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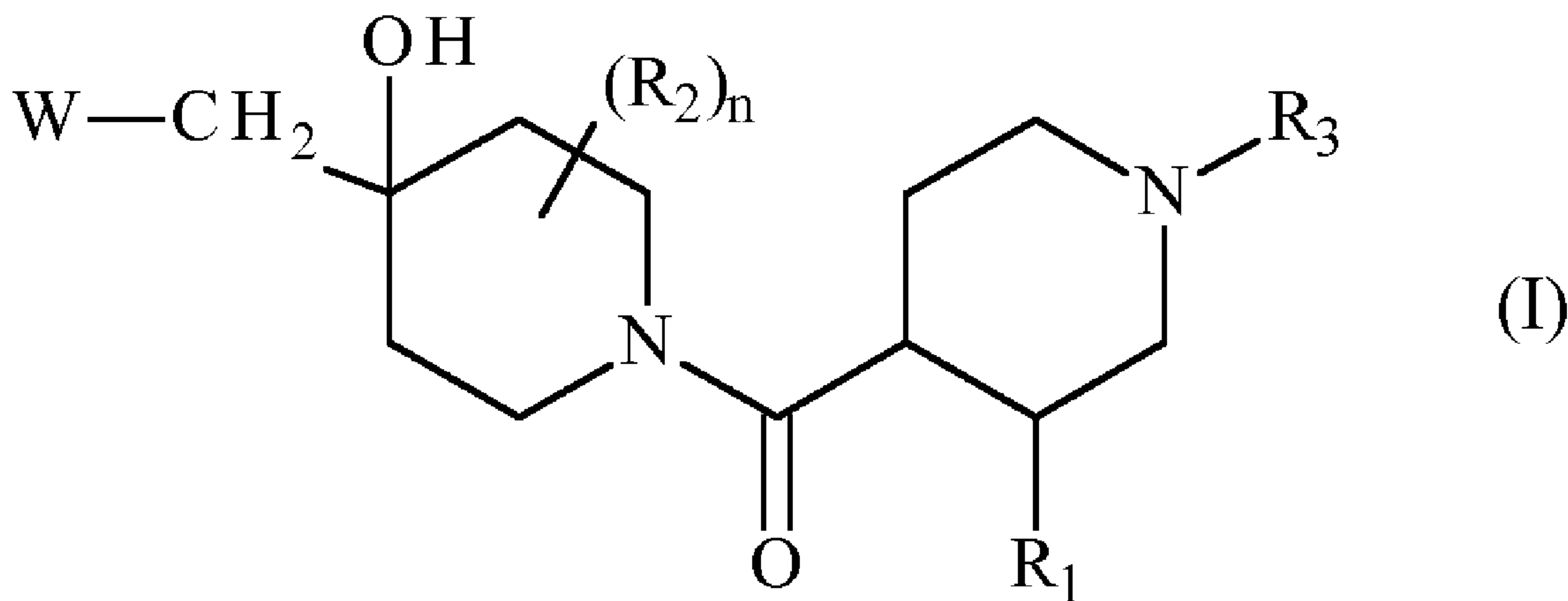
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...

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(54) Title: NEW PIPERIDINYL DERIVATIVES, A PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abrégé/Abstract:

Compounds of formula (I) wherein R_1 , R_2 , R_3 , n and W are as defined in the description. Medicaments.

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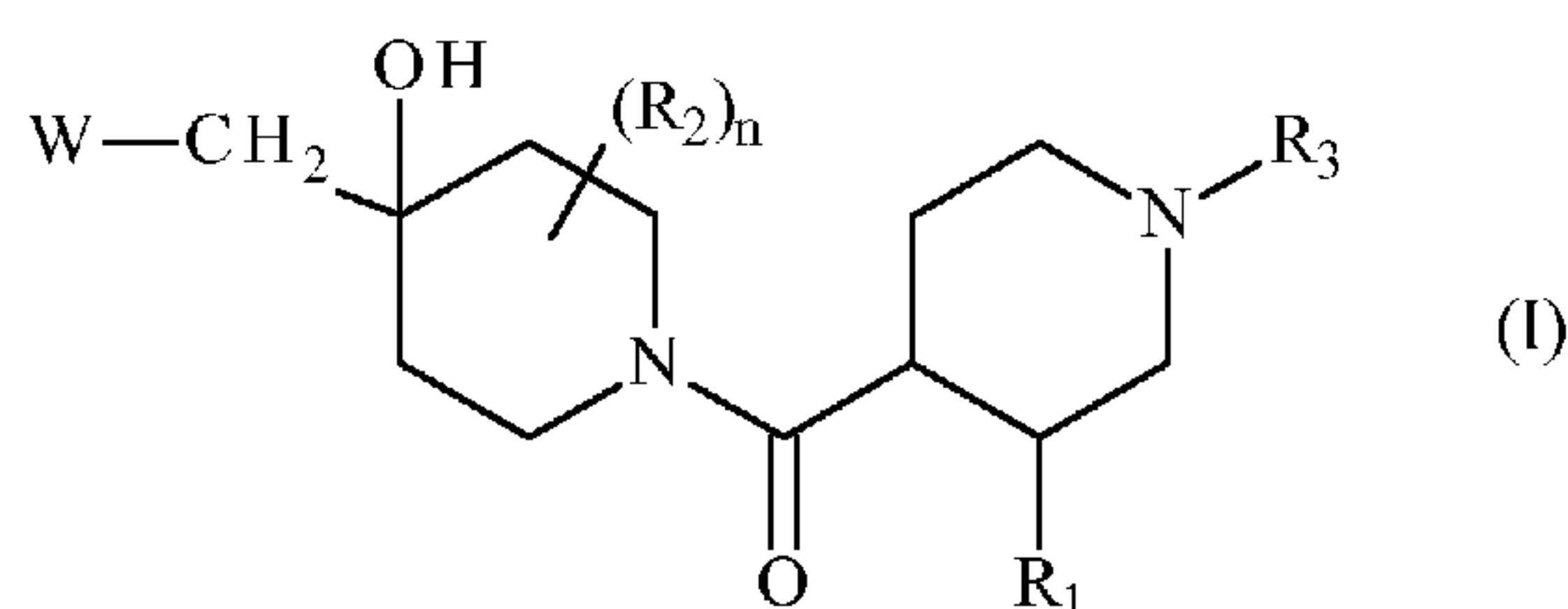
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NEW PIPERIDINYL DERIVATIVES, A PROCESS FOR THEIR PREPARATION
AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to new piperidiny l derivatives, to a process for their preparation and to pharmaceutical compositions containing them.

The compounds of the present invention are new and have very valuable pharmacological characteristics in the field of apoptosis and oncology.

5 Ubiquitination is a process controlling essential cellular functions such as protein turnover and homeostasis, protein activation and localisation. Ubiquitin is a 76 amino acids polypeptide which is covalently attached to postranslationnaly modified protein substrates via an isopeptide bond. Deubiquinating enzymes (DUBs) are in majority cysteine proteases that cleave the ubiquitin-ubiquitin bond or ubiquitin-protein bond at the Cter glycine of
10 Ubiquitin. Approximately 100 DUBs regulate the thousands ubiquitinated proteins and then some redundancy of deubiquitinase substrates regulation are observed.

Dysregulation of DUBs have been associated with several diseases such as neurodegenerative and infectious diseases (Edelman et al., *Expert Rev. Mol. Med.* 2011, 13, 1-17) and human malignancies (Pal et al., *Cancer Res.* 2014, 74, 4955-4966).
15 Accordingly, overexpression of DUBs or increase of their activity have been associated to numerous types of cancers (Luise et al., *Plos One* 2011, 6, e15891; Rolen et al., *Mol. Carcinog.* 2006, 45, 260-269) and poor prognosis.

Ubiquitin Specific Protease 7 (USP7), also known as Herpes-virus-Associated Ubiquitin-Specific Protease (HAUSP), belongs to the deubiquitinating family. USP7 has been
20 reported to stabilize numerous oncogenes involved in survival and proliferations *via* cell cycle progression, apoptosis, DNA repair, DNA replication and epigenetic factors regulation (Nicholson et al., *Cell Biochem. Biophys.* 2011, 60, 61-68). In addition, USP7 has been shown to regulate immune response via inflammation and Treg modulation (Van Loosdregt et al., *Immunity* 2013, 39, 259-27; Colleran et al., *Proc. Natl. Acad. Sci. USA*
25 2013, 110, 618-623). USP7 has also been implicated in other pathologic states such as neurodevelopmental disorder (Hao et al., *Mol. Cell* 2015, 59, 956-969) and viral infection (Holowaty et al., *Biochem. Soc. Trans.* 2004, 32, 731-732).

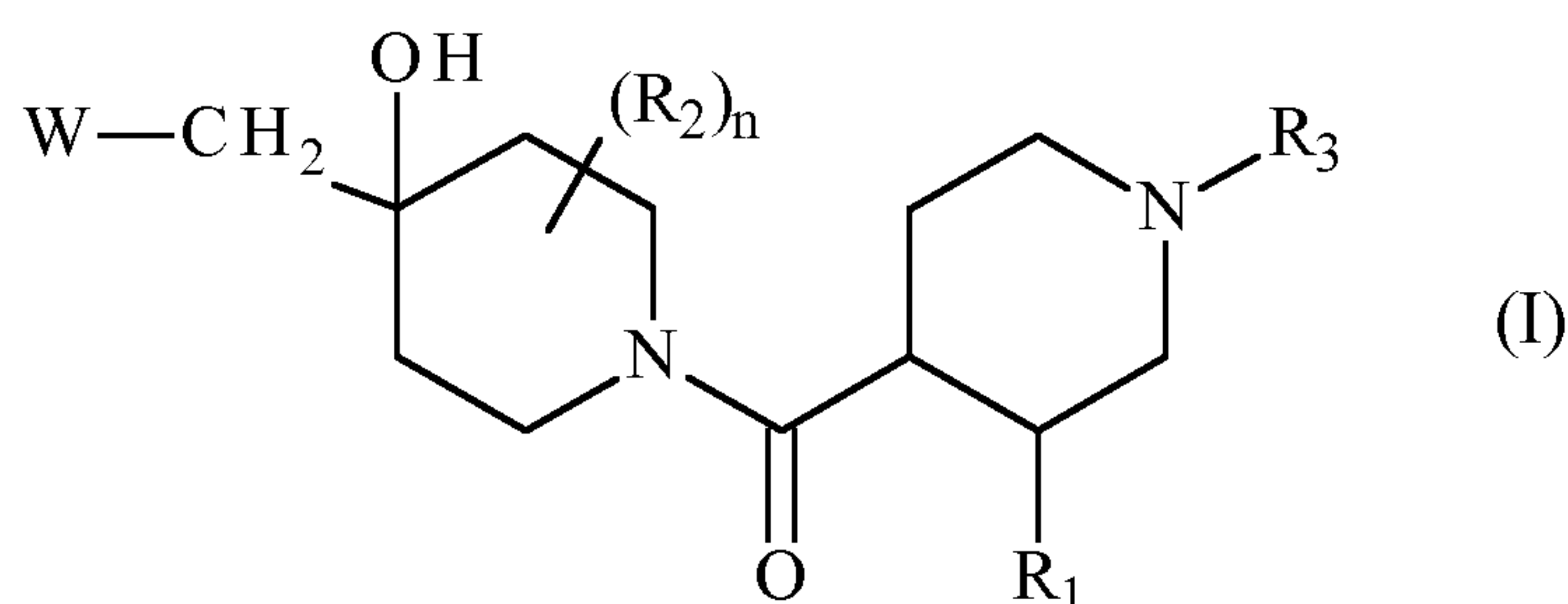
USP7 overexpression has been associated with late stages of cancers and poor prognosis in lung, neuroblastoma, myeloma, prostate, colon and breast cancers. Although some
30 inhibitors have been published in the literature, most of them were not selective and, to

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date, no USP7 inhibitors have entered the clinic (Kemp et al., *Progress in Medicinal Chemistry* 2016, 55, 149-192). There is, therefore, a therapeutic need for compounds that inhibit the activity of the protein USP7.

In addition to being new, the compounds of the present invention have pro-apoptotic and/or anti-proliferative properties making it possible to use them in pathologies involving a defect in apoptosis, such as, for example, in the treatment of cancer and of immune and auto-immune diseases.

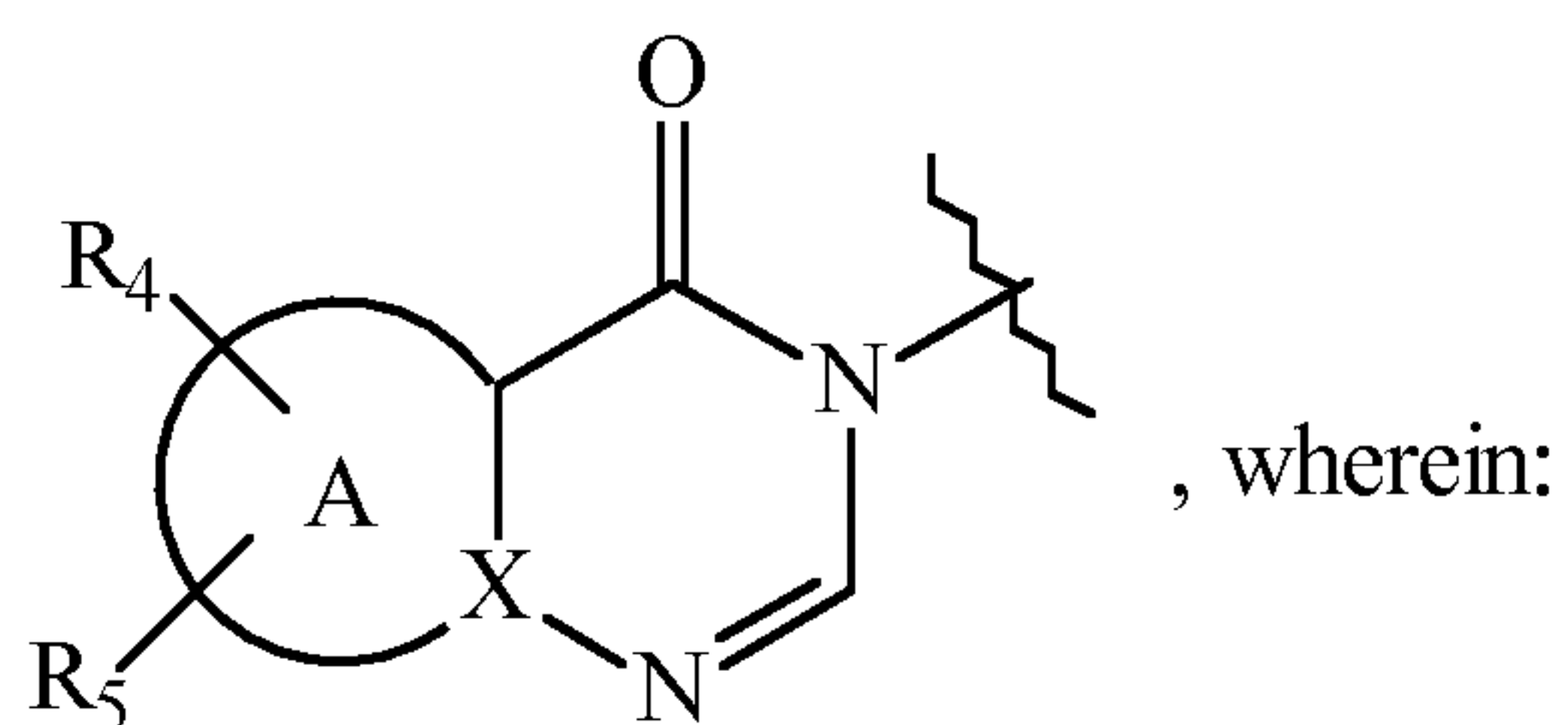
The present invention relates more especially to compounds of formula (I):



wherein:

