

[0028] A preferred group of compounds of formula (I) is a group in which X\(_1\), X\(_2\), X\(_3\) and X\(_4\), are as disclosed hereabove wherein when X\(_2\) is C-R\(_1\) and R\(_1\) is X\(_5\)-R\(_5\), then X\(_5\) is not a single bond.

[0029] Preferably, X\(_1\), X\(_2\) and X\(_3\) are the same or different and are C-R\(_1\), in which R\(_1\) is selected from:
- Q1, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 fluorine atoms, OR, COOR or NR\(_3\)R\(_4\) in which R\(_3\) and R\(_4\) are the same or different and are selected from hydrogen or lower alkyl, or R\(_3\) and R\(_4\), together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X\(_5\)-R\(_5\) in which X\(_5\) is a single bond and R\(_5\) is selected from aryl, preferably phenyl, heteroaryl, preferably pyridyl, or a bicyclic group, preferably indolyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3,

in which Q1 and Q3 are the same or different and are selected from
- hydrogen, halogen, CN, lower alkyl,
- OR\(_2\), C(=O)OR\(_2\), NR\(_3\)R\(_4\), C(=O)NR\(_3\)R\(_4\) or SO\(_2\)NR\(_3\)R\(_4\) in which R\(_2\), R\(_3\) and R\(_4\) are the same or different and are selected from:
- hydrogen,
- lower alkyl, Q4-heteroaryl in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and (CH\(_2\))\(_n\) in which n is an integer selected from 0, 1, 2 or 3;
these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO₂H, C(=O)-NH-SO₂-CH₃, OR₆, COOR⁵ or NR⁶R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR⁸ in which R and R⁸ are hydrogen or lower alkyl, and

- R⁶ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,

- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,

- H, or,

- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

A preferred group of compounds of formula (I) is a group in which X₁, X₂, X₃ and X₄, are as disclosed hereabove where in X₂ is C-R¹ and R¹ is X₅-R⁶, then X³ is not a single bond.

A preferred group of compounds is the group in which one of X₁, X₂, X₃ is C-R¹ in which R¹ is hydrogen while the others are identical or different and are C-R¹ in which R¹ is selected from:

- Q₁, or

- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q₂:

- the group X⁵-R⁶ in which,

- X⁵ is selected from a single bond or lower alkylene, optionally interrupted with 1 heteroatom chosen from O, S and N; and

- R⁶ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃, heteroaryl or lower alkyl optionally substituted with Q₃; in which Q₁, Q₂, Q₃ are the same or different and are selected from

- hydrogen, halogen, CN, NO₂, SO₂H,

- OR₆, OC(=O)R₆, C(=O)OR₆, SR₆, S(=O)R₆, C(=O)-NH-SO₂-CH₃, NR₆R₇, Q-R₆, Q-NR₆R₇, NR₆²-Q-NR₆R₇ or NR₆³-Q-R₆ in which Q is selected from C(=NR), C(=O), C(=S) or SO₂, R is selected from hydrogen or lower alkyl and R², R³ and R⁴ are the same or different and are selected from:

- hydrogen,

- lower alkyl optionally interrupted with C(=O), Q₄-aryl, Q₄-heteroaryl, Q₄-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂ or N, or Q₄-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂ or N, in which

- Q₄ is selected from (CH₂)n, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR’ or NR’R’’ in which R’ and R’’ are the same or different and are selected from hydrogen or lower alkyl;

- n is an integer selected from 0, 1, 2, 3 or 4;

- these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH₃, SO₂H, SO₂CH₃, CF₃, C(=O)-NH-SO₂-CH₃, OR₆, COOR₆, C(=O)R₆, NR₆R₇, C(=O)NR₆R₇ or SO₂NR₆R₇, in which R⁶ and R₇ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR₈ in which R and R₈ are hydrogen or lower alkyl, and,

- R⁶ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO₂ or N, and which may be substituted with,
- (CH₂)n-Q₅, in which n is an integer selected from 0, 1, 2 and 3, and Q₅ is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R'', C(=O)NR'R'' or COOR in which R' and R'' are the same or different and are selected from,
- H, or,
- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R'' together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

[0032] A preferred group of compounds of formula (I) is a group in which X₁, X₂, X₃ and X₄, are as disclosed hereabove wherein when X₁ is C-R₁ and R' is X⁵-R⁶, then X⁵ is not a single bond.

[0033] A preferred group of compounds is the group in which one of X₁, X₂ and X₃ is C-R¹ in which R¹ is hydrogen while the others are identical or different and are C-R¹ in which R¹ is selected from:

- Q₁, or
- lower alkyl or lower alkenyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups halogen or with OR¹, COOR¹ or NR¹R² in which R³ and R⁴ are the same or different and are selected from hydrogen or lower alkyl; or R³ and R⁴, together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X⁵=R⁶ in which X⁵ is a single bond and R⁶ is selected from aryl, preferably phenyl, heteroaryl, preferably pyridyl, or a bicyclic group, preferably indolyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃, in which Q₁ and Q₃ are the same or different and are selected from

- halogen, CN, lower alkyl,
- OR², C(=O)OR², NR²R³, C(=O)NR²R³ or SO₂NR²R³ in which R², R³ and R⁴ are the same or different and are selected from:
  - hydrogen,
  - lower alkyl, Q₄-heteroaryl in which Q₄ is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and (CH₂)n, in which n is an integer selected from 0, 1, 2 or 3; these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO₂H, C (=O)-NH-SO₂-C₇H₅, OR⁶, COOR⁶ or NR⁶R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NR⁸ in which R and R⁸ are hydrogen or lower alkyl, and,
  - R⁶ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl; or,
- a lower alkyl optionally substituted with OR¹, NR¹R², C(=O)NR¹R² or COOR in which R¹ and R² are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl, in which R¹ is hydrogen or lower alkyl and,

R' and R'' together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

[0034] A preferred group of compound is the group disclosed hereabove in which X₃ is C-R¹ in which R¹ is hydrogen.

[0035] Preferably, X₃ is C-R¹, in which R¹ is selected from:

- hydrogen or halogen, preferably Cl, or,
- X⁵-R⁶ in which X⁵ is a single bond and R⁶ is aryl, preferably phenyl or heteroaryl, preferably pyridyl, optionally substituted with one, two or three groups which are the same or different and which are selected from halogen, CN, CF₃, SO₂Me, OR⁶, COOR⁶, NR⁶R⁷, SO₂NR⁶R⁷ and CONR⁶R⁷ in which R⁶ and R⁷ are the same or different and
are selected from hydrogen and lower alkyl.

[0036] Preferably, X₃ is C-R¹, in which R¹ is selected from hydrogen or halogen, preferably Cl. Preferably, X₃ is C-R¹ in which R¹ is hydrogen.

[0037] Preferably, X₁ is C-R¹, in which R¹ is selected from:

- hydrogen, halogen, preferably Cl or Br, OR², COR², COOR², CONR²R³ in which R² and R³ are the same or different and are selected from

- hydrogen,
- lower alkyl, Q₄-aryl, Q₄-heteroaryl, Q₄-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, or Q₄-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, in which

- Q₄ is selected from (CH₂)ₙ, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl;
- n is an integer selected from 0, 1, 2 or 3;

these groups being unsubstituted or substituted with lower alkyl, CN, C(=O)-NH-SO₂-CH₃, OR⁶, SO₃H, CONR⁶R⁷, COOR⁶, COR⁶ or NR⁶R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH₂, COOH, OH, or R⁶ and R⁷, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with,

- (CH₂)ₙ-Q₅, in which n is an integer selected from 0, 1, 2 and 3, and Q₅ is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- COR’ or lower alkyl optionally substituted with OR’, NR’R” or COOR’ in which R’ and R” are the same or different and are selected from hydrogen or lower alkyl;

- lower alkyl optionally substituted with CN, SO₃H, OR³, NR³R⁴, COOR³ or CONR³R⁴ in which R³ and R⁴ are the same or different and are selected from hydrogen and lower alkyl optionally substituted with OH, COOH or NH₂;
- the group X⁵-R⁸ in which X⁵ is a lower alkylene optionally interrupted with a heteroatom selected from O and N and R⁸ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2 or 3 heteroatoms chosen from O, S or N and cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N, these groups being unsubstituted or substituted with OR³ or COOR³ in which R³ is selected from hydrogen and lower alkyl; R⁸ and R⁹, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,

- (CH₂)ₙ-Q₅, in which n is an integer selected from 0, 1, 2 and 3, and Q₅ is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- C(=O)-R’ or a lower alkyl optionally substituted with OR’, NR’R”, C(=O)NR’R” or COOR’ in which R’ and R” are the same or different and are selected from hydrogen or lower alkyl.

[0038] Preferably, X₁ is C-R¹, in which R¹ is selected from hydrogen, halogen, preferably Cl or Br, or OR² in which R² is selected from:

- hydrogen,
- lower alkyl, unsubstituted or substituted with CN, C(=O)-NH-SO₂-CH₃, OR⁶, SO₃H, COOR⁶ or NR⁶R⁷,
- Q₄-oxadiazole, Q₄-tetrazole, Q₄-morpholine, Q₄-furan, Q₄-isoxazole, in which Q₄ is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and (CH₂)ₙ in which n is an integer selected from 1 and 2;

these groups being unsubstituted or substituted with CH₃, OR⁶ or COOR⁶, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH₂ or COOH.

[0039] Preferably, X₂ is C-R¹, in which R¹ is X⁵-R⁸, in which
- $X^5$ is a single bond,
- $R^5$ is phenyl or pyridyl,
- optionally substituted with a lower alkyl, and,
- substituted with $C(=O)NR^3R^4$ in which $R^3$ and $R^4$ together with the nitrogen atom to which they are linked, form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO$_2$ or N, and which may be substituted with:
  - a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or
  - a lower alkyl optionally substituted with OR', $NR'R^*$, C(=O)NR$R^*$ or COOR' in which $R'$ and $R^*$ are the same or different and are selected from H or lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl; or
  - $R'$ and $R^*$ together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

[0040] Preferably, $X_2$ is C-$R^1$, in which $R^1$ is $X^5$-$R^5$, in which

- $X^5$ is a single bond,
- $R^5$ is phenyl,
- optionally substituted with a methyl, and
- substituted with $C(=O)NR^3R^4$ in which $R^3$ and $R^4$ together with the nitrogen atom to which they are linked, form a 6-membered heterocyclic ring, which may contain one or two nitrogen atoms, and which may be substituted with,
  - a 6-membered heterocyclic ring, which may contain one or two nitrogen atoms and which may be substituted with a lower alkyl, or,
  - a lower alkyl optionally substituted with OR', $NR'R^*$, C(=O)NR$R^*$ or COOR' in which $R'$ and $R^*$ are the same or different and are selected from,
    - H, or,
    - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,
  - $R'$ and $R^*$ together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

[0041] In each of all the group of compounds defined above, the following substitutions are further preferred:
Preferably, Z is O.

[0042] Preferably, A is unsubstituted cyclohexyl.
Preferably Z is O and A is unsubstituted cyclohexyl.

[0043] Preferably Z is O, A is unsubstituted cyclohexyl, $X_3$ is C-$R^1$ in which $R^1$ is hydrogen and $X_4$ is C-$R^1$, in which $R^1$ is selected from F, Cl, Br, CF$_3$, or methyl.

In the following and in the foregoing text:

[0044] Halogen includes fluoro, chloro, bromo, and iodo. Preferred halogens are F and Cl.
Lower alkyl includes straight and branched carbon chains having from 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, isopropyl, tert-butyl and the like.
Lower alkenyl includes straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one double bond. Examples of such alkenyl groups are ethenyl, 3-buten-1-yl, 2-ethenylbutyl, 3-hexen-1-yl, and the like.
Lower alkynyl includes straight and branched hydrocarbon radicals having from 2 to 6 carbon atoms and at least one triple bond. Examples of such alkynyl groups are ethynyl, 3-butyn-1-yl, propynyl, 2-butyn-1-yl, 3-pentyn-1-yl, and the like.
Lower haloalkyl includes a lower alkyl as defined above, substituted with one or several halogens. A preferred haloalkyl is trifluoromethyl.
Aryl is understood to refer to an aromatic carbocycle containing between 6 and 10, preferably 6, carbon atoms. A preferred aryl group is phenyl.
Heteroaryl includes aromatic cycles which have from 5 to 10 ring atoms, from 1 to 4 of which are independently selected
from the group consisting of O, S, and N. Preferred heteroaryl groups have 1, 2, 3 or 4 heteroatoms in a 5- or 6-membered aromatic ring. Examples of such groups are tetrazole, pyridyl, thienyl and the like. Preferred cycloalkyl contain from 3 to 8 carbon atoms. Examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term "interrupted" means that in a backbone chain, a carbon atom is replaced by an heteroatom or a group as defined herein. For example, in cycloalkyl or cycloalkenyl optionally interrupted with C(=O) or with 1 heteroatom chosen from O, S, S(=O), SO₂ or N, the term "interrupted" means that C(=O) or a heteroatom can replace a carbon atom of the ring. Example of such groups are morpholine or piperazine.

Cycloalkenyl includes 3- to 10- membered cycloalkyl containing at least one double bond.

Heterocyclic ring include heteroaryl as defined above and cycloalkyl or cycloalkenyl, as defined above, interrupted with 1, 2 or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N.

Bicyclic substituents refer to two cycles, which are the same or different and which are chosen from aryl, heterocyclic ring, cycloalkyl or cycloalkenyl, fused together to form said bicyclic substituents. A preferred bicyclic substituent is indolyl.

Preferred compounds are:

8'-Chlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-methylspiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-fluorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one.

5',8'-dichlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Bromospiro[cycloheptane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
6',8'-dichlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-iodospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-methoxyspiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-phenylspiro[cycloheptane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-phenylspiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-methylspiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-pyridyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(4-pyridyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
6'-[(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
6'-[(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(1H-indol-5-yl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(2-pyridyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(4-(methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(4-(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(4-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro6'-[(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
Among the compounds mentioned above, the following compounds are more preferred:

8'-Chlorospiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
8'-methylspiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
8'-bromospiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
8'-fluorospiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
5,8'-diclorospiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
8'-bromospiro[cyclohexane-1-4'-3,4'-dihydro]quinazolin]-2'(1H)-one,
6'-8'-dichlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one
8'-chloro-6'-iodospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-methoxyspirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenylspiro[cycloheptane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-phenoxydipropylcarboxamide)
8'-chloro-6'-pyridyldipropylcarboxamide)
8'-chloro-6'-pyridylspiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-[3-pyridyldipropylcarboxamide)
8'-chloro-6'-[4-pyridyldipropylcarboxamide)
6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-[1H-indol-5y]spiro[cyclohexane-1-4'[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-methylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-[3-(N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-[2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-[3-(N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(6'-(3-[4-methyl-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(3-[2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-2'-cyanoiminospirocyclohexane-1-4'-[3',4'-dihydro]quinazoline,
8'-chloro-6'-(4-[4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-[4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-[4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(4-[4-(2-hydroxy-ethoxy)-ethyl]-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methoxyspirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
5'-8'-difluorospiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(methylisopropylamino)-cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-dimethylaminooethoxy]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(methylamino)ethoxy]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-5'-(3-sulphopropoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-y]methoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-carboxy-furan-2-y]methoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-cyanomethoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(1H-tetrazol-5-yl]methoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-Chloro-5'-(5-hydroxy-[1,2,4]oxadiazol-3-y]methoxy)spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
6'-(4-carboxyphenyl)-8'-chloro-5'-methoxyspirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
6'-(3-carboxyphenyl)-8'-chloro-5'-methoxyspirocyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
8'-chloro-6'-(2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one,
Among the compounds mentioned above, the following compounds are more preferred:

8\textsuperscript{-}-bromo-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}-dichloro-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}-Bromo-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}-chloro-6\textsuperscript{-}-methoxy-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}-chloro-6\textsuperscript{-}-phenyl-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}-chloro-6\textsuperscript{-}·(3-pyridyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
6\textsuperscript{-}·(4-carboxyphenyl)-8\textsuperscript{-}-chloro-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
6\textsuperscript{-}·(3-carboxyphenyl)-8\textsuperscript{-}-chloro-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(1H-indol-5-yl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(6'-(2-pyridyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(3-dimethylamino-prop-1-ynyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(3-methylamino-prop-1-ynyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(4-methyl-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(3-N-dimethylamino-propylcarboxamide)phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(2-N-dimethylamino-ethylcarboxamide)phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(3-(3-N-dimethylamino-propylcarboxamide)phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(3-(4-methyl-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-pyrimidin-2-yl-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl)-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
8\textsuperscript{-}·(5-carboxymethoxy-8-chloro-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
5\textsuperscript{-}·(carboxypropoxy-8-chloro-spiro[cyclohexane-1-4\textsuperscript{-}·(3',4'-dihydro)quinazolin]-2\textsuperscript{(1'H)-one},
An alternative method for preparing a compound of formula (I) in which $X_1$ is as defined in the summary of the invention, to obtain said compound of formula (I).

An alternative method for preparing a compound of formula (I) in which $X_1$, $X_2$, $X_3$, $X_4$, and $A$ are as defined in the summary of the invention, comprises:

(1) reacting a compound (2a)
in which $X_1$, $X_2$, $X_3$ and $X_4$ are as defined in the summary of the invention with a group $P\cdot LG$ in which $P$ is a protecting group and $LG$ is a leaving group to obtain compound (2b)

(2) reacting compound (2b) with $R\cdot Li$ in which $R$ is lower alkyl and then with a ketone of formula

in which $A$ is as defined in the summary of the invention to obtain compound (2c)

(3) removing the protecting group $P$ either under reductive conditions, acidic condition or basic condition to obtain compound (2d)
(4) reacting compound (2d) with a group O=C=N-H to obtain compound (2e).

(5) reacting compound (2e) with an acid to obtain said compound of formula (I),

(6) isolating said compound of formula (1).

The compounds utilized in the invention include pharmaceutically acceptable derivatives of compounds of formula (I), defined as solvates, hydrates, pharmaceutically acceptable salts and polymorphs (different crystalline lattice descriptors). Pharmaceutically acceptable salts of a compound of formula (I) include salts having a basic part and salts having an acidic part.

The expression pharmaceutically acceptable salt of a compound of formula (I) having a basic part should be understood to refer to the addition salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic acids such as, for example, hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic, hydroxymaleic, benzoic, tumatic and toluenesulfonic acid salts, and the like. The various quaternary ammonium salts of the derivatives (I) are also included in this category of compounds of the invention. In addition, the expression pharmaceutically acceptable salt of a compound of formula (I) having an acidic part is understood to refer to the usual salts of the compounds of formula (I) which may be formed from non-toxic inorganic or organic bases such as, for example, the hydroxides of alkali metals and alkaline-earth metals (sodium, potassium, magnesium and calcium), amines (dibenzylethelenediamine, trimethylamine, piperidine, pyrrolidine, benzylamine and the like) or alternatively quaternary ammonium hydroxides such as tetramethylammonium hydroxide. (See also “Pharmaceutical salts” by Berge S.M. et al. (1997) J. Pharm. Sci. 66: 1-19, which is incorporated herein by reference.).

Pharmaceutical compositions.

[0049] The products of the invention are administered in the form of compositions, which are appropriate for the nature, and severity of the complaint to be treated. The daily dose in humans is usually between 1 mg and 1 g of product, which may be taken in one or more individual doses. The compositions are prepared in forms which are compatible with the intended route of administration, such as, for example, tablets, coated tablets, capsules, mouthwashes, aerosols, powders for inhalation, suppositories, enemas, foams (such as rectal foams) gels or suspensions. These compositions are prepared by methods which are familiar to those skilled in the art and comprise from 0.5 to 60% by weight of active principle (compound of the invention) and 40 to 99.5% by weight of a pharmaceutical vehicle or carrier which is appropriate and compatible with the active principle and the physical form of the intended composition.

[0050] Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants,
suspension agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders, tablets, cachets or encapsulated forms for capsules preferably contain 5% to about 70% of the active component. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrose, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

[0051] Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration. The drug may be delivered as a spray (either in a pressurized container fitted with an appropriate valve or in a non-pressurized container fitted with a metering valve).

[0052] Liquid form preparations include solutions, suspensions, and emulsions.

[0053] Sterile water or water-propylene glycol solutions of the active compounds may be mentioned as an example of liquid preparations suitable for parenteral administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solutions.

[0054] Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavouring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

[0055] For preparing suppository preparations, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify. Enemas are obtained according to known procedures to prepare solutions adapted for rectal administration. Foams are prepared according to known methods (these foams can notably be similar to those used to administer a drug such as 5-ASA for treating rectocolitis).

[0056] Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of drug. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packaged tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Use in treatment.

[0057] The compounds of the invention are PDE inhibitors, and particularly PDE7 inhibitors. These compounds have low IC_{50} values, typically at most 5 \mu M, preferably below 1 \mu M, and even below 100 nM.

[0058] It has been shown according to the invention that compounds of the invention are selective PDE7 inhibitors. "selective PDE7 inhibitors" refers to a compound which have an IC_{50} for PDE7 at least 5 times lower than the IC_{50} for a PDE distinct from PDE7, and preferably at least 10 times, 15 times, 20 times, 30 times, 40 times, 50 times or 100 times lower than the IC_{50} value for a PDE distinct from PDE7.

A PDE distinct from PDE7 refers preferably to a PDE chosen from PDE1, PDE3, PDE4 or PDE5.

[0059] In particular, it has been shown according to the invention that the compounds of the invention, and more particularly the family of compounds given as examples in the present description, have an IC_{50} value for the enzyme PDE7 which is often 100 times lower than the value of their IC_{50} for a PDE distinct from PDE7, in particular PDE1, PDE3, PDE4 or PDE5.

[0060] Compounds of the invention can be used in the treatment of various diseases, as they can modulate inflammatory and immunological processes due to the increase of intracellular cAMP levels.

[0061] The diseases that can be treated are T-cell-related diseases, AE-cell-related diseases and immune disorders, such as autoimmune diseases, osteoarthritis, rheumatoid arthritis, multiple sclerosis, osteoporosis, asthma, COPD, cancer, AIDS, inflammation, allergy and various inflammatory disorders such as, for example, inflammatory bowel disease (IBD).

Processes for synthesising the compounds of general formula (I)

[0062] The compounds according to the present invention can be obtained by carrying out several synthetic processes. Some of these synthetic processes (protocols A-H) are described below.

[0063] The solvent, reaction time, temperature, catalyst if any, can be varied in all steps described below for all routes, as the skilled man will appreciate.
Protocol A:

In scheme 1, $X_1$, $X_2$, $X_3$, $X_4$ and $A$ are as defined in the summary of the invention. The starting materials are either commercially available or can be prepared according to routes known to the skilled person. If the starting urea in step 3 is not commercially available, it can be prepared by treating the corresponding isocyanate with ammonia in a solvent such as tetrahydrofuran (step 1) or treating the corresponding aniline with a isocyanate in an organic solvent such as dichloromethane or acetonitrile (step 2).

In step 3, the urea is converted into the desired quinazolinone by reacting it with a cyclic ketone in polyphosphoric acid at 80-130°C.

Protocol B:
In scheme 2, X₁, X₂, X₃, X₄ and A are as defined in the summary of the invention, LG is a leaving group and R is lower alkyl. The starting compounds are either commercially available or can be prepared according to routes known to the skilled person.

In step 1, compound (2a) is reacted with dialkyl-carbamoyl chloride to form the desired N,N dialkyl-carbamate or thio-carbamate according to routes known to the skilled person. See Poirier, M.; Simard, M.; Wuest, J.D.; Organometallics, 1996, 15 (4), 1296-1300.

Other protecting groups may be used as oxygen-based directed metalation groups such as OMe, OMOM, OP(OR₂), OPO(NMe)₂. See Snieckus, Chem. Rev., 1990, 90, 879-933.

The aniline derivative is protected as a t-buty carbamate or as a pivaloyl amide according to routes known to the skilled person. See Tet. Lett., 1994, 35 (48), 9003-9006.

In step 2, compound (2b) is converted to a dilithium salt thereof by reaction with an excess of lithium compound-forming agent such as t-butyllithium in a mixed solvent of anhydrous ether (for example, diethyl ether and tetrahydrofuran) and alkane (for example pentane), and reacted with an appropriate ketone. The reaction is carried out at low temperature (between -78°C and 0°C) to give the expected tertiary alcohol. The organolithium intermediate can also be formed by halogen-metal exchange. The organolithium can also be transmetallated into another organometallic reagent such as a cerate (with anhydrous cerium trichloride for example) prior to treatment with the ketone.

In step 3, the protecting group is removed according to routes known to the skilled person either under acidic condition or under basic condition to give compound (2d).

In step 4, compound (2d) is reacted with an appropriate isocyanate to obtain compound (2e).

In step 5, treating compound (2e) with an acid (mineral acid or Lewis acid) triggers cyclisation to give compound (2f).

Protocol C:

[0066]
In scheme 3, \( X_1, X_2, X_3, X_4 \) and \( A \) are as defined in the summary of the invention, \( R^9 \) is alkyl, aryl, alkylsulfonyl or arylsulfonyl, \( R \) is lower alkyl and \( Y \) may be O, S or NH.

An alternative method of preparing compound of the present invention is shown below and proceeds through the reaction of the organolithium intermediate with an imine.

In step 1, compound (3a) is converted to a dilithium salt thereof by reaction with an excess of lithium compound-forming agent such as t-butyllithium in a mixed solvent of anhydrous ether (for example, diethyl ether and tetrahydrofuran) and alkane (for example pentane). The resulting organolithium is reacted with an appropriate imine at low temperature to give the expected tertiary amine (3b). The organolithium can also be transmetallated into another organometallic reagent such as a cerate (with anhydrous cerium trichloride for example) prior to treatment with the ketone. In step 2, the protecting group is removed according to routes known to the skilled person under acidic condition or under basic condition to give compound (3c).

In step 3, compound (3c) is reacted with a compound selected from a carbonic acid halide such as phosgene, a carbonic acid diester, 1,1'-carbonyldiimidazole and so on to obtain compound (3d).

Protocol D:

[0067]
In scheme 4, $X_1$, $X_3$, $X_4$ and $A$ are as defined in the summary of the invention.