- ◆ R_1 represents an aryl group or a heteroaryl group,
- ◆ R_2 represents a hydrogen atom or a halogen atom,
- ◆ R_3 represents a hydrogen atom, a linear or branched (C_1 - C_6)alkyl group, a linear or branched halo(C_1 - C_6)alkyl, a $-C(O)-R_8$ group, a $-C(O)-OR_8$ group,
- ◆ n is an integer equal to 0, 1 or 2,

- ◆ W represents the group



- A represents a heteroaryl ring,
- X represents a carbon atom or a nitrogen atom,
- R_4 represents a hydrogen atom, a halogen atom, a linear or branched (C_1 - C_6)alkyl group, a linear or branched (C_2 - C_6)alkenyl group, a linear or branched (C_2 - C_6)alkynyl group, a $-Y_1-NR_6R_7$ group, a $-Y_1-OR_6$ group,

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a linear or branched halo(C₁-C₆)alkyl group, an oxo group, a -Y₁-Cy₁ group, a -Cy₁-R₇ group, a -Cy₁-OR₇ group, or a -Y₁-NR₆-C(O)-R₇ group,

- R₅ represents a hydrogen atom, a halogen atom, a linear or branched (C₁-C₆)alkyl group, a cyano group, or a -hydroxy(C₁-C₆)alkyl group,

5 ▪ R₆ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, or a -Y₂-Si[(C₁-C₄)alkyl]₃ group,

- R₇ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, or a -Y₂-Cy₂ group,

10 ▪ Y₁ and Y₂ independently of one another represent a bond or a linear or branched (C₁-C₄)alkylene group,

- ♦ R₈ represents a hydrogen atom or a linear or branched (C₁-C₆)alkyl group,

- ♦ Cy₁ and Cy₂ independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group,

it being understood that:

15 - “aryl” means a phenyl, naphthyl, or indanyl group,

- “heteroaryl” means any mono- or fused bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen,

20 - “cycloalkyl” means any mono- or fused bi-cyclic non-aromatic carbocyclic group containing from 3 to 7 ring members,

- “heterocycloalkyl” means any non-aromatic mono- or fused bi-cyclic group containing from 3 to 10 ring members, and containing from 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined

25 to be substituted by from 1 to 4 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl, linear or branched (C₂-C₆)alkynyl, linear or branched halo(C₁-C₆)alkyl, -Y₁-OR', -Y₁-NR'R'', -Y₁-S(O)_m-R', oxo (or *N*-oxide where appropriate), nitro, cyano, -C(O)-R', -C(O)-OR', -O-C(O)-R', -C(O)-NR'R'', -Y₁-NR'-C(O)-R'', -Y₁-NR'-C(O)-OR'', halogen, cyclopropyl, and pyridinyl which can be

30 substituted by a linear or branched (C₁-C₆)alkyl group,

it being understood that R' and R'' independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₁-C₆)alkoxy group, a linear or branched halo(C₁-C₆)alkyl, a linear or branched hydroxy(C₁-C₆)alkyl group, a linear or branched (C₁-C₆)alkoxy(C₁-C₆)alkyl group, a phenyl group, a cyclopropylmethyl group, a tetrahydropyranyl group, or the substituents of the pair (R', R'') form together with the nitrogen atom carrying them a non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen a second heteroatom selected from oxygen and nitrogen, it being understood that the nitrogen in question may be substituted by from 1 to 2 groups representing a hydrogen atom, or a linear or branched (C₁-C₆)alkyl group,

and it being understood that m is an integer equal to 0, 1 and 2,

their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

Among the pharmaceutically acceptable acids there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphonic acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, citric acid, ascorbic acid, oxalic acid, methanesulphonic acid, camphoric acid etc.

Among the pharmaceutically acceptable bases there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, triethylamine, tert-butylamine etc.

Among the heteroaryl groups there may be mentioned, without implying any limitation, pyrrolyl, furyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, pyridinonyl, indolyl, dihydroindolyl, dihydroisoindolyl, indazolyl, dihydrocyclopentathienyl, benzothienyl, tetrahydrobenzothienyl, benzofuranyl, imidazopyridinyl, benzotriazolyl, benzodioxolyl, dihydrobenzodioxinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl,

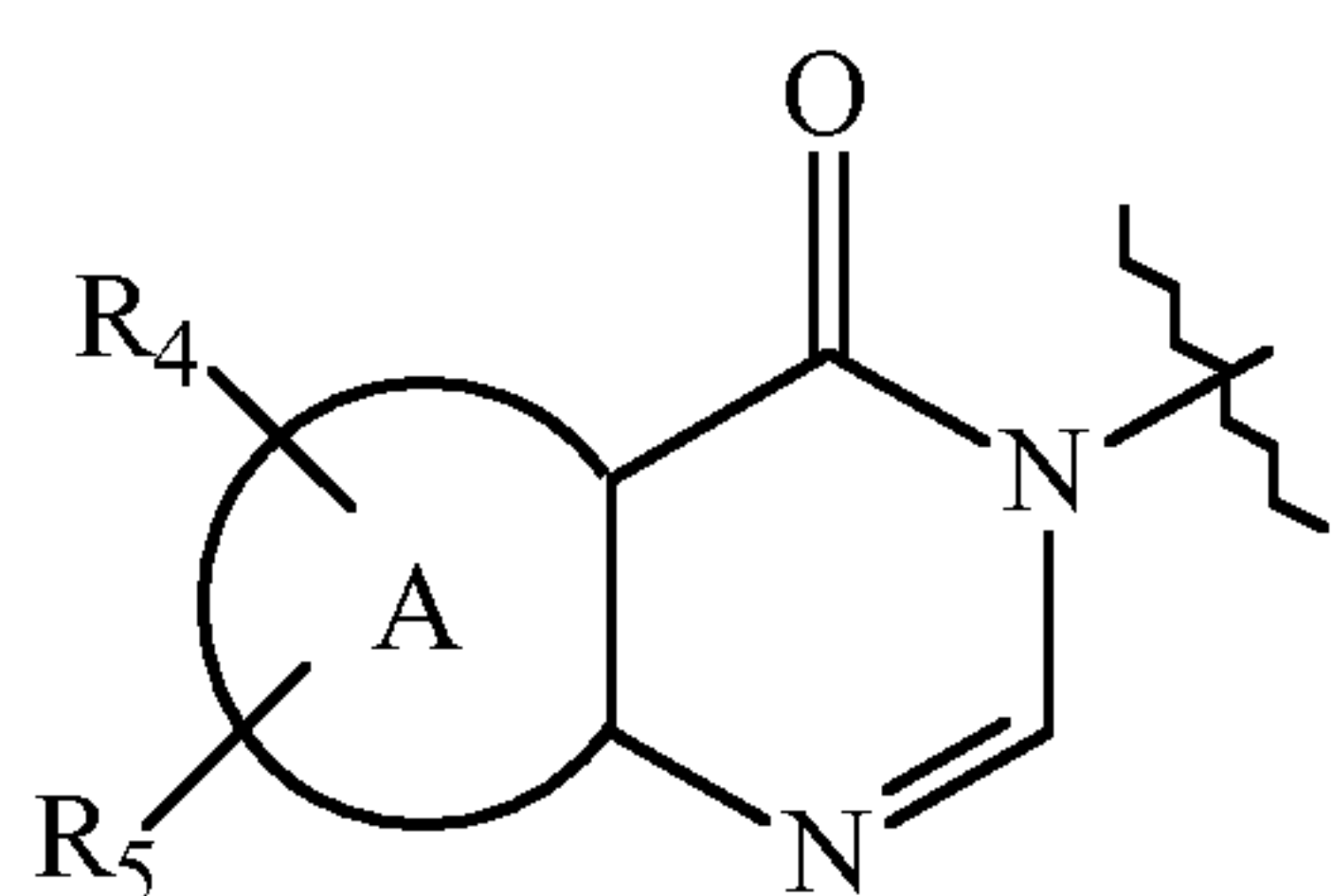
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tetrahydroisoquinoliny, quinoxaliny, dihydroquinoxaliny, dihydrothienodioxiny, quinazolinony, pyrrolopyridaziny, dihydropyrroliziny, tetrahydroindoliziny, etc.

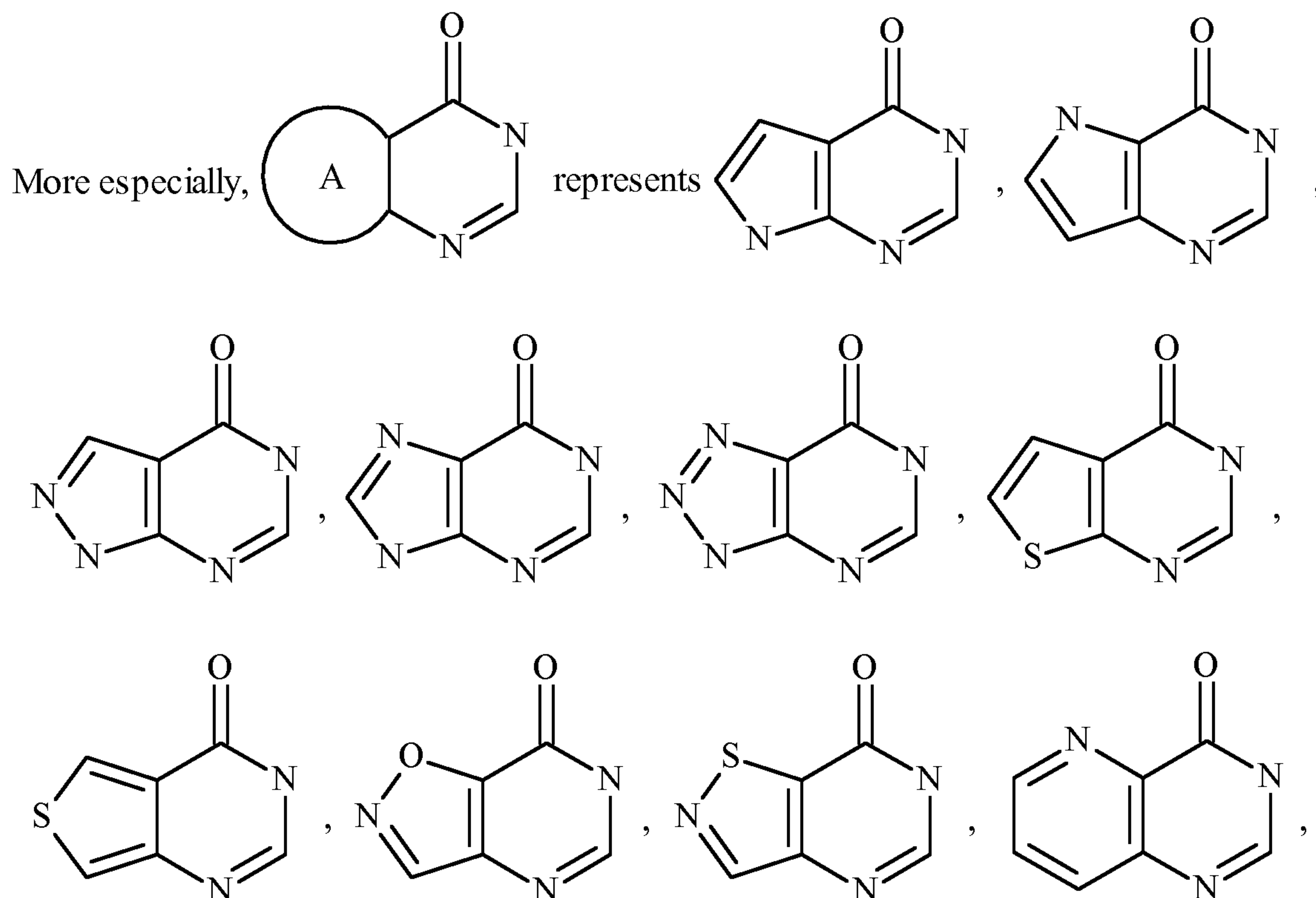
Among the cycloalkyl groups there may be mentioned, without implying any limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.

5 Among the heterocycloalkyl groups there may be mentioned, without implying any limitation, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, etc.

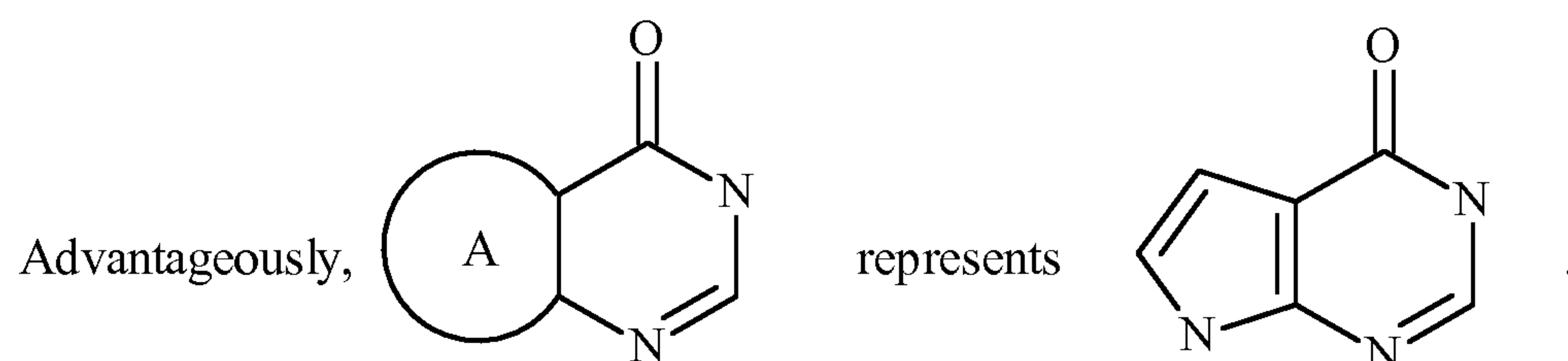
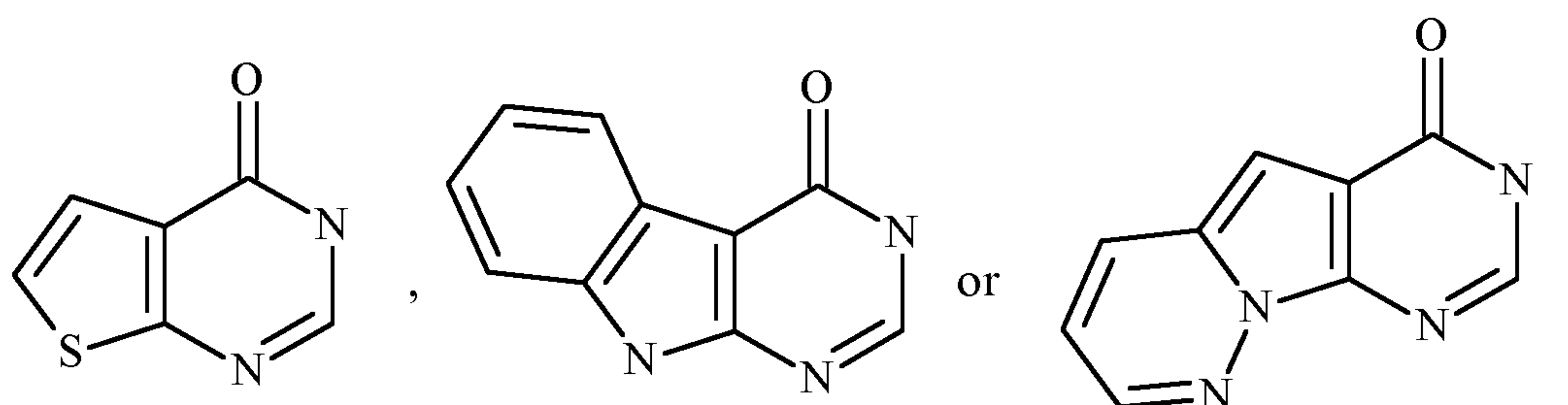
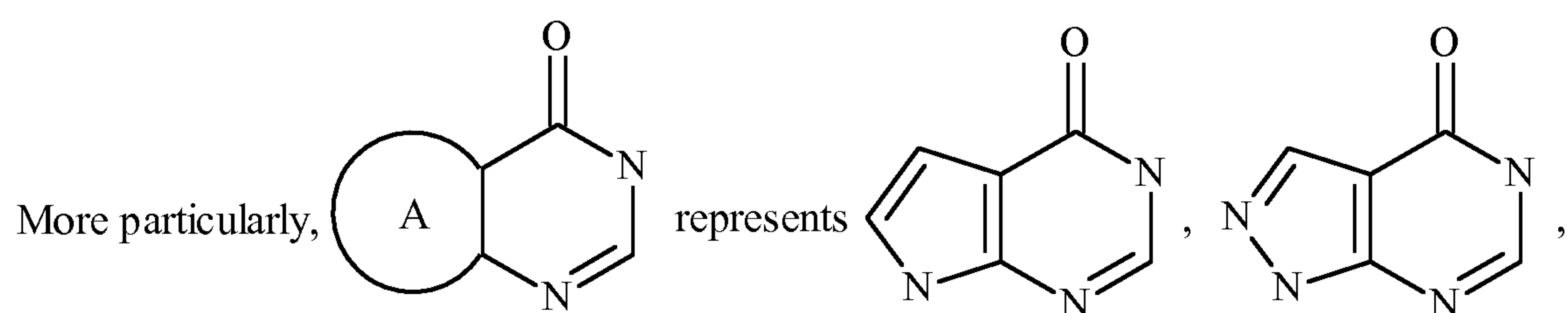
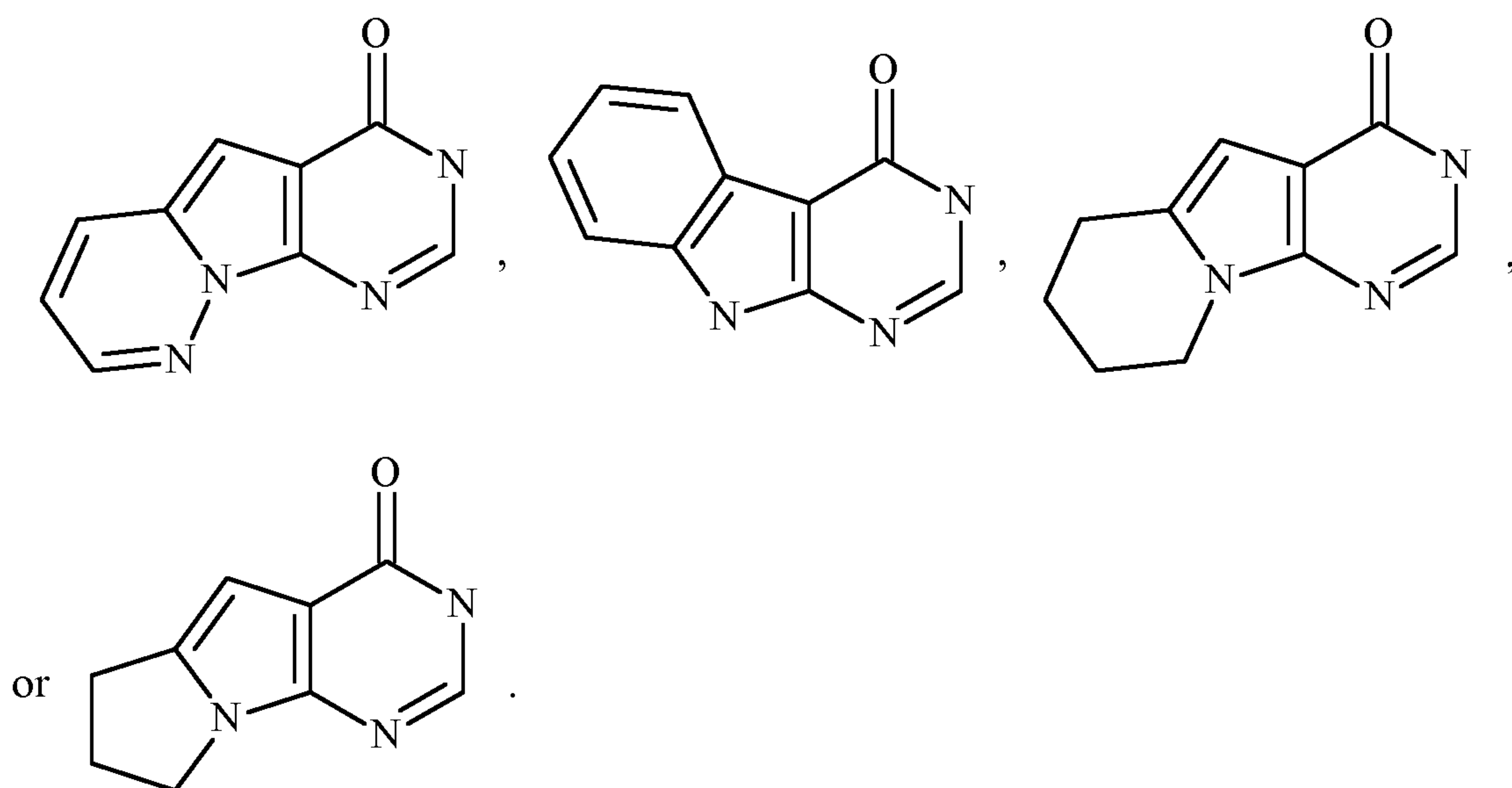
In another embodiment of the invention, W advantageously represents the group



wherein R₄, R₅ and A are as defined for formula (I).



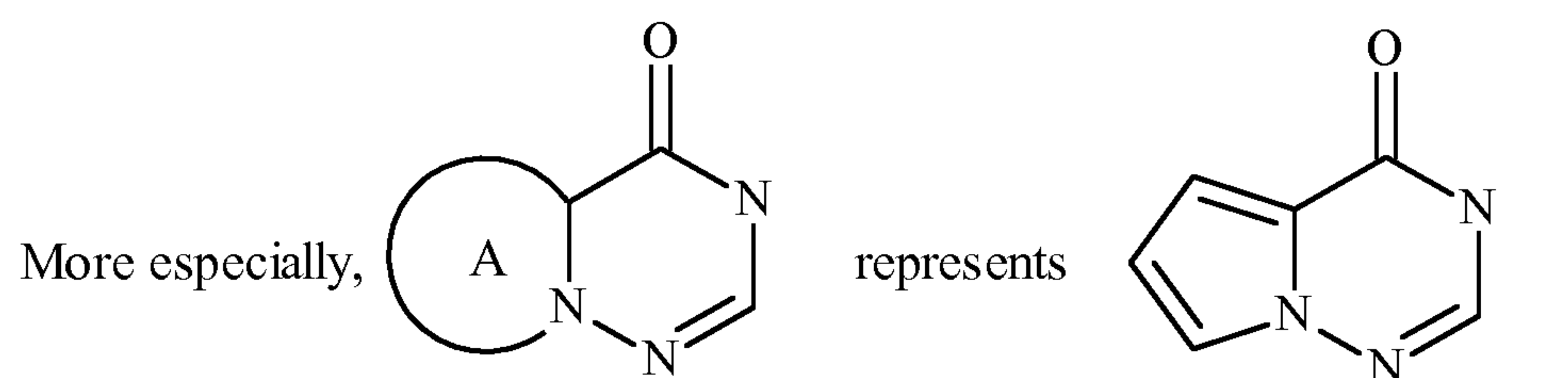
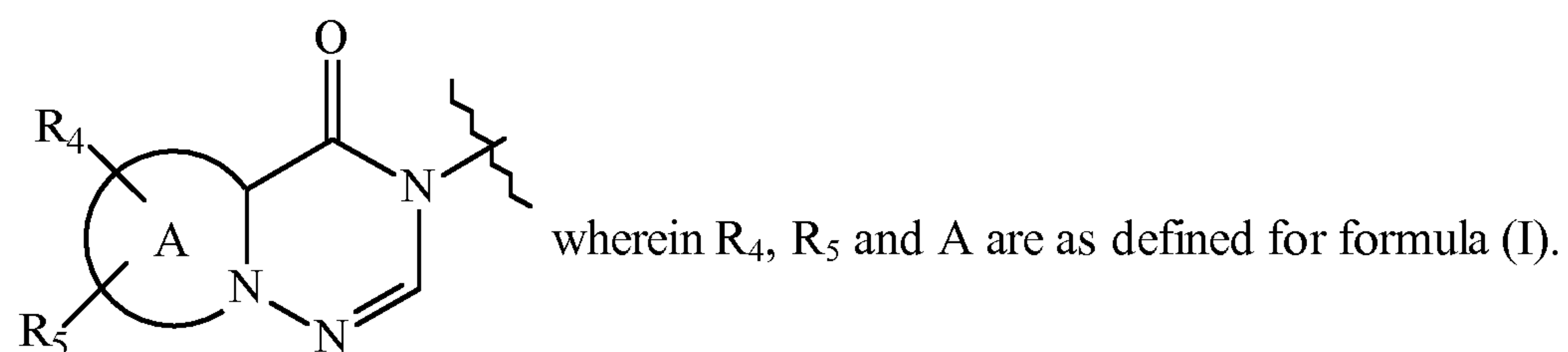
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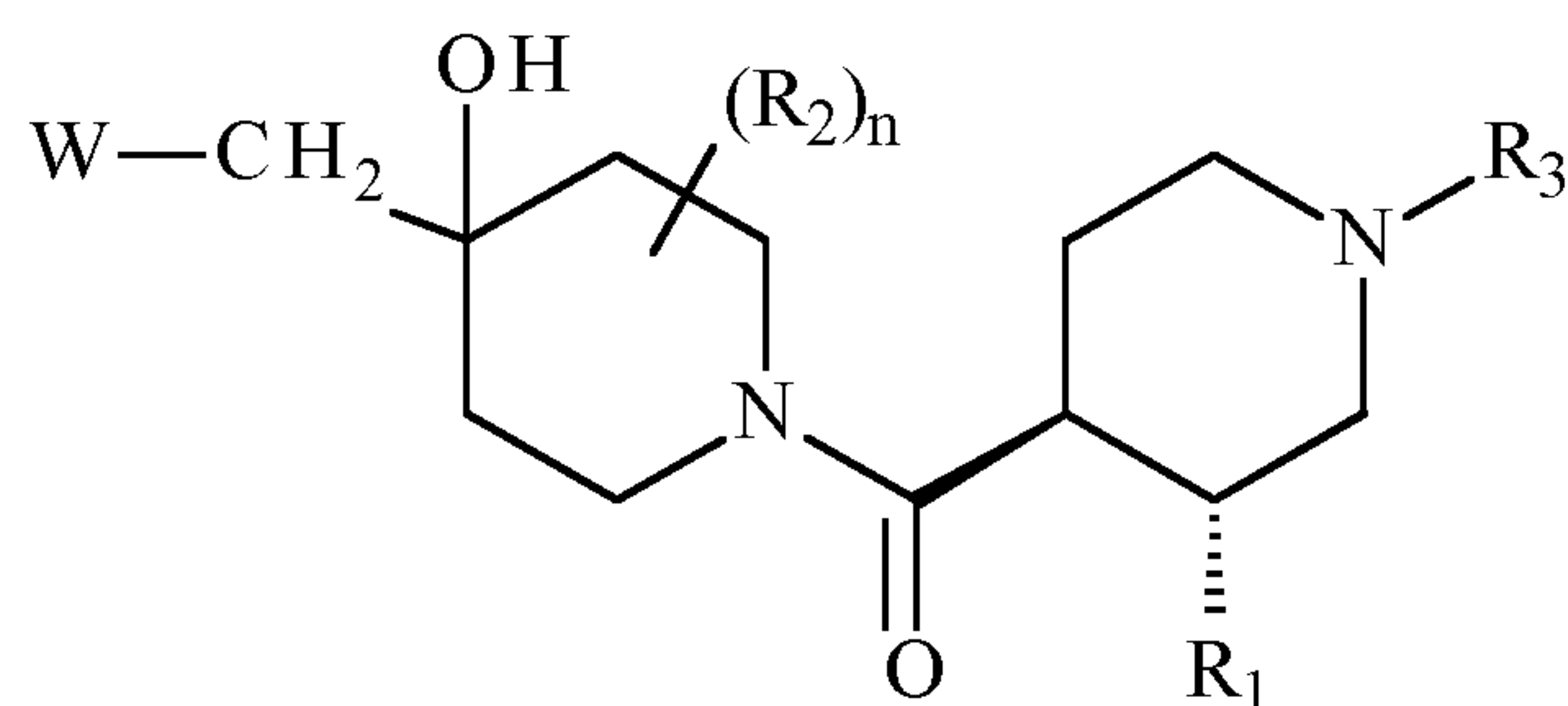
In another embodiment of the invention, W advantageously represents the group