The starting tricyclic compound is reacted with an electrophile $E^+$ such as halonium or acylium in presence or absence of an activating agent in an organic solvent. Various solvents and reaction conditions for this aromatic electrophilic substitution can be used depending on the electrophile and will be easily determined by the skilled person. For instance, the starting material can be treated with a source of halonium such as N-iodo or N-bromosuccinimide in dimethylformamide at 60-70°C to give the corresponding halide. In another example, the starting material can be reacted with an acyl halide and aluminium trichloride, as Lewis acid, in a solvent such as dichloroethane at 80°C.

Protocol E:

In scheme 5, $X_1$, $X_3$ and $A$ are as defined in the summary of the invention and $X_2$ is not CH.

The starting tricyclic compound is reacted with an electrophile $E^+$ in presence or not of an activating agent in an organic solvent. This aromatic electrophilic substitution is similar to Protocol D except that in this case, since $X_2$ is different from CH, the substitution is oriented in position 8. Similarly to Protocol D, various solvents and reaction conditions for this aromatic electrophilic substitution can be used depending on the electrophile and will be easily determined by the skilled person.

Protocol F:

Scheme 6
In scheme 6, $X_1, X_2, X_3, X_4, Z$ and $A$ are as defined in the summary of the invention, $R$ is alkenyl, alkynyl, aryl or heteroaryl and $R'$ is H or alkyl.

The starting aryl or heteroaryl iodide or bromide is subjected to a palladium-catalyzed cross-coupling reaction with an organometallic species, such as a boronate ester, a boronic acid, an organozinc ($\text{Hal}=\text{halogen}$) or a trialkylstannane in the presence of base when needed. The organometallic species can be replaced with a terminal alkene or alkyne in the coupling reaction. When an alkyne is used, a source of copper(I), such as copper iodide, can be added. Various palladium catalysts, solvents and reaction conditions can be used for these coupling reactions and will be easily determined by the skilled person. For example, the starting aryl or heteroaryl iodide or bromide can be reacted with a boronic acid in dimethylformamide at $80^\circ\text{C}$ in the presence of tetrakis(triphenylphosphine)palladium as catalyst and an aqueous solution of potassium carbonate as a base.

Protocol G:

[0070]
In scheme 7, $X_1$, $X_2$, $X_3$, $X_4$, Z, $R^2$, $R^3$, $R^4$ and A are as defined in the summary of the invention and R is selected from aryl, alkenyl, alkynyl or heteroaryl.

In step 1, the starting aryl or heteroaryl iodide or bromide is treated with bis(pinacolato)diboron under palladium catalysis to give the corresponding boronate ester. Various palladium catalysts, solvents and reaction conditions can be used and will be easily determined by the skilled person. For example, the starting heteroaryl iodide or bromide can be reacted with bis(pinacolato)diboron in dimethylformamide at 80°C in the presence of tetrakis(triphenylphosphine)palladium as catalyst. The resulting boronate ester is then coupled to an aryl, alkenyl, alkynyl or heteroaryl iodide, bromide or triflate catalyzed by a palladium species (step 2). Again, various palladium catalysts, solvents and reaction conditions can be used for this coupling reactions and will be easily determined by the skilled person. For instance, the boronate ester is reacted with an aryl, alkenyl, alkynyl or heteroaryl iodide in dimethylformamide at 80°C in the presence of sodium acetate as base and tetrakis(triphenylphosphine)palladium as catalyst to give the coupled product.

In step 3, the boronate ester is hydrolyzed to the corresponding boronic acid. This can be done by treating it with acid, e.g. an aqueous solution of hydrochloric acid, in an organic solvent, e.g. methanol. The resulting boronic acid is coupled,

(step 4) under air with a phenol or heteroaryl alcohol, or,
(step 5) with a primary or secondary amine, heteroarylamine, aniline, amide, sulfonamide, urea, carbamate or imide, in the presence of a base such as triethylamine or pyridine and a source of copper(II) such as copper(II) acetate in a solvent like dichloromethane. Molecular sieves, 4Å or 3Å, can be added to the reaction mixture.

In [0071] step 3, the boronate ester is hydrolyzed to the corresponding boronic acid. This can be done by treating it with acid, e.g. an aqueous solution of hydrochloric acid, in an organic solvent, e.g. methanol. The resulting boronic acid is coupled,
In scheme 8, $X_2$, $X_3$, $X_4$, and $A$ are as defined in the summary of the invention, $R$ is alkyl or $C(=O)$-alkyl and $LG$ is a leaving group.

In step 1, the starting methoxy derivative is demethylated with boron tribromide in a solvent such as dichloromethane. The resulting phenol intermediate is treated in step 2 with an electrophile such as an alkyl halide, an acyl halide or the like in the presence of a base such as potassium carbonate, cesium carbonate or sodium hydride in a solvent like dimethylformamide.

**Synthesis Examples**

**Reference Example 1**

6'-Methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

**Reference Example 2**

6'-Phenylspiro[cycloheptane-1-4'-{(3',4'-dihydro)quinazolin}]-2'(1'H)-one
The title compound was obtained as a white powder (23.3 g, 38% yield). mp = 180-182°C. 

$^1$H NMR $[(CD_3)_2SO]$ $\delta$ 9.28 (br s, 1H, NH), 7.59 (m, 2H), 7.43 (m, 4H), 7.30 (m, 1H), 7.0 (br s, 1H, NH), 6.88 (m, 1H), 2.01 (m, 2H), 1.89 (m, 2H), 1.77 (m, 2H), 1.58 (m, 6H).

**Example 1**

8'-Chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[0078\]

$X_1 = CH, X_2 = CH, X_3 = CH, X_4 = C-Cl, A = cyclohexyl, X = NH, Z = O, Y = NH.$

**Example 2**

8'-Methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[0080\]

$X_1 = CH, X_2 = CH, X_3 = CH, X_4 = C-CH_3, A = cyclohexyl, X = NH, Z = O, Y = NH.$

**Example 3**

8'-Bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[0082\]

$X_1 = CH, X_2 = CH, X_3 = CH, X_4 = C-Br, A = cyclohexyl, X = NH, Z = O, Y = NH.$

**Example 4**

8'-Fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[0084\]

$X_1 = CH, X_2 = CH, X_3 = CH, X_4 = C-F, A = cyclohexyl, X = NH, Z = O, Y = NH.$
The title compound was prepared according to protocol A, using 2-fluorophenyl urea (0.77 g, 5 mmol) and cyclohexanone (0.55 mL, 5.5 mmol, 1.1 equiv.) in polyphosphoric acid (20 g). The aqueous layer was extracted with CH$_2$Cl$_2$/MeOH (2/1). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH : 99/1 to 95/5) followed by recrystallization in toluene to give 272 mg (23% yield) of the title compound as a white solid. mp = 221 °C

1H NMR [(CD$_3$)$_2$SO] $\delta$ 9.12 (br s, 1H, NH), 7.11 (d, $J = 7.8$ Hz, 1H), 7.05 (m, 1H), 6.94 (br s, 1H, NH), 6.90 (m, 1H), 1.81-1.61 (m, 7H), 1.50 (m, 2H), 1.25 (m, 1H).

Reference Example 3

6'-Methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X$_1$ =CH, X$_2$ =C-CH$_3$, X$_3$ =CH, X$_4$ =CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-methylphenyl urea (1.5 g, 10 mmol) and cyclohexanone (1.1 mL, 11 mmol, 1.1 equiv.) in polyphosphoric acid (38 g). The aqueous layer was extracted with CH$_2$Cl$_2$/MeOH (2/1). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH : 99/1 to 90/10) followed by recrystallization in toluene to give 405 mg (18% yield) of the title compound as a white solid. mp = 229°C

1H NMR [(CD$_3$)$_2$SO] $\delta$ 9.01 (br s, 1H, NH), 7.05 (s, 1H), 6.91 (d, $J = 8.0$ Hz, 1H), 6.68-6.66 (m, 2H), 2.22 (s, 3H), 1.76 - 1.61 (m, 7H), 1.50 (m, 2H), 1.23 (m, 1H).

Example 5

5',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X$_1$ =C-Cl, X$_2$ =CH, X$_3$ =CH, X$_4$ =C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 2,5-dichlorophenyl urea (0.615 g, 3 mmol) and cyclohexanone (0.50 mL, 5 mmol, 1.6 equiv.) in polyphosphoric acid (15 g). The aqueous layer was extracted with CH$_2$Cl$_2$/MeOH (2/1). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH : 99/1 to 92/8) followed by recrystallization in toluene to give 56 mg (7% yield) of the title compound as a white solid. mp = 243°C

1H NMR [(CD$_3$)$_2$SO] $\delta$ 8.35 (br s, 1H, NH), 7.35 (d, $J = 8.5$ Hz, 1H), 7.21 (br s, 1H, NH), 7.01 (d, $J = 9.0$ Hz, 1H), 2.50 (ddd, $J = 13.5$, 13.5, 4.5 Hz, 2H), 1.83 (m, 2H), 1.68-1.51 (m, 5H), 1.24 (m, 1H).

Reference Example 4

6'-Phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X$_1$ =CH, X$_2$ =C-phenyl, X$_3$ =CH, X$_4$ =CH, A=cyclohexyl, X=NH, Z=O, Y=NH.

The title compound was prepared according to protocol A, using 4-phenyl-phenyl urea (0.67 g, 3.15 mmol) and cyclohexanone (0.50 mL, 5 mmol, 1.6 equiv.) in polyphosphoric acid (16 g). The aqueous layer was extracted with CH$_2$Cl$_2$/MeOH (2/1). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH : 99/1 to 90/92) followed by recrystallization in toluene to give 410 mg (13% yield) of the title compound as a white solid. mp = 213°C

1H NMR [(CD$_3$)$_2$SO] $\delta$ 9.25 (br s, 1H, NH), 7.62 (d, $J = 7.4$ Hz, 2H), 7.52 (d, $J = 1.6$ Hz, 1H), 7.42 (m, 3H), 7.30 (t, $J = 7.3$ Hz, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 6.83 (br s, 1H, NH), 1.84 - 1.79 (m, 6H), 1.63 (m, 1H), 1.53 (m, 2H), 1.30 (m, 1H).
Example 6

8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ X_1=CH, X_2=CH, X_3=CH, X_4=Br, A=\text{cycloheptyl}, X=\text{NH}, Z=O, Y=\text{NH}. \]

[0092]

The title compound was prepared according to protocol A, using 2-bromophenyl urea (0.6 g, 2.8 mmol) and cycloheptanone (0.5 mL, 4.2 mmol, 1.5 equiv.) in polyphosphoric acid (22 g). The aqueous layer was extracted with \( \text{CH}_2\text{Cl}_2/\text{MeOH} \) (2/1). The organic extracts are dried over MgSO\(_4\), filtered and concentrated. The crude material was purified by flash chromatography on silica gel (\( \text{CH}_2\text{Cl}_2/\text{MeOH} : 99/1 \) to 90/10) and the resulting powder was washed with diisopropyl ether. The title compound was obtained as a white powder (0.12 g, 14% yield). mp = 215-217°C

\[^1\text{H} \text{NMR} (\text{CD}_3\text{SO}) \delta 7.87 \text{ (br s, 1H, NH)}, 7.44 \text{ (d, } J=7.8 \text{ Hz, 1H)}, 7.31 \text{ (br s, 1H, NH)}, 7.28 \text{ (d, } J=7.8 \text{ Hz, 1H)}, 6.90 \text{ (t, } J=7.8 \text{ Hz, 1H)}, 1.96-1.84 \text{ (m, 4H)}, 1.76-1.71 \text{ (m, 2H)}, 1.56 \text{ (m, 6H)}. \]

Example 7

6',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0094]

\[ X_1=CH, X_2=\text{C-Cl}, X_3=\text{CH}, X_4=\text{C-Cl}, A=\text{cyclohexyl}, X=\text{NH}, Z=O, Y=\text{NH}. \]

[0095]

A solution of Example 1 (100.2 mg, 0.4 mmol) in dimethylformamide (2 mL) was treated with N-chlorosuccinimide (80 mg, 0.6 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (\( \text{CH}_2\text{Cl}_2/\text{MeOH} : 100/0 \) to 90/10) and reverse phase HPLC (C18 column, gradient of acetonitrile in water : 50/50 to 95/5) to give the title compound as a white solid (48% yield). mp = 245°C

\[^1\text{H} \text{NMR} (\text{CDCl}_3) \delta 7.26 \text{ (m, 1H)}, 7.19 \text{ (br s, 1H, NH)}, 7.10 \text{ (m, 1H)}, 5.80 \text{ (br s, 1H, NH)}, 1.97 \text{ (m, 2H)}, 1.82-1.57 \text{ (m, 7H)}, 1.29 \text{ (m, 1H)}. \]

Example 8

8'-Chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0096]

\[ X_1=CH, X_2=\text{C-I}, X_3=\text{CH}, X_4=\text{C-Cl}, A=\text{cyclohexyl}, X=\text{NH}, Z=O, Y=\text{NH}. \]

[0097]

To a solution of Example 1 (5 g, 20 mmol) in trifluoroacetic acid (25 mL) were subsequently added N-iodosuccinimide (6 g, 22 mmol, 1.1 equiv.) and sulfuric acid (4 mL). The resulting solution was heated to 55°C overnight, concentrated under reduced pressure, taken into dichloromethane and washed twice with water. The reaction mixture was concentrated and purified by flash chromatography on silica gel (\( \text{CH}_2\text{Cl}_2/\text{MeOH} : 97/3 \)) to give 4.5 g (73% yield) of the title compound as a yellowish solid. mp = 261°C

\[^1\text{H} \text{NMR} ([\text{CDCl}_3]_2) \delta 8.64 \text{ (br s, 1H, NH)}, 7.64 \text{ (d, } J=2.0 \text{ Hz, 1H)}, 7.56 \text{ (d, } J=1.0 \text{ Hz, 1H)}, 7.22 \text{ (br s, 1H, NH)}, 1.76-1.59 \text{ (m, 7H)}, 1.49 \text{ (m, 2H)}, 1.25 \text{ (m, 1H)}. \]

Example 9

8'-Chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0098]

\[ X_1=CH, X_2=\text{C-phenyl}, X_3=\text{CH}, X_4=\text{C-Cl}, A=\text{cyclohexyl}, X=\text{NH}, Z=O, Y=\text{NH}. \]

[0099]

A solution of Reference Example 4 (232 mg, 0.79 mmol) in dimethylformamide (4 mL) was treated with N-chlorosuccinimide (80 mg, 0.6 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (\( \text{CH}_2\text{Cl}_2/\text{MeOH} : 99/1 \) to 90/10) to give the title compound as a white solid (41%
Example 10

8'-Chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{X}_1 = \text{CH}, \text{X}_2 = \text{C-O-CH}_3, \text{X}_3 = \text{CH}, \text{X}_4 = \text{C-Cl}, \text{A} = \text{cyclohexyl}, \text{X} = \text{NH}, \text{Z} = \text{O}, \text{Y} = \text{NH} \]

A solution of Reference Example 1 (500 mg, 2.03 mmol) in dimethylformamide (10 mL) was treated with N-chlorosuccinimide (300 mg, 2.24 mmol, 1.1 equiv.) at 60°C overnight. The reaction mixture was concentrated and purified by flash chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}/MeOH: 99/1 to 90/10) followed by recrystallization in toluene to give 76 mg (13% yield) of the title compound as a white solid. mp = 226°C

\[ \text{H} \text{ NMR} \ (\text{CDCl}_3) \delta 8.20 \ (\text{br s}, 1\text{H}, \text{NH}), 6.96 \ (\text{br s}, 1\text{H}, \text{NH}), 6.92 \ (\text{m}, 1\text{H}), 3.73 \ (\text{s}, 3\text{H}), 1.72 - 1.61 \ (\text{m}, 7\text{H}), 1.62 \ (\text{m}, 2\text{H}), 1.26 \ (\text{m}, 1\text{H}). \]

Example 11

8'-Chloro-6'-phenylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{X}_1 = \text{CH}, \text{X}_2 = \text{C-phenyl}, \text{X}_3 = \text{CH}, \text{X}_4 = \text{C-Cl}, \text{A} = \text{cycloheptyl}, \text{X} = \text{NH}, \text{Z} = \text{O}, \text{Y} = \text{NH} \]

A solution of Reference Example 2 (150 mg, 0.49 mmol) in dimethylformamide (2 mL) was treated with N-chlorosuccinimide (75 mg, 0.56 mmol, 1.1 equiv.) at 60°C overnight. The reaction mixture was concentrated then purified by flash chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}/MeOH: 99/1 to 90/10) to give 158 mg (95% yield) of the title compound as a yellowish solid. mp = 201 °C

\[ \text{H} \text{ NMR} \ (\text{CDCl}_3) \delta 7.51-7.41 \ (\text{m}, 6\text{H}), 7.36 \ (\text{m}, 2\text{H}), 5.90 \ (\text{br s}, 1\text{H}, \text{NH}), 2.75-2.01 \ (\text{m}, 4\text{H}), 1.77-1.43 \ (\text{m}, 8\text{H}). \]

Example 12

8'-Chloro-6'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{X}_1 = \text{CH}, \text{X}_2 = \text{C-CH}_3, \text{X}_3 = \text{CH}, \text{X}_4 = \text{C-Cl}, \text{A} = \text{cyclohexyl}, \text{X} = \text{NH}, \text{Z} = \text{O}, \text{Y} = \text{NH} \]

A solution of Reference Example 3 (350 mg, 1.51 mmol) in dimethylformamide (7 mL) was treated with N-chlorosuccinimide (305 mg, 2.3 mmol, 1.5 equiv.) at 60°C overnight. The reaction mixture was concentrated and purified by flash chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}/MeOH: 99/1 to 90/10). The resulting solid was triturated with methanol to give the title compound as a white solid (28% yield). mp = 266°C

\[ \text{H} \text{ NMR} \ (\text{CD}_3\text{SO}) \delta 8.23 \ (\text{br s}, 1\text{H}, \text{NH}), 7.11 \ (\text{m}, 2\text{H}), 7.03 \ (\text{br s}, 1\text{H}, \text{NH}), 2.23 \ (\text{s}, 3\text{H}), 1.77 - 1.61 \ (\text{m}, 7\text{H}), 1.51 \ (\text{m}, 2\text{H}), 1.25 \ (\text{m}, 1\text{H}). \]

Example 13

8'-Chloro-6'-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{X}_1 = \text{CH}, \text{X}_2 = \text{C-(3-pyridyl)}, \text{X}_3 = \text{CH}, \text{X}_4 = \text{C-Cl}, \text{A} = \text{cyclohexyl}, \text{X} = \text{NH}, \text{Z} = \text{O}, \text{Y} = \text{NH} \]

A solution of Reference Example 8 (0.5 g, 1.4 mmol) in dimethylformamide (5 mL) were subsequently added 3-pyridylboronic acid (0.22 g, 1.7 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL).
mixture was degassed by bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine) palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, triturated with water and filtered. The resulting solid was triturated with ethyl acetate, filtered and purified by flash chromatography on silica gel (CH$_2$Cl$_2$/EtOAc : 80/20 to 50/50) to give 140 mg (30% yield) of the title compound as white solid. mp = 246°C

$^1$H NMR [(CD$_3$)$_2$SO] $\delta$ 8.93 (br s. 1H, NH), 8.55 (m, 2H), 8.10 (m, 1H), 7.71 (d, $J$ = 1.5 Hz, 1H), 7.65 (d, $J$ = 1.5 Hz, 1H), 7.45 (dd, $J$ = 8.0, 5.0 Hz, 1H), 7.19 (br s, 1H. NH), 1.91 - 1.77 (m, 6H), 1.63 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 14

8'-Chloro-6'-(4-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[X$_1$=CH, X$_2$=C-(4-pyridyl), X$_3$=CH, X$_4$=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH]

To a suspension of Example 8 (0.5 g, 1.4 mmol) in dimethylformamide (5 mL) were subsequently added 4-pyridylboronic acid (0.22 g, 1.7 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine) palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, washed with water and ethyl acetate then purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 97/3 to 95/5) to give 40 mg (10% yield) of the title compound as white solid. mp = 320-321°C

$^1$H NMR [(CD$_3$)$_2$SO] $\delta$ 8.64 (br s, 1H, NH), 8.59 (d, $J$ = 6.0 Hz, 2H), 7.80-7.72 (m, 4H), 7.22 (br s, 1H. NH), 1.99-1.77 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 15

6'-(4-Carboxyphenyl)-8'chlorospiro[cyclohexane-1-4'-(3,4-dihydro)quinazolin]-2'(1'H)-one

[X$_1$=CH, X$_2$=C-(4-carboxyphenyl), X$_3$=CH, X$_4$=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH]

To a suspension of Example 8 (1 g, 2.8 mmol) in dimethylformamide (10 mL) were subsequently added 4-carboxyphenylboronic acid (0.55 g, 3.35 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (3 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine) palladium (120 mg, 0.1 mmol, 0.04 equiv.) was added. After heating to reflux overnight, the mixture was concentrated under reduced pressure, taken into dichloromethane and washed with water. The aqueous layer was acidified to pH 2 and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to a third of its volume and filtered. The resulting solid was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 97/3 to 95/5) to give 250 mg (40% yield) of the title compound as white solid. mp = 309°C

$^1$H NMR [(CD$_3$)$_2$SO] $\delta$ 12.95 (br s, 1H, OH), 8.58 (brs, 1H, NH), 7.98 (d, $J$ = 8.5 Hz, 2H), 7.83 (d, $J$ = 8.5 Hz, 2H), 7.70 (d, $J$ = 1.5 Hz, 1H), 7.65 (s, 1H), 7.20 (br s, 1H, NH), 1.93 -1.78 (m, 6H), 1.64 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 16

6'-(3-Carboxyphenyl)-8'chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[X$_1$=CH, X$_2$=C-(3-carboxyphenyl), X$_3$=CH, X$_4$=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH]

To a suspension of Example 8 (1 g, 2.8 mmol) in dimethylformamide (10 mL) were subsequently added 3-carboxyphenylboronic acid (0.55 g, 3.35 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (3 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine) palladium (120 mg, 0.1 mmol, 0.04 equiv.) was added. After heating to reflux overnight, the mixture was concentrated under reduced pressure, taken into dichloromethane and washed with water. The aqueous layer was acidified to pH 1 and filtered to give 330 mg (58% yield) of the title compound as white solid. mp = 300°C
Example 17

8'-Chloro-6'-(1H-indol-5-yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0114]

X₁=CH, X₂=C-indol-5-yl, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0115] To a suspension of Example 8 (0.5 g, 1.4 mmol) in dimethylformamidine (5 mL) were subsequently added 5-indotylboronic acid (0.26 g, 1.6 mmol, 1.2 equiv.) and a 2M aqueous solution of potassium carbonate (1.5 mL). The mixture was degassed by bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine) palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After heating to 80°C overnight, the mixture was concentrated under reduced pressure, taken into ethyl acetate and washed three times with water. The residue was then purified by flash chromatography on silica gel (CH₂Cl₂/EtOAc: 80/20) to give 210 mg (44% yield) of the title compound as white solid. mp = 257°C

1H NMR [(CD₃)₂SO] δ 11.12 (br s, 1H, NH), 8.40 (br s, 1H, NH), 7.83 (s, 1H), 7.56 (m, 2H), 7.44 (d, J = 8.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.11 (s, 1H), 6.47 (br s, 1H, NH), 1.89 -1.78 (m, 6H), 1.64 (m, 1H), 1.55 (m, 2H), 1.32 (m, 1H).

Example 18

8'-Chloro-6'-(2-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0116]

X₁=CH, X₂=C-(2-pyridyl), X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0117] To a solution of Example 8 (0.5 g, 1.3 mmol) in tetrahydrofuran (5 mL) was added a 0.5 M solution of 2-pyridylzinc bromide in tetrahydrofuran (60 mL, 30 mmol, 23 equiv.). The mixture was degassed bubbling nitrogen for 30 minutes and tetrakis(triphenylphosphine)palladium (60 mg, 0.05 mmol, 0.04 equiv.) was added. After refluxing for 4 h, additional tetrakis(triphenylphosphine)palladium (100 mg) and toluene (5 mL) were added. After heating to 90°C overnight, the mixture was diluted with dichloromethane and washed three times with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (CH₂Cl₂/EtOAc: 90/10) to give 50 mg (2% yield) of the title compound as a solid. mp = 251°C

1H NMR [(CD₃)₂SO] δ 8.64 (br s, 1H, NH), 7.45 (dd, J = 5.0, 1.0 Hz, 1H), 8.04-8.01 (m, 3H), 7.85 (td, J = 7.5, 2.0 Hz, 1H), 7.32 (m, 1H), 7.21 (br s, 1H, NH), 1.89 - 1.83 (m, 6H), 1.66 (m, 1H), 1.56 (m, 2H), 1.32 (m, 1H).

Example 19

8'-Chloro-6'-(3-dimethylamino-prop-1-ynyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0118]

X₁=CH, X₂=C-(3-dimethylaminoprop-1-ynyl), X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0119] To a suspension of Example 8 (0.5 g, 1.4 mmol) in pyrrolidine (10 mL) were subsequently added 1-dimethylamino-2-propyne (0.170 mL, 1.6 mmol, 1.2 equiv.), toluene (10 mL) and tetrakis(triphenylphosphine) palladium (80 mg, 0.07 mmol, 0.05 equiv.). After heating to 45°C overnight, the mixture was filtered, diluted with ethyl acetate and washed twice with a 1 M aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with ethyl acetate. The combined extracts were dried over sodium sulfate, concentrated under reduced pressure and to give 60 mg (13% yield) of the title compound as yellowish solid. mp = 208°C

1H NMR [(CD₃)₂SO] δ 8.63 (br s, 1H, NH), 7.37 (d, J = 1.5 Hz, 1H), 7.34 (s, 1H), 7.19 (br s, 1H, NH), 3.43 (s, 2H), 2.24 (s, 6H), 1.81 - 1.72 (m, 6H), 1.62 (m, 1H), 1.50 (m, 2H), 1.27 (m, 1H).
Example 20

8-Chloro-6'(3-methy lamino-prop-1-ynyl)s piro[ cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X₁ = CH, X₂ = C-(3-methy lamino-prop-1-ynyl), X₃ = CH, X₄ = C-Cl, A = cyclohexyl, X = NH, Z = O, Y = NH

Example 21

8-Chloro-6'[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X₁ = CH, X₂ = C-(4-(4-methyl-piperazine-1-carbonyl)phenyl), X₃ = CH, X₄ = C-Cl, A = cyclohexyl, X = NH, Z = O, Y = NH

Example 22

8-Chloro-6'[4-(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

X₁ = CH, X₂ = C-[4-(3-N-dimethylamino-propylcarboxamide)phenyl], X₃ = CH, X₄ = C-Cl, A = cyclohexyl, X = NH, Z = O, Y = NH

Example 23

To a solution of Example 8 (0.2 g, 0.5 mmol) in dimethylformamide (3 mL) were subsequently added N-methylpropargylamine (0.1 mL, 1 mmol, 2 equiv.) and triethylamine (1 mL, 7 mmol, 14 equiv.). The mixture was degassed bubbling nitrogen for 30 minutes then tetrakis(triphenylphosphate)palladium (20 mg, 0.025 mmol, 0.05 equiv.) and copper(I) iodide (20 mg, 0.1 mmol, 0.02 equiv.) were added. After heating to 80°C overnight, the mixture was diluted with dichloromethane and washed three times with water. The organic layer was dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by flash chromatography on silica gel (CH₂Cl₂/MeOH : 98/2 to CH₂Cl₂/MeOH/NH₄OH : 96/3/1) to give 40 mg (25% yield) of the title compound as a solid. mp = 188°C

1H NMR [(CD₃)₂SO] δ 8.62 (br s, 1H, NH), 7.33 (s, 1H), 7.32 (s, 1H), 7.19 (br s, 1H, NH), 3.50 (br s, 2H), 2.35 (br s, 3H), 1.76 - 1.73 (m, 6H), 1.61 (m, 1H), 1.50 (m, 2H), 1.26 (m, 1H).