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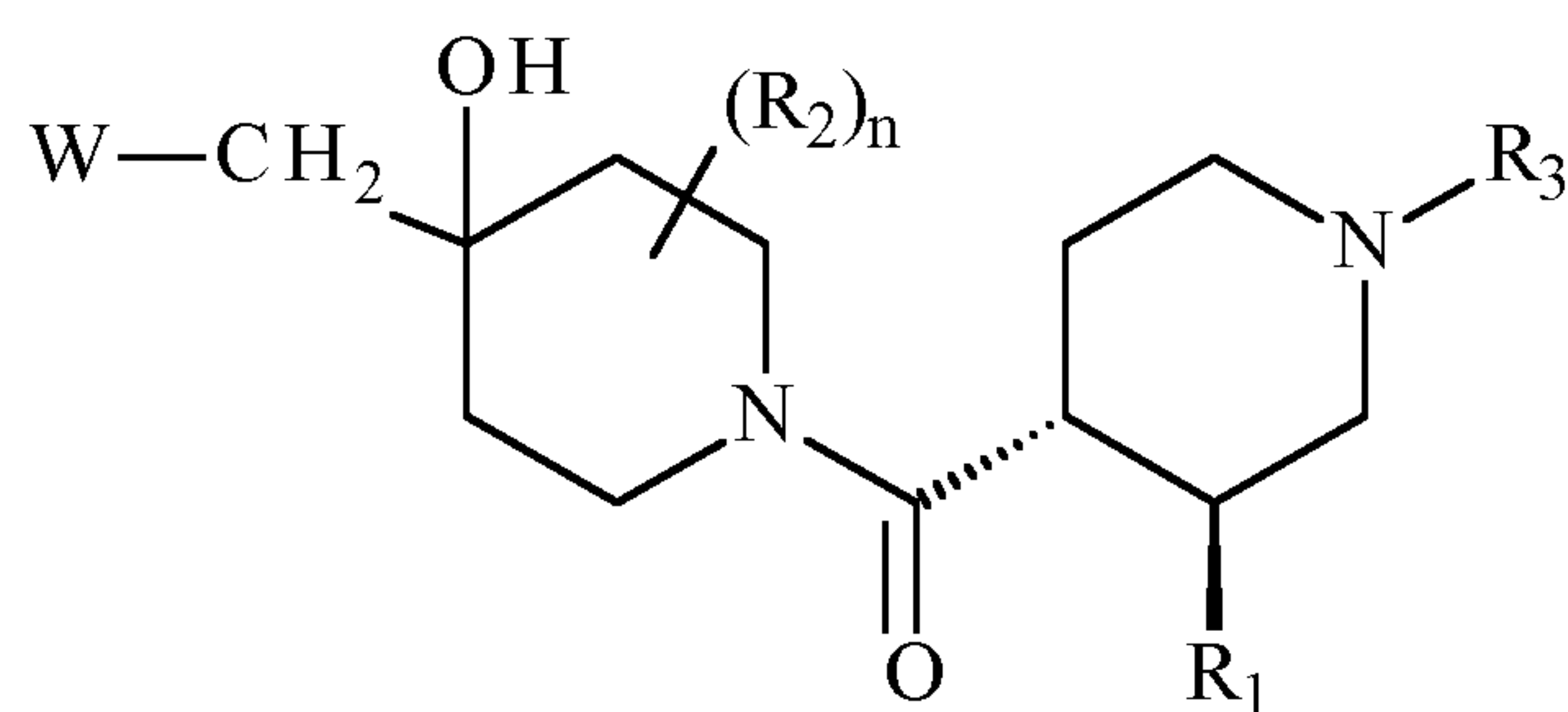
R_1 advantageously represents a phenyl group.

Advantageously, the compounds of formula (I) display a *trans* configuration as follows:



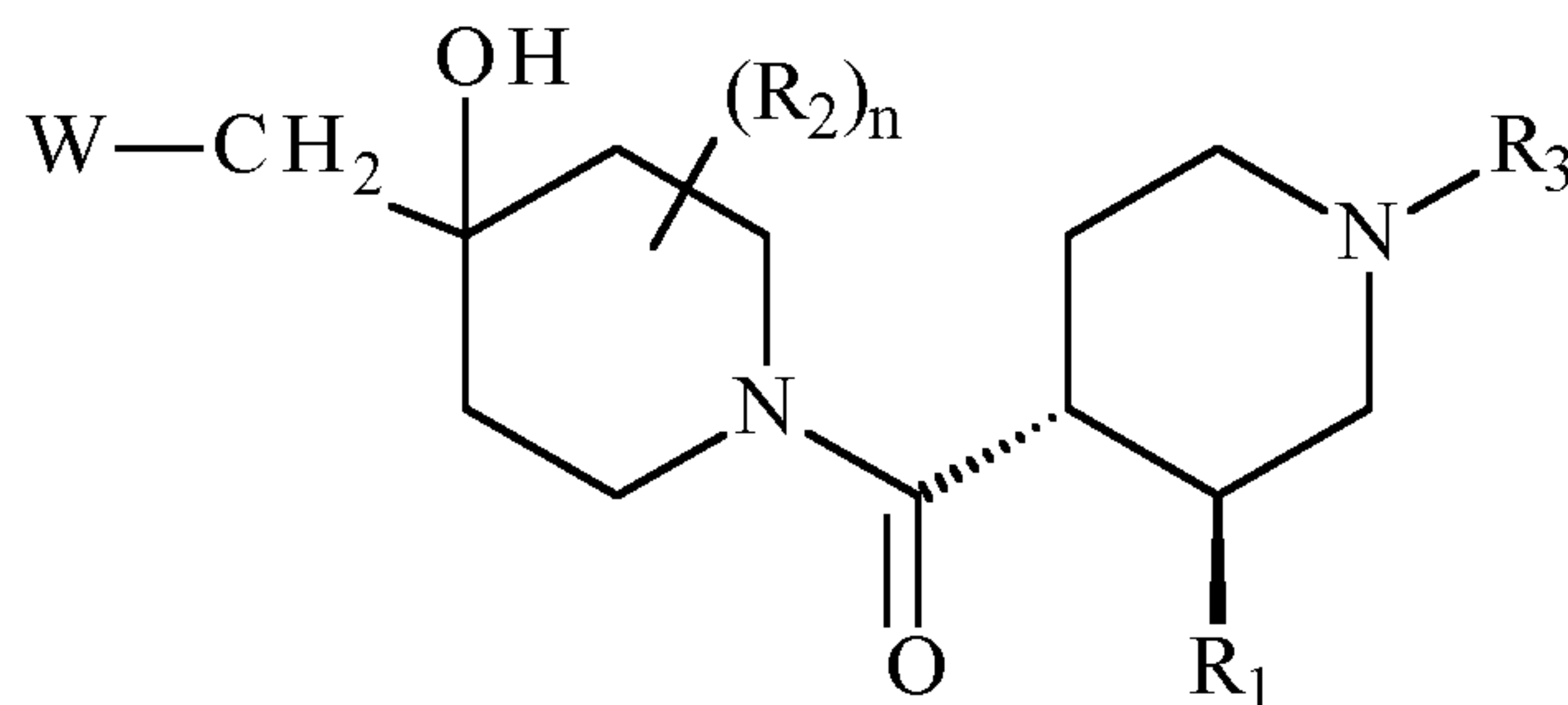
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or



More preferably, the compounds of formula (I) display a *trans* configuration as follows:

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Preferably, R_2 represents a hydrogen atom.

In some preferred embodiment of the invention, R_3 represents a hydrogen atom, a methyl group, a $-\text{CH}_2-\text{CH}(\text{CH}_3)_2$ group, a $-\text{CH}_2-\text{CF}_3$ group, a $-\text{C}(\text{O})-\text{CH}_3$ group, a $-\text{C}(\text{O})-\text{CH}(\text{CH}_3)_2$ group, a $-\text{C}(\text{O})-\text{CH}_2-\text{C}(\text{CH}_3)_3$ group, or a $-\text{C}(\text{O})-\text{OC}(\text{CH}_3)_3$ group.

In the preferred compounds of the invention, R_4 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_2-C_6) alkenyl group, a linear or branched (C_2-C_6) alkynyl group, a $-\text{Y}_1-\text{NR}_6\text{R}_7$ group, a $-\text{Y}_1-\text{OR}_6$ group, a linear or branched halo (C_1-C_6) alkyl group, a $-\text{Y}_1-\text{Cy}_1$ group, a $-\text{Cy}_1-\text{R}_7$ group, or a $-\text{Cy}_1-\text{OR}_7$ group.

Advantageously, Cy_1 represents a phenyl group, a naphthyl group, a thienyl group, a thiazolyl group, a pyrazolyl group, an imidazolyl group, a pyridinyl group, a pyrimidinyl group, a pyridinonyl group, a benzodioxolyl group, a dihydrobenzodioxinyl group, a cyclopropyl group, a cyclobutyl group, or a piperidinyl group.

Advantageously, R_5 represents a hydrogen atom, an iodine atom, a chlorine atom, a methyl group or a $-\text{CH}_2-\text{OH}$ group.

In the preferred compounds of the invention, R_6 represents a hydrogen atom, a methyl group, or a $-(\text{CH}_2)_2-\text{Si}(\text{CH}_3)_3$ group.

R_7 preferably represents a hydrogen atom, a methyl group, or a $-\text{CH}_2-\text{Cy}_2$ group. Preferably, Cy_2 represents a phenyl group.

Among the preferred compounds of the invention there may be mentioned:

- *tert*-butyl (3*S*,4*S*)-4-({4-hydroxy-4-[(4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)methyl]piperidin-1-yl} carbonyl)-3-phenylpiperidine-1-carboxylate;
- *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[4-oxo-7-(pyridin-2-yl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl} piperidin-1-yl) carbonyl]-3-phenylpiperidine-1-carboxylate;
- 5 - *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[7-(4-methoxyphenyl)-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl} piperidin-1-yl) carbonyl]-3-phenylpiperidine-1-carboxylate;
- *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[1-(4-methoxyphenyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl} piperidin-1-yl) carbonyl]-3-phenylpiperidine-1-carboxylate;
- 10 - *tert*-butyl (3*R*,4*R*)-4-[(4-{[7-(4-fluoro-3-methoxyphenyl)-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl}-4-hydroxypiperidin-1-yl) carbonyl]-3-phenylpiperidine-1-carboxylate;
- *tert*-butyl (3*R*,4*R*)-4-[(4-{[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl}-4-hydroxypiperidin-1-yl) carbonyl]-3-phenylpiperidine-1-carboxylate;
- 15 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 5-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;
- 20 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-7-(pyridin-2-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 25 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(4-fluorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 30 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl] carbonyl} piperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

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- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(3-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(4-fluorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 5 - 7-(3-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(4-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 10 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(3-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 15 - 7-(4-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(4-fluoro-3-methoxyphenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-(2-methylpropyl)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 20 - 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-fluorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 25 - (3*R*,4*R*)-4-[(4-hydroxy-4-{[1-(4-methoxyphenyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl}piperidin-1-yl)carbonyl]-1,1-dimethyl-3-phenylpiperidinium;
- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-(2-methylpropanoyl)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 30 - 4-one;

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- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(3-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

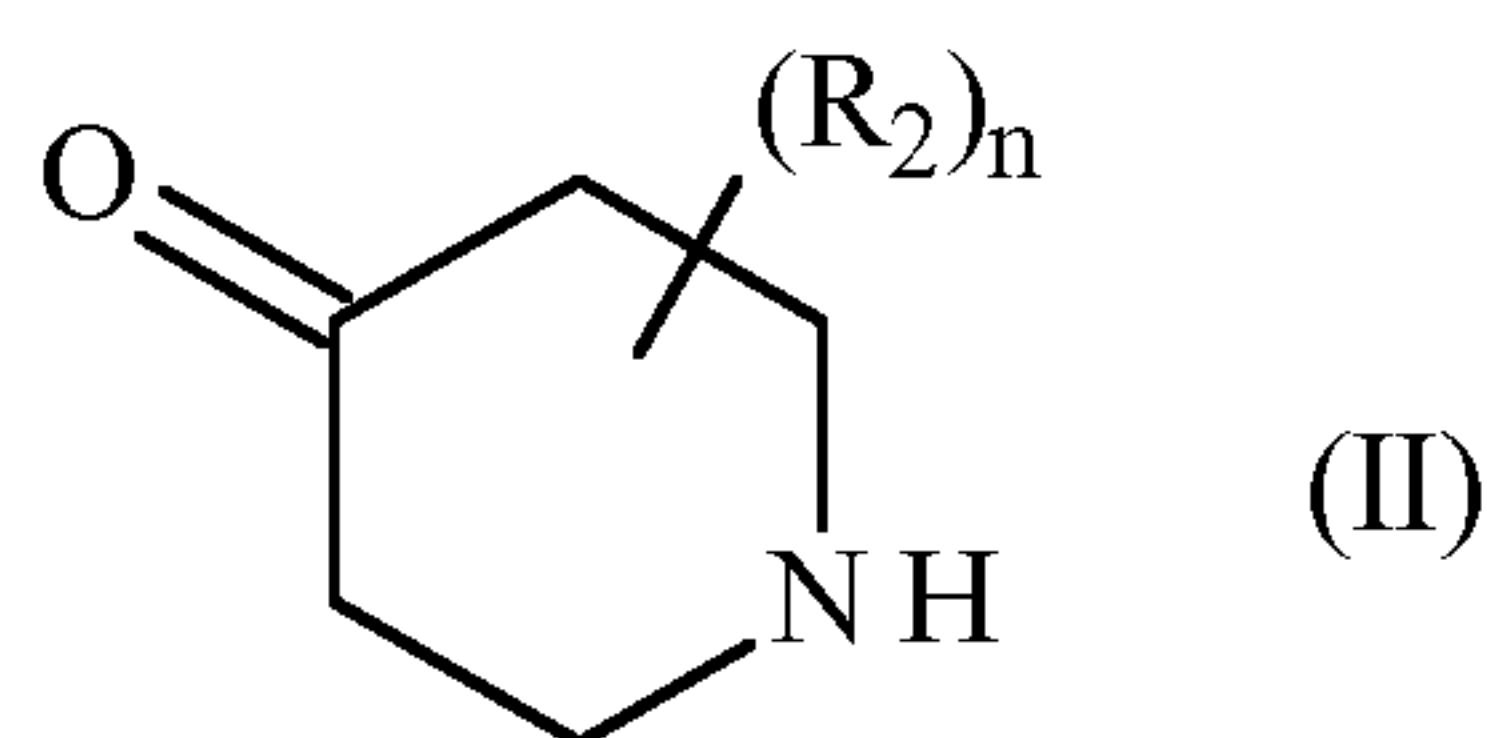
5 - 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(3-chlorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-chlorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

10 - 3-[(1-{[(3*R*,4*R*)-1-(2,2-dimethylpropanoyl)-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

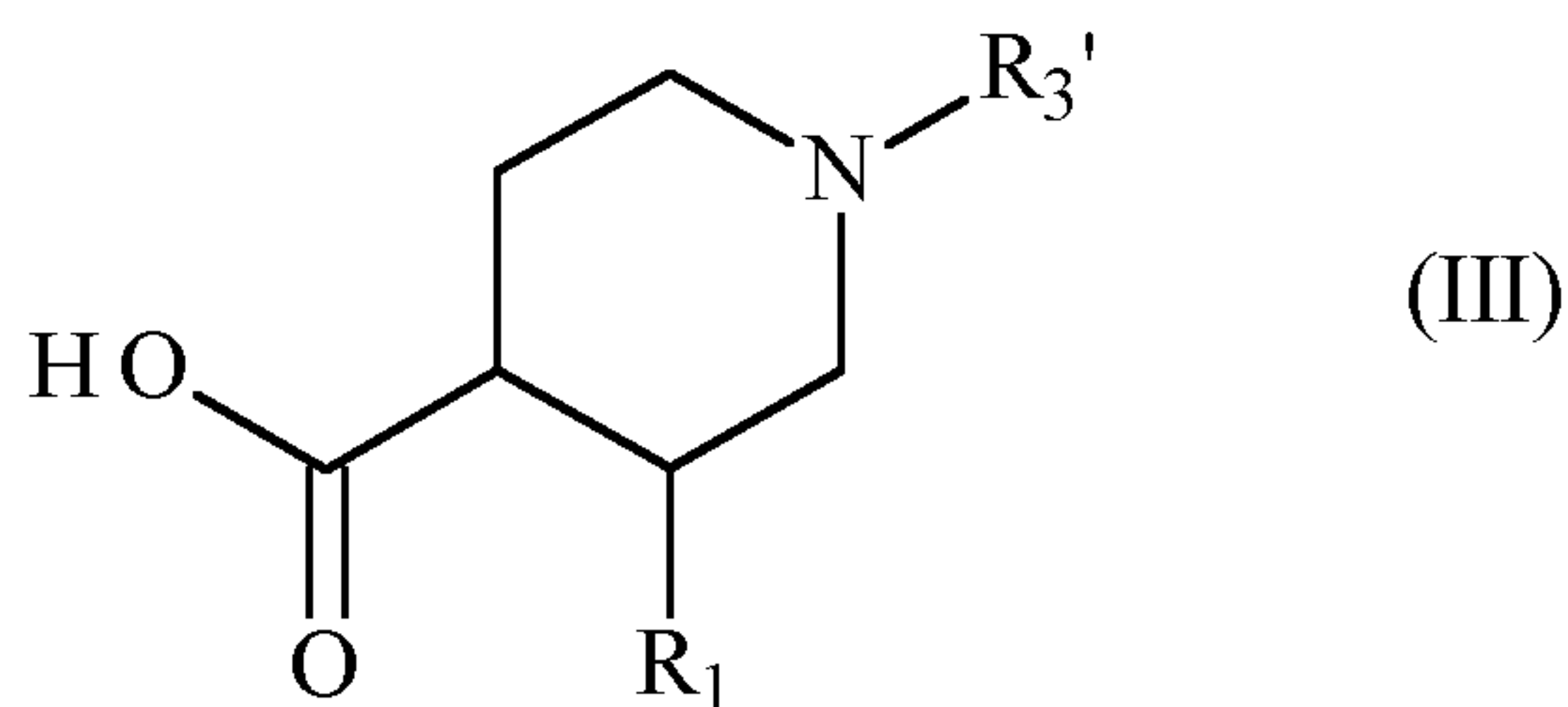
- 3-[(1-{[(3*R*,4*R*)-1-(3,3-dimethylbutanoyl)-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

15 The invention relates also to a process for the preparation of compounds of formula (I), which process is characterized in that there is used as starting material the compound of formula (II):



wherein R_2 and n are as defined for formula (I),

20 which is subjected to coupling with a compound of formula (III):

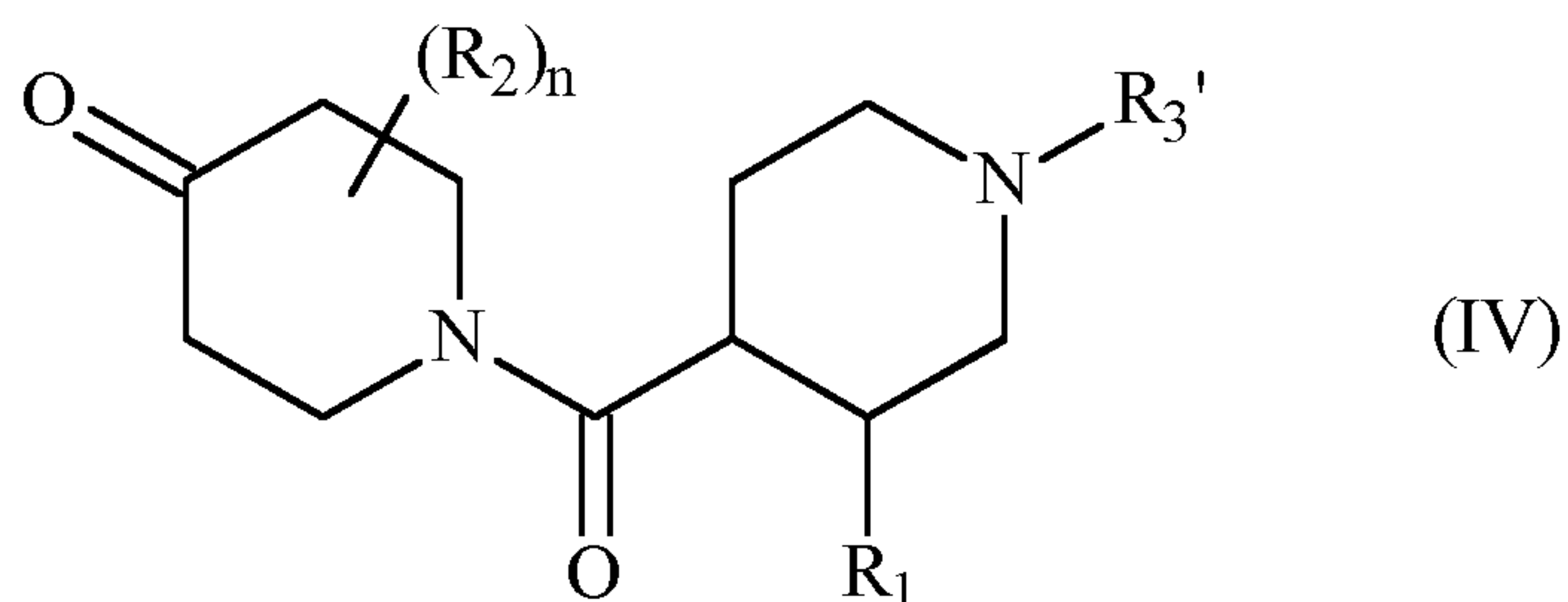


wherein R_1 is as defined for formula (I), and R_3' represents a $-C(O)-OR_8$ group wherein R_8

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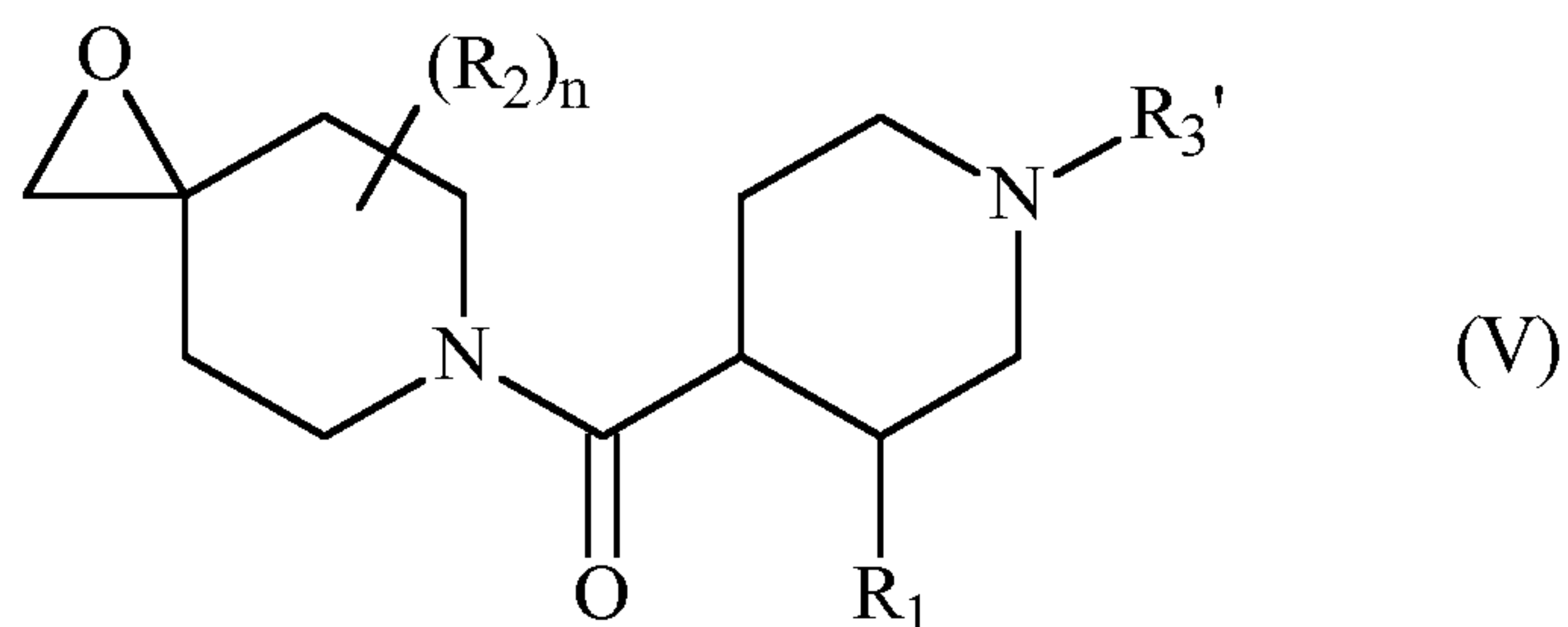
is as defined for formula (I),

to yield the compound of formula (IV):



wherein R_1 , R_2 , R_3' and n are as defined hereinbefore,

- 5 compound of formula (IV) which is further converted to an epoxide compound of formula (V):



wherein R_1 , R_2 , R_3' and n are as defined hereinbefore,

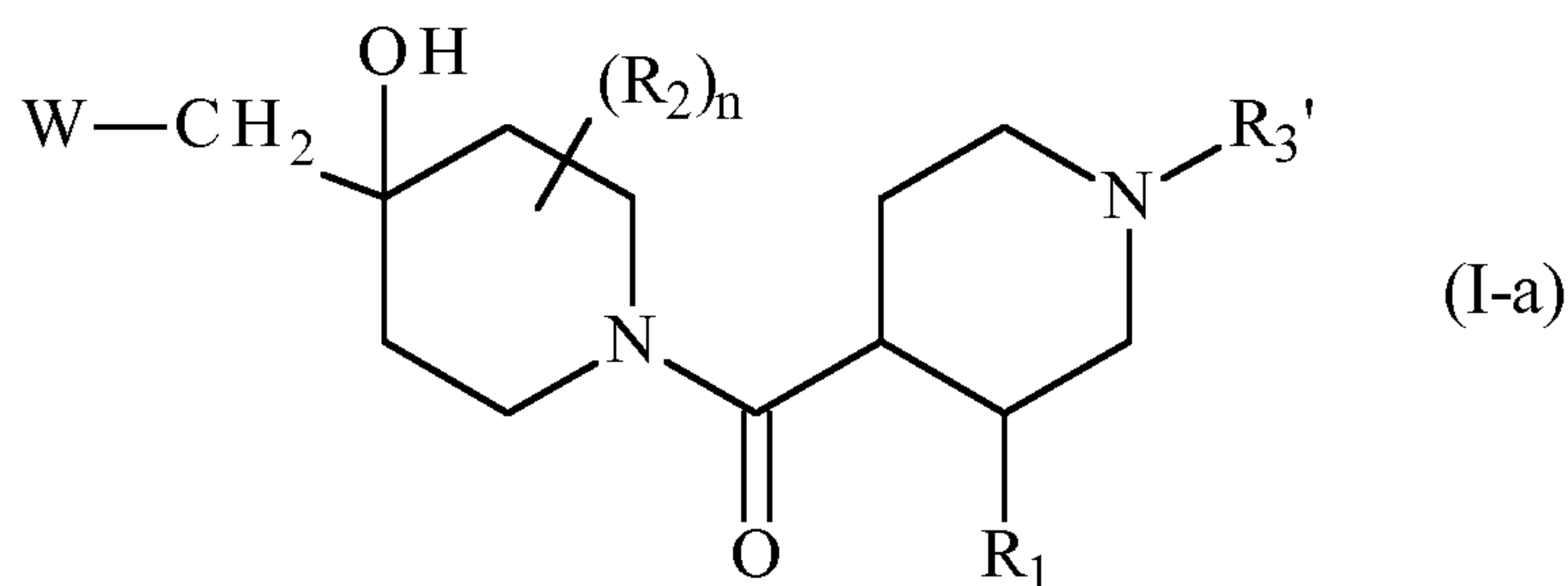
- 10 compound of formula (V) which is further subjected to coupling with compound of formula (VI):



wherein W is as defined for formula (I),

to yield the compound of formula (I-a), a particular case of the compounds of formula (I):

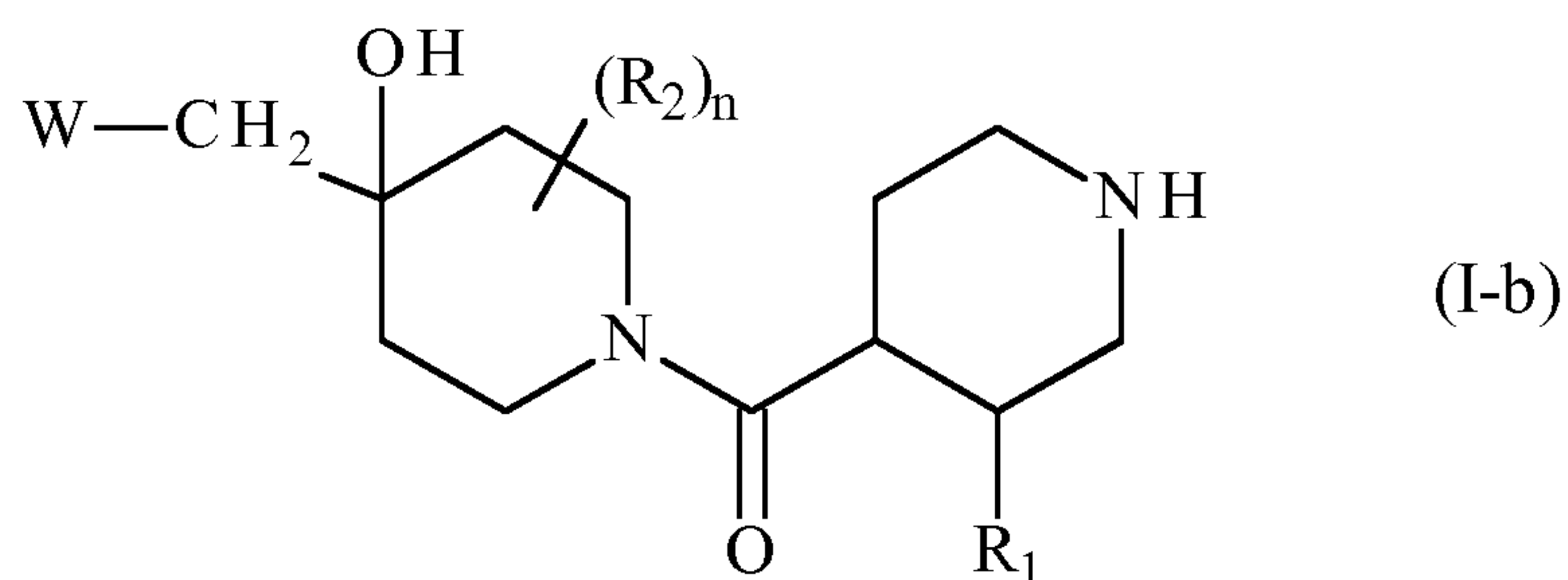
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wherein R_1 , R_2 , R_3' , n and W are as defined hereinbefore,

which compound of formula (I/a) may then, if required, be subjected to a reaction removing the R_3' group,

5 to yield the compound of formula (I-b), a particular case of the compounds of formula (I):