Example 24

To a suspension of Example 15 (100 mg, 0.27 mmol) in toluene (3 mL) was added thionyl chloride (0.03 mL, 0.4 mmol, 1.5 equiv.). The resulting mixture was heated to reflux for 2 hours, then twice concentrated under reduced pressure and taken into toluene. To the resulting solid in toluene (2 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 1-methylpiperazine (0.04 mL, 0.32 mmol, 1.2 equiv.). After stirring overnight, the mixture was diluted with dichloromethane and washed twice with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (CH₂Cl₂/MeOH : 97/3) to give 20 mg (16% yield) of the title compound as white solid. mp = 277°C

1H NMR [(CD₃)₂SO] δ 8.55 (br s, 1H, NH), 7.80 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.61 (s, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.18 (br s, 1H, NH), 3.60 (br m, 4H), 3.08 (br m, 4H), 2.67 (br s, 3H), 1.91 - 1.72 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 25

To a suspension of Example 15 (122 mg, 0.33 mmol) in toluene (3 mL) was added thionyl chloride (0.04 mL, 0.5 mmol, 1.5 equiv.). The resulting mixture was heated to reflux overnight, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.1 mL, 0.54 mmol, 1.6 equiv.) and 3-dimethylaminopropyamine (0.03 mL, 0.26 mmol, 0.8 equiv.). After stirring for 4 h, the mixture was diluted with dichloromethane and washed twice with water and a 1N aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 40 mg (34% yield) of the title compound as white solid. mp = 232°C

1H NMR [(CD₃)₂SO] δ 8.59-8.55 (m, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 1.5 Hz, 1H), 7.63 (s, 1H), 7.18 (br s, 1H, NH), 3.29 (m, 2H), 2.26 (t, J = 7.0 Hz, 2H), 2.14 (s, 6H), 1.92 - 1.77 (m, 6H), 1.67 (m, 3H), 1.31 (m, 1H).
Example 23

8'-Chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0126]

X₁=CH, X₂=C-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl], X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0127]  To a suspension of Example 15 (150 mg, 0.4 mmol) in toluene (3 mL) was added thionyl chloride (0.03 mL, 0.41 mmol, 1.0 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the resulting solid in toluene (3 mL) was added triethylamine (0.14 mL, 0.8 mmol, 2 equiv.) and 2-dimethylaminoethylamine (0.04 mL, 0.32 mmol, 0.8 equiv.). After stirring overnight, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1 N aqueous solution of hydrochloric acid. The aqueous layer was basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 100 mg (56% yield) of the title compound as white solid. mp = 234°C

1H NMR [(CD₃)₂SO] δ 8.54 (br s, 1H, NH), 8.44 (t, J = 5.5 Hz, 1H), 7.91 (d, J = 8.5 Hz, 2H), 7.79 (d, J= 8.5 Hz, 2H), 7.69 (d, J = 1.5 Hz, 1H), 7.63 (d, J = 1.5 Hz, 1H), 7.17 (br s, 1H, NH), 3.37 (q, J = 6.5 Hz, 2H), 2.45 (t, J = 6.5 Hz, 2H), 2.22 (s, 6H), 1.90 - 1.74 (m; 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.32 (m, 1H).

Example 24

8'-Chloro-6'-[3-(3-N-dimethylamino-propylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0128]

X₁=CH, X₂=C-[3-(3-N-dimethylamino-propylcarboxamide)phenyl], X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0129]  To a suspension of Example 16 (100 mg, 0.27 mmol) in toluene (10 mL) was added thionyl chloride (0.1 mL, 1.3 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (10 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 3-dimethylaminopropylamine (0.03 mL, 0.21 mmol, 0.8 equiv.). After stirring for 3 h, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1 N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 30 mg (30% yield) of the title compound as white solid. mp = 208°C

1H NMR [(CD₃)₂SO] δ 8.60 (m, 1H), 8.54 (br s, 1H, NH), 8.03 (br s, 1H, NH), 7.83 (d, J = 7.5 Hz, 2H), 7.78 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 1.5 Hz, 1H), 7.60 (s, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.17 (br s, 1H, NH), 3.29 (m, 2H), 3.27 (t, J = 7.0 Hz, 2H), 2.14 (s, 6H), 1.85- 1.78 (m; 6H), 1.67 (m, 3H), 1.55 (m, 2H), 1.30 (m, 1H).

Example 25

8'-Chloro-6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0130]

X₁=CH, X₂=C-[3-(4-methyl-piperazine-1-carbonyl)-phenyl], X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0131]  To a suspension of Example 16 (100 mg, 0.27 mmol) in toluene (5 mL) was added thionyl chloride (0.03 mL, 0.4 mmol, 1.5 equiv.). The resulting mixture was heated to reflux for 3 hours, then twice concentrated under reduced pressure and taken into toluene. To the resulting solid in toluene (5 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 1-methylpiperazine (0.024 mL, 0.21 mmol, 0.8 equiv.). After stirring overnight, the mixture was diluted with
dichloromethane and washed twice with water. The organic layer was concentrated under reduced pressure, taken into ethyl acetate and washed with 1 N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 60 mg (61% yield) of the title compound as white solid. mp = 207°C

$^1$H NMR [(CD$_3$)$_2$SO] δ 8.52 (br s, 1H, NH), 7.76 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.65 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.16 (br s, 1H, NH), 3.64 (br m, 4H), 2.32 (br m, 4H), 2.20 (s, 3H), 1.89 - 1.77 (m, 6H), 1.64 (m, 1H), 1.53 (m, 2H), 1.32 (m, 1H).

Example 26

8'-Chloro-6'-(3-[2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one

$[0132]$ $X_1=$CH, $X_2=$C-[3-[2-N-dimethylamino-ethylcarboxamide)phenyl], $X_3=$CH, $X_4=$C-Cl, A=cyclohexyl, $X=$NH, $Z=O$, $Y=NH$

$[0133]$ To a suspension of Example 16 (100 mg, 0.27 mmol) in toluene (10 mL) was added thionyl chloride (0.1 mL, 1.3 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (10 mL) was added triethylamine (0.1 mL, 0.54 mmol, 2 equiv.) and 2-(1-piperazinyl)pyrimidine (0.024 mL, 0.21 mmol, 0.8 equiv.). After stirring for 3 h, the mixture was concentrated, diluted with dichloromethane and washed twice with water and a 1 N aqueous solution of hydrochloric acid. The aqueous layer was washed with ethyl acetate, basified to pH 9 and extracted twice with dichloromethane. The combined organic extracts were concentrated under reduced pressure to give 40 mg (40% yield) of the title compound as white solid. mp = 225°C

$^1$H NMR [(CD$_3$)$_2$SO] δ 8.55 (br s, 1H, NH), 8.51 (t, J= 5.5 Hz, 1H), 8.05 (br s, 1H, NH), 7.84 (d, J = 7.5 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.18 (br s, 1H, NH), 3.39 (q, J = 6.5 Hz, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.19 (s, 6H), 1.89 - 1.78 (m, 6H), 1.65 (m, 1H), 1.54 (m, 2H), 1.31 (m, 1H).

Example 27

8'-Chloro-2'-cyanoiminospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]

$[0134]$ $X_1=$CH, $X_2=$CH, $X_3=$CH, $X_4=$C-Cl, A=cyclohexyl, $X=$NH, $Z_1=$NH-CN, $Y=N$

$[0135]$ 2',8'-Dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline] (2 mmol) and cyanamide (3 g) were heated to 60°C overnight. The mixture was cooled to room temperature and water was added. The aqueous solution was extracted with CH$_2$Cl$_2$. The organic extracts were washed with saturated aqueous NaCl, dried over Na$_2$SO$_4$, filtered and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/ EtOAc : 90/10) to afford the title compound as a white solid (260 mg, 23%). mp = 193-195°C

$^1$H NMR [(CD$_3$)$_2$SO] δ 9.45 (br s, 1H, NH), 8.05 (br s, 1H, NH), 7.42 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 1.81-1.57 (m, 9H), 1.28 (m, 1H).

Example 28

8'-Chloro-6'-(4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one

$[0136]$ $x_1=$ CH, $x_2=$ C-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl], $x_3=$ CH, $x_4=$ C-Cl, A= cyclohexyl, $X_5= NH$, $Z= O$, $Y= NH$

$[0137]$ To a suspension of Example 15 (185 mg, 0.5 mmol) in toluene (10 mL) was added thionyl chloride (0.19 mL, 1.9 mmol, 5 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (4 mL) was added triethylamine (0.15 mL, 1 mmol, 2 equiv.) and 2-(1-piperazinyl)pyrimidine
(100 mg, 0.6 mmol, 1.2 equiv.). After heating to 80°C for 1 h, the mixture was diluted with dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the resulting solid was purified by flash chromatography on silica gel (CH₂Cl₂/MeOH : 97/3) to give 210 mg (81% yield) of the title compound as white solid. mp = 271°C

1H NMR [(CD₃)₂SO] δ 8.30 (br s, 1H, NH), 8.15 (d, J = 4.5 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.44 (t, J = 4.5 Hz, 1H), 6.43 (t, J = 4.5 Hz, 1H), 3.57-3.27 (m, 8H), 1.69 - 1.54 (m, 6H), 1.41 (m, 1H), 1.30 (m, 2H), 1.07 (m, 1H).

Example 29

8'-Chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0138] X₁ = CH, X₂ = C-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl], X₃ = CH, X₄ = C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

[0139] To a suspension of Example 15 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 2 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 1-[2-(morpholin-4-yl)-ethyl]-piperazine (64 mg, 0.3 mmol, 0.8 equiv.). After stirring for 2 h, the mixture was diluted with dichloromethane, washed with water and washed with a 1 M aqueous solution of sodium hydroxyde. The organic layer was dried over sodium sulfate, concentrated under reduced pressure and the resulting solid was triturated with ethyl acetate/methanol to give 106 mg (50% yield) of the title compound as white solid. mp = 264°C

1H NMR [(CD₃)₂SO] δ 8.53 (br s, 1H, NH), 7.75 (m, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.43 (m, 2H), 7.17 (br s, 1H, NH), 3.53 (m, 8H), 2.50-2.36 (m, 12H), 1.84 - 1.78 (m, 6H), 1.63 (m, 1H), 1.56 (m, 2H), 1.29 (m, 1H).

Example 30

8'-Chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0140] X₁ = CH, X₂ = C-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl], X₃ = CH, X₄ = C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH

[0141] To a suspension of Example 15 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 4-[2-(piperazin-1-yl)-acetyl]-morpholine (130 mg, 0.6 mmol, 1.5 equiv.). After stirring overnight, the mixture was diluted with dichloromethane, washed with water and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, concentrated under reduced pressure and the resulting solid was triturated with ethyl acetate/methanol to give 0.1 g (45% yield) of the title compound as white solid. mp = 239°C

1H NMR [(CD₃)₂SO] δ 8.53 (br s, 1H, NH), 7.74 (d, J = 8.0 Hz, 2H), 7.66 (s, 1H), 7.60 (s, 1H), 7.44 (d, J = 8.0 Hz, 2H), 7.17 (br s, 1H, NH), 3.58-3.22 (m, 14H), 2.50 (m, 4H), 1.88 - 1.79 (m, 6H), 1.64 (m, 1H), 1.55 (m, 2H), 1.30 (m, 1H).

Example 31

8'-Chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0142] X₁ = CH, X₂ = C-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl], X₃ = CH, X₄ = C-Cl, A= cyclohexyl, X= NH, Z= O, Y= NH
To a suspension of Example 15 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure. To the resulting solid in toluene (2 mL) was added triethylamine (0.11 mL, 0.8 mmol, 2 equiv.) and 1-hydroxyethylethoxy-piperazine (77 mg, 0.4 mmol, 1.1 equiv.). After stirring for 2 h, the mixture was diluted with dichloromethane and washed with water and washed with a 1 M aqueous solution of sodium hydroxyde. The organic layer was dried over sodium sulfate, concentrated under reduced pressure to give 0.06 g (29% yield) of the title compound as white solid. mp = 100°C.

**Example 32**

**8'-chloro-5'-'methoxyspiro[cyclohexane-1'-4'-(3',4'-dihydro)Quinaxolin1-2'(1'H)-one**

**Formula (I):**

\[X_1 = \text{C-} \text{OCH}_3, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\]

**Preparation of (2-Chloro-5-methoxy-phenyl)-urea (intermediate 1)**

A solution of 2-chloro-5-methoxyaniline (5 g, 25.76 mmol) and potassium cyanate (5.22 g, 64.41 mmol) in a mixture of acetic acid (125 mL) and water (12.5 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue taken into a mixture of CH$_2$Cl$_2$ and an aqueous saturated solution of NaHCO$_3$. The layers were separated, the aqueous one being extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The crude material was purified by flash chromatography on silica gel (cyclohexane/ EtOAc/ MeOH: 80/20/2) to give 2.06 g (40%) of intermediate 1.

**1H NMR [(CD$_3$)$_2$SO] \[\delta 7.97 \text{ (br s, 1H, NH)}, 7.85 \text{ (d, J = 3.0 Hz, 1H)}, 7.27 \text{ (d, J = 9.0 Hz, 1H)}, 6.54 \text{ (dd, J = 9.0, 3.0 Hz, 1H)}, 6.4 \text{ (br s, 2H)}, 3.71 \text{ (s, 3H)}.**

**Preparation of Example 32**

Example 32 was prepared according to protocol A using intermediate 1 (1g, 4.98 mmol), polyphosphoric acid (15 g) and cyclohexanone (0.88 mL, 7.47 mmol). After completion, ice was added, the precipitate was filtered and washed with cold water. The residue was recrystallized in ethanol to afford the title compound as a white powder (0.6 g, 78% yield) (purity 99.54%) mp = 228.5-230.5°C.

**1H NMR [(CD$_3$)$_2$SO] \[\delta 7.93 \text{ (br s, 1H, NH)}, 7.27 \text{ (d, J = 8.9 Hz, 1H)}, 7.00 \text{ (br s, 1H, NH)}, 6.65 \text{ (d, J = 8.9 Hz, 1H)}, 3.79 \text{ (s, 3H)}, 2.45-2.38 \text{ (m, 2H)}, 1.84-1.74 \text{ (m, 2H)}, 1.63-1.56 \text{ (m, 3H)}, 1.46 \text{ (m, 2H)}, 1.23-1.13 \text{ (m, 1H)}.**

**Example 33**

5',8'-Difluorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

**Formula (I):**

\[X_1 = \text{C-F}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-F}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\]

**Preparation of 2,5-difluorophenyl urea (intermediate 2)**

To a solution of 2,5-difluorophenyl isocyanate (1 g, 6.45 mmol) in tetrahydrofuran (50 mL) at 0°C was added a 28% aqueous solution of ammonia (30 mL). The mixture was stirred for 1h allowing the temperature to warm up to room temperature, then concentrated under reduced pressure, taken into water and filtered. The solid was washed twice with water and with ether then dried at 65°C under reduced pressure to give 740 mg (67%) of intermediate 2.

**1H NMR [(CD$_3$)$_2$SO] \[\delta 8.53 \text{ (br s, 1H, NH)}, 8.02 \text{ (m, 1H)}, 7.21 \text{ (m, 1H)}, 6.72 \text{ (m, 1H)}, 6.29 \text{ (br s, 2H, NH$_2$)}.**
Preparation of Example 33

The title compound was prepared according to protocol A using intermediate 2 (740 mg, 4.3 mmol), polyphosphoric acid (20 g) and cyclohexanone (0.70 mL, 6.75 mmol). The crude product was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 100/0 to 95/5) followed by recrystallization in toluene to give the title compound as a white solid (28 mg, 3% yield) (purity 99%) mp = 194-195°C.

$^1$H NMR [(CD$_3$)$_2$SO] δ 9.26 (br s, 1H, NH), 7.13 (m, 1H), 7.05 (br s, 1H, NH), 6.71 (m, 1H), 2.01 (m, 2H), 1.86-1.75 (m, 4H), 1.64 (m, 1H), 1.49 (m, 2H), 1.18 (m, 1H).

Example 34

8'-Chloro-5'-methylspiro[cyclohexane-1.4'1-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I):

Example 34

Preparation of (2-chloro-5-methyl-phenyl)urea (intermediate 3)

A solution of 2-chloro-5-methylaniline (10 g, 70.6 mmol) and potassium cyanate (14.3 g, 176 mmol) in a mixture of acetic acid (340 mL) and water (34 mL) was stirred at room temperature during 4 hours. The solvent was evaporated and the residue taken into a mixture of CH$_2$Cl$_2$ and an aqueous saturated solution of NaHCO$_3$. The precipitate was filtered, washed with dichloromethane and dried under vacuum to give 12.6 g (97%) of intermediate 3.

$^1$H NMR [(CD$_3$)$_2$SO] δ 8.05 (s, 1H, NH), 7.96 (s, 1H), 7.23 (d, 1H), 6.75 (d, 1H), 6.37 (br s, 2H), 2.24 (s, 3H).

Preparation of Example 34

The title compound was prepared according to protocol A using intermediate 3 (12.6 g, 68.2 mmol), polyphosphoric acid (150 g) and cyclohexanone (8.5 mL, 81.9 mmol). After completion, the mixture was poured into ice and water and stirred 45 minutes. The precipitate was filtered and washed with cold water, with diethyl ether and dried under vacuum to give 3.1 g of the title product. The residue was recrystallized in ethanol to afford the title compound as a white powder (0.06 g, 17% yield) (purity with HPLC: 99.9%).

$^1$H NMR [(CD$_3$)$_2$SO] δ 8.02 (s, 1H, NH), 7.20 (d, J = 8.04 Hz, 1H), 6.89 (br s, 1H, NH), 6.57 (d, J = 8.03 Hz, 1H), 2.47 (s, 3H), 2.02-2.18 (m, 2H), 1.70-1.90 (m, 4H), 1.62-1.80 (m, 1H), 1.14-1.60 (m, 2H), 1.20-1.35 (m, 1H).

Example 35

8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1.4'1-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I):

Example 35

The title compound was prepared according to protocol D. To a stirred solution of Example 1 (1 g, 4 mmol) in glacial acetic acid (15 mL) was sequentially added trioxane (0.55 g, 6 mmol, 1.5 equiv.) and a 48% aqueous solution of hydrobromic acid (5 mL). The mixture was heated to 95°C overnight, poured on ice. The precipitate was filtered, washed twice with water then with ether to give 1.39 g of 8'-Chloro-6'-bromomethylspiro[cyclohexane-1.4'1-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid. The crude bromomethyl derivative (150 mg, 0.43 mmol) was treated with morpholine (0.100 mL, 1.1 mmol, 2.6 equiv.) in DMF (3 mL) overnight. The mixture was concentrated under reduced pressure, taken into ethyl acetate, extracted with 1N aqueous HCl. The aqueous layer was washed twice with ether, basified to pH 9 and extracted three times with ethyl acetate. The combined organic layers were washed three times with water and brine and concentrated under reduced pressure. The crude material was purified by recrystallization in toluene to give the title compound (102 mg, 68%) (purity 97%) as a white solid. mp = 223°C.

$^1$H NMR [(CD$_3$)$_2$SO] δ 8.33 (br s, 1H, NH), 7.21 (s, 1H), 7.18 (s, 1H), 7.08 (br s, 1H, NH), 3.56 (m, 4H), 3.39 (s, 2H), 2.32 (m, 2H), 1.84-1.49 (m, 9H), 1.25 (m, 1H).
Example 36

8'-Chloro-5'-hydroxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): \( X_1 = \text{C-OH}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

The title compound was prepared according to protocol H. To a stirred solution of Example 32 (0.83 g, 2.95 mmol) in CH\(_2\)Cl\(_2\) (100 mL) boron tribromide (1 N in CH\(_2\)Cl\(_2\), 21.8 mL, 21.8 mmol) was added at 0°C. The mixture was stirred at room temperature for 48 h, poured into a saturated aqueous solution of NaHCO\(_3\) and extracted with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtered and concentrated. The crude material was purified by precipitation in Et\(_2\)O to afford the title compound as a white solid (0.25 g, 32%). (purity 97.6%) mp = 252-254°C.

\( ^1\)H NMR [(CD\(_3\))\(_2\)SO] \( \delta \) 9.90 (br s, 1H), 7.75 (br s, 1H), 7.08 (d, \( J = 8.7 \) Hz, 1H), 6.97 (br s, 1H, NH), 6.43 (d, \( J = 8.7 \) Hz, 1H), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.24-1.07 (m, 1H).

Example 37

8'-Chloro-5'-hydroxy-6'-iodo-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): \( X_1 = \text{C-OH}, X_2 = \text{C-I}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

To a stirred suspension of Example 36 (10 g, 37.5 mmol) in trifluoroacetic acid (150 mL) at 0 to 5°C was added N-iodosuccinimide (9.47 g, 41.2 mmol) in portions over 10 minutes. The reaction mixture was stirred at 0 to 5°C for 2 hours. The mixture was poured onto a mixture of water (700 mL) and ice (300 mL). The resulting brown solid was filtered and washed with water (250 mL) followed by heptane (4 x 40mL). The solid was pulled dry on the filter bed for 2 hours and then slurried in a mixture of dichloromethane (30 mL) and methanol (5 mL). The dark pink precipitate was filtered and washed with dichloromethane (3 x 20mL) to afford the titled compound (12.2 g, 31.0 mmol, 83%).

\( ^1\)H NMR [(CD\(_3\))\(_2\)SO] \( \delta \) 9.10 (s, 1H), 8.25 (s, 1H), 7.81 (s, 1H), 7.18 (s, 1H), 2.70 (m, 2H), 1.95 (m, 2H), 1.75 (m, 3H), 1.60 (m, 2H), 1.28 (m, 1H).

Example 38

8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): \( X_1 = \text{C-OCH}_3, X_2 = \text{C-I}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

To a stirred suspension of Example 37 (16.27 g, 41.4 mmol) in DMF (325 mL) was added DBU (7.5 mL, 50.1 mmol) followed by methyl iodide (6.8 mL, 109 mmol) at 20 to 25 °C. The reaction mixture was stirred for 3 hours. The mixture was poured into water (1625 mL) and the resulting solid was filtered and washed with water (500 mL) followed by heptane (2 x 150 mL). The solid was stirred in ethyl acetate containing 10% methanol (100 mL) for 10 minutes. The precipitate was filtered and washed with EtOAc (25 mL), TBME (10 mL) and dried \( \textit{in vacuo} \) at 50°C to afford the titled compound as a fawn solid (14.4 g, 35.5 mmol, 86%).

\( ^1\)H NMR [(CDCl\(_3\))] \( \delta \) 7.67 (s, 1H), 7.18 (s, 1H), 5.68 (s, 1H), 3.83 (s, 3H), 2.23 (td, \( J = 13.6, 4.5, 2H \)), 1.90 (m, 2H), 1.70 (m, 3H), 1.51 (m, 2H), 1.25 (m, 1H).

Example 39

8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

Formula (I): \( X_1 = \text{C-CH}_3, X_2 = \text{C-CN}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

To a stirred suspension of Example 37 (16.27 g, 41.4 mmol) in DMF (325 mL) was added DBU (7.5 mL, 50.1 mmol) followed by methyl iodide (6.8 mL, 109 mmol) at 20 to 25 °C. The reaction mixture was stirred for 3 hours. The mixture was poured into water (1625 mL) and the resulting solid was filtered and washed with water (500 mL) followed by heptane (2 x 150 mL). The solid was stirred in ethyl acetate containing 10% methanol (100 mL) for 10 minutes. The precipitate was filtered and washed with EtOAc (25 mL), TBME (10 mL) and dried \( \textit{in vacuo} \) at 50°C to afford the titled compound as a fawn solid (14.4 g, 35.5 mmol, 86%).

\( ^1\)H NMR [(CDCl\(_3\))] \( \delta \) 7.67 (s, 1H), 7.18 (s, 1H), 5.68 (s, 1H), 3.83 (s, 3H), 2.23 (td, \( J = 13.6, 4.5, 2H \)), 1.90 (m, 2H), 1.70 (m, 3H), 1.51 (m, 2H), 1.25 (m, 1H).
EP 1 373 224 B1

Formula (I): $X_1 = \text{C-}O\text{CH}_3$, $X_2 = \text{C-CN}$, $X_3 = \text{CH}$, $X_4 = \text{C-Cl}$, $A = \text{cyclohexyl}$, $X = \text{NH}$, $Z = \text{O}$, $Y = \text{NH}$

[0162] To a stirred solution of Example 38 (3g, 7.38mmol) in NMP (60mL) at 18 to 20°C was added copper (I) cyanide (555mg, 6.2mmol). The mixture was heated to 150°C for 4 days, quenched into ice/water (300mL) and the crude product filtered off. The crude product was dissolved in EtOAc (2x 200mL) and washed with 33% NH$_3$(aq) solution (2x 200mL). The organic layer was further washed with brine (2x 100mL) and water (2x 100mL) and dried over MgSO$_4$, filtered and concentrated in vacuo at 40°C to give the crude product (1.2g, 3.92mmol). The crude product (650mg, 2.12mmol) was purified by preparative HPLC to yield the title compound as a pale yellow solid (97mg, 3.27mmol, 4%) (purity 96%).