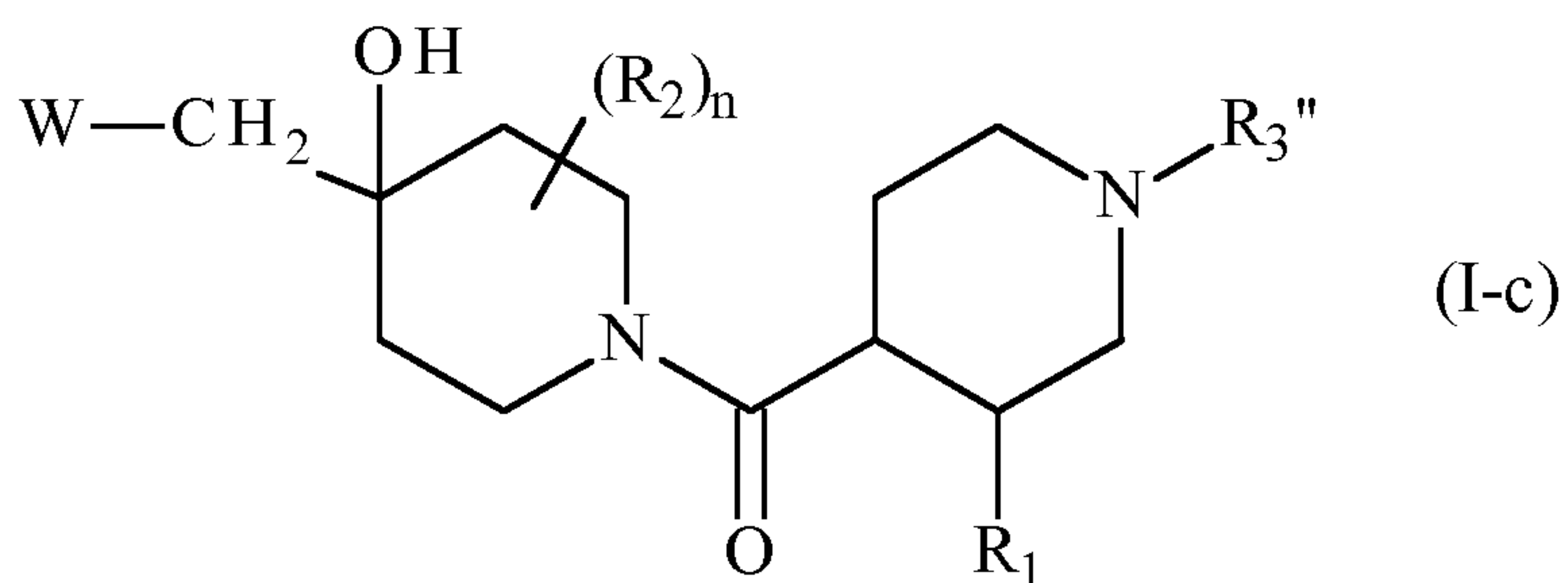


wherein R_1 , R_2 , n and W are as defined hereinbefore,

which compound of formula (I/b) may then, if required, be subjected to a coupling reaction with compound of formula $R_3''\text{-Cl}$ wherein R_3'' represents a linear or branched (C₁-C₆)alkyl group, a linear or branched halo(C₁-C₆)alkyl, or a -C(O)-R₈ group wherein R₈ is as defined for formula (I),

10

to yield the compound of formula (I-c), a particular case of the compounds of formula (I):



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wherein R_1 , R_2 , R_3'' , n and W are as defined hereinbefore,

which compounds of formulae (I/a) to (I/c), which constitute the totality of the compounds of formula (I), may then be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that at any moment considered appropriate during the course of the process described above, some groups (hydroxy, amino...) of the starting reagents or of the synthesis intermediates can be protected, subsequently deprotected and functionalized, as required by the synthesis.

The compounds of formulae (II), (III), (VI) and R_3'' -Cl are either commercially available or can be obtained by the person skilled in the art using conventional chemical reactions described in the literature.

Pharmacological studies of the compounds of the invention have shown pro-apoptotic and/or anti-proliferative properties. The ability to reactivate the apoptotic process in cancerous cells is of major therapeutic interest in the treatment of cancers and of immune and auto-immune diseases.

Among the cancer treatments envisaged there may be mentioned, without implying any limitation, treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukemia, cancer of the colon, esophagus and liver, lymphoblastic leukemia, acute myeloid leukemia, lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer, pancreatic cancer and small-cell lung cancer. More especially, the compounds according to the invention will be useful in the treatment of chemo-, targeted therapy- or radio-resistant cancers.

The present invention relates also to pharmaceutical compositions comprising at least one compound of formula (I) in combination with one or more pharmaceutically acceptable excipients.

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Among the pharmaceutical compositions according to the invention there may be mentioned more especially those that are suitable for oral, parenteral, nasal, per- or trans-cutaneous, rectal, perlingual, ocular or respiratory administration, especially tablets or dragées, sublingual tablets, sachets, paquets, capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels, and drinkable or injectable ampoules.

The pharmaceutical compositions according to the invention comprise one or more excipients or carriers selected from diluents, lubricants, binders, disintegration agents, stabilisers, preservatives, absorbents, colorants, sweeteners, flavourings etc.

By way of non-limiting example there may be mentioned:

- ♦ *as diluents*: lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycerol,
- ♦ *as lubricants*: silica, talc, stearic acid and its magnesium and calcium salts, polyethylene glycol,
- ♦ *as binders*: magnesium aluminium silicate, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and polyvinylpyrrolidone,
- ♦ *as disintegrants*: agar, alginic acid and its sodium salt, effervescent mixtures.

The dosage varies according to the sex, age and weight of the patient, the administration route, the nature of the therapeutic indication, or of any associated treatments, and ranges from 0.01 mg to 1 g per 24 hours in one or more administrations.

Furthermore, the present invention relates also to the combination of a compound of formula (I) with anti-cancer agents selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors, protein-protein interaction inhibitors, immunomodulators, E3 ligase inhibitors, chimeric antigen receptor T-cell therapy and antibodies, and also to pharmaceutical compositions comprising that type of combination and their use in the manufacture of medicaments for use in the treatment of cancer.

The combination of a compound of formula (I) with an anticancer agent may be administered simultaneously or sequentially. The administration route is preferably the oral

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route, and the corresponding pharmaceutical compositions may allow the instantaneous or delayed release of the active ingredients. The compounds of the combination may moreover be administered in the form of two separate pharmaceutical compositions, each containing one of the active ingredients, or in the form of a single pharmaceutical composition, in which the active ingredients are in admixture.

The compounds of formula (I) may also be used in combination with radiotherapy in the treatment of cancer.

The following Preparations and Examples illustrate the invention but do not limit it in any way.

10 General Procedures

All reagents obtained from commercial sources were used without further purification. Anhydrous solvents were obtained from commercial sources and used without further drying.

Flash chromatography was performed on ISCO CombiFlash Rf 200i with pre-packed silica-gel cartridges (RediSep[®] R_f Gold High Performance).

Thin layer chromatography was conducted with 5 x 10 cm plates coated with Merck Type 60 F254 silica-gel.

Microwave heating was performed in an Anton Parr MonoWave or CEM Discover[®] instrument.

Preparative HPLC purifications were performed on an HANBON NP7000 Liquid Chromatography system with a Gemini-NX[®] 5 μ M C18, 250 mm $\times$ 50 mm i.d. column running at a flow rate of 99.9 mL min⁻¹ with UV diode array detection (210 – 400 nm) using 5 mM aqueous NH₄HCO₃ solution and MeCN as eluents unless specified otherwise.

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Analytical LC-MS: The compounds of the present invention were characterized by high performance liquid chromatography-mass spectroscopy (HPLC-MS) on Agilent HP1200 with Agilent 6140 quadrupole LC/MS, operating in positive or negative ion electrospray ionisation mode. Molecular weight scan range is 100 to 1350. Parallel UV detection was
5 done at 210 nm and 254 nm. Samples were supplied as a 1 mM solution in ACN, or in THF/H₂O (1:1) with 5 µL loop injection. LCMS analyses were performed on two instruments, one of which was operated with basic, and the other with acidic eluents.

Basic LCMS: Gemini-NX, 3 µm, C18, 50 mm × 3.00 mm i.d. column at 23 °C, at a flow rate of 1 mL min⁻¹ using 5 mM ammonium bicarbonate (Solvent A) and acetonitrile
10 (Solvent B) with a gradient starting from 100 % Solvent A and finishing at 100 % Solvent B over various/certain duration of time.

Acidic LCMS: ZORBAX Eclipse XDB-C18, 1.8 µm, 50 mm × 4.6 mm i.d. column at 40 °C, at a flow rate of 1 mL min⁻¹ using 0.02 % v/v aqueous formic acid (Solvent A) and 0.02 % v/v formic acid in acetonitrile (Solvent B) with a gradient starting from 100%
15 Solvent A and finishing at 100 % Solvent B over various/certain duration of time.

¹H-NMR measurements were performed on Bruker Avance III 500 MHz spectrometer and Bruker Avance III 400 MHz spectrometer, using DMSO-d₆ or CDCl₃ as solvent. ¹H NMR data is in the form of delta values, given in part per million (ppm), using the residual peak of the solvent (2.50 ppm for DMSO-d₆ and 7.26 ppm for CDCl₃) as internal standard.
20 Splitting patterns are designated as: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), m (multiplet), brs (broad singlet), brd (broad doublet), brt (broad triplet), brq (broad quartet), brm (broad multiplet), vbrs (very broad singlet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplets), dq (doublet of quartet), ddd (doublet of doublet of doublets), dm (doublet of multiplets), tm (triplet of multiplets), qm
25 (quartet of multiplets).

Combination gas chromatography and low resolution mass spectrometry were performed on Agilent 6850 gas chromatograph and Agilent 5975C mass spectrometer using 15 m × 0.25 mm column with 0.25 µm HP-5MS coating and helium as carrier gas. Ion source: EI⁺, 70 eV, 230 °C, quadrupole: 150 °C, interface: 300 °C.

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HRMS were determined on a Shimadzu IT-TOF, ion source temperature 200 °C, ESI +/-, ionization voltage: (+-)4.5 kV. Mass resolution min. 10000.

Elementary analyses were performed on a Thermo Flash EA 1112 Elemental Analyzer.

List of abbreviations

5	Abbreviation	Name
	abs.	absolute
	aq.	aqueous
	Ar	argon
	AtaPhos*PdCl ₂	bis(di- <i>tert</i> -butyl(4-dimethylaminophenyl)phosphine)
10		dichloropalladium(II)
	Boc	<i>tert</i> -butoxycarbonyl
	cc.	concentrated
	DCM	dichloromethane
	DEE	diethyl ether
15	DIPO	diisopropyl oxide
	disp.	dispersion
	DMEDA	<i>N,N'</i> -dimethylethylenediamine
	DMF	dimethylformamide
	EDC.HCl	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide
20		hydrochloride
	EEO	ethyl ethanoate
	eq.	equivalent
	iPr ₂ NH	isopropylamine
	LC	liquid chromatography
25	LDA	lithium diisopropylamide
	MeCN	acetonitrile
	MSM	methylsulfinylmethane
	MTBE	<i>tert</i> -butyl methylether

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PDO	p-dioxane
Pd ₂ (dba) ₃	tris(dibenzylideneacetone)dipalladium
r.t.	room temperature
sat.	saturated
5 TFA	trifluoroacetic acid
THF	tetrahydrofuran

General Procedure 1*Step 1:*

10 To a stirred solution of 4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidine (**Preparation R1a**; 1.84 g, 12 mmol, 1 eq.) in abs. DMF (15 ml) sodium-hydride (720 mg, 60 % disp. in mineral oil, 18 mmol, 1.5 eq.) was added, and stirred for 10 minutes at r.t. under Ar. Alkylating agent (13.18 mmol) was added to the reaction mixture and stirred for 1-6 hours at r.t. The mixture was poured into water (150 ml), then it was extracted with EEO (3 x 150 ml). The combined organic layer was washed with water, brine, dried over MgSO₄, and evaporated.

15 *Step 2:*

A part of this residue (1.36 mmol) and lithium-hydroxide monohydrate (571 mg, 13.62 mmol, 10 eq.) were stirred in PDO-water (40 ml, 1:1 v/v) mixture at 110 °C for 7-36 hours. The reaction mixture was neutralized with 1 N aq. HCl solution. The resulted precipitate was filtered off, washed with water and dried.

20 **General Procedure 2***Step 1:*

Preparation R1a (460 mg, 3 mmol, 1 eq.), heteroaryl/aryl-boronic acid (7.5 mmol) and copper(II)-acetate (817 mg, 4.5 mmol) were stirred in pyridine (10 ml) at 50-60 °C for 16-72 hours.

25 Work-up 1:

- 20 -

The mixture was evaporated to Celite, purified by flash chromatography (heptane-EEO, gradient).

Work-up 2:

5 The mixture was filtered, the resulted filtrate was purified by preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient).

Step 2:

10 The resulted compound (1.36 mmol) and lithium-hydroxide monohydrate (571 mg, 13.62 mmol, 10 eq.) were stirred in PDO-water (40 ml, 1:1 v/v) mixture at 110 °C for 7-24 hours. The reaction mixture was neutralized with 1 N aq. HCl solution. The resulted precipitate was filtered off, washed with water and dried.

General Procedure 3

Step 1:

15 **Preparation R1b** (746 mg, 5 mmol, 1 eq.), heteroaryl/aryl-iodide (10 mmol), CuI (286 mg, 1.5 mmol, 0.3 eq.), *R,R*-diaminocyclohexane (171 mg, 1.5 mmol, 0.3 eq.), anhydrous K₃PO₄ (4.24 g, 20 mmol, 4 eq.) was stirred in diglyme (15 ml) for 6-16 hours at 120 °C under N₂ atmosphere.

Work-up1:

20 After the reaction completed, the mixture was diluted with water (200 ml) (or. 25 % aq. NH₃) and cooled to r.t. The mixture was filtered, and washed with water (3x30 ml), aq. NH₃ solution (40 ml, 25 %), water (3 x 50 ml), heptane (50 then 30 ml), dried in vacuum.

Work-up2:

The reaction mixture was evaporated to Celite, then purified by flash chromatography (heptane:EEO, gradient).

Step 2:

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The corresponding 4-methoxy-7-aryl-pyrrolo[2,3-*d*]pyrimidine (61.3 mmol, 1 eq.), cc. HCl aqueous solution (10 ml, ~12.2 M, 122.5 mmol, 2 eq.) and PDO (70 ml) was stirred at 100 °C for 0.5-2 hours. After the reaction completed, the mixture was partially evaporated. The formed suspension was filtered and the solid on the filter was washed with water and dried.

General procedure 4

Step 1:

Preparation R1a (154 mg, 1 mmol, 1 eq.), di-*tert*-butyl-diazodicarboxylate (690 mg, 3 mmol, 3 eq.), triphenylphosphine (786 mg, 3 mmol, 3 eq.) and corresponding alcohol (3 mmol, 3 eq.) were stirred in abs. toluene (10 ml) under Ar atmosphere at 50 °C for 2 hours. The reaction mixture was evaporated, taken in THF and purified by preparative LC (on C-18 Gemini-NX 5µm column, 5 mM aqueous NH₄HCO₃-MeCN, gradient).

Step 2:

A part of this residue (4-chloro-7-aryl/alkyl-pyrrolo[2,3-*d*]pyrimidine) (1.36 mmol) and lithium-hydroxide monohydrate (571 mg, 13.62 mmol) were stirred in PDO-water (40 ml, 1:1 v/v) mixture at 110 °C for 7-24 hours. The reaction mixture was neutralized with 1 N aq. HCl solution. The resulted precipitate was filtered off, washed with water and dried.

General procedure 5

Pyrimidine-4-one derivative (1 mmol), epoxide compound **Preparation R1c** (400.5 mg, 1 mmol, 1 eq.) and K₂CO₃ (276.4 mg, 2 mmol, 2 eq.) were stirred in DMF (5 ml) at 75 °C for 2-8 hours.

Work-up 1:

The mixture was poured into ice-water mixture. The resulted precipitate was filtered off, washed with water, and dried.

Work-up 2:

The reaction mixture was filtered, the solid was washed with DMF. The resulted filtrate

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was purified by preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient).

General procedure 6

Compound obtained in **General Procedure 5** (~ 1 mmol) was stirred in aq. HCl solution (1 N, 10 ml, 10 mmol, 10 eq.) and PDO (5 ml) for 1-3 hours at 75 °C.

Work-up1:

The mixture was cooled to about 0-5 °C with ice bath and the white precipitate was filtered off, dried in vacuum (resulted HCl salt).

Work-up2:

The mixture was totally evaporated, and was used to the further step (resulted HCl salt).

Work-up3:

The mixture was purified by preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient, resulted as free base).

General procedure 7

Compound obtained in **General Procedure 6** (1 mmol, 1 eq.), alkyl-X (1 mmol, 1 eq.) and K₂CO₃ (483 mg, 3.5 mmol, 3.5 eq.) were stirred in DMF (10 ml) at r.t. for 4-16 hours.

Work-up1:

The mixture was poured into ice-water mixture. The resulted precipitate was filtered off, washed with water, and dried.

Work-up2:

The mixture was filtered and the filtrate was injected to preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient).

General procedure 8

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Compound obtained in **General Procedure 6** (2.7 mmol), EDC.HCl (1.183 g, 6.172 mmol) and corresponding carboxylic acid (2.7 mmol) were stirred in pyridine (25 ml) at r.t. for 16 hours.

Work-up1:

5 The reaction mixture was evaporated, the residue was taken in DMF and injected to preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient).

Work-up2:

10 The reaction mixture was evaporated and the residue was triturated with water. The resulted solid was filtered off.

Preparation R1b: 4-methoxy-7H-pyrrolo[2,3-d]pyrimidine

Preparation R1a (100 g, 0,651 mol, 1 eq.), NaOH (31,26 g, 0,781 mol, 1.2 eq.) and MeOH (400 ml) was stirred at 90 °C for 24 hours. The mixture was quenched with water (1200 ml) and cooled to r.t. with ice bath. The mixture was stirred for 30 minutes, and
15 filtered through a glass filter. The precipitate was washed with water (3 x 100 ml) then dried and **Preparation R1b** is obtained as white solid. HRMS calculated for C₇H₇N₃O: 149.0589; found 150.0667 [(M+H)⁺ form].

¹H-NMR (400 MHz, MSM-d₆): δ = 12.02 (vbrs, 1 H), 8.37 (s, 1 H), 7.35 (d, 1 H), 6.47 (d, 1 H), 4.02 (s, 3 H).

20 ¹³C-NMR (100 MHz, MSM-d₆): δ ppm 162.6, 152.9, 150.8, 124.6, 104.8, 98.3, 53.7.

Preparation R1c: tert-butyl (3R,4R)-4-(2-oxa-6-azaspiro[2.5]octane-6-carbonyl)-3-phenyl-piperidine-1-carboxylate

Step 1: tert-butyl (3R,4R)-4-(4-oxopiperidine-1-carbonyl)-3-phenyl-piperidine-1-carboxylate

25 4-piperidone hydrochloride hydrate (0.969 g, 6.3 mmol), EDC.HCl (3.623 g, 18.9 mmol) and (3R,4R)-1-tert-butoxycarbonyl-3-phenyl-piperidine-4-carboxylic acid (1.928 g,

- 24 -

6.3 mmol) were dissolved in pyridine (10 mL) and stirred at r.t. for 16 hours. The reaction mixture was evaporated to Celite, purified by flash chromatography (DCM:MeOH, gradient) to give the product of the title. HRMS calculated for $C_{22}H_{30}N_2O_4$: 386.2206; found 409.2093 $[(M+Na)^+ \text{ form}]$.

5 $^1\text{H-NMR}$ (500 MHz, MSM- d_6): δ = 1.42 (s, 9 H), 4.14-1.50 (m, 16 H), 7.32-7.15 (m, 5 H).

Step 2: Preparation R1c

tert-Butyl (3R,4R)-4-(4-oxopiperidine-1-carbonyl)-3-phenylpiperidine-1-carboxylate (60 g, 155 mmol 1 eq.) and trimethylsulfoxonium-iodide (85.41 g, 388 mmol, 2.5 eq.) was charged into a round bottom flask and dissolved/suspended in MeCN (150 ml) and MTBE (150 ml). NaOH (15.5 g, 388 mmol, 2.5 eq.) was dissolved in water (21.6 ml) (~40 % solution). The aq. NaOH solution was added to the mixture and stirred at 60 °C for 2 hours. After the reaction completed, the mixture was cooled to r.t., filtered through a Celite bed, the filter cake was washed with MTBE (2 x 60 ml). Water (150 ml) was added to the organic layer and after extraction the layers were separated. The aq. layer was extracted with further MTBE (2 x 60 ml). The combined organic layers were dried over $MgSO_4$, and after filtration evaporated to give **Preparation R1c** as beige solid foam. HRMS calculated for $C_{23}H_{32}N_2O_4$: 400.2362; found 423.2247 $[(M+Na)^+ \text{ form}]$. $^1\text{H-NMR}$ (500 MHz, MSM- d_6): δ = 1.41 (s, 9 H), 1.79-0.86 (m, 6 H), 2.61-2.51 (m, 2 H), 4.16-2.73 (m, 10 H), 7.33-7.18 (m, 5 H).

20 **Preparation R2b: 7-(pyridin-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 3** starting from **Preparation R1b** and 2-iodopyridine as reagents, **Preparation R2b** was obtained. HRMS calculated for $C_{11}H_8N_4O$: 212.0698; found 213.0774 $[(M+H)^+ \text{ form}]$.

25 $^1\text{H-NMR}$ (500 MHz, MSM- d_6): δ (ppm) 12.29 (s, 1 H), 8.55 (dd, 1 H), 8.47 (dd, 1 H), 8.06 (brs, 1 H), 8.03 (t, 1 H), 7.9 (d, 1 H), 7.4 (t, 1 H), 6.7 (d, 1 H).

$^{13}\text{C-NMR}$ (125 MHz, MSM- d_6): δ (ppm) 149.1, 145, 139.4, 122.5, 122, 116.9, 104.

$^{15}\text{N-NMR}$ (50.6 MHz, MSM- d_6): δ (ppm) 171.2.

Preparation R2c: 7-(4-methoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

- 25 -

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodoanisole as reagents, **Preparation R2c** was obtained. HRMS calculated for $C_{13}H_{11}N_3O_2$: 241.0851; found 242.0929 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.04 (brs, 1 H), 7.92 (d, 1 H), 7.58 (dd, 1 H), 7.4 (d, 1 H), 7.08 (d, 1 H), 6.65 (d, 1 H), 3.81 (s, 3 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 158.8, 147.3, 144.4, 130.9, 126.1, 124.4, 114.8, 109.4, 103.1, 55.9.

Preparation R2e: 7-(4-fluoro-3-methoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-fluoro-4-iodo-2-methoxybenzene as reagents, **Preparation R2e** was obtained. HRMS calculated for $C_{13}H_{10}N_3O_2F$: 259.0757; found 260.0818 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.1 (s, 1 H), 7.95 (s, 1 H), 7.51 (d, 1 H), 7.48 (dd, 1 H), 7.38 (dd, 1 H), 7.27 (ddd, 1 H), 6.68 (d, 1 H), 3.9 (s, 3 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 144.7, 124.5, 117, 116.5, 111, 103.4, 56.8.

Preparation R2g: 7-methyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and iodomethane as alkylating agent, **Preparation R2g** was obtained. HRMS calculated for $C_7H_7N_3O$: 149.0589; found 150.0668 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 11.85 (brs, 1 H), 7.88 (brs, 1 H), 7.09 (d, 1 H), 6.44 (d, 1 H), 3.70 (m, 1 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.7, 143.8, 125.1, 108.1, 101.7, 31.8.

Preparation R2h: 7-ethyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and iodoethane as reagents, **Preparation R2h** was obtained. HRMS calculated for $C_8H_9N_3O$: 163.0746; found 164.0823 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 11.38 (brs., 1 H), 7.87 (d, $J=2.0$ Hz, 1 H), 7.16 (d, $J=3.4$ Hz, 1 H), 6.45 (d, $J=3.4$ Hz, 1 H), 4.14 (q, $J=7.1$ Hz, 2 H), 1.34 (t, $J=7.1$ Hz, 3 H).

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Preparation R2i: 7-(prop-2-yn-1-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1b** (instead of **Preparation R1a**) and 3-bromoprop-1-yne as reagents (without the hydrolysis step), the crude methoxypyrimidine product (400 mg, 2.3 mmol) was dissolved in PDO (4 ml) and aqueous HCl solution (37 %, 0.18 ml) was added. The mixture was heated for 100 °C for 30 minutes in a Schlenk tube. After cooling, DIPO (4 ml) was added to the reaction mixture and the resulted precipitate was filtered off and dried to give **Preparation R2i**. HRMS calculated for C₉H₇N₃O: 173.0589; found 174.0665 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.98 (brs, 1 H), 7.93 (s, 1 H), 7.19 (d, 1 H), 6.5 (d, 1 H), 4.98 (d, 2 H), 3.42 (t, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.6, 147.3, 144.3, 123.6, 102.5, 79.4, 76, 34.1.

Preparation R2j: 7-cyclopropyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and cyclopropylboronic acid as reagents, **Preparation R2j** was obtained. HRMS calculated for C₉H₉N₃O: 175.0746; found 176.0819 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.88 (brs., 1 H), 7.89 (brs., 1 H), 7.05 (d, 1 H), 6.4 (d, 1 H), 3.53 (m, 1 H), 1.06-0.92 (m, 4 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 148.9, 143.8, 123.4, 108.8, 101.6, 27.5, 6.6.

Preparation R2k: 7-(buta-2,3-dien-1-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1b** (instead of **Preparation R1a**) and 4-bromobuta-1,2-diene as reagents (without the hydrolysis step), the crude methoxypyrimidine product (300 mg, 1.65 mmol) was dissolved in PDO (4 ml) and aq. HCl solution (37 %, 0.18 ml) was added. The mixture was heated for 100 °C for 30 minutes in a Schlenk tube. After cooling, the reaction mixture was evaporated to give **Preparation R2k**. HRMS calculated for C₁₀H₉N₃O: 187.0745; found 188.0821 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.91 (brs, 1 H), 7.89 (s, 1 H), 7.12 (d, 1 H), 6.46 (d, 1 H), 5.48 (m, 1 H), 4.87 (m, 2 H), 4.73 (m, 2 H).

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¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 208.3, 158.7, 147.4, 143.9, 123.9, 108.2, 102.1, 88.3, 78.1, 43.

Preparation R2l: 7-(cyclopropylmethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and cyclopropylmethyl bromide as reagents, **Preparation R2l** was obtained. HRMS calculated for C₁₀H₁₁N₃O: 189.0902; found 190.0980 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.84 (s, 1 H), 7.87 (s, 1 H), 7.2 (d, 1 H), 6.45 (d, 1 H), 3.97 (d, 2 H), 1.21 (m, 1 H), 0.52-0.35 (m, 4 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.3, 143.7, 124, 108.1, 101.7, 49, 12.3, 4.07.

Preparation R2m: 7-(2-methylpropyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and 1-bromo-2-methylpropane as reagents, **Preparation R2m** was obtained. HRMS calculated for C₁₀H₁₃N₃O: 191.1059; found 192.1132 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.84 (brs, 1 H), 7.86 (s, 1 H), 7.12 (d, 1 H), 6.45 (d, 1 H), 3.92 (d, 2 H), 2.1 (sept., 1 H), 0.82 (d, 6 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.7, 143.7, 124.5, 108, 101.6, 52, 29.6, 20.2.

Preparation R2n: 9-methyl-3H-pyrimido[4,5-b]indol-4-one

Preparation R1b (500 mg, 3.06 mmol) and 2,5-dimethoxytetrahydrofuran (810 mg, 6.13 mmol, d= 1.02, 795 μl) in 5 ml 1,4-dioxane were heated up to 100 °C for 102 hours, then 5ml 1N HCl was added. It was dissolved in DMF and purified by preparative LC (on C-18 Gemini-NX 5μm column, 5 mM aqueous NH₄HCO₃-MeCN, gradient) to give **Preparation R2n**. HRMS calculated for C₁₁H₉N₃O: 199.0746; found 200.0827 [(M+H)⁺ form].

¹H-NMR(500 MHz, dmso-d6) δ ppm 12.33 (brs, 1 H), 8.21 (s, 1 H), 7.63 (dm, 1 H), 7.41 (ddd, 1 H), 7.29 (td, 1 H), 3.86 (s, 3 H)

¹³C-NMR(500 MHz, dmso-d6) δ ppm 158.5, 153.5, 148.1, 137, 124.6, 122, 121.8, 121, 110.7, 100.1, 28.5

Preparation R2o: 7-(cyclobutylmethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and (bromomethyl)cyclobutane as reagents, **Preparation R2o** was obtained. HRMS calculated for $C_{11}H_{13}N_3O$: 203.1059; found 204.1134 $[(M+H)^+]$ form].

5 ^1H -NMR (500 MHz, MSM-d6): δ (ppm) 11.83 (brs, 1 H), 7.87 (d, 1 H), 7.12 (d, 1 H), 6.43 (d, 1 H), 4.13 (d, 2 H), 2.72 (m, 1 H), 1.92/1.74 (m+m, 4 H), 1.82 (m, 2 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 143.7, 124.2, 101.7, 49.6, 36, 25.6, 18.

Preparation R2p: 7-[2-(dimethylamino)ethyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

10 Using **General Procedure 1** starting from **Preparation R1a** and 2-bromo-*N,N*-dimethylethylamine hydrobromide as reagents, **Preparation R2p** was obtained. HRMS calculated for $C_{10}H_{14}N_4O$: 206.1168; found 207.1242 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 11.84 (brs, 1 H), 7.88 (brd, 1 H), 7.16 (d, 1 H), 6.44 (d, 1 H), 4.19 (t, 2 H), 2.6 (t, 2 H), 2.16 (s, 6 H).

15 ^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.5, 143.7, 124.4, 108.1, 101.7, 59.2, 45.5, 42.6.

Preparation R2q: 7-phenyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and iodobenzene as reagents, **Preparation R2q** was obtained. HRMS calculated for $C_{12}H_9N_3O$: 211.0746; found 212.083 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.1 (brs, 1 H), 7.95 (d, 1 H), 7.71 (m, 2 H), 7.54 (m, 2 H), 7.5 (d, 1 H), 7.4 (m, 1 H), 6.69 (d, 1 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.3, 144.6, 137.8, 129.7, 127.4, 124.6, 124.1, 109.8, 103.6.