**Example 40**

8'-Chloro-5'-[2-(4-morpholino)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0163]

Formula (I): $X_1 = \text{C-}O\text{CH}_2\text{CH}_2-(4'-\text{morpholinyl})$, $X_2 = \text{CH}$, $X_3 = \text{CH}$, $X_4 = \text{C-Cl}$, $A = \text{cyclohexyl}$, $X = \text{NH}$, $Z = \text{O}$, $Y = \text{NH}$

[0164] The title compound was prepared according to protocol H. To a stirred solution of Example 36 (1 g, 3.93 mmol) in DMF (30 mL) under nitrogen at 18 to 20°C was added 60% sodium hydride dispersion (0.16 g, 3.93 mmol). The mixture was stirred for 15 minutes before 4-(2-chloroethyl)morpholine (0.59 g, 3.93 mmol) was added. The mixture was then heated to 100°C for 1.5 hours. After cooling to room temperature the reaction mixture was added to water (300 mL). The resulting solid was filtered and washed with water (50 mL). The crude solid was dried in vacuo at 45°C and subsequent purification by column chromatography (silica 60 g, eluting with 5% methanol in dichloromethane) afforded the title compound (0.48 g, 1.23 mmol, 32%) as a cream solid after drying in vacuo at 50°C. (purity 96.9%)

**Example 41**

8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0165]

Formula (I): $X_1 = \text{C-}O\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, $X_2 = \text{CH}$, $X_3 = \text{CH}$, $X_4 = \text{C-Cl}$, $A = \text{cyclohexyl}$, $X = \text{NH}$, $Z = \text{O}$, $Y = \text{NH}$

[0166] To a stirred solution of Example 36 (6g, 22.5mmol) in DMF (20mL) at 18 to 20°C was added a solution of potassium carbonate (2M, 9.42mL, 18.84mmol) followed by 2-dimethyl-aminoethyl chloride hydrochloride (2M, 37.7mL, 75.4mmol). The mixture was heated to 100°C for 18 hours and allowed to cool to 18 to 20°C. The reaction mixture was added to water (1.5L) and extracted with EtOAc (2x1L). The combined organic layer was washed with brine (1L) and separated. The combined organic fractions were dried over MgSO$_4$, filtered and concentrated in vacuo at 40°C to give the crude material (4.7g, 13.9mmol). The crude product was purified by TBME wash (60mL) and charcoal (5g) treatment in DCM (200mL) and column chromatography (silica; gradient elution, 100% DCM to 50% in DCM:EtOAc:DCM:MeOH; 2:10:1) to yield the title compound as a pale yellow solid (2.34g, 6.93mmol, 31 %) (purity 99%)

**Example 42**

8'-Chloro-5'-[2-aminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0167]
Preparation of 8'-Chloro-5'-[2-methanesulphonylethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 4)

[0168] To a stirred solution of Example 51 (5 g, 1.61 mmol) and triethylamine (1.95 g, 1.93 mmol) in dichloromethane (200 mL) at 0 to 5°C was added a solution of methanesulphonyl chloride (2.21 g, 1.93 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at 20 to 25°C for 5 hours. The mixture was washed with water (2 x 100 mL) and the organic phase was dried over magnesium sulphate. Filtration and concentration in vacuo afforded intermediate 4 as an off-white solid (5.4 g, 1.39 mmol, 86%).

1H NMR [CDCl3] δ 7.13 (d, J = 9.1 Hz, 1H), 6.99 (s, 1H), 6.38 (d, J = 9.1 Hz, 1H), 5.60 (s, 1H), 4.53 (m, 2H), 4.20 (m, 2H), 3.00 (s, 3H), 2.47 (td, J = 13.6, 4.5 Hz, 2H), 1.59-1.78 (m, 5H), 1.48 (m, 2H), 1.28 (m, 1H).

Preparation of Example 42

[0169] Intermediate 4 (1.0 g, 2.57 mmol) was stirred with a solution of ammonia in ethanol (40 mL) at 70°C in a sealed pressure vessel for 21 hours. The ethanol was removed by evaporation in vacuo at 40°C to leave a fawn coloured solid residue (0.81 g). 2N-Hydrochloric acid (40 mL) was added (no dissolution occurred), the acidic aqueous suspension was treated with 2N-sodium hydroxide to pH 12. The aqueous mixture was extracted twice with ethyl acetate containing 10 % methanol (45 mL and 80 mL). The combined ethyl acetate was washed once with water (50 mL), dried over magnesium sulphate, filtered and concentrated in vacuo at 40°C to give a pink solid residue. The crude amine was purified by column chromatography (silica 20 g, eluting with 4% triethylamine and 16% methanol in ethyl acetate) to yield the title compound (0.23 g, 0.71 mmol, 69%) as an off-white solid after drying in vacuo at 50°C (purity 99%).

1H NMR (d6 DMSO) δ 1.21 (m, 1H), 1.54 (m, 2H), 1.68 (m, 3H), 1.85 (m, 2H), 2.41 (s, 3H), 2.58 (m, 2H), 2.95 (t, J = 5.7Hz, 2H), 4.08 (t, J = 5.7Hz, 2H), 6.70 (t, J = 8.9Hz, 1H), 7.12 (s, 1H), 7.31 (d, J = 8.9Hz, 1H), 8.02 (s, 1H).

Example 43

8'-Chloro-5'-[2-(methylamino)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0170] Formula (I): X1=C-OCH2CH2NHCH3, X2=CH, X3=CH, X4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0171] Intermediates 4 (0.4 g, 1.03 mmol) was stirred with a solution of methylvamine in ethanol (27 mL) at 70°C for 7 hours. The ethanol was removed by evaporation in vacuo at 40°C and the residue was partitioned between water (25 mL) and ethyl acetate (50 mL), adding 2M-sodium hydroxide to pH 12. The ethyl acetate was washed once with water (15 mL), dried over magnesium sulphate and concentrated in vacuo at 40°C to give a pink solid residue. The crude amine was purified by column chromatography (silica 20 g, eluting with 4% triethylamine and 16% methanol in ethyl acetate) to yield the title compound (0.23 g, 0.71 mmol, 69%) as an off-white solid after drying in vacuo at 50°C (purity 99%).

1H NMR (d6 DMSO) δ 1.21 (m, 1H), 1.54 (m, 2H), 1.68 (m, 3H), 1.85 (m, 2H), 2.41 (s, 3H), 2.58 (m, 2H), 2.95 (t, J = 5.7Hz, 2H), 4.08 (t, J = 5.7Hz, 2H), 6.70 (t, J = 8.9Hz, 1H), 7.12 (s, 1H), 7.31 (d, J = 8.9Hz, 1H), 8.02 (s, 1H).

Example 44

8'-Chloro-5'-[2-(2-aminoethoxy)ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0172] Formula (I): X1=C-OCH2CH2OCH2CH2NH2, X2=CH, X3=CH, X4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0173] To a stirred solution of Example 36 (1.07 g, 4.0 mmol) in DMF (20 mL) at room temperature was added potassium
carbonate (1.22 g, 8.8 mmol) and 2-[2-(2-chloroethoxy)ethyl]-1H-isooindole-1,3(2H)-dione (1.22 g, 4.8 mmol). The mixture was heated at 100°C for 8 hours. More potassium carbonate (1.22 g) and 2-[2-(2-chloroethoxy)ethyl]-1H-isooindole-1,3(2H)-dione (1.22 g) were added and the stirred mixture was heated at 100°C for a further 9 hours. After cooling to 18 to 20°C the reaction mixture was added to water (200 mL). The resulting solid was filtered and washed with water (50 mL). The solid was purified by column chromatography (silica 50 g, eluting with 5% methanol in dichloromethane) to yield the phthalimide intermediate (1.0 g, 2.06 mmol, 52%) as a pink glassy solid.

To a stirred suspension of the phthalimide intermediate (0.9 g, 1.86 mmol) in ethanol (23 mL) was added hydrazine hydrate (0.28 mL, 5.64 mmol). The mixture was heated at 60°C for 4 hours. 2M-Hydrochloric acid (36 mL) was added and the reaction was heated at reflux for 1.25 hours. Cooling to 18 to 20°C afforded a solid that was isolated by filtration and washed with water (10 mL). The pH of the filtrate was adjusted to 14 by the addition of 2M-sodium hydroxide (2 mL), the crude amine precipitated and was filtered and washed with water (10 mL) and TBME (10 mL). The amine was purified by column chromatography (silica 20 g, eluting with 4% triethylamine and 16% methanol in ethyl acetate) to yield the title compound (0.43 g, 1.21 mmol, 65%) as a white solid after drying in vacuo at 50°C. (purity 98%)

1H NMR (360 MHz, d6-DMSO) δ 1.40 (m, 1H), 1.65 (m, 2H), 1.75 (m, 3H), 2.00 (m, 2H), 2.77 (m, 2H), 3.65 (t, J = 5.9Hz, 2H), 3.95 (m, 2H), 4.29 (m, 2H); 6.81 (d, J = 9.0Hz, 1H), 7.16 (s, 1H), 7.35 (d, J = 9.1Hz, 1H), 8.13 (s, 1H).

Example 45

8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0174]

Formula (I):  X1=C-OCH2CH2CH2N(CH3)2, X2=CH, X3=CH, X4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0175] To a stirred solution of Example 36 (1.5g, 5.63mmol) in DMF (20mL) at 18 to 20°C was added a solution of potassium carbonate (2M, 9.42mL, 18.84mmol) followed by 3-dimethylaminopropyl chloride hydrochloride (1.02g, 6.45mmol). The mixture was heated to 100°C for 18 h. It was then added to water (400mL) and extracted with EtOAc (2x400mL). The combined organic layer was then washed with water (300mL) and separated. Dried with MgSO4, concentrated in vacuo at 40°C to give crude material (1.27g, 3.61mmol). The crude product was purified by charcoal (1g) treatment in DCM (120mL) and column chromatography (silica; gradient elution, 100% EtOAc to 50% in DCM to EtOAc:DCM:MeOH; 2:10:1) to yield the desired product as an off-white solid (305mg, 0.87mmol, 15%) (purity 99%)

1H NMR (360 MHz, d6-DMSO) δ 1.40-1.53 (m, 1H), 1.65-1.78 (m, 2H), 1.85-2.0 (m, 5H), 2.2 (m, J = 7.3, 6.3Hz, 2H), 2.45 (s, 6H), 2.67 (t, J = 7.3Hz, 2H), 2.75 (ddd, J = 4.6, 13.6 & 13.6Hz, 2H), 4.22 (t, J = 6.3Hz, 2H), 5.71-5.75 (br s, 1H), 6.68 (d, J = 9.1Hz, 1H), 7.16-7.20 (brs, 1H), 7.35 (d, J = 9.1Hz, 1H).

Example 46

8'-Chloro-5'-ethoxycarbonylmethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0176]

Formula (I):  X1=C-OCH2CO2CH2CH3, X2=CH, X3=CH, X4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

[0177] The title compound was prepared according to protocol H. To a stirred solution of Example 63 (0.5 g, 1.96 mmol) in DMF (10 mL) at 18 to 20°C was added potassium carbonate (0.6 g, 4.31 mmol) and ethyl bromoacetate (0.36 g, 2.16 mmol). The mixture was heated at 100°C for 1.5 hours, cooled to room temperature and then added to water (100 mL). The resulting solid was filtered and washed with water (50 mL) and heptane (20 mL). Drying in vacuo at 50°C afforded the title compound (0.6 g, 1.7 mmol, 87%) as an off-white solid.

1H NMR (360 MHz, CDCl3) δ 7.2 (d, J = 9.1 Hz, 1H), 7.03 (s, 1H), 6.37 (d, J = 9.1 Hz, 1H), 5.60 (s, 1H), 4.64 (s, 2H), 4.30 (q, J = 7.3 Hz, 2H), 2.70 (td, J = 13.2, 4.1 Hz, 2H), 1.80 (m, 4H), 1.55 (m, 3H), 1.45 (m, 1H), 1.35 (t, J = 7.3 Hz, 3H).
Example 47

5'-Carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0178]

Formula (I): \( X_1 = \text{C-OCH}_2\text{CO}_2\text{H}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y=\text{NH} \)

[0179] A solution of potassium hydroxide (0.32 g, 5.65 mmol) in water (1.1 mL) was added to a stirred suspension of the crude Example 46 (0.4 g, 1.13 mmol) in THF (30 mL) at room temperature. The mixture was stirred for 24 hours before the THF was removed by evaporation in vacuo at 40°C. Water (20 mL) was added to the residue and the mixture was washed once with ethyl acetate (10 mL). The aqueous solution was acidified to pH 1 with concentrated hydrochloric acid to afford an off-white solid. The solid was filtered and washed with water (10 mL) and heptane (5 mL). The solid was purified by column chromatography (silica 10 g, eluting with 10% acetic acid in ethyl acetate) to yield the title (0.15 g, 0.46 mmol, 41%) as an off-white solid after drying in vacuo at 50°C. (purity 98.9%) mp = 284-286°C.

1H NMR [(CD3)2SO] \( \delta \) 13.05 (br s, 1H), 7.95 (br s, 1H), 7.24 (d, \( J = 9.0 \) Hz, 1H), 6.99 (br s, 1H, NH), 6.54 (d, \( J = 9.0 \) Hz, 1H), 4.69 (s, 2H), 2.61 (m, 2H), 1.77 (m, 2H), 1.55 (m, 3H), 1.45 (m, 2H), 1.30 (m, 1H).

Example 48

5'-Carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0180] Formular (I): \( X_1 = \text{C-OCH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

[0181] To a stirred solution of Example 36 (1.07 g, 4 mmol) in DMF (20 mL) at 18 to 20°C was added potassium carbonate (1.22 g, 8.8 mmol) and ethyl 4-bromobutyrate (0.82 g, 4.2 mmol). The mixture was heated at 100°C for 2 hours, cooled to room temperature and added to water (200 mL). The mixture was extracted with ethyl acetate (2 x 200 mL). The combined extracts were washed with water (100 mL), dried over magnesium sulfate and evaporated in vacuo at 50°C to afford a solid residue. Trituration of the residue with heptane (10 mL) afforded the intermediate ethyl ester (1.27 g, 3.33 mmol, 84%) as a pink solid after drying in vacuo at 50°C.

1H NMR (360 MHz, CDCl3) \( \delta \) 1.11 (t + m, 4H), 1.38 (m, 2H), 1.58 (m, 5H), 2.01 (m, 2H), 2.38 (m, 4H), 3.87 (t, \( J = 5.7 \)Hz, 2H), 4.01 (q, \( J = 6.3 \)Hz, 2H), 5.46 (s, 1H), 6.32 (d, \( J = 8.1 \) Hz, 1H), 6.87 (s, 1H), 7.02 (d, \( J = 8.1 \) Hz, 1H).

6N-Hydrochloric acid (10 mL) was added to a stirred suspension of the ethyl ester (0.9 g, 2.36 mmol) in dioxane (6 mL) at 18 to 20°C. The mixture was stirred under reflux for 2.5 hours. After cooling to 18 to 20°C the solid was filtered and washed with water (50 mL) and TBME (5 mL). The solid was triturated with TBME (30 mL) to afford the title compound (0.64 g, 1.79 mmol, 76%) as an off-white solid after drying in vacuo at 50°C. (purity 98%).

1H NMR (360 MHz, d6 DMSO) \( \delta \) 1.03 (m, 1H), 1.34 (m, 2H), 1.47 (m, 3H), 1.68 (m, 2H), 1.80 (m, 2H), 2.30 (m, 4H), 3.87 (t, \( J = 6.3 \)Hz, 2H), 6.40 (d, \( J = 9.0 \) Hz, 1H), 6.90 (s, 1H), 7.11 (d, \( J = 9.0 \) Hz, 1H), 7.80 (s, 1H), 12.05 (br s, 1H).

Example 49

8'-Chloro-5'-[3-sulphopropoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0182] Formular (I): \( X_1 = \text{C-OCH}_2\text{CH}_2\text{CH}_2\text{SO}_3\text{H}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH} \)

[0183] The title compound was prepared according to protocol H. To a stirred solution of Example 63 (1 g, 3.93 mmol) in DMF (20 mL) at 18 to 20°C was added potassium carbonate (1.19 g, 8.65 mmol) followed by sodium 3-bromopropanesulphonate (0.97 g, 4.32 mmol). The mixture was heated at 100°C for 6 hours, cooled to room temperature and then added to water (300 mL). The resulting solution was acidified to pH 1 with concentrated hydrochloric acid. The aqueous mixture was washed with ethyl acetate (200 mL) and evaporated in vacuo to dryness at 70°C. The residue
was treated with TBME (200 mL) and a small amount of white solid was filtered and discarded. Decanting away the TBME from the filtrate isolated a pale yellow insoluble oil. Remaining DMF was removed from the oil by further evaporation in vacuo at 70°C. The resulting gum was triturated with acetonitrile (10 mL) to yield the title compound (0.11 g, 0.28 mmol, 7%) as a white solid after drying in vacuo at 50°C.

\[ \text{Example 50} \]

8'-Chloro-5'-(2-(tetrahydro-pyran-2-yloxy)-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{Formula (I):} \quad X_1 = \text{C-OCH}_2\text{CH}_2\text{O-(tetrahydro-pyran-2-yl)}, \quad X_2 = \text{CH}, \quad X_3 = \text{CH}, \quad X_4 = \text{C-Cl}, \quad A = \text{cyclohexyl}, \quad X = \text{NH}, \quad Z = \text{O}, \quad Y = \text{NH} \]

\[ \text{Example 51} \]

8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{Example 52} \]

8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{Example 53} \]

8'-Chloro-5'-(2-bromoethoxy)-tetrahydro-2H-pyran (0.45 g, 2.16 mmol). The mixture was heated at 100°C for 3.2 hours, cooled to room temperature and then added to water (100 mL). The resulting solid was filtered and washed with water (50 mL) followed by heptane (20 mL). Drying in vacuo at 50°C afforded the title compound (0.69 g, 1.75 mmol, 90%) as an off-white solid.

\[ \text{Example 54} \]

8'-Chloro-5'-(2-hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{Example 55} \]

8'-Chloro-5'-(5-ethoxycarbonyl-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

\[ \text{Example 56} \]

8'-Chloro-5'-(6-ethoxycarbonyl-furanyl)methoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one
0.95 mmol) and 5-Chloromethyl-furan-2-carboxylic acid ethyl ester (0.29 mL, 1.87 mmol). The mixture was stirred at room temperature for 2 h. After completion, the solvent was removed under reduced pressure and a mixture of water and EtOAc was added. The layer were separated, the aqueous one being extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The solid was purified by column chromatography (silica 10 g, eluting with CH₂Cl₂/MeOH: 99/1 to 98/2) to yield the title compound (0.75 g, 96%) as a white solid after drying in vacuo at 50°C.

1H NMR [(CD₃)₂SO] δ 7.98 (br s, 1H, NH), 7.30-7.28 (m, 2H), 7.01 (br s, 1H, NH), 6.80-6.76 (m, 2H), 5.2 (s, 2H), 4.28 (q, J = 7.0 Hz, 2H), 2.43-2.4 (m, 2H), 1.75-1.72 (m, 2H), 1.56-1.53 (m, 3H), 1.40 (m, 2H), 0.97 (m, 1H).

Example 53

8'-Chloro-5'-(5-carboxy-furan-2-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0190]

Formula (I): X₁=C-OCH₂-(5-carboxy-furan-2-yl), X₂=CH, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

A solution of lithium hydroxide monohydrate (0.85 g, 20 mmol) in water (1.35 mL), EtOH (11 mL) and MeOH (67 mL) was added to a stirred suspension of the crude Example 52 (0.6 g, 1.43 mmol) in CH₂Cl₂ (17 mL) at room temperature. The mixture was stirred for 48 h before the solvents were removed by evaporation in vacuo at 40°C. Water was added to the residue and the mixture was acidified with concentrated aqueous HCl and extracted with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The solid was purified by column chromatography (silica 5 g, eluting with CH₂Cl₂/MeOH: 70/30) to yield the title compound (0.05 g, 9%) as a white solid after drying in vacuo at 50°C. (purity 98%)

1H NMR [(CD₃)₂SO] δ 13.10 (s, 1H), 7.96 (br s, 1H, NH), 7.29 (d, J = 9.1 Hz, 1H), 7.12 (br s, 1H, NH), 6.99 (s, 1H), 6.79 (d, J = 9.1 Hz, 1H), 6.70 (br s, 1H), 5.15 (s, 2H), 2.43-2.40 (m, 2H), 1.70 (m, 2H), 1.55-1.52 (m, 3H), 1.40 (m, 2H), 0.98-1.00 (m, 1H).

Example 54

8'-Chloro-5'-cyanomethoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0192]

Formula (I): X₁=C-OCH₂-CN, X₂=CH, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

The title compound was prepared according to protocol H. To a stirred solution of Example 36 (2 g, 7.85 mmol) in DMF (30 mL) at 18 to 20°C was added potassium carbonate (2.39 g, 17.3 mmol) followed by bromoacetonitrile (1.04 g, 8.64 mmol). The mixture was heated at 100°C for 2 hours, cooled to 18 to 20°C and added to water (300 mL). The resulting solid was filtered and washed with water (60 mL). Drying in vacuo at 50°C afforded crude title compound (2.35 g). The crude product was purified by column chromatography (silica 70 g eluting with 10% methanol in dichloromethane) to yield title compound (1.72 g, 5.6 mmol, 72%) as a fawn solid after drying in vacuo at 50°C. (purity = 97%) mp = 193-195°C.

1H NMR [(CD₃)₂SO] δ 8.12 (br s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 7.07 (br s, 1H, NH), 6.75 (d, J = 9.0 Hz, 1H), 5.24 (s, 2H), 2.34 (m, 2H), 1.80 (m, 2H), 1.63 (m, 3H), 1.47 (m, 2H), 1.20 (m, 1H).

Example 55

8'-Chloro-5'-(1H-tetrazol-5-ylmethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0194]

Formula (I): X₁=C-OCH₂-(1H-tetrazol-5-yl), X₂=CH, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Example 54 (0.05 g, 0.16 mmol), trimethyltin azide (0.05 mL, 0.179 mmol) and toluene (2 mL) were mixed and
refluxed under nitrogen for 15 h. 10M NaOH (0.02 ml, 0.2 mmol) was added and the mixture was stirred at room temperature overnight. The upper layer was removed, hexane was added to the residue, the resulting mixture was stirred for 30 min, hexane was removed. This operation was repeated three times, and EtOAc was added, the precipitate was filtered and washed with EtOAc. The residue was taken into CH₂Cl₂ and 1 M HCl (1 ml, 1 mmol) and concentrated under reduced pressure. The precipitate was washed successively with water and MeOH to give the title compound (0.04 g, 71 %) as a white powder (purity = 98.1%) mp = 287-289°C.

1H NMR [{CD₃}₂SO] δ 8.02 (br s, 1H), 7.34 (d, J = 8.9 Hz, 1H), 7.01 (br s, 1H), 6.82 (d, J = 8.9 Hz, 1H), 5.47 (s, 2H), 2.35 (m, 2H), 1.73 (m, 2H), 1.50 (m, 3H), 1.36 (m, 2H), 0.88 (m, 1H).

Example 56

8'-Chloro-5'-[5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy]-spiro[cyclohexane-1-4'-[3',4'-dihydro) quinazolin]-2'(1'H)-one

[0196]

Formula (I): X₁=C-OCH₂(5-hydroxy-[1,2,4]oxadiazol-3-yl), X₂=CH, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Preparation of 8'-chloro-5'-[N-hydroxycarbamimidoylmethoxy]-spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one (intermediate 5)

[0197]  To a mixture of Example 54 (0.6 g, 1.96 mmol) and hydroxylamine hydrochloride (0.186 g, 2.94 mmol) in ethanol (7 ml) was added sodium hydroxide (0.114 g, 2.85 mmol) dissolved in the minimum of water. The reaction mixture was heated to reflux for 24h with stirring. After cooling, the solvent was concentrated under reduced pressure. The residue was taken into CH₂Cl₂, the precipitate was filtered, washed with CH₂Cl₂ and dried under vacuum at 45°C to afford intermediate 5 in a quantitative yield.

1H NMR [{CD₃}₂SO] δ 9.34 (br s, 1H, OH), 7.94 (br s, 1H, NH), 7.73 (d, J = 9.0 Hz, 1H), 6.98 (br s, 1H, NH), 6.70 (d, J = 9.0 Hz, 1H), 5.61 (s, 2H), 4.40 (br s, 2H, NH₂), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.24-1.07 (m, 1H).

Preparation of Example 56

[0198]  To a mixture of intermediate 5 (0.3 g, 0.885 mmol) and ethyl chloroformate (0.13 mL, 1.3 mmol) in anhydrous CHCl₃ (4 mL) was added triethylamine (0.22 mL, 1.6 mmol). The reaction mixture was stirred at room temperature for 30 min, hexane was removed. This operation was repeated three times, and EtOAc was added, the precipitate was filtered and washed with EtOAc. The residue was taken into CH₂Cl₂ and 1 M HCl (1 mL, 1 mmol) and concentrated under reduced pressure. The precipitate was washed successively with water and MeOH to give the title compound (0.04 g, 71 %) as a white powder (purity = 98.1%) mp = 287-289°C.

1H NMR [{CD₃}₂SO] δ 9.34 (br s, 1H, OH), 7.94 (br s, 1H, NH), 7.73 (d, J = 9.0 Hz, 1H), 6.98 (br s, 1H, NH), 6.70 (d, J = 9.0 Hz, 1H), 5.61 (s, 2H), 4.40 (br s, 2H, NH₂), 2.58-2.54 (m, 2H), 1.83-1.72 (m, 2H), 1.62-1.53 (m, 3H), 1.46 (m, 2H), 1.28-1.20 (m, 1H), 1.23(t, J = 7.7 Hz, 3H).

A mixture [ethoxycarbonyl]oxy]amino intermediate (0.275 g, 0.67 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.4 mL, 2.67 mmol) in CH₃CN (4 mL) was refluxed for 24h with stirring. The reaction mixture was concentrated under reduced pressure and taken into a mixture of CH₂Cl₂ and aqueous 1 M HCl. The layers were separated and the aqueous one being extracted three times with CH₂Cl₂. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to yield the title compound (0.17 g, 70%) as a white solid after drying in vacuo at 50°C.

1H NMR [{CD₃}₂SO] δ 12.86 (brs, 1H), 8.04 (br s, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.03 (br s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 5.07 (s, 2H), 2.42-2.36 (m, 2H), 1.78-1.74 (m, 2H), 1.59-1.56 (m, 3H), 1.44 (m, 2H), 1.11 (m, 1H).

Example 57

8'-chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-[3',4'-dihydro]quinazolin]-2'(1'H)-one

[0199]

Formula (I): X₁=C-OCH₂CH₂N(CH₃)₂, X₂=C-I, X₃=CH, X₄=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH

Z=O, Y=NH
The title compound was prepared according to protocol H. To a stirred solution of Example 41 (1.5 g, 4.44 mmol) in trifluoroacetic acid (15 mL) were subsequently added N-iodosuccinimide (1.1 g, 4.89 mmol, 1.1 equiv.) and sulfuric acid (4 mL). The resulting solution was stirred for 4 h, and then ethyl acetate and water were added. The organic layer was separated. The aqueous layer was twice washed with ethyl, basified to pH 9 with 30% aqueous sodium hydroxide then extracted three times with ethyl acetate. The combined organic extracts were washed with water, brine and concentrated under reduced pressure to give 1.95 g (95%) of the title compound as a white solid. (purity 99%)

Example 58

6'-{4-Carboxyphenyl}-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-{3',4'-dihydro}quinazolin]-2'(1'H)-one

Formula (I):

\[ \begin{align*}
X_1 &= \text{C-}O\text{CH}_3, \\
X_2 &= \text{C-}(4\text{-carboxyphenyl}), \\
X_3 &= \text{CH}, \\
X_4 &= \text{C-}Cl, \\
A &= \text{cyclohexyl}, \\
X &= \text{NH}, \\
Z &= \text{O}, \\
Y &= \text{NH}
\end{align*} \]

The title compound was prepared according to protocol F. To a stirred solution of Example 38 (7 g, 17.2 mmol) in DMF (84 mL) at 18 to 20°C was added a solution of 4-carboxyphenyl-boronic acid (343 mg, 20.64 mmol) and potassium carbonate (2M, 34 mL, 68 mmol) under N2. After degassing the mixture by bubbling with N2 for 2 h, tetrakis (triphenylphosphine) palladium (1.33 g, 1.147 mmol) was added. The solution was heated to 100°C for 18 h. It was then added to water (1L) and EtOAc (1L). The desired product was precipitated and collected by filtration to give the crude product (3.5 g, 51%). The aqueous filtrate was separated and acidified to pH 1 with concentrated HCl (20 mL). The white solid was collected by filtration (2.7 g, 39%). The crude products were combined and purified by column chromatography (silica 80 g; gradient elution, 20% DCM in EtOAc to 50% DCM in MeOH) to give the title compound (1.77 g, 4.41 mmol, 18%) as an off-white solid. (purity = 99.4%) mp = 309-311 °C.

1H NMR (CDCl3) \( \delta \) 8.27 (s, 1H), 7.98 (d, \( J = 8.0 \) Hz, 2H), 7.50 (d, \( J = 8.0 \) Hz, 2H), 7.29 (s, 1H), 6.98 (s, 1H), 3.18 (s, 3H), 2.25 (m, 2H), 1.80 (m, 4H), 1.61 (m, 1H), 1.48 (m, 2H), 1.19 (m, 1H).

Example 59

6'-{3-Carboxyphenyl}-8'-chloro-5'-methoxyspiro[cyclohexane-1-4'-{3',4'-dihydro}quinazolin]-2'(1'H)-one

Formula (I):

\[ \begin{align*}
X_1 &= \text{C-}O\text{CH}_3, \\
X_2 &= \text{C-}(3\text{-carboxyphenyl}), \\
X_3 &= \text{CH}, \\
X_4 &= \text{C-}Cl, \\
A &= \text{cyclohexyl}, \\
X &= \text{NH}, \\
Z &= \text{O}, \\
Y &= \text{NH}
\end{align*} \]

The title compound was prepared according to protocol F. To a stirred solution of Example 38 (1.75 g, 4.30 mmol) in DMF (30 mL) at 18 to 20°C was added a solution of 3-carboxyphenyl-boronic acid (0.86 g, 5.18 mmol) and potassium carbonate (2M, 8.5 mL, 17mmol) under N2. The mixture was degassed by bubbling with N2 for 2 h, tetrakis (triphenylphosphine) palladium (331 mg, 0.286 mmol) was added. The solution was heated to 100°C for 24 h and allowed to cool to 18 to 20°C. The reaction mixture was added to water (200 mL) and EtOAc (300 mL). The desired product was precipitated and collected by filtration, dried in vacuo at 40°C to yield the title compound (567 mg, 1.42 mmol, 33%) as a light brown solid. (purity = 96%)

1H NMR ((CD3)2SO) \( \delta \) 13.06 (br s, 1H), 8.30 (br s, 1H), 8.04 (s, 1H), 7.94 (d, \( J = 8.1 \) Hz, 1H), 7.74 (d, \( J = 8.0 \) Hz, 1H), 7.58 (t, \( J = 8.0 \) Hz, 1H), 7.34 (s, 1H), 7.01 (br s, 1H), 3.21 (s, 3H), 2.30 (m, 2H), 1.87-1.78 (m, 4H), 1.67-1.64 (m, 1H), 1.53-1.50 (m, 2H), 1.24 (m, 1H).

Example 60

8'-Chloro-6'-{2-[4-methyl-piperazine-1-carbonyl]phenyl}spiro[cyclohexane-1-4'-{3',4'-dihydro}quinazolin]-2'(1'H)-one

Formula (I):

\[ \begin{align*}
X_1 &= \text{C-}O\text{CH}_3, \\
X_2 &= \text{C-}(4\text{-carboxyphenyl}), \\
X_3 &= \text{CH}, \\
X_4 &= \text{C-}Cl, \\
A &= \text{cyclohexyl}, \\
X &= \text{NH}, \\
Z &= \text{O}, \\
Y &= \text{NH}
\end{align*} \]
Preparation of (2-bromo-phenyl)-(4-methyl-piperazin-1-yl)-methanone (intermediate 6)

[0206] To a solution of 2-bromobenzoyl chloride (2 g, 9 mmol) in toluene (30 mL) was added N-methylpiperazine (2 mL, 18 mmol, 2 equiv.). The resulting mixture was stirred overnight. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was taken into dichloromethane, washed with water. The organic layer was concentrated under reduced pressure to give 2g (77% yield) of intermediate 6.

\[ \text{H NMR } [\text{CDCl}_3] \ \delta \ 7.60 \text{ (m, 1H)}, 7.35 \text{ (m, 1H)}, 7.20 \text{ (m, 2H)}, 3.90-3.80 \text{ (m, 2H)}, 3.40-3.20 \text{ (m, 2H)}, 2.60-2.40 \text{ (m, 3H)}, 2.30 \text{ (s, 3H)}, 2.30-2.25 \text{ (m, 1H)}. \]

Preparation of Example 60

[0207] To a suspension of Example 8 (200 mg, 0.5 mmol) in dimethylformamide (6 mL) were subsequently added sodium acetate (130 mg, 1.6 mmol, 3 equiv.) and bis(pinacolato)diboron (152 mg, 0.6 mmol). The mixture was degassed by bubbling nitrogen and tetrakis(triphenylphosphine)palladium (30 mg, 0.026 mmol, 0.05 equiv.) was added. The resulting mixture was heated to 45°C overnight, then additional bis(pinacolato)diboron (635 mg, 2.5 mmol, 1 equiv.) was added. The mixture was concentrated under reduced pressure, the resulting solid was crystallized in toluene/methanol to give 10 mg (16% yield) of the title compound as a white solid. mp = 250°C

\[ \text{H NMR } [(\text{CD}_3)_2\text{SO}] \ \delta \ 8.58 \text{ (br s, 1H), 7.50-7.49 (m, 2H), 7.43 (m, 1H), 7.33-7.28 (m, 3H), 7.18 (br s, 1H), 3.70 (m, 1H), 3.20 (m, 1H), 2.95 (m, 1H), 2.78 (m, 1H), 2.38 (m, 1H), 2.10 (m, 1H), 1.98 (s, 3H), 1.86-1.75 (m, 6H), 1.62-1.48 (m, 4H), 1.24-1.16 (m, 2H).} \]

Example 61

8'-Chloro-6'-(2-methyl-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0208] Formula (I): \ \ X_1=\text{CH, } X_2=\text{C-(2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl), } X_3=\text{CH, } X_4=\text{C-Cl, } A=\text{cyclohexyl, } X=\text{NH, } Z=\text{O, } Y=\text{NH}

Preparation of (4-Bromo-3-methyl-phenyl)-(4-methyl-piperazin-1-yl)-methanone (intermediate 7)

[0209] To a solution of 4-bromo-3-methylbenzoyl chloride (0.5 g, 2 mmol) in toluene (6 mL) was added N-methylpiperazine (0.5 mL, 4 mmol, 2 equiv.). The resulting mixture was stirred overnight. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was taken into ethyl acetate and washed with water. The organic layer was washed three times with HCl (1 N), then the mixture was concentrated under reduced pressure, the resulting solid was crystallized in toluene/methanol to give 0.2 g (34% yield) of intermediate 7.

Preparation of Example 61
tetrakis(triphenylphosphine) palladium (100 mg, 0.087 mmol, 0.035 equiv.) was added. The mixture was heated to 90°C overnight and concentrated under reduced pressure. The residue was taken into ethyl acetate, washed once with water. The organic layer was concentrated under reduced pressure and the resulting solid was washed with ethyl acetate to give 0.7 g (78% yield) of boronate. To a suspension of the boronate (200 mg, 0.5 mmol) in dimethylformamide (3 mL) were subsequently added intermediate 7 (200 mg, 0.7 mmol, 1.4 equiv.) and sodium acetate (123 mg, 1.5 mmol, 3 equiv.). The mixture was degassed by bubbling nitrogen and tetrakis(triphenylphosphine)palladium (29 mg, 0.025 mmol, 0.05 equiv.) was added. After heating to 90°C overnight, the mixture was concentrated under reduced pressure, taken into dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and purified by flash chromatography on silica gel (dichloromethane/methanol: 97/3 to 95/5) and the resulting solid was crystallized in toluene/methanol to give 10 mg (6% yield) of the title compound as a white solid. mp = 184°C.

**Example 62**

8'-Chloro-6'-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0211]

Formula (I):

\[ X_1 = \text{CH}, \quad X_2 = \text{C}-(4-(\text{piperazine-1-carbonyl})\text{phenyl}), \quad X_3 = \text{CH}, \quad X_4 = \text{C-Cl}, \quad A=\text{cyclohexyl}, \quad X=\text{NH}, \quad Z=\text{O}, \quad Y=\text{NH} \]

[0212] To a suspension of Example 15 (400 mg, 1.08 mmol) in toluene (4 mL) was added thionyl chloride (0.2 mL, 2.16 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 h, then concentrated under reduced pressure taken into THF (8 mL). To a 0.135 M solution of the acyl chloride in THF (4 mL, 0.54 mmol) was added triethylamine (0.1 mL, 0.15 mmol, 3 equiv.) and piperazine (70 mg, 0.81 mmol, 1.5 equiv.). After stirring for 2 days, the mixture was concentrated, taken into dichloromethane, washed with water and extracted with a 1N aqueous solution of HCl. The aqueous layer was washed twice with dichloromethane, basified to pH 9 and extracted three times with dichloromethane. The combined organic extracts were concentrated under reduced pressure and purified by flash chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 99/1 to 95/5) to give 181 mg (75% yield) of the title compound as a white solid. mp = 184°C.

1H NMR [(CD$_3$)$_2$SO] $\delta$ 8.50 (br s, 1H, NH), 7.30-7.23 (m, 5H), 7.15 (br s, 1H, NH), 3.60-3.37 (m, 4H), 2.33-2.27 (m, 7H), 2.20 (s, 3H), 1.78 (m, 6H), 1.62 (m, 1H), 1.5 (m, 2H), 1.24 (m, 1H).

**Example 63**

8'-Chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0213]

Formula (I):

\[ X_1 = \text{CH}, \quad X_2 = \text{C}-(4-(\text{carbamoyl-phenyl}), X_3 = \text{CH}, \quad X_4 = \text{C-Cl}, \quad A=\text{cyclohexyl}, \quad X=\text{NH}, \quad Z=\text{O}, \quad Y=\text{NH} \]

[0214] To a suspension of Example 15 (1g, 2.7 mmol) in toluene (10 mL) was added thionyl chloride (0.4 mL, 5.4 mmol, 2 equiv.). The resulting mixture was heated to reflux overnight. The precipitate was isolated by filtration, washed with toluene and dried under reduced pressure to give 0.9 g (90% yield) of the acyl chloride. To a suspension of the acyl chloride (100 mg, 0.25 mmol) in toluene (2 mL) was added a 0.5M solution of ammonia in dioxane (1 mL, 0.5 mmol, 2 equiv.). The mixture was stirred overnight and concentrated under reduced pressure. The residue was taken into dichloromethane and washed with water. The organic layer was concentrated under reduced pressure and the resulting solid was purified by flash chromatography on silica gel (dichloromethane/methanol: 97/3) to give 10 mg (66% yield) of the title compound as a white solid. mp = 327°C.

1H NMR [(CD$_3$)$_2$SO] $\delta$ 8.55 (br s, 1H, NH), 8.02 (br s, 1H, NH), 7.78 (d, $J = 8.5$ Hz, 2H), 7.66 (s, 1H), 7.63 (s, 1H), 7.48 (d, $J = 8.0$ Hz, 2H), 7.17 (br s, 1H, NH), 3.57 (br m, 4H), 2.96 (br m, 4H), 1.92-1.77 (m, 6H), 1.64 (m, 1H), 1.54 (m, 2H), 1.28 (m, 1H).
Example 64

8'-Chloro-6'-(4-(1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0215]

Formula (I): \(X_1 = \text{CH}, X_2 = \text{C-(4-(1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl}, X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\)

[0216] To a suspension of Example 15 (150 mg, 0.4 mmol) in toluene (2 mL) was added thionyl chloride (0.06 mL, 0.8 mmol, 2 equiv.). The resulting mixture was heated to reflux for 3 hours, and then concentrated under reduced pressure. The resulting solid was added to a solution of 1-(N-methylpiperidin-4-yl)piperazine (100 mg, 0.6 mmol, 1.5 equiv.) and triethylamine (0.1 mL, 0.8 mmol, 2 equiv.) in toluene (2 mL). After stirring overnight, the mixture was diluted with dichloromethane and washed with a saturated solution of sodium bicarbonate. The organic layer was concentrated under reduced pressure. The resulting solid was washed with ethyl acetate/methanol and crystallized in ethyl acetate/methanol to give 70 mg (33% yield) of the title compound as a white solid. mp = 181 °C.

\[\text{1H NMR } [(\text{CD}_3)_2\text{SO}] \delta 8.53 \text{ (br s, 1H, NH), 7.75 (d, } J = 8\text{Hz, 2H), 7.65 (s, 1H), 7.60 (s, 1H), 7.43 (d, } J = 8\text{Hz, 2H), 7.17 (br s, 1H, NH), 3.59-3.31 \text{ (br m, 7H), 2.78-2.75 (m, 2H), 2.16-2.12 (m, 4H), 1.88-1.29 (m, 17H).}\]

Example 65

8'-Chloro-5'-methoxy-6'-(4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0217]

Formula (I): \(X_1 = \text{C-CH}_3, X_2 = \text{C-(4-(4-methyl-piperazine-1-carbonyl)phenyl), X_3 = CH, X_4 = C-Cl, A = cyclohexyl, X = NH, Z = O, Y = NH}\)

[0218] To a stirred solution of Example 58 (1 g, 2.55 mmol) in DCM (15 mL) at 18 to 20°C was added a solution of thionyl chloride (0.6 g, 5 mmol) and DMF (0.8 mL). The mixture was stirred at 18 to 20°C for 2 h. The resulting mixture was concentrated in vacuo at 55°C. Toluene (10 mL) was added to the intermediate and concentrated in vacuo at 55°C. (This procedure was repeated to ensure all the unreacted thionyl chloride was removed.). The crude intermediate was dissolved in toluene (10 mL) and N-methyl piperazine (0.5 g, 5 mmol) was added. The reaction was stirred for 15 h at 18 to 20°C and concentrated in vacuo at 55°C. The crude product was purified by column chromatography (silica 35 g; 60% EtOAc in MeOH) to yield title compound as a pale brown solid (0.35 mmol, 14%) (purity 95%).

\[\text{1H NMR } [(\text{CD}_3)_2\text{SO}] \delta 1.25 \text{ (m, 1H), 1.54 (m, 2H), 1.68 (m, 1H), 1.83 (m, 4H), 2.22 (s, 3H), 2.32 (m, 6H), 3.25 (s, 3H), 3.36-3.40 (br s, 2H), 3.56-3.70 (br s, 2H), 7.05-7.09 (br s, 1H), 7.36 (s, 1H), 7.47 (d, } J = 8.3\text{Hz, 2H), 7.58 (d, } J = 8.3\text{Hz, 2H), 8.36-8.40 (br s, 1H).}\]

Example 66

8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0219]

Formula (I): \(X_1 = \text{CH}, X_2 = \text{CH}; X_3 = \text{CH}, X_4 = \text{C-Cl}, A = \text{cyclohexyl, X = NH, Z = O, Y = NH}\)

[0220] The title compound was prepared according to protocol A using 2-trifluoromethylphenylurea (500 mg, 2.45 mmol), polyphosphoric acid (3 g) and cyclohexanone (0.3 mL, 2.89 mmol). The crude product was purified by flash chromatography on silica gel (hexane/EtOAc : 10/0 to 50/50) followed by reverse-phase chromatography on a C18 column (water/acetonitrile : 90/10 to 0/100) to give the title compound (13 mg, 2% yield).

\[\text{1H NMR } [(\text{CDCl}_3)] \delta 7.46 \text{ (m, 2H), 7.07 (m, 1H), 7.01 (br s, 1H, NH), 5.60 (br s, 1H, NH), 2.00 (m, 2H), 1.83-1.57 (m, 7H), 1.30 (m, 1H).}\]

Example 67

8'-Bromo-6'-(4-(1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0221]

Formula (I): \(X_1 = \text{CH}, X_2 = \text{CH}; X_3 = \text{CH}, X_4 = \text{C-Br}, A = \text{cyclohexyl, X = NH, Z = O, Y = NH}\)
Example 67

8'-Chloro-6'-cyanomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0221]

Formula (I): $X_1=CH, X_2=C-CH_2CN, X_3=CH, X_4=C-Cl, A=cyclohexyl, X=NH, Z=O, Y=NH$

[0222] The title compound was prepared according to protocol D. To a stirred solution of Example 1 (1g, 4 mmol) in glacial acetic acid (15 mL) was sequentially added trioxane (0.55 g, 6 mmol, 1.5 equiv.) and a 48% aqueous solution of hydrobromic acid (5 mL). The mixture was heated to 95°C overnight, poured on ice. The precipitate was filtered, washed twice with water then with ether to give 1.39 g of 8'-Chloro-6'-bromomethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one as a white solid. The crude bromomethyl derivative (256 mg, 74 mmol) was treated with sodium cyanide (40 mg, 82 mmol, 1.1 equiv.) in DMF (10 mL) and was heated to 60°C for two hours. The mixture was concentrated under reduced pressure, taken into water, extracted twice with $\text{CH}_2\text{Cl}_2$, dried over $\text{Na}_2\text{SO}_4$, filtered and concentrated under reduced pressure. The crude material was purified twice by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2$/MeOH: 99/1 followed by cyclohexane/EtOAc : 60/40 + 2% $\text{NH}_4\text{OH}$), to give the title compound (60 mg, 28%) (purity 95%) as a white solid. mp = 239°C

$^1\text{H}$ NMR [(CD$_3$)$_2$SO] $\delta$ 8.50 (br s, 1H, NH), 7.30-7.29 (d, 2H), 7.15 (br s, 1H, NH), 3.94 (s, 2H), 1.81-1.68 (m, 7H), 1.54-1.50 (m, 2H), 1.25 (m, 1H).

Example 68

8'-Chloro-5'-[3-dimethylamino-2-hydroxy-propoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one

[0223]

$X_1=C-\text{OCH}_2\text{CH(OH)}\text{CH}_2\text{N(CH}_3)_2, X_2=CH, X_3=CH, X_4=C-\text{Cl}, A=cyclohexyl, X=\text{NH}, Z=O, Y=\text{NH}$

[0224] Preparation of 8'-Chloro-5'-[oxiran-2-ylmethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one (intermediate 8)

To a stirred solution of Example 36 (5g, 18.75 mmol) in DMF (80 mL) at 18 to 20°C was added anhydrous potassium carbonate (6.5g, 46.9 mmol) followed by epibromohydrin (2.83 g, 20.6 mmol) in one portion. The mixture was heated to 80°C for 2 h and then 90°C for 2 h. The crude mixture was quenched into water (800 mL) and extracted with $\text{EtOAc}$ (2x1L). The organic layer was dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo at 40°C to give the crude product (3.4g, 57% yield). The crude product was subjected to column chromatography on silica gel (CH$_2$Cl$_2$/MeOH: 99:1) to give the title compound (60 mg, 28%) (purity 95%) as a white solid. mp = 239°C

$^1\text{H}$ NMR [(CD$_3$)$_2$SO] $\delta$ 6.96 (d, $J=8.8$ Hz, 1H), 6.76-6.79 (br s, 1H), 6.24 (d, $J=8.8$ Hz, 1H), 5.30-5.35 (br s, 1H), 4.09 (dd, $J=2.8$, 10.9 Hz, 1H), 3.67 (dd, $J=6.3$, 10.9 Hz, 1H), 3.16 (m, 1H), 2.73 (dd, $J=4.3$, 4.8 Hz, 1H), 2.53 (dd, $J=2.5$, 4.8 Hz, 1H), 2.28-2.38 (m, 2H), 1.45-1.61 (m, 5H), 1.23-1.36 (m, 2H), 1.04-1.15 (m, 1H).

Preparation of example 68

[0225] To a stirred solution of dimethylamine in EtOH (17 mL, 5.6 M, 95.2 mmol) at 18 to 20°C was added intermediate 8 (730 mg, 2.26 mmol) in one portion. The mixture was heated to 40°C for 2.6 h. The solid was filtered, washed with EtOH (40 mL) and dried in vacuo at 40°C to yield the desired product as a white solid (515 mg, 1.4 mmol, 62%) (purity 98%).

$^1\text{H}$ NMR [(CD$_3$)$_2$SO] $\delta$ 7.10 (d, $J=9.0$ Hz, 1H), 6.90-6.94 (br s, 1H), 6.42 (d, $J=9.0$ Hz, 1H), 5.44-5.50 (br s, 1H), 3.99 (m, 1H), 3.91 (m, 2H), 3.50-3.54 (br s, 1H), 2.52 (m, 3H), 2.33 (dd, $J=12.1$, 3.5 Hz, 1H), 2.27 (s, 6H), 1.59-1.76 (m, 5H), 1.38-1.52 (m, 2H), 1.18-1.30 (m, 1H).

51
Example 69

8'-Chloro-5'-{(3-methylamino-2-hydroxy-propano)-spiro[cyclohexane-1-4'-{(3',4'-dihydro)quinazolin}]-2'} (1'H)-one

[0226]

\[X_1 = \text{C}-\text{OCH}_2\text{CH(OH)CH}_2\text{NHCH}_3, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\]

[0227] To a stirred solution of methylamine in EtOH (12mL, 8M, 96mmol) at 18 to 20°C was added intermediate 8 (500mg, 1.55mmol) in one portion. The mixture was heated to 40°C for 2 h. A further portion of methylamine in EtOH (10mL, 8M, 80mmol) was added and the reaction heated at 40°C for another 20mins. The mixture was concentrated in vacuo at 40°C and TBME (30mL) was added. The white solid (390mg, 1.1 mmol) formed was filtered to give the crude product (390mg, 1.1 mmol). The material was dissolved in DCM (20mL) and heated to 35°C for ten minutes in the presence of charcoal (2g). The suspension was filtered through a pad of celite, washed with DCM (20mL) and concentrated in vacuo at 40°C to yield the title compound as a white solid (200mg, 36% yield) (purity 97.3%).

\[1H\text{ NMR } [(CD_3)_2SO] \delta 7.21 (d, J = 9.0 Hz, 1H), 7.00-7.06 (br s, 1H), 6.54 (d, J = 9.0 Hz, 1H), 5.55-5.59 (br s, 1H), 4.04 (m, 2H), 4.13 (m, 1H), 2.90 (dd, J = 3.8, 12.0 Hz, 1H), 2.80 (dd, J = 8.4, 12.0 Hz, 1H), 2.60 (m, 2H), 2.54 (s, 3H), 2.05-2.25 (br s, 2H), 1.70-1.88 (m, 5H), 1.48-1.63 (m, 1H).

Example 70

8'-Chloro-5'-{2-{ethoxycarbonylmethyl-amino}-ethoxy}-spiro[cyclohexane-1-4'-{(3',4'-dihydro)quinazolin}]-2' (1'H)-one

[0228]

\[X_1 = \text{C}-\text{OCH}_2\text{CH}_2\text{NHCH}_2\text{COOCH}_2\text{CH}_3, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\]

[0229] To a stirred suspension of intermediate 4 (2.0g, 5.14mmol) in acetonitrile (28mL) was added a solution of ethyl glycinate (3.72g, 3.6mmol) in acetonitrile (12mL). The mixture was stirred under reflux for 24 hours. Concentration in vacuo at 40°C afforded an orange oil (5g) which was subjected to column chromatography (silica 110g, eluting with 50% to 100% EtOAc in heptane followed by 90% EtOAc in DCM) to give the title compound (450mg, 22% yield) as a white solid after drying in vacuo at 45°C.

\[1H\text{ NMR } [(CD_3)_2SO] \delta 7.94-7.98 (br s, 1H). 7.24 (d, J = 9.0 Hz, 1H). 7.01-7.05 (br s, 1H), 6.62 (d, J = 9.0 Hz, 1H), 4.08 (t, J = 7.1 Hz, 2H), 4.01 (t, J = 5.6 Hz, 2H), 3.41 (s, 2H), 2.95 (t, J = 5.6 Hz, 2H), 2.45-2.55 (m, 2H), 2.12 (br s, 1H), 1.70-1.85 (m, 2H), 1.52-1.63 (m, 3H), 1.40-1.49 (m, 2H), 1.21-1.25 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H).

Example 71

8'-Chloro-5'-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-{(3',4'-dihydro)quinazolin}]-2' (1'H)-one hydrochloride

[0230]

\[X_1 = \text{C}-\text{OCH}_2\text{CH}_2\text{NHCH}_2\text{COOH}, X_2 = \text{CH}, X_3 = \text{CH}, X_4 = \text{Cl}, A = \text{cyclohexyl}, X = \text{NH}, Z = \text{O}, Y = \text{NH}\]

[0231] To a stirred solution of Example 70 (600mg, 1.52 mmol) in 1,4-dioxane (8mL) was added a solution of HCl (6N, 10.5mL) at 18 to 20°C. The reaction mixture was heated to 90°C for 2 h. It was then quenched onto water (100mL) and washed with DCM (200mL). The aqueous layer was concentrated and dried in vacuo at 60°C to give title compound (614mg, 99.9% yield) as a white solid (purity 95.9%).

\[1H\text{ NMR } (400 MHz, CD_3OD) \delta 7.07 (d, J = 9.1 Hz, 1H), 6.56 (d, J = 9.1 Hz, 1H), 4.17 (t, J = 5.6 Hz, 2H), 3.86 (s, 2H), 3.39 (t, J = 5.6 Hz, 2H), 2.24-2.34 (m, 2H), 1.40-1.60 (m, 7H), 1.15-1.26 (m, 1H).
Biological results

In vitro inhibition of the phosphodiesterase 7 and of other phosphodiesterases

The capacity of the compounds of the invention to inhibit cyclic nucleotide phosphodiesterases was evaluated by measuring their IC\textsubscript{50} (concentration necessary to inhibit the enzymatic activity by 50 %).

PDE3A3, PDE4D3, PDE7A1 were cloned and expressed in insect cells Sf21 using the baculovirus expression system and we uses directly the cell culture supernatant as enzyme source. The source of PDE1 and of PDE5 were human cell lines (respectively TPH1 human monocytes and MCF7 human caucasian breast adenocarcinoma).

They were obtained partially purified on an anion exchange column (Mono Q) according to a method adapted from Lavan B.E., Lakey T., Houslay M.D. Biochemical Pharmacology, 1989, 38 (22), 4123-4136.

Measurement of the enzymatic activity for the various types of PDE was then made according to a method adapted from W.J. Thompson et al. 1979, Advances in Cyclic Nucleotide Research, Vol. 10 : 69-92, ed. G. Brooker et al. Raven Press, NY. The substrate used was cGMP for PDE1 and PDE5 and cAMP for PDE 3, PDE 4 and PDE 7. The substrate concentration was 0.2\muM for PDE 1, PDE 3 and PDE 5, 0.25\muM for PDE 4 and 50\muM for PDE 7.

The enzymatic reaction was stopped after 1 hour for PDE 1, PDE 3 and PDE 5 and 10 minutes for PDE 4 and PDE 7.

In order to determine their IC\textsubscript{50}, compounds of the invention were assayed at 8 to 11 concentrations ranging from 0.02nM to 100\muM for PDE 4 and PDE 7 and at least at 6 concentrations ranging from 0.1\muM to 30\muM for PDE 1, 3 and 5.

The IC\textsubscript{50} (\muM) were determined for some of the compounds of the invention, and the IC\textsubscript{50} of most of the compounds of examples 1 to 71 were comprise between 0.008 \muM and 18 \muM.

The activity of some of the most active compounds are summarized in the following table:

<table>
<thead>
<tr>
<th>Example number</th>
<th>IC\textsubscript{50} PDE7 (\muM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.014</td>
</tr>
<tr>
<td>9</td>
<td>0.016</td>
</tr>
<tr>
<td>17</td>
<td>0.012</td>
</tr>
<tr>
<td>21</td>
<td>0.018</td>
</tr>
<tr>
<td>24</td>
<td>0.02</td>
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<tr>
<td>28</td>
<td>0.008</td>
</tr>
<tr>
<td>29</td>
<td>0.015</td>
</tr>
<tr>
<td>30</td>
<td>0.013</td>
</tr>
<tr>
<td>31</td>
<td>0.013</td>
</tr>
</tbody>
</table>

These results show that the compounds of the invention inhibit PDE7 at very low concentrations, with some IC\textsubscript{50} values lower than 100nM. The results of the assays with other PDE (1, 3, 4 and 5) show IC\textsubscript{50} values often superior to 1\muM or even 10 \muM.

It demonstrates that compounds of the invention are strong and selective PDE7 inhibitors.

Claims

1. Compounds having the following formula (I) :
in which:

\[ X_1, X_2 \text{ and } X_3 \text{ are the same or different and are selected from } C^-R^1, \text{ in which} \]

\[ R^1 \text{ is selected from:} \]

- Q1, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being - unsubstituted or substituted with 1, 2 or 3 groups Q2;
- the group X5-R5 in which,
  - X5 is selected from a single bond or lower alkylene, optionally interrupted with 1 heteroatom chosen from O, S, or N; and
  - R5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S(=O), SO2 or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO2 or N, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q3, heteroaryl or lower alkyl optionally substituted with Q3;

\[ \text{in which Q1, Q2, Q3 are the same or different and are selected from:} \]

- hydrogen, halogen, CN, NO2, SO2H,
- OR2, OC(=O)R2, C(=O)OR2, SR2, S(=O)2CH3, NR3R4, Q-R2, Q-NR3R4, NR2-Q-NR3R4 or NR3-Q-R2 in which Q is selected from C(=NR), C(=O), C(=S) or SO2, R is selected from hydrogen or lower alkyl and R2, R3 and R4 are the same or different and are selected from:
  - hydrogen,
  - lower alkyl optionally interrupted with C(=O), Q4-aryl, Q4-heteroaryl, Q4-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S(=O), SO2 or N, or Q4-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO2 or N, in which
    - Q4 is selected from (CH2)n, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR', or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;
    - n is an integer selected from 0, 1, 2, 3 or 4;
    - these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH3, SO2H, SO2CH3, C(=O)-NH-SO2-CH3, CF3, OR6, COOR6, C(=O)R6, NR6R7, C(=O)NR6R7 or SO2NR6R7, in which R6 and R7 are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR6 in which R and R6 are hydrogen or lower alkyl, and,
    - R6 and R7, and/or R3 and R4, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO2 or N, and which may be substituted with,
    - (CH2)n-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
    - a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are
2. A compound according to claim 1 in which X₁, X₂ and X₃ are the same or different and are C-R¹, in which R¹ is selected from:

- hydrogen, halogen, CN, SO₂H, NO₂, CF₃, OR², SR², NR²R³, COOR², CONR²R³, SO₂CH₃, SO₂NR²R³ in which R² and R³ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with halogen, CN, OR₆, COOR₆, NR₆R⁷, SO₂NR₆R⁷ or C(=O)NR₆R⁷ in which R₆ and R⁷ are the same or different and are selected from hydrogen or lower alkyl and halogen, CN, OR₆, COOR₆, NR₆R⁷, SO₂NR₆R⁷ or C(=O)NR₆R⁷ in which R₆ and R⁷, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from halogen, CN, OR₆, COOR₆, NR₆R⁷, SO₂NR₆R⁷ or C(=O)NR₆R⁷ in which R₆, R⁷ and R₈ are the same or different and are selected from hydrogen or lower alkyl, and, R₈ and R⁹, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring;
- the group X₅R⁵ in which:
  - X₅ is selected from a lower alkylene or a single bond, and,
  - R⁵ is selected from phenyl, pyridyl or indolyl,

these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃ in which Q₃ is selected from:

- halogen, CN, SO₂H, NO₂, CF₃, OR², OC(=O)R², C(=O)OR², NH-C(=O)R², NR³R⁴, SO₂NR³R⁴ or C(=O)NR³R⁴ in which R², R³ and R⁴ are the same or different and are selected from:

- hydrogen, lower alkyl unsubstituted or substituted with one or several groups selected from halogen, OR₆, COOR₆ or NR₆R⁷ in which R₆ and R⁷ are the same or different and are selected from hydrogen or lower alkyl and,
- R₆ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or
N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C (=O) NR'R" or COOR' in which R' and R" are the same or different and are selected from,
  - H, or,
  - lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

3. A compound according to claim 1 in which X₁, X₂ and X₃ are the same or different and are C-R¹, in which R¹ is selected from:
- Q₁, or
- lower alkyl, lower alkenyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 groups Q₂;
- the group X⁵-R⁶ in which,
  - X⁵ is selected from:
    - a single bond,
    - a lower alkylene, optionally interrupted with 1 heteroatom chosen from O, S and N;
  - R⁶ is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N, cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S, S(=O), SO₂ or N, or a bicyclic group,
  - these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃, heteroaryl or lower alkyl optionally substituted with Q₃;

in which Q₁, Q₂, Q₃ are the same or different and are selected from:
- hydrogen, halogen, CN, NO₂, SO₂H,
- OR², OC(=O)R², C(=O)OR², SR², S(=O)R², C(=O)-NH-SO₂-CH₃, NR³R⁴, Q-R², Q-NR³R⁴, NR²-Q-NR³R⁴ or NR³-Q-R² in which Q is selected from C(=NR), C(=O), C(=S) or SO₂, R is selected from hydrogen or lower alkyl and R², R³ and R⁴ are the same or different and are selected from:
- hydrogen,
- lower alkyl optionally interrupted with C(=O), Q₄-aryl, Q₄-heteroaryl, Q₄-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂ or N, or Q₄-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, S(=O), SO₂ or N, in which
- Q₄ is selected from (CH₂)n, lower alkyl interrupted with one heteroatom selected from O, S or N, lower alkenyl or lower alkynyl, these groups being optionally substituted with lower alkyl, OR' or NR'R" in which R' and R" are the same or different and are selected from hydrogen or lower alkyl;
  - n is an integer selected from 0, 1, 2, 3 or 4;
- these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, halogen, CN, CH₃, SO₃H, SO₂CH₃, CF₃, C(=O)NH-SO₂CH₃, OR⁵, COOR⁶, C(=O)R⁶, NR⁶R⁷, C(=O)NR⁶R⁷ or SO₂NR⁶R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR⁸ in which R and R⁸ are hydrogen or lower alkyl, and,
- R⁵ and R⁷, and/or R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O), SO₂ or N, and which may be substituted with,
- (CH₂)ₙ-Q₅, in which n is an integer selected from 0, 1, 2 and 3, and Q₅ is a 4- to 8- membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
- H, or,
- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

4. A compound according to claim 3, in which X₁, X₂, and X₃ are the same or different and are C-R¹, in which R¹ is selected from:
- Q₁, or
- lower alkyl or lower alkynyl, these groups being unsubstituted or substituted with 1, 2 or 3 fluorine atoms, OR², COOR³ or NR³R⁴ in which R³ and R⁴ are the same or different and are selected from hydrogen or lower alkyl, or R³ and R⁴, together with the nitrogen atom to which they are linked, may also form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N;
- the group X⁵-R⁵ in which X⁵ is a single bond and R⁵ is selected from aryl, heteroaryl, or a bicyclic group, these groups being unsubstituted or substituted with 1, 2 or 3 groups selected from Q₃,
in which Q₁ and Q₃ are the same or different and are selected from
- hydrogen, halogen, CN, lower alkyl,
- OR², C(=O)OR², NR³R⁴, C(=O)NR³R⁴ or SO₂NR³R⁴ in which R², R³ and R⁴ are the same or different and are selected from:
- hydrogen,
- lower alkyl, Q₄-heteroaryl in which Q₄ is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and (CH₂)ₙ in which n is an integer selected from 0, 1, 2 or 3;
these groups being unsubstituted or substituted with 1 or 2 groups selected from lower alkyl, CN, SO₂H, C(=O)-NH-SO₂-CH₃, OR⁶, COOR⁶ or NR⁶R⁷, in which R⁶ and R⁷ are the same or different and are selected from hydrogen or lower alkyl optionally substituted with one or two groups selected from OR, COOR or NRR⁸ in which R and R⁸ are hydrogen or lower alkyl, and
- R⁶ and R⁷, and/or, R³ and R⁴, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,
- a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N and which may be substituted with a lower alkyl, or,
- a lower alkyl optionally substituted with OR', NR'R", C(=O)NR'R" or COOR' in which R' and R" are the same or different and are selected from,
- H, or,
- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,

R' and R" together with the nitrogen atom to which they are linked, can form a 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N.

5. A compound according to claim 3, in which X₁ is C-R¹, in which R¹ is selected from hydrogen, halogen, OR², COOR², COOR² or CONR²R³ in which R² and R³ are the same or different and are selected from
- hydrogen,
- lower alkyl, Q₄-aryl, Q₄-heteroaryl, Q₄-cycloalkyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, or Q₄-cycloalkenyl optionally interrupted with C(=O) or with 1 or 2 heteroatoms chosen from O, S, or N, in which
A compound according to any one of claims 3, 5 and 6 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2, COOH or OH; R^6 and R^7 together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with.

- (CH_2)_n-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- COR^3 or lower alkyl optionally substituted with OR^3, NR^6R^7, C(=O)NR^6R^7 or COOR^3 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl;
- lower alkyl optionally substituted with CN, SO_2H, OR^3, NR^3R^4, COOR^3 or CONR^3R^4 in which R^3 and R^4 are the same or different and are selected from hydrogen and lower alkyl optionally substituted with OH, COOH or NH_2;
- the group X^5-R^5 in which X^5 is a lower alkylene optionally interrupted with a heteroatom selected from O and N and R^5 is selected from aryl, heteroaryl, cycloalkyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N and cycloalkenyl optionally interrupted with C(=O) or with 1, 2, or 3 heteroatoms chosen from O, S or N, these groups being unsubstituted or substituted with OR^3 or COOR^3 in which R^3 is selected from hydrogen and lower alkyl; R^5 and R^4, together with the nitrogen atom to which they are linked, can form a 4- to 6-membered heterocyclic ring, which may contain one or two heteroatoms selected from O or N, and which may be substituted with,
- (CH_2)_n-Q5, in which n is an integer selected from 0, 1, 2 and 3, and Q5 is a 4- to 8-membered heterocyclic ring which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
- C(=O)-R^4 or a lower alkyl optionally substituted with OR^4, NR^6R^7, C(=O)NR^6R^7 or COOR^4 in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl.  

6. A compound according to claim 3 in which X_1 is C-R^1, in which R^1 is selected from hydrogen, halogen or OR^2 in which R^2 is selected from

- hydroxyl,
- lower alkyl, unsubstituted or substituted with CN, C(=O)-NH-SO_2-CH_3, OR^6, SO_3H, COOR^6 or NR^6R^7;
- Q4-oxadiazole, Q4-tetrazole, Q4-morpholine, Q4-furan, Q4-isoxazole, in which Q4 is selected from lower alkyl interrupted with one heteroatom selected from O, S or N and (CH_2)_n, in which n is an integer selected from 1 and 2, these groups being unsubstituted or substituted with CH_3, OR^6 or COOR^6, in which R^6 and R^7 are the same or different and are selected from hydrogen or lower alkyl, optionally substituted with NH_2 or COOH.

7. A compound according to any one of claims 3, 5 and 6 in which X_2 is C-R^1, in which R^1 is X^5-R^5, in which

- X^5 is a single bond,
- R^5 is phenyl or pyridyl,

- optionally substituted with a lower alkyl and,
- substituted with C(=O)NR^3R^4 in which R^3 and R^4 together with the nitrogen atom to which they are linked, form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S, S(=O),SO_2 or N, and which may be substituted with,
- a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N and which may be substituted with a lower alkyl, or,
A compound according to claim 1, selected from the group consisting of:

- a lower alkyl optionally substituted with OR', NR'R', C (=O) NR'R' or COOR' in which R' and R" are the same or different and are selected from,
- H, or,
- lower alkyl optionally substituted with OR or COOR in which R is hydrogen or lower alkyl and,
- R' and R" together with the nitrogen atom to which they are linked, can form a 4- to 8-membered heterocyclic ring, which may contain one or two heteroatoms selected from O, S or N.

8. A compound according to any one of claims 3 to 7 in which one of X₁, X₂ and X₃ is C-R¹ in which R¹ is hydrogen while the others are identical or different and are C-R¹ in which R¹ is other than hydrogen.

9. A compound according to claim 8, in which X₃ is C-R¹ in which R¹ is hydrogen.

10. A compound according to any one of claims 3 to 8, in which X₃ is C-R¹, in which R¹ is selected from:

- hydrogen or halogen, or.
- X⁵-R⁵ in which X⁵ is a single bond and R⁵ is aryl or heteroaryl, optionally substituted with one, two or three groups which are the same or different and which are selected from halogen, CN, CF₃, SO₂Me, OR₂, COOR₂, NR²R₃, SO₃NR²R₃ and CONR²R³ in which R² and R³ are the same or different and are selected from hydrogen or lower alkyl.

11. A compound according to claim 10 in which X₃ is C-R¹, in which R¹ is selected from hydrogen or halogen.

12. A compound according to claim 1, selected from the group consisting of:

- 8'-Chlorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-methylspro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-bromospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-fluorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 5',8'-dichlorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-Bromospiro[cycloheptane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 6',8'-dichlorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-iodospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-8'-methoxyspiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-phenylspirospiro[cycloheptane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-phenylspirospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-methylspirospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(3-pyridyl)spirospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(4-pyridyl)spirospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 6'-(3-carboxyphenyl)-8'-chlorospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(1H-indol-5yl)spirospiro[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(2-pyridyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(3-dimethylamino-prop-1-ynyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(3-methylamino-prop-1-ynyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(4-(4-methyl-piperazine-1-carbonyl)phenyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(4-(3-N-dimethylamino-propylcarboxamide)phenyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(4-(2-N-dimethylamino-ethylcarboxamide)phenyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
- 8'-chloro-6'-(3-(3-N-dimethylamino-propylcarboxamide)phenyl)spirospe[cyclohexane-1'-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-2'-cyanoimino-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline
8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5',8'-difluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-(morpholin-4-yl)methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-hydroxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(4-morpholin-4-yl)-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-dimethylaminoethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-aminothoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(aminomethyl)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(2-aminothoxy)ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-dimethylaminopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-ethoxy-carbonylmethoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-sulphopropoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[2-(tetrahydro- pyran- 2- yloxy)-ethoxy]-spiro [cyclohexane- 1-4'-(3', 4'- dihydro) quinazolin]- 2'(1'H)-one,
8'-Chloro-5'-[2-(hydroxy-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[5-ethoxy-carbonyl- furan- 2- yl methoxy]-spiro [cyclohexane- 1-4'-(3', 4'- dihydro) quinazolin]- 2'(1'H)-one,
8'-Chloro-5'-[5-carboxy-furan-2-ylmethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-cyano-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[1(H)-tetrazol-5-ylmethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[5-hydroxy-[1,2,4] oxadiazo-3- yl methoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-iodo-5'-[2-dimethylamino-ethoxy]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-[4-carboxyphenyl]-8'-chloro-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
6'-[3-carboxyphenyl]-8'-chloro-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[2-(4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-6'-[4-[(1-methyl-piperidin-4-yl)-piperazine-1-carbonyl]phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-chloro-5'-methoxy-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Trifluoromethylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-6'-cyano-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-dimethylamino-2-hydroxy-propoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8'-Chloro-5'-[3-methylamino-2-hydroxy-propoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
10. A compound according to claim 1, selected from the group consisting of:

8'-chloro-5'-(2-[(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2' (1'H)-one hydrochloride,

8'-Chloro-5'-(2-methanesulfonylamo-2-oxo-ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro) quinazolin]-2' (1'H)-one, and

8'-Chloro-5'-(2-[(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazol
lin]-2'(1'H)-one;

or a pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

13. A compound according to claim 1, selected from the group consisting of:

8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-phenylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,

8'-chloro-6'-[3-(pyridyl)]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(pyridyl)]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

6'-(4-carboxyphenyl)-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one.

8'-[3-(4-carboxyphenyl)]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[1H-indol-5-yl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[2-(pyridyl)]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-dimethylamino-prop-1-ynyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-methylamino-prop-1-ynyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(3-N-dimethylamino-prop[carboxamide])phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(3-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(4-methyl-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[3-(2-N-dimethylamino-ethylcarboxamide)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-pyrimidin-2-yl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-morpholin-4-yl-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-morpholin-4-yl-2-oxo-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-6'-[4-(4-(2-hydroxy-ethoxy)-ethyl)-piperazine-1-carbonyl)-phenyl]spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-methoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-methylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-hydroxySpiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-cyano-5'-methoxy-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-(4-morpholin)]ethoxy)-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

5'-carboxymethoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

5'-carboxypropoxy-8'-chloro-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-chloro-5'-[3-sulphopropoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[2-(hydroxy-ethoxy)]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[5-(ethoxycarbonyl-furan-2-ylmethoxy)]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-[5-carboxy-furan-2-ylmethoxy)]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-cyano methoxy]-spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,

8'-Chloro-5'-(1H-tetrazol-5-ylmethyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazolin]-2'(1'H)-one,
8’-Chloro-5’-(5-hydroxy-[1,2,4]oxadiazol-3-ylmethoxy)-spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
6’-(4-carboxyphenyl)-8’-chloro-5’-methoxy spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
6’-(3-carboxyphenyl)-8’-chloro-5’-methoxy spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-chloro-6’-[2-methyl-4-(4-methyl-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-chloro-6’-[4-(piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-chloro-6’-[4-carbamoyl-phenyl]spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-chloro-6’-[4-(1-methyl-piperidin-4-yl)-piperazine-1-carbonyl)phenyl]spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-Chloro-5’-[2-(carboxymethyl-amino)-ethoxy]-spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one hydrochloride.
8’-Chloro-5’-[2-methanesulfonylamino-2-oxo-ethoxy]-spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.
8’-Chloro-5’-[2-(5-methyl-isoxazol-3-ylmethyl)-amino]ethoxy]spiro[cyclohexane-1-4’-(3’,4’-dihydro)quinazolin]-2’(1’H)-one.

or a pharmaceutically acceptable salt, solvate, hydrate or polymorph thereof.

14. A compound according to any one of claims 1 to 13 for use as a medicament.
15. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13 in combination with an appropriate carrier.
16. Use of a compound according to any one of claims 1 to 13 for the preparation of a medicament for the prevention or the treatment of disorders for which therapy by a PDE7 inhibitor is relevant.
17. Use according to claim 16 in which said disorder is selected from T-cell-related diseases, autoimmune diseases, osteoarthritis, multiple sclerosis, osteoporosis, chronic obstructive pulmonary disease, asthma, cancer, acquired immune deficiency syndrome, allergy or inflammatory bowel disease.
18. A method for preparing a compound of formula (I) according to claim 1 in which Z is O comprising reacting a substituted urea of formula

\[ \text{in which } X_1, X_2, X_3 \text{ and } X_4, \text{ are as defined in claim 1, with a cyclic ketone of formula} \]

\[ \text{in which } A \text{ is as defined in claim 1, to obtain said compound of formula (I) and isolating said compound of formula (I).} \]
19. A method for preparing a compound of formula (I) according to claim 1 in which X1, X2, X3, X4 and A are as defined in claim 1 said method comprising,

\[ \text{(1) reacting a compound (2a)} \]
in which $X_1$, $X_2$, $X_3$ and $X_4$ are as defined in claim 1 with a group $P$-$LG$ in which $P$ is a protecting group and $LG$ is a leaving group to obtain compound (2b).

(2) reacting compound (2b) with $R$-Li in which $R$ is lower alkyl and then with a ketone of formula

in which $A$ is as defined in claim 1 to obtain compound (2c).

(3) removing the protecting group $P$ either under reductive conditions, acidic condition or basic condition to obtain compound (2d).
(4) reacting compound (2d) with a group \( O=\text{C}=\text{N}- \) to obtain compound (2e)

(5) reacting compound (2e) with an acid to obtain said compound of formula (I),
(6) isolating said compound of formula (I).

**Patentansprüche**

1. Verbindungen mit der folgenden Formel (I):

   \[
   \begin{array}{c}
   \text{(I)}
   \end{array}
   \]

   worin:

   \( X_1, X_2 \) und \( X_3 \) dasselbe oder verschieden sind und ausgewählt sind aus \( C-\text{R}^1 \), worin

   \( \text{R}^1 \) ausgewählt aus:

   - \( \text{Q1} \) oder
   - Niederalkyl, Niederalkenyln oder Niederalkinyl, wobei diese Gruppen unsubstituiert oder mit 1, 2 oder 3
     \( \text{Q2} \)-Gruppen substituiert sind;
   - der Gruppe \( \text{X}^5-\text{R}^5 \), worin

   \( \text{X}^5 \) ausgewählt ist aus einer Einfachbindung oder Niederalkylen, gegebenenfalls unterbrochen von 1
   Heteroatom, ausgewählt aus O, S oder N; und
wobei diese Gruppen unsubstituiert oder substituiert sind mit 1, 2 oder 3 Gruppen, ausgewählt aus Q3, Heteroaryl oder Niederalkyl, gegebenenfalls substituiert mit Q3,

worin Q1, Q2, Q3 dasselbe oder verschieden sind und ausgewählt sind aus:

- Wasserstoff, Halogen, CN, NO₂, SO₃H,
- OR², OC(=O)R², C(=O)OR², SR², S(=O)R², C(=O)-NH-SO₂-CH₃, CF₃, OR⁶, COOR⁶, C(=O)R⁶, NR⁷R⁷, C(=O)NR⁷R⁷ oder SO₂NR⁷R⁷ ausgewählt sind, wobei R⁶ und R⁷ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl; gegebenenfalls substituiert mit einer oder zwei Gruppen, ausgewählt aus OR, COOR oder NRR⁷, wobei R und R⁸ Wasserstoff oder Niederalkyl sind, und
- R⁶ und R⁷ und/oder R³ und R⁴ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome enthalten kann, die aus O, S, S(=O), SO₂ oder N ausgewählt sind, und der substituiert sein kann mit

- (CH₂)n=O₂, worin n eine ganze Zahl ist, die aus 0, 1, 2 und 3 ausgewählt ist, und Q⁵ ein 4- bis 8gliedriger heterocyclischer Ring ist, der ein oder zwei Heteroatome enthalten kann, die aus O, S oder N ausgewählt sind, und der mit einer Niederalkylgruppe substituiert sein kann, oder
- einer Niederalkylgruppe, gegebenenfalls substituiert mit OR⁷, NRR⁷, C(=O)NR⁷R⁷ oder COOR⁷, worin R⁷ und R⁸ dasselbe oder verschieden sind und ausgewählt sind aus:

- H oder
- Niederalkyl, gegebenenfalls substituiert mit OR oder COOR, worin R Wasserstoff oder Niederalkyl ist, und

R⁷ und R⁸ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome enthalten kann, die aus O, S oder N ausgewählt sind;

X₄ für C-R¹ steht, worin R¹ ausgewählt ist aus F, Cl, Br, CF₃ und CH₃; Z für O oder N-CN steht; und
A für unsubstituiertes Cyclohexyl oder unsubstituiertes Cycloheptyl steht; oder deren tautomer Formen, deren racemische Formen oder deren Isomere und deren pharmazeutisch annehmbare Salze, Solvate, Hydrate und Polymorphe; wobei es sich versteht, dass:

Niederalkylen und Niederalklylen gerade und verzweigte Kohlenstoffketten mit 1 bis 6 Kohlenstoffatomen bedeuten;
Niederalskenyl gerade und verzweigte Kohlenwasserstoffreste mit 2 bis 6 Kohlenstoffatomen und mindestens einer Doppelbindung bedeutet; Niederalkynyl gerade und verzweigte Kohlenwasserstoffreste mit 2 bis 6 Kohlenstoffatomen und mindestens einer Dreifachbindung bedeutet; Cycloalkyl einen gesättigten carbocyclischen Ring bedeutet, der 3 bis 8 Ringkohlenstoffatome enthält; Cycloalkenyl einen ungesättigten, nicht-aromatischen carbocyclischen Ring bedeutet, der 3 bis 10 Ringkohlenstoffatome und mindestens eine Doppelbindung enthält; Aryl sich auf einen aromatischen Carbocycle bezieht, der zwischen 6 und 10 Kohlenstoffatome enthält; Heteroaryl einen aromatischen Cyclus mit 5 bis 10 Ringatomen bezeichnet, von denen 1 bis 4 unabhängig voneinander aus der Gruppe, bestehend aus O, S und N, ausgewählt sind; ein heterocyclischer Ring Heteroaryl wie oben definiert und Cycloalkyl oder Cycloalkenyl, unterbrochen von 1, 2 oder 3 Heteroatomen, ausgewählt aus O, S, S(=O), SO₂ oder N, beinhaltet; eine bicyclische Gruppe zwei Cylken bezeichnet, die dieselben oder verschieden sind und die ausgewählt sind aus Aryl, einem heterocyclischen Ring, Cycloalkyl oder Cycloalkenyl, die unter Bildung der bicyclischen Gruppe miteinander kondensiert sind.

2. Verbindung gemäß Anspruch 1, worin X₁, X₂ und X₃ dasselbe oder verschieden sind und für C-R¹ stehen, worin R¹ ausgewählt ist aus:

- Wasserstoff, Halogen, CN, SO₃H, NO₂, CF₃, OR², SR², NR²R³, COR², COOR², CONR²R³, SO₂CH₃, SO₃HNR²R³, worin R² und R³ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, gegebenenfalls substituiert mit Halogen, CN, OR₆, COOR₆, NR₆R₇, SO₂NR₆R₇ oder C(=O)NR₆R₇, worin R₆ und R₇ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, und R⁶ und R⁷ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können;
- Niederalkyl, Niederalkynyl oder Niederalkynyl, wobei diese Gruppen unsubstituiert oder mit 1, 2 oder 3 Gruppen substituiert sind, die aus Halogen, CN, SO₃H, OR², COOR², NR₄R⁵, SO₂NR₄R⁵ oder C(=O)NR₄R⁵ ausgewählt sind, worin R⁴, R⁵ und R⁶ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, und R⁴ und R⁵ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können;
- der Gruppe X⁵-R⁵, in der
  - X⁵ ausgewählt ist aus Niederalkylren oder einer Einfachbindung und
  - R⁵ ausgewählt ist aus Phenyl, Pyridyl oder Indolyl,

wobei diese Gruppen unsubstituiert oder substituiert sind mit 1, 2 oder 3 Gruppen, ausgewählt aus Q₃, Heteraryl oder Niederalkyl, gegebenenfalls substituiert mit Q₃,

worin Q₃ ausgewählt ist aus:

- Halogen, CN, SO₃H, NO₂, CF₃, OR², OC(=O)R², C(=O)R², C(=O)OR², NH-C(=O)R², NR₆R⁷, SO₂NR₆R⁷ oder C(=O)NR₆R⁷, worin R², R⁶ und R⁷ dasselbe oder verschieden sind und ausgewählt sind aus:
- Wasserstoff, Niederalkyl, unsubstituiert oder substituiert mit einer oder mehreren Gruppen, ausgewählt aus Halogen, OR₆, COOR₆ oder NR₆R⁷, worin R₆ und R⁷ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, und
- R₆ und R⁷ und/oder R³ und R⁴ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann und der substituiert sein kann, mit
  - einem 4- bis 8-gliedrigen heterocyclischen Ring, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N enthalten kann und der mit einer Niederalkylgruppe substituiert sein kann, oder
  - einem Niederalkyl, gegebenenfalls substituiert mit OR⁴, NR⁴, C(=O)NR⁴R⁵ oder COOR⁴, worin R⁴ und R⁵ dasselbe oder verschieden sind und ausgewählt sind aus:
    - H oder
    - Niederalkyl, gegebenenfalls substituiert mit OR oder COOR, worin R Wasserstoff oder Niederalkyl
ist, und

R' und R" zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann.

3. Verbindung gemäß Anspruch 1, worin X₁, X₂ und X₃ dasselbe oder verschieden sind und für C·R¹ stehen, worin R¹ ausgewählt ist aus:

- Q1 oder
  - Niederalkyl, Niederalkenyl oder Niederalkinyl, wobei diese Gruppen unsubstituiert oder mit 1, 2 oder 3 Q2-Gruppen substituiert sind;
  - der Gruppe X²-R⁵, worin

    - X² ausgewählt ist aus:
      - einer Einfachbindung,
      - einem Niederalkylring, gegebenenfalls unterbrochen von 1 Heteroatom, ausgewählt aus O, S und N;

    - R⁵ ausgewählt ist aus Aryl, Heteroaryl, Cycloalkyl, gegebenenfalls unterbrochen von C(=O) oder von 1, 2 oder 3 Heteroatomen, ausgewählt aus O, S, S(=O), SO₂ oder N, Cycloalkenyl, gegebenenfalls unterbrochen von C(=O) oder von 1, 2 oder 3 Heteroatomen, ausgewählt aus O, S, S(=O), SO₂ oder N, oder einer bicyclischen Gruppe,

wobei diese Gruppen unsubstituiert oder substituiert sind mit 1, 2 oder 3 Gruppen, ausgewählt aus Q3, Heteroaryl oder Niederalkyl, gegebenenfalls substituiert mit Q3;

worin Q1, Q2, Q3 dasselbe oder verschieden sind und ausgewählt sind aus:

- Wasserstoff, Halogen, CN, NO₂, SO₂H,
- OR², OC(=O)R², C(=O)OR², SR², S(=O)R², C(=O)·NH·SO₂·CH₃, NR³R⁴, Q·R², Q·NR³R⁴, NR²·Q·NR³R⁴ oder NR³·Q·R², worin Q ausgewählt ist aus C(=NR), C(=O), C(=S) oder SO₂; R ausgewählt ist aus Wasserstoff oder Niederalkyl und R², R³ und R⁴ dasselbe oder verschieden sind und ausgewählt sind aus:

  - Wasserstoff,
  - Niederalkyl, gegebenenfalls unterbrochen von C(=O), Q₄-Aryl, Q₄-Heteroaryl, Q₄-Cycloalkyl, gegebenenfalls unterbrochen von C(=O) oder von 1 oder 2 Heteroatomen, ausgewählt aus O, S, S(=O), SO₂ oder N, oder Q₄-Cycloalkenyl, gegebenenfalls unterbrochen von C(=O) oder von 1 oder 2 Heteroatomen, ausgewählt aus O, S, S(=O), SO₂ oder N, worin

    - Q₄ ausgewählt ist aus (CH₃)ₙ, Niederalkyl, unterbrochen von einem Heteroatom, ausgewählt aus O, S oder N, Niederalkenylin oder Niederalkinyl, wobei diese Gruppen gegebenenfalls substituiert sind mit Niederalkyl, OR² oder NR³R⁴, worin R' und R" dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl;
    - n eine ganze Zahl ist, die aus 0, 1, 2, 3 oder 4 ausgewählt ist;

    - wobei diese Gruppen unsubstituiert oder substituiert sind mit 1 oder 2 Gruppen, ausgewählt aus Niederalkyl, Halogen, CN, CH₃, SO₂H, SO₂CH₃, CF₃, C(=O)·NH·SO₂·CH₃, OR⁶, COOR⁶, C(=O)R⁶, NR⁶R⁷, C(=O)NR⁶R⁷ oder SO₂NR⁶R⁷, worin R⁶ und R⁷ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, gegebenenfalls substituiert mit einer oder zwei Gruppen, ausgewählt aus OR, COOR oder NRR⁶, worin R und R⁸ Wasserstoff oder Niederalkyl sind, und
    - R⁶ und R⁷ und/oder R³ und R⁴ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O, S, S(=O), SO₂ oder N, enthalten kann und der mit einer Niederalkylgruppe substituiert sein kann, oder
    - einem Niederalkyl, gegebenenfalls substituiert mit OR², NR³R⁴, C(=O) NR³R⁴ oder COOR⁶, worin R' und
R* dasselbe oder verschieden sind und ausgewählt sind aus

- H oder
- Niederalkyl, gegebenenfalls substituiert mit OR oder COOR, worin R Wasserstoff oder Niederalkyl

ist und

R' und R* zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann.

10 4. Verbindung gemäß Anspruch 3, worin X₁, X₂ und X₃ dasselbe oder verschieden sind und für C-R¹ stehen, worin R¹ ausgewählt ist aus:

- Q₁ oder
- Niederalkyl oder Niederalkynyl, wobei diese Gruppen unsubstituiert oder substituiert sind mit 1, 2 oder 3 Fluoratomen, OR³, COOR³ oder NR³R⁴, worin R³ und R⁴ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl oder Niederalkylnyl oder R³ und R⁴ zusammen mit dem Stickstoffatom, an das sie gebunden sind, auch einen 6-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus C oder N, enthalten kann;

- der Gruppe X⁵-R⁵, worin X⁵ eine Einfachbindung ist und R⁵ ausgewählt ist aus Aryl, Heteroaryl oder einer bicyclischen Gruppe, wobei diese Gruppen unsubstituiert oder substituiert sind mit 1, 2 oder 3 Gruppen, ausgewählt aus Q₃,

wobei Q₁ und Q₃ dasselbe oder verschieden sind und ausgewählt sind aus

- Wasserstoff, Halogen, CN, Niederalkyl,
- OR², C(=O)OR², NR³R⁴, C(=O)NR³R⁴ oder SO₂NR³R⁴, worin R³, R⁴ und R⁵ dasselbe oder verschieden sind und ausgewählt sind aus:

- Wasserstoff,
- Niederalkyl, Q₄-Heteroaryl, worin Q₄ ausgewählt ist aus Niederalkyl, unterbrochen von einem Heteroatom, ausgewählt aus O, S oder N, und (CH₂)m, worin n eine ganze Zahl ist, die aus 0, 1, 2 oder 3 ausgewählt ist; wobei diese Gruppen unsubstituiert oder substituiert sind mit 1 oder 2 Gruppen, ausgewählt aus Niederalkyl, CN, SO₂H, C(=O)-NH₂, OR⁶, COOR⁶ oder NR₆R⁷,

worin R⁶ und R⁷ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, gegebenenfalls substituiert mit einer oder zwei Gruppen, ausgewählt aus OR, COOR oder NRR₆, worin R und R⁶ Wassertstoff oder Niederalkyl sind, und

- R⁶ und R⁷ und/oder R³ oder R⁴ zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 6-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O oder N, enthalten kann und der substituiert sein kann mit:

- einem 6-gliedrigen heterocyclischen Ring, der ein oder zwei Heteroatome, ausgewählt aus O oder N, enthalten kann und der substituiert sein kann mit einem Niederalkyl, oder
- einem Niederalkyl, gegebenenfalls substituiert mit OR⁴, NR'R⁵, C(=O) NR'R⁵ oder COOR⁴, worin R' und R* dasselbe oder verschieden sind und ausgewählt sind aus

- H oder
- Niederalkyl, gegebenenfalls substituiert mit OR oder COOR, worin R Wassertstoff oder Niederalkyl

ist, und

R' und R* zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 6-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O oder N, enthalten kann.

5. Verbindung gemäß Anspruch 3, worin X₄ für C-R¹ steht, worin R¹ ausgewählt ist aus Wasserstoff, Halogen, OR², COR², COOR² oder CONR²R³, worin R² und R³ dasselbe oder verschieden sind und ausgewählt sind aus

- Wasserstoff,
- Niederalkyl, Q₄-Aryl, Q₄-Heteroaryl, Q₄-Cycloalkyl, gegebenenfalls unterbrochen von C(=O) oder von 1 oder
2 Heteroatomen, ausgewählt aus O, S oder N, oder
Q4-Cycloalkenyl, gegebenenfalls unterbrochen von C(=O) oder von 1 oder 2 Heteroatomen, ausgewählt aus O, S oder N, worin

- Q4 ausgewählt ist aus (CH2)n, Niederalkyl, unterbrochen von einem Heteroatom, ausgewählt aus O, S oder N, Niederalkenyl oder Niederalkynyl;
- n eine ganze Zahl ist, die aus 0, 1, 2 oder 3 ausgewählt ist;
- wobei diese Gruppen unsubstituiert oder substituiert sind mit Niederalkyl, CN, OR6, SO3H, C(=O)-NH-SO2-CH3, CONR6R7, COOR6, COR6 oder NR6R7,
worin R6 und R7 dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, gegebenenfalls substituiert mit NH2, COOH oder OH;
R6 und R7 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 8-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann und der substituiert sein kann mit:

- (CH2)n-Q5, worin n eine ganze Zahl ist, die aus 0, 1, 2 und 3 ausgewählt ist, und Q5 ein 4- bis 8-gliedriger heterocyclischer Ring ist, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann und der mit einem Niederalkyl substituiert sein kann, oder
- COR1 oder Niederalkyl, gegebenenfalls substituiert mit OR1, NR1R2, C(=O)NR1R2 oder COOR1, worin R1 und R2 dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl;

- Niederalkyl, gegebenenfalls substituiert mit CN, SO3H, OR3, NR3R4, COOR3 oder CONR3R4, worin R3 und R4 dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff und Niederalkyl, gegebenenfalls substituiert mit OH, COOH oder NH2;
- der Gruppe X5-R5, worin X5 ein Niederalkyl, gegebenenfalls unterbrochen von einem Heteroatom, ausgewählt aus O und N, ist und R5 ausgewählt ist aus Aryl, Heteroaryl, Cycloalkyl, gegebenenfalls unterbrochen von C (=O) oder von 1, 2 oder 3 Heteroatomen, ausgewählt aus O, S oder N, Cycloalkenyl, gegebenenfalls unterbrochen von C(=O) oder von 1, 2 oder 3 Heteroatomen, ausgewählt aus O, S oder N,

wobei diese Gruppen unsubstituiert oder substituiert sind mit OR3 oder COOR3, worin R3 ausgewählt ist aus Wasserstoff und Niederalkyl;
R3 und R4 zusammen mit dem Stickstoffatom, an das sie gebunden sind, einen 4- bis 6-gliedrigen heterocyclischen Ring bilden können, der ein oder zwei Heteroatome, ausgewählt aus O oder N, enthalten kann und der substituiert sein kann mit

- (CH2)n-Q5, worin n eine ganze Zahl ist, die aus 0, 1, 2 und 3 ausgewählt ist, und Q5 ein 4- bis 8-gliedriger heterocyclischer Ring ist, der ein oder zwei Heteroatome, ausgewählt aus O, S oder N, enthalten kann und der mit einem Niederalkyl substituiert sein kann, oder
- C(=O)-R1' oder einem Niederalkyl, gegebenenfalls substituiert mit OR1', NR1'R2, C(=O)NR1'R2 oder COOR1', worin R1' und R2 dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl.

6. Verbindung gemäß Anspruch 3, worin X1 für C-R1 besteht, worin R1 ausgewählt ist aus Wasserstoff, Halogen oder OR2, worin R2 ausgewählt ist aus

- Wasserstoff,
- Niederalkyl, unsubstituiert oder substituiert mit CN, C(=O)-NH-SO2-CH3, OR6, SO3H, COOR6 oder NR6R7;
- Q4-Oxadiazol, Q4-Tetrazol, Q4-Morpholin, Q4-Furan, Q4-Isoxazol, worin Q4 ausgewählt ist aus Niederalkyl, unterbrochen von einem Heteroatom, ausgewählt aus O, S oder N, und (CH2)n, worin n eine ganze Zahl ist, die aus 1 und 2 ausgewählt ist;

wobei diese Gruppen unsubstituiert oder substituiert sind mit CH3, OR6 oder COOR6, worin R6 und R7 dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl, gegebenenfalls substituiert mit NH2 oder COOH.

7. Verbindung gemäß einem der Ansprüche 3, 5 und 6, worin X2 für C-R1 besteht, worin R1 für X5-R5 steht, worin

- X5 eine Einfachbindung ist,
Verbindung gemäß einem der Ansprüche 3 bis 7, worin eines aus X₁, X₂ und X₃ für C-R¹ steht, worin R¹ Wasserstoff ist, während die anderen identisch oder verschieden sind und für C-R¹ stehen, worin R¹ nicht für Wasserstoff steht.

9. Verbindung gemäß Anspruch 8, worin X₃ für C-R¹ steht, worin R¹ für Wasserstoff steht.

10. Verbindung gemäß einem der Ansprüche 3 bis 8, worin X₃ für C-R¹ steht, worin R¹ ausgewählt ist aus:

- Wasserstoff oder Halogen, oder
- X⁵-R⁵, worin X⁵ eine Einfachbindung ist und R⁵ Aryl oder Heteroaryl ist, gegebenenfalls substituiert mit einer, zwei oder drei Gruppen, die dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff, CN, CF₃, SO₂Me, OR², COOR², NR²R³, SΟ₂NR²R³ und CONR²R³, worin R² und R³ dasselbe oder verschieden sind und ausgewählt sind aus Wasserstoff oder Niederalkyl.

11. Verbindung gemäß Anspruch 10, worin X₃ für C-R¹ steht, worin R¹ ausgewählt ist aus Wasserstoff oder Halogen.

12. Verbindung gemäß Anspruch 1, ausgewählt aus der Gruppe, bestehend aus:

8'-Chlorspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Methyglyspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Bromspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Fluorspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5',8'-Dichlorspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Bromspiro[cycloheptan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
6',8'-Dichlorspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-iodspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-methoxyspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-phenylspiro[cycloheptan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-phosphyspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-methylylspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(3-pyridyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(4-pyridyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
6'-[(4-Carboxyphenyl)-8'-chlorospiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
6'-[(3-Carboxyphenyl)-8'-chloorospiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[1H-indol-5-yl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(2-pyridyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(3-dimethylaminoprop-1-yl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(3-methylaminoprop-1-yl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[(4-(4-methylpiperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(4-(3-N-dimethylaminopropylcarboxamid)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(3-(4-methylpiperazin-1-carbonyl)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(3-(4-N-dimethylaminopropylcarboxamid)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(4-(4-pyrimidin-2-yl)piperazin-1-carbonyl)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(4-(4-(2-morpholin-4-y1)piperazin-1-carbonyl)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(3-(4-(2-morpholin-4-y1-2-oxoethyl)piperazin-1-carbonyl)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(4-(4-[(2-hydroxyethoxy)ethyl]piperazin-1-carbonyl)phenyl)spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-methoxypropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on, 5'-8'-Difluoropropyloxcyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-methylpropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on, 8'-Chlor-6'-[m(morpholin-4-y1)methylpropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-hydroxypropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-(iodopropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[m(morpholin-4-y1)methylpropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(4-morpholin-4-y1)ethoxyxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(dimethylaminooxyethoxy)xycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(aminooxyethoxy)xycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(methylaminooxyethoxy)xycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(a(minoxyethoxy)xycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[3-dimethylaminopropoxyxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[ethoxyxycarbonylmethylpropoxyxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxymethoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chloropropyloxycyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Trifluormethyspirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-cyanomethylspirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[3-dimethylamino-2-hydroxypropoxy]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[3-methylamino-2-hydroxypropoxy]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(ethoxycarbonylmethylamino)ethoxy]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(carboxymethylamino)ethoxy]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on-Hydrochlorid,
or ein pharmazeutisch annehmbares Salz, Solvat, Hydrat oder Polymorphes davon.

13. Verbindung gemäß Anspruch 1, ausgewählt aus der Gruppe, bestehend aus:
8'-Bromspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-methoxySpiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Bromspiro[cycloheptan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-methoxyspirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-phenylspiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-pyridyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-pyridyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
6'-[4-(Carboxyphenyl)]-8'-chlorSpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
6'-[3-Carboxyphenyl)]-8'-chlorSpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[1H-indol-5-yl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[2-pyridyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-dimethylaminoprop-1-yl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-methylyaminoprop-1-yl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(4'-methylpiperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(3-N-dimethylaminopropylcarboxyamid)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(2-N-dimethylaminoethylcarboxyamid)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-N-dimethylaminopropylcarboxyamid)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-[4'-methylpiperazin-1-carbonyl]phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[3-(2-N-dimethylaminoethylcarboxyamid)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(4-pyrimidin-2-yl)piperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(2-morpholin-4-ylethyl)piperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-6'-[4-(2-hydroxyethoxy)ethyl)piperazin-1-carbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
8'-Chlor-5'-nmethoxySpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-methylspirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-hydroxySpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-6'-cyano-5'-methoxySpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[2-(morpholin-4-yl-2-oxoethyl)piperazin-1-earbonyl)phenyl]spiro[cyclohexan-1-4'-(3',4'-dihydro)-chinazolin]-2'(1'H)-on,
5'-Carboxymethoxy-8'-chlorSpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
5'-Carboxypropoxy-8'-chlorSpirocyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
8'-Chlor-5'-[3-sulffopropoxy]spiro[cyclohexan-1-4'-(3',4'-dihydro)chinazolin]-2'(1'H)-on,
Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, worin X
Verwendung gemäß Anspruch 16, wobei die Störung ausgewählt ist aus T-
Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 13 in Kom-
Verbindung gemäß einem der Ansprüche 1 bis 13 zur Verwendung als ein Arzneimittel.
Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, in der Z für O steht, umfassend das
worin A wie in Anspruch 1 definiert ist, um die Verbindung der Formel (I) zu erhalten, und Isolieren der Verbindung
oder ein pharmazeutisch verträgliches Salz, Solvat, Hydrat oder Polymorphes davon.
Verbindung gemäß einem der Ansprüche 1 bis 13 zur Verwendung als ein Arzneimittel.
Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem der Ansprüche 1 bis 13 in Kombi-
Verwendung einer Verbindung gemäß einem der Ansprüche 1 bis 13 zur Herstellung eines Arzneimittels zur Prä-
Verwendung gemäß Anspruch 16, wobei die Störung ausgewählt ist aus T-Zellenvermittelten Krankheiten, Autoim-
Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, in der Z für O steht, umfassend das
worin X₁, X₂, X₃ und X₄ wie in Anspruch 1 definiert sind, mit einem cyclischen Keton der Formel
worin A wie in Anspruch 1 definiert ist, um die Verbindung der Formel (I) zu erhalten, und Isolieren der Verbindung
der Formel (I).
Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1, worin X₁, X₂, X₃, X₄ und A wie in
Anspruch 1 definiert sind, wobei das Verfahren die folgenden Stufen umfasst:
(1) Umsetzen einer Verbindung (2a)

worin $X_1$, $X_2$, $X_3$ und $X_4$ wie in Anspruch 1 definiert sind, mit einer Gruppe $P$-$LG$,
worin $P$ für eine Schutzgruppe steht und $LG$ für eine Abgangsgruppe steht, um eine Verbindung (2b) zu erhalten

(2) Umsetzen der Verbindung (2b) mit $R$-$Li$, worin $R$ eine Niederalkylgruppe ist, und dann mit einem Keton der Formel

worin $A$ wie in Anspruch 1 definiert ist, um eine Verbindung (2c) zu erhalten

(3) Entfernen der Schutzgruppe $P$ entweder unter reduktiven Bedingungen, saurer Bedingung oder basischer Bedingung, um Verbindung (2d) zu erhalten
(4) Umsetzen der Verbindung (2d) mit einer Gruppe O=C=N-, um eine Verbindung (2e) zu erhalten

(5) Umsetzen der Verbindung (2e) mit einer Säure, um die Verbindung der Formel (I) zu erhalten,
(6) Isolieren der Verbindung der Formel (I).

Revendications

1. Composés répondant à la formule (I) suivante:

   dans laquelle:
   
   X₁, X₂ et X₃ sont identiques ou différents et sont choisis parmi des groupes C-R¹, dans lesquels R¹ est choisi entre :
   
   - Q1, ou
   - un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes Q₂ ;
   
   - le groupe X⁵-R⁵ dans lequel
   
   - X⁵ est choisi entre une liaison simple et un groupe alkylène inférieur, facultativement interrompu avec un hétéroatome choisi entre O, S et N ; et
   - R⁵ est choisi entre des groupes aryle, hétéroaryle, cycloalkyle facultativement interrompu avec un groupe
C(=O) ou avec 1, 2 ou 3 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, cycloalcényle facultativement interrompu avec un groupe C(=O)

ou avec 1, 2 ou 3 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, ou un groupe bicyclique,

ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes choisis entre des groupes Q₃, hétéroaryle et alkyle inférieur facultativement substitué avec Q₃ ;

dans lesquels Q₁, Q₂, Q₃ sont identiques ou différents et sont choisis entre

- un atome d’hydrogène, un atome d’halogène, des groupes CN, NOₓ, SOₓH,
- un groupe OR², OC(=O)R², C(=O)OR², SR², S(=O)₂R², C(=O)NH-SOₓ₂CH₃, NR₃R₄, O-R₂Q-NR₃R₄, NR²Q₄ ou NR³-Q-R² dans lequel Q est choisi entre des groupes C(=O), C(=S) et SO₂, R est choisi entre un atome d’hydrogène et un groupe alkyle inférieur et R², R³ et R⁴ sont identiques ou différents et sont choisis entre :

- Q₄ est choisi entre des groupes (CH₂)ₙ, alkyle inférieur interrompu avec un hétéroatome choisi entre O, S et N, alcényle inférieur ou alcynyle inférieur, ces groupes étant facultativement substitués avec un substituant alkyle inférieur, OR’ ou NR’R” dans lequel R’ et R” sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur ;
- n représente un nombre entier choisi entre 0, 1, 2, 3 et 4 ;

ces groupes étant non substitués ou substitués avec 1 ou 2 groupes choisis entre des groupes alkyle inférieur, halogéno, CN, CH₃, SO₂H, SO₂CH₃, C(=O)-NH-SO₂CH₃, CF₃, OR⁶, COO(CH₂)₆, C(=O)R⁶, NR⁶R⁷, C(=O)NR⁶R⁷ et SO₂NR⁶R⁷, dans lesquels R⁶ et R⁷ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur facultativement substitué avec un ou deux groupes choisis entre des groupes OR, COOR et NRR⁸ dans lesquels R et R⁸ représentent des atomes d’hydrogène ou des groupes alkyle inférieur, et - R⁶ et R⁷, et/ou R³ et R⁴, conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S, S(=O), SO₂ et N, et qui peut être substitué avec,

- un groupe (CH₂)ₙ-Q₅, dans lequel n représente un nombre entier choisi entre 0, 1, 2 et 3, et Q₅ représente un noyau hétérocyclique tétra- à octogonal qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec un substituant alkyle inférieur, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR’, NR’R” ou COOR’ dans lequel R’ et R” sont identiques ou différents et sont choisis entre :

- H, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR ou COOR dans lequel R représente un atome d’hydrogène ou un groupe alkyle inférieur, et

R’ et R”, conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N ;

X₄ représente un groupe C-R¹, dans lequel R¹ est choisi entre des groupes F, Cl, Br, CF₃ et CH₃ ;
Z représente un O ou un groupe N-CN ; et
A représente un groupe cyclohexyle non substitué ou cycloheptyl non substitué ;
or leurs formes tautomères, leurs formes racémiques ou leurs isomères et leurs sels, produits de solvatation, hydrates et formes polymorphes pharmaceutiquement acceptables ;
étant entendu que :

les expressions "alkyle inférieur" et "alkylène inférieur" désignent des chaînes carbonées droites et ramifiées ayant 1 à 6 atomes de carbone ;
Composé suivant la revendication 1, dans lequel X, X2 et X3 sont identiques ou différents et représentent un groupe C-R1, dans lequel R1 est choisi entre :  
- un atome d'hydrogène, un atome d'halogène, des groupes CN, SO2H, NO2, CF3, OR2, SR2, NR2R3, COR2, COOR2, CONR2R3R4, SO2CH3, SO2NR2R3, dans lesquels R2 et R3 sont identiques ou différents et sont choisis entre un atome d'hydrogène et un groupe alkyloxy inférieur facultativement substitué avec un atome d'halogène, un groupe CN, OR, COOR, NR2R3, SO2NR2R3, dans lesquels R2 et R3 sont identiques ou différents et sont choisis entre un atome d'halogène et un groupe alkyloxy inférieur, et R6 et R7, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal ;  
- un groupe alkyloxy inférieur, alcènyle inférieur ou alcynyle inférieur, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes choisis entre des groupes halogéno, OR, COOR, NR2R3, SO2NR2R3 et C (=O) NR2R3 dans lesquels R2, R3 et R4 sont identiques ou différents et sont choisis entre un atome d'halogène et un groupe alkyloxy inférieur, et R3 et R4, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal ;  
- le groupe X5-R6, dans lequel  
- X5 est choisi entre un groupe alkyloxy inférieur et une liaison simple, et  
- R6 est choisi entre des groupes phényle, pyridyle et indolye, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes choisis entre des groupes Q3, hétéroatome et alkyloxy inférieur facultativement substitué avec Q3, Q3 étant choisi entre des groupes :  
- halogéno, CN, SO2H, NO2, CF3, OR2, OC(=O)R2, C(=O)OR2, C(=O)OR2, NH-C(=O)OR2, NR3R4, SO2NR3R4 et C(=O)NR3R4 dans lesquels R2, R3 et R4 sont identiques ou différents et sont choisis entre :  
- un atome d'hydrogène, un groupe alkyloxy inférieur non substitué ou substitué avec un ou plusieurs groupes choisis entre des groupes halogéno, OR, COOR et NR3R4 dans lesquels R2 et R3 sont identiques ou différents et sont choisis entre un atome d'halogène et un groupe alkyloxy inférieur, et les groupes R6 et R7, et/ou R3 et R4, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N, et qui peut être substitué avec  
- un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec un substituant alkyloxy inférieur, ou  
- un groupe alkyloxy inférieur facultativement substitué avec un groupe OR, NR3R4, C (=O) NR3R4 ou COOR dans lequel R2 et R3 sont identiques ou différents et sont choisis entre  
- H, ou  
- un groupe alkyloxy inférieur facultativement substitué avec un substituant OR ou COOR dans lequel R représente un atome d'halogène ou un groupe alkyloxy inférieur, et R2 et R3, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra-
octagonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N.

3. Composé suivant la revendication 1, dans lequel X₁, X₂ et X₃ sont identiques ou différents et représentent un groupe C-R¹, dans lequel R¹ est choisi entre :

- un groupe Q₁, ou
- un groupe alkyle inférieur, alcényle inférieur ou alcynyle inférieur, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes Q₂;
- le groupe X²-R³, dans lequel X² est choisi entre :
  - une liaison simple,
  - un groupe alkylène inférieur, facultativement interrompu avec 1 hétéroatome choisi entre O, S et N ;

- R⁵ est choisi entre des groupes aryle, hétéroaryle, cycloalkyle facultativement interrompu avec un groupe C(=O) ou avec 1, 2 ou 3 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, cycloalcényle facultativement interrompu avec un groupe C(=O) ou avec 1, 2 ou 3 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, ou un groupe bicyclique, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes choisis entre des groupes Q₃, hétéroaryle et alkyle inférieur facultativement substitué avec Q₃ ;

dans lequel Q₁, Q₂ et Q₃ sont identiques ou différents et sont choisis entre :

- un atome d’hydrogène, un atome d’halogène, des groupes CN, NO₂, SO₃H, un groupe OR², OC(=O)R², C(=O)OR², SR², S(=O)R², C(=O)-NH-SO₂-CH₃, NR³R⁴, Q-R², Q-NR³R⁴, NR²-Q- NR³R⁴ ou NR³-Q-R² dans lequel Q est choisi entre des groupes C(=N), C(=O), C(=S) et SO₂, R est choisi entre un atome d’hydrogène et un groupe alkyle inférieur et R², R³ et R⁴ sont identiques ou différents et sont choisis entre :

- un atome d’hydrogène,
- un groupe alkyle inférieur facultativement interrompu avec un groupe C(=O), Q4-aryle, Q4-hétéroaryle, Q4-cycloalkyle facultativement interrompu avec un groupe C(=O) ou avec 1 ou 2 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, ou Q4-cycloalcényle facultativement interrompu avec un groupe C(=O) ou avec 1 ou 2 hétéroatomes choisis entre O, S, S(=O), SO₂ et N, dans lesquels

- Q₄ est choisi entre des groupes (CH₃)ₙ, alkyle inférieur interrompu avec un hétéroatome choisi entre O, S et N, alcényle inférieur ou alcynyle inférieur, ces groupes étant facultativement substitués avec un substituant alkyle inférieur, OR² ou NR²R² dans lequel R² et R³ sont identiques ou différents ;
- n représente un nombre entier choisi entre 0, 1, 2, 3 et 4 ;
- ces groupes étant non substitués ou substitués avec 1 ou 2 groupes choisis entre des groupes alkyle inférieur, halogène, CN, CH₃, SO₂H, SO₂CH₃, CF₃, C(=O)-NH-SO₂-CH₃, OR⁵, COOR⁶, C(=O)R⁶, NR⁴R⁷, C(=O)NR⁴R⁷ et SO₂NR⁴R⁷, dans lesquels R⁶ et R⁷ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur facultativement substitué avec un ou deux groupes choisis entre des groupes OR, COOR et NRR⁶ dans lesquels R et R⁸ représentent des atomes d’hydrogène ou des groupes alkyle inférieur, et

- R⁶ et R⁷, et/ou R⁸ et R⁹, conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S, SO₂ et N, et qui peut être substitué avec :

- un groupe (CH₂)ₙ-Q₅, dans lequel n représente un nombre entier choisi entre 0, 1, 2 et 3, et Q₅ représente un noyau hétérocyclique tétra- à octogonal qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec un substituant alkyle inférieur, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR¹, NR¹R¹, C(=O)NR¹R¹ ou COOR¹ dans lequel R¹ et R² sont identiques ou différents et sont choisis entre :
- H, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR ou COOR dans lequel R représente un atome d'hydrogène ou un groupe alkyle inférieur, et

R' et R", conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N.

4. Composé suivant la revendication 3, dans lequel X₁, X₂ et X₃ sont identiques ou différents et représentent un groupe C-R¹, dans lequel R¹ est choisi entre :

- un groupe Q₁, ou
- un groupe alkyle inférieur ou alcynyle inférieur, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 atomes de fluor, des groupes OR₂, COOR₂ ou NR₃R₄ dans lesquels R₂ et R₄ sont identiques ou différents et sont choisis entre un atome d'hydrogène et un groupe alkyle inférieur, ou bien R₃ et R₄, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former également un noyau hétérocyclique hexagonal, qui peut contenir un ou deux hétéroatomes choisis entre O et N;
- le groupe X⁵-R⁵ dans lequel X⁵ représente une liaison simple et R⁵ est choisi entre un groupe aryle, un hétéroaryle et un groupe bicyclique, ces groupes étant non substitués ou substitués avec 1, 2 ou 3 groupes choisis parmi des groupes Q₃,

dans lesquels Q₁ et Q₃ sont identiques ou différents et sont choisis entre :

- un atome d'hydrogène, un atome d'halogène, un groupe CN, un groupe alkyle inférieur,
- un groupe OR₂, C(=O)OR₂, NR₃R₄, C(=O)NR₃R₄ ou SO₂NR₃R₄ dans lequel R₂, R₃ et R₄ sont identiques ou différents et sont choisis entre :

- un atome d'hydrogène,
- un groupe alkyle inférieur, Q₄-hétéroaryle dans lequel Q₄ est choisi entre un groupe alkyle inférieur interrompu avec un hétéroatome choisi entre O, S et N et un groupe (CH₂)ₙ dans lequel n représente un nombre entier choisi entre 1, 2, et 3 ; ces groupes étant non substitués ou substitués avec 1 ou 2 groupes choisis entre des groupes alkyle inférieur, CN, SO₂H, C(=O)-NH-SO₂CH₃, OR₆, COOR₆ et NR₆R₇, dans lesquels R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d'hydrogène et un groupe alkyle inférieur interfacultativement substitué avec un ou deux groupes choisis entre des groupes OR, COOR et NRR⁸ dans lesquels R et R⁸ représentent un atome d'hydrogène ou un groupe alkyle inférieur, et
- R₆ et R₇, et/ou R³ et R⁴, conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O et N, et qui peut être substitué avec :

- un noyau hétérocyclique hexagonal, qui peut contenir un ou deux hétéroatomes choisis entre O et N et qui peut être substitué avec un substituant alkyle inférieur, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR¹, NR¹R", C(=O)NR¹R" ou COOR¹ dans lequel R¹ et R" sont identiques ou différents et sont choisis entre :

- H, ou
- un groupe alkyle inférieur facultativement substitué avec un substituant OR ou COOR dans lequel R représente un atome d'hydrogène ou un groupe alkyle inférieur, et

R' et R", conjointement avec l'atome d'azote auquel ils sont liés, peuvent former un noyau hétérocyclique hexagonal qui peut contenir un ou deux hétéroatomes choisis entre O et N.

5. Composé suivant la revendication 3, dans lequel X₁ représente un groupe C-R¹, dans lequel R¹ est choisi entre un atome d'hydrogène, un atome d'halogène, des groupes OR², COR² COOR² et CONR²R³ dans lesquels R² et R³ sont identiques ou différents et sont choisis entre :

- un atome d'hydrogène,
- un groupe alkyle inférieur, Q₄-aryle, Q₄-hétéroaryle, Q₄-cycloalkyle facultativement interrompu avec un groupe C(=O) ou avec 1 ou 2 hétéroatomes choisis entre O, S et N, ou Q₄-cycloalényle facultativement interrompu avec un groupe C(=O) ou avec 1 ou 2 hétéroatomes choisis entre O, S et N, dans lesquels :
Composé suivant la revendication 3, dans lequel X repré
- Q4 est choisi entre des groupes (CH₂)ₙ, alkyle inférieur interrompu avec un hétéroatome choisi entre O, S et N, alcényle inférieur ou alcynyle inférieur;
- n représente un nombre entier choisi entre 0, 1, 2 et 3;

ces groupes étant non substitués ou substitués avec des substituants alkyle inférieur, CN, OR₆, SO₃H, C(=O)-NH-SO₂-CH₃, CONR₆R₇, COOR₆, COR₆ ou NR₆R₇,
dans lesquels R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur, facultativement substitué avec un substituant NH₂, COOH ou OH ;
R₆ et R₇, conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N, et qui peut être substitué avec
- un groupe (CH₂)ₙ- Q₅, dans lequel n représente un nombre entier choisi entre 0, 1, 2 et 3, et Q₅ représente un noyau hétérocyclique tétra- à octogonal qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec un substituant alkyle inférieur, ou
- un groupe COR₆ ou alkyle inférieur facultativement substitué avec un substituant OR₆, NR₆R₇, C(=O)NR₆R₇ ou COOR₆ dans lequel R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur ;
- un groupe alkyle inférieur facultativement substitué avec un substituant CN, SO₃H, OR₃, NR₃R₄, COOR₃,
dans lequel R₃ et R₄ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur substitué avec un substituant OH, COOH ou NH₂ ;
- le groupe X₅-R₅ dans lequel X₅ représente un groupe alkylène inférieur facultativement interrompu avec un hétéroatome choisi entre O et N et R₅ est choisi entre des groupes aryle, hétéroatome, cycloalkyle facultativement interrompu avec un groupe C(=O) ou avec 1, 2 ou 3 hétéroatomes choisis entre O, S et N et cycloalkénylamine substituée avec un substituant OR₆, NR₆R₇, C(=O)NR₆R₇ ou COOR₆ dans lequel R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur ;
R₃ et R₄, conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O et N, et qui peut être substitué avec :
- un groupe (CH₂)ₙ-Q₅ dans lequel n représente un nombre entier choisi entre 0, 1, 2 et 3 et Q₅ représente un noyau hétérocyclique tétra- à octogonal qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec :
- un groupe C(=O)-R₇ ou un groupe alkyle inférieur facultativement substitué avec un substituant OR₆, NR₆R₇,
C(=O)NR₆R₇ ou COOR₆ dans lequel R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur.

6. Composé suivant la revendication 3, dans lequel X₁ représente un groupe C-R₁, dans lequel R₁ est choisi entre un atome d’hydrogène et un atome d’halogène ou un groupe OR₂ dans lequel R₂ est choisi entre :
- un atome d’hydrogène,
- un groupe alkyle inférieur, non substitué ou substitué avec un substituant CN, C(=O)-NH-SO₂-CH₃, OR₆,
SO₃H, COOR₆ ou NR₆R₇;
- un groupe Q₄-oxadiazole, Q₄-tétrazole, Q₄-morpholine, Q₄-furanne, Q₄-isoxazole, dans lequel Q₄ est choisi entre un groupe alkyle inférieur interrompu avec un hétéroatome choisi entre O, S et N et un groupe (CH₂)ₙ,
dans lequel n représente un nombre entier choisi entre 1 et 2 ;

ces groupes étant non substitués ou substitués avec un substituant CH₃, OR₆ ou COOR₆, dans lequel R₆ et R₇ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur, facultativement substitué avec un substituant NH₂ ou COOH.

7. Composé suivant l’une quelconque des revendications 3, 5 et 6, dans lequel X₂ représente un groupe C-R₁, dans lequel R₁ représente un groupe X₅ₗ-R₅, dans lequel
- x₅ représente une liaison simple
- R₅ représente un groupe phényle ou pyridyle,
- substitué avec un substituant C(=O)NR'R'' dans lequel R³ et R⁴, conjointement avec l’atome d’azote auquel ils sont liés, forment un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S, S(=O), SO₂ et N, et qui peut être substitué avec  

- un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre O, S et N et qui peut être substitué avec un substituant alkyle inférieur, ou 

- un groupe alkyle inférieur facultativement substitué avec un substituant OR', NR'R'', C(=O)NR'R'' ou COOR dans lequel R' et R" sont identiques ou différents et sont choisis entre 

- H ou 

- un groupe alkyle inférieur facultativement substitué avec un substituant OR ou COOR dans lequel R représente un atome d’hydrogène ou un groupe alkyle inférieure, et 

R' et R", conjointement avec l’atome d’azote auquel ils sont liés, peuvent former un noyau hétérocyclique tétra- à octogonal, qui peut contenir un ou deux hétéroatomes choisis entre 0, S et N. 

8. Composé suivant l’une quelconque des revendications 3 à 7, dans lequel un des groupes X₁, X₂ et X₃ représente un groupe C-R¹ dans lequel R¹ représente un atome d’hydrogène, tandis que les autres sont identiques ou différents et représentent un groupe C-R¹ dans lequel R¹ est autre qu’un atome d’hydrogène. 

9. Composé suivant la revendication 8, dans lequel X₃ représente un groupe C-R¹ dans lequel R¹ représente un atome d’hydrogène. 

10. Composé suivant l’une quelconque des revendications 3 à 8, dans lequel X₃ représente un groupe C-R¹, dans lequel R¹ est choisi entre :

- un atome d’hydrogène ou un atome d’halogène, ou 

- un groupe X⁵-R⁵ dans lequel X⁵ représente une liaison simple et R⁵ représente un atome aryle ou hétéroaire, facultativement substitué avec un, deux ou trois groupes qui sont identiques ou différents et qui sont choisis entre des groupes halogène, CN, CF₃, SO₂Me, OR², COOR² NR²R³, SO₂NR²R³ et CONR²R³, dans lesquels R² et R³ sont identiques ou différents et sont choisis entre un atome d’hydrogène et un groupe alkyle inférieur. 

11. Composé suivant la revendication 10, dans lequel X₃ représente un groupe C-R¹ dans lequel R¹ est choisi entre un atome d’hydrogène et un atome d’halogène. 

12. Composé suivant la revendication 1, choisi dans le groupe consistant en :

8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-méthylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-bromospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-fluorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
5',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-bromospiro[cycloheptane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
6',8'-dichlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-iodospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-méthoxyspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-phénylspiro[cycloheptane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-phénylspiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-méthylspirom[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-3-(3-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-4-(pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
6'-[4-carboxyphényl]-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
6'-[3-carboxyphényl]-8'-chlorospiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-(1H-indol-3'-yl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-(2'-pyridyl)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-(3-diméthylamino-prop-1-yny)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one,  
8'-chloro-6'-(3-méthylamino-prop-1-yny)spiro[cyclohexane-1-4'-(3',4'-dihydro)quinazoline]-2'(1'H)-one.
8'-chloro-6'-[4-(4-méthyl-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-diméthylamino-propylcarboxamide)-phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-diméthylamino-éthylcarboxamide)-phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-(4-méthyl-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-diméthylamino-éthylcarboxamide)-phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-cyanoiminospirocyclohexane-1-4'-](3',4'-dihydro)quinazoline
8'-chloro-6'-[4-(4-pyrimidine-2-yl-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-morpholine-4-yl-éthyl)-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-morpholine-4-yl-2-oxo-éthyl)-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-hydroxy-éthoxy)éthyl]-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-méthoxydipropyl[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
5',8'-difluoro(spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-méthylspropiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-hydroxy-6'-iodo-spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-iodo-5'-méthoxy-spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-cyano-5'-méthoxy-spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(4-morpholine-4-yl)éthoxy]-éthoxy]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(diméthylaminéthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(aminoéthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(méthylaminéthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(aminoéthoxy)éthoxy]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[3-diméthylaminopropoxy]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-éthoxy-carboxylméthoxyspropiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
5'-carboxyméthoxy-8'-chloro-spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
5'-carboxipropoxy-8'-chloro-spirocyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[3-sulfopropoxy]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(tétrahydro- pyranne-2-yloxy)-éthoxy]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[2-(hydroxy-éthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[5-(carboxy-carbonyl-furanne-2-ylméthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
45'-chloro-5'-[5-(carboxy-furanne-2-ylméthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-cyano-méthoxyspropiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[1H-tétrazole-5-ylméthoxy]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-5'-[5-hydroxy-][1,2,4]oxiadazole-3-ylméthoxy]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-iodo-5'-[2-(diméthylaminéthoxy)]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
6'-[4-carboxyphényl]-8'-chloro-5'-méthoxyspropiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
6'-[3-carboxyphényl]-8'-chloro-5'-méthoxyspropiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[2-(4-méthyl-pipérazine-1-carbonyl)phényl]-spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[2-méthyl-4-(4-méthyl-pipérazine-1-carbonyl)phényl]spiro[cyclohexane-1-4'-](3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(1-méthyl-pipéridine-4-yi)pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-chloro-5'-méthoxy-6'-[4-(4-méthyl-pipérazine-1-carbonyl]-phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-trifluorométhyl]spiro[cyclohexane-1-4'-3',4'-dihydro]-quinazoline]-2'(1'H)-one,
8'-chloro-6'-cyanométhyl]spiro[cyclohexane-1-4'-3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-chloro-5'-(3-diméthylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
8'-chloro-5'-(3-méthylamino-2-hydroxy-propoxy)-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
8'-chloro-5'-(2-(éthoxycarboxylméthyl-amino)-éthoxy]-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
chlorhydrate de 8'-chloro-5'-[2-(carboxylméthyl-amino)-éthoxy]-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
8'-chloro-5'-(2-éthanesulfonylemarnino-2-oxo-éthoxy)-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
et 8'-chloro-5'-(2-[(5-méthyl-isoxazole-3-ylméthyl)-amino]-éthoxy]-spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'-(1'H)-one,
ou un de ses sels, produits de solvatation, hydrates ou une de ses formes polymorphes, pharmaceutiquement acceptables.

13. Composé suivant la revendication 1, choisi dans le groupe consistant en :

8'-bromospiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
5',8'-dichlorospiro[cyclohexane-1-4'(3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-bromospiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-méthoxySpiro[cyclohexane-1-4'-3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-chloro-6'-phénylspiro[cyclohexane-1-4'-3',4'-dihydro)-quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-pyridyl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-pyridyl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
6'-[4-carboxyphényl]-8'-chlorospiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
6'-[3-carboxyphényl]-8'-chlorospiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[1H-indol-5y]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[2-pyridyl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-diméthylamino-prop-1-ynyl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-diméthylamino-prop-1-ynyl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(4-méthyl-pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(3-N-diméthylamino-propylcarboxamid)phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-N-diméthylamino-éthylcarboxamid)phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-(3-N-diméthylamino-propylcarboxamid)phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-(4-méthyl-pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[3-(2-N-diméthylamino-éthylcarboxamid)phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(4-pyrimidine-2-yi-pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(4-morpholine-4-yi-éthyl) pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(4-morpholine-4-yi-éthyl) pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
8'-chloro-6'-[4-(2-hydroxy-éthoxy)-éthyl]pipérazine-1-carbonyl]phényl]spiro[cyclohexane-1-4'-3',4'-dihydro)quinazoline]-2'(1'H)-one,
Utilisation d'un composé suivant l'une quelconque des revendications 1 à 13 pour la préparation d'un médicament

Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 13 en association avec un support approprié.

ou un de ses sels, produits de solvatation,hydrates ou une de ses formes polymorphes, pharmaceutiquement acceptables.

14. Composé suivant l'une quelconque des revendications 1 à 13, destiné à être utilisé comme médicament.

15. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 13 en association avec un support approprié.

16. Utilisation d’un composé suivant l’une quelconque des revendications 1 à 13 pour la préparation d’un médicament destiné à la prévention ou au traitement de troubles pour lesquels une thérapie avec un inhibiteur de PDE7 est intéressante.

17. Utilisation suivant la revendication 16, dans laquelle ledit trouble est choisi entre des maladies en rapport avec les lymphocytes T, des maladies auto-immunes, l’arthrose, la sclérose en plaques, l’ostéoporose, la maladie pulmonaire obstructive chronique, l’asthme, le cancer, le syndrome d'immunodéficience acquise, l’allergie et une maladie intestinale inflammatoire.

18. Procédé pour la préparation d’un composé de formule (I) suivant la revendication 1, dans lequel Z représente O, comprenant la réaction d’une urée substituée de formule

\[
\begin{align*}
&\text{Z} \quad \text{NH}_2 \\
\end{align*}
\]

dans laquelle X_1, X_2, X_3 et X_4 répondent aux définitions figurant dans la revendication 1, avec une cétone cyclique
19. Procédé pour la préparation d'un composé de formule (I) suivant la revendication 1, dans lequel X₁, X₂, X₃ et X₄ et A répondent aux définitions figurant dans la revendication 1, ledit procédé comprenant :

(1) la réaction d'un composé (2a)

(2) la réaction du composé (2b) avec un composé de formule R-LI, dans lequel R représente un groupe alkyle inférieur et ensuite avec une cétone de formule dans laquelle A répond à la définition figurant dans la revendication 1, pour obtenir le composé (2c)
(3) l'élimination du groupe protecteur P dans des conditions réductrices, des conditions acides ou des conditions basiques, pour obtenir le composé (2d).

(4) la réaction du composé (2d) avec un groupe \( O=C=N-H \) pour obtenir le composé (2e).

(5) la réaction du composé (2e) avec un acide pour obtenir ledit composé de formule (I).

(6) l'isolement dudit composé de formule (I).
REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

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Non-patent literature cited in the description

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