Preparation R2s: 7-(pyrimidin-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

25 **Preparation R1b** (300 mg, 2.011 mmol, 1 eq.), 2-chloropyrimidine (2.413 mmol, 1.2 eq.) and anhydrous K_2CO_3 (417 mg, 3.017 mmol, 1.5 eq.) was heated in DMF (10 ml) at 150 °C for 2 hours. The reaction mixture was filtered and purified by preparative LC (on

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C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient) to give 4-methoxy-7-pyrimidin-2-yl-pyrrolo[2,3-*d*]pyrimidine.

Then the obtained product (0.633 mmol, 1 eq.), 1M HCl aqueous solution (3 ml) and PDO (60 ml) were stirred at 100 °C for 1 hour. After the reaction completed, the mixture was evaporated and purified by preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient) to give **Preparation R2cj**. HRMS calculated for C₁₀H₇N₅O: 213.0651; found 214,0735 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.19 (brs, 1 H), 8.94 (d, 1 H), 8.01 (s, 1 H), 7.78 (d, 1 H), 7.54 (t, 1 H), 6.71 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 159.7, 158.7, 156, 148.1, 145.2, 123.3, 120.1, 111.4, 104.5.

Preparation R2t: 6,8-dimethylpyrimido[5,4-*b*]indolizin-4(3*H*)-one

Preparation R1b (1.74 g, 11.67 mmol) was dissolved in DMF (80 ml) and cooled to 0 °C. Sodium hydride (60 % disp., 1.87 g, 46.67 mmol) was slowly added and the solution was stirred for 30 minutes at 0 °C. Hydroxylamine-O-sulfonic acid (2.11 g, 18.67 mmol) was added to the reaction mixture and allowed to warm up to r.t. and stirred for 20 hours. Water (100 ml) was added to the reaction mixture and extracted with DCM (4 x 50 ml). The combined organic layers were washed with water, dried over MgSO₄ and evaporated.

A part of the resulted *N*-amino compound (300 mg, 1.83 mmol) and acetylacetone (206 μ l, 201 mg 2.01 mmol) were dissolved in 5 ml acetic acid and heated up to 120 °C for 2 hours and 30 minutes, then TFA (5 ml) was added. It was heated at 120 °C for more 18 hours. Then 1 ml water and 10 ml methanol were added, then it was evaporated. The residue was purified by preparative LC (on C-18 Gemini-NX 5 μ m column, 5 mM aqueous NH₄HCO₃-MeCN, gradient) to give **Preparation R2t**. HRMS calculated for C₁₁H₁₀N₄O: 214.0855; found 215.0935 [(M+H)⁺ form].

¹H-NMR(500 MHz, dmso-d6) δ ppm 12.16 (s, 1 H), 8 (s, 1 H), 6.89 (s, 1 H), 6.68 (d, 1 H), 2.45 (d, 3 H), 2.44 (s, 3 H)

¹³C-NMR(500 MHz, dmso-d6) δ ppm 159.7, 152.5, 143.4, 141.2, 138.9, 127.7, 115.5, 109.8, 91.2, 21.9, 17.4

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Preparation R2u: 7-(1-methyl-1H-imidazol-4-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodo-1-methyl-1H-imidazole as reagents, **Preparation R2u** was obtained. HRMS calculated for C₁₀H₉N₅O: 215.0807; found 216.0879 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 9.24-7.3 (vbrs, 3 H), 7.51 (d, 1 H), 6.72 (brs, 1 H), 3.77 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 121.7, 103.5, 35.

¹⁵N-NMR (50.6 MHz, MSM-d6): δ (ppm) 153.

Preparation R2v: 7-(thiophen-3-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and thiophene-3-boronic acid pinacol ester as reagents, **Preparation R2v** was obtained. HRMS calculated for C₁₀H₇N₃OS: 217.0310; found 218.0390 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.14 (s, 1 H), 7.99 (d, 1 H), 7.92 (dd, 1 H), 7.71 (dd, 1 H), 7.68 (dd, 1 H), 7.57 (d, 1 H), 6.66 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.6, 147, 144.8, 136.3, 127, 123.8, 123.3, 115.1, 109.5, 103.5.

Preparation R2w: 7-(thiophen-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-iodothiophene as reagents, **Preparation R2w** was obtained. HRMS calculated for C₁₀H₇N₃OS: 217.0310; found 218.0384 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.2 (brs, 1 H), 8.03 (s, 1 H), 7.58 (d, 1 H), 7.43 (dd, 1 H), 7.39 (dd, 1 H), 7.07 (dd, 1 H), 6.69 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.5, 147.2, 145.3, 138.7, 126, 124.3, 122.8, 119.2, 109.4, 104.2.

Preparation R2x: 7-(2,2,2-trifluoroethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and 2,2,2-trifluoroethyl trifluoromethanesulfonate as reagents, **Preparation R2x** was obtained. HRMS calculated for C₈H₆N₃OF₃: 217.0463; found 218.0543 [(M+H)⁺ form].

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¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.08 (brs, 1 H), 7.97 (s, 1 H), 7.19 (d, 1 H), 6.57 (d, 1 H), 5.06 (q, 2 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.5, 148.4, 144.9, 124.7, 124.4, 108.8, 103.2, 45.1.

5 ¹⁹F-NMR (376.5 MHz, MSM-d6): δ (ppm) -70.3.

Preparation R2y: 7-(1,3-thiazol-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-iodothiazole as reagents, **Preparation R2ck** was obtained. HRMS calculated for C₉H₆N₄OS: 218.0262; found 219.0335 [(M+H)⁺ form].

10 ¹H-NMR (500 MHz, MeCN-d3) δ ppm 8.5 (s, 1 H), 7.62 (d, 1 H), 7.52 (d, 1 H), 7.22 (d, 1 H), 6.51 (d, 1 H).

¹³C-NMR (125 MHz, MeCN-d3) δ ppm 154.5, 137.9, 116.8, 114.8, 104.2.

Preparation R2z: 7-[3-(dimethylamino)propyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

15 Using **General Procedure 1** starting from **Preparation R1a** and 3-dimethylaminopropyl chloride hydrochloride as reagents, **Preparation R2z** was obtained. HRMS calculated for C₁₁H₁₆N₄O: 220.1324; found 221.1401 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.84 (brs, 1 H), 7.88 (s, 1 H), 7.13 (d, 1 H), 6.44 (d, 1 H), 4.12 (t, 2 H), 2.15 (t, 2 H), 2.1 (s, 6 H), 1.85 (p, 2 H).

20 ¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.4, 143.8, 124.2, 108.2, 101.7, 56.4, 45.6, 43, 28.6.

Preparation R2aa: 7-(3-methylphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

25 Using **General Procedure 3** starting from **Preparation R1b** and 3-iodotoluene as reagents, **Preparation R2aa** was obtained. HRMS calculated for C₁₃H₁₁N₃O: 225.0902; found 226.098 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.08 (brs, 1 H), 7.95 (d, 1 H), 7.52 (brs, 1 H), 7.49 (dm, 1 H), 7.46 (d, 1 H), 7.41 (t, 1 H), 7.22 (brd., 1 H), 6.67 (d, 1 H), 2.39 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.3, 144.6, 139.2, 137.8, 129.5, 128.1, 125.2, 124.2, 121.8, 109.7, 103.5, 21.4.

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Preparation R2ab: 7-(4-methylphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodotoluene as reagents, **Preparation R2ab** was obtained. HRMS calculated for C₁₃H₁₁N₃O: 225.0902; found 226.0987 [(M+H)⁺ form].

5 ¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.06 (brs, 1 H), 7.93 (s, 1 H), 7.58 (dm, 1 H), 7.44 (d, 1 H), 7.33 (dm, 1 H), 6.66 (d, 1 H), 2.37 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.3, 144.5, 136.8, 135.4, 130.1, 124.5, 124.1, 109.6, 103.4, 21.

Preparation R2ac: 7-benzyl-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

10 Using **General Procedure 1** starting from **Preparation R1a** and benzyl bromide as reagents, **Preparation R2ac** was obtained. HRMS calculated for C₁₃H₁₁N₃O: 225.0902; found 226.0986 [(M+H)⁺ form].

¹H-NMR (400 MHz, MSM-d6): δ (ppm) 11.91 (brs, 1 H), 7.91 (s, 1 H), 7.36-7.17 (m, 5 H), 7.2 (d, 1 H), 6.49 (d, 1 H), 5.34 (s, 2 H).

15 ¹³C-NMR (100 MHz, MSM-d6): δ (ppm) 144.1, 124.3, 102.2, 48.1.

Preparation R2ad: 6-methyl-7-phenyl-3H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and iodobenzene as reagents, 4-methoxy-7-phenyl-pyrrolo[2,3-d]pyrimidine was obtained (without hydrolysis).

This crude product (450 mg, 2 mmol) was dissolved in THF (18 ml) stirred at -78 °C, then
20 LDA solution (1.8 M, 1.7 ml, 3 mmol) was added. After one hour of stirring at -78 °C, iodomethane (190 µl, 3 mmol) solution in THF (5 ml) was added, and continued stirring for 90 minutes. Then the reaction mixture was diluted with brine (10 ml), evaporated to Celite and purified by flash chromatography (Hexane-EEO=7-1).

The resulted crude product (400 mg, 1.6 mmol) was dissolved in cc. HCl aqueous solution
25 (330 µl, ~12.2 M, 4 mmol) and PDO (5 ml) was stirred at 100 °C for 2 hours. After the reaction completed, the mixture was partially evaporated and the formed suspension was filtered. The solid on the filter was washed with water and dried to give **Preparation R2de**. HRMS calculated for C₁₃H₁₁N₃O: 225.0902; found 226.0985 [(M+H)⁺ form].

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¹H-NMR(500 MHz, MSM-d6) δ ppm 11.94 (s, 1 H), 7.76 (d, 1 H), 7.55 (tm, 2 H), 7.49 (tm, 1 H), 7.4 (dm, 2 H), 6.41 (d, 1 H), 2.17 (d, 3 H).

¹³C-NMR(125 MHz, MSM-d6) δ ppm 158.4, 143.6, 136.2, 132.6, 129.6, 128.7, 128.5, 100.9, 13.3.

5 **Preparation R2ae: 7-(4-fluorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 3** starting from **Preparation R1b** and 4-fluoroiodobenzene as reagents, **Preparation R2ae** was obtained. HRMS calculated for C₁₂H₈FN₃O: 229.0651; found 230.0714 [(M+H)⁺ form].

10 ¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.12 (brs, 1 H), 7.95 (d, 1 H), 7.74 (m, 2 H), 7.48 (d, 1 H), 7.39 (m, 2 H), 6.68 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.7, 126.8, 124.2, 116.4, 103.5.

Preparation R2ai: 6-chloro-7-phenyl-3H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and iodobenzene as reagents, 4-methoxy-7-phenyl-pyrrolo[2,3-d]pyrimidine was obtained (without hydrolysis).

15 The crude product (394 mg, 1.75 mmol) was dissolved in THF (14 ml) stirred at -78 °C, then LDA solution (1.8 M, 1.2 ml, 2.16 mmol) was added. After one hour of stirring at -78 °C, hexachloroethane (632 mg, 2.63 mmol) solution in THF (5 ml) was added, and continued stirring for 90 minutes. Then the reaction mixture was diluted with brine (10 ml), evaporated to Celite and purified by flash chromatography (Hexane-EEO=9-1).

20 The resulted crude product (110 mg, 0.42 mmol) was dissolved in cc. HCl aqueous solution (82 µl, ~12.2 M, 1 mmol) and PDO (5 ml) was stirred at 100 °C for 2 hours. After the reaction completed, the mixture was partially evaporated and the formed suspension was filtered. The solid on the filter was washed with water and dried to give **Preparation R2dh**. HRMS calculated for C₁₂H₈N₃OCl: 245.0356; found 246.043 [(M+H)⁺ form].

25 ¹H-NMR(500 MHz, MSM-d6) δ ppm 12.16 (s, 1 H), 7.88 (s, 1 H), 7.6-7.52 (m, 5 H), 6.78 (s, 1 H).

¹³C-NMR(125 MHz, MSM-d6) δ ppm 157.6, 148.2, 145.3, 101.6.

Preparation R2aj: 6-iodo-7-methyl-3H-pyrrolo[2,3-d]pyrimidin-4-one

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To a stirred solution of **Preparation R1a** (8 g, 52.1 mmol) in abs. DMF (50 ml) was cooled down to 0 °C, then sodium-hydride (3.13 g, 60 % disp. in mineral oil, 78.2 mmol, 1.5 eq.) was added, and stirred for 20 minutes at r.t. under Ar. Methyl iodide (8.2 g, 57.2 mmol, d=2.28, 3.6 ml) was added to the reaction mixture and stirred for 1.5 hours at r.t. The mixture was poured into water (50 ml). Solid compound was formed, which was filtered off.

A part of the resulted *N*-methylated compound (500 mg, 2.98 mmol) was dissolved in 5 ml abs. THF and cooled down to -78 °C. Then 2M LDA (1.7 ml, 3.4 mmol) was added dropwise. The mixture was stirred at -78°C for 1 hour, then iodide (757 mg, 2.98 mmol) was added. The solution was allowed to warm to r.t. and stirred for 22 hours, then 5 ml water was added. Solid compound was formed and filtered off to give **Preparation R2aj**. HRMS calculated for C₇H₆IN₃O: 274.9556; found 275.9634 [(M+H)⁺ form].

¹H-NMR(500 MHz, dmso-d₆) δ ppm 11.97 (s, 1 H), 7.85 (s, 1 H), 6.79 (s, 1 H), 3.64 (s, 3 H)

¹³C-NMR(500 MHz, dmso-d₆) δ ppm 157.3, 149.1, 144.2, 111.4, 110.3, 80.4, 33.2

Preparation R2al: 6-iodo-7-(2-trimethylsilylethoxymethyl)-3H-pyrrolo[2,3-d]pyrimidin-4-one

233 mg (0.82mmol) 2-[(4-chloropyrrolo[2,3-d]pyrimidin-7-yl)methoxy]ethyl-trimethylsilane was dissolved in 4 ml dry THF and cooled down to -78 °C and 500 µL (1.8 M stock solution, 0.9 mmol, 1.1 eq.) LDA was added. The mixture was stirred under nitrogen for 40 minutes at -78 °C then 208 mg iodine (0.82 mmol, 1 eq.) was added and allowed to warm to r.t. It was stirred for 40 minutes, then water was added. The solution was extracted with EEO (2 x 15 ml), combined organic phase was dried (magnesium sulfate) and evaporated. The residue was purified by flash chromatography (Eluent: heptane-EEO gradient).

Resulted crude 2-[(4-chloro-6-iodo-pyrrolo[2,3-d]pyrimidin-7-yl)methoxy]ethyl-trimethylsilane was solved in 3 ml PDO and 3 ml water and 166 mg (3.98 mmol) lithium hydroxide hydrate was added. The mixture was heated and stirred at 110 °c for 5 hours. The solution was cooled to r.t., then 1 N HCl was added till pH 3-4. Solid compound was formed, which was filtered off, and washed with water, **Preparation R2al** was obtained.

HRMS calculated for C₁₂H₁₈IN₃O₂Si: 391.0213; found 392.0298 [(M+H)⁺ form].

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¹H-NMR(500 MHz, DMSO-d₆) δ ppm 12.1 (brs, 1 H), 7.91 (d, 1 H), 6.84 (s, 1 H), 5.45 (s, 2H), 3.51(m, 2H), 0.82 (m, 2H), -0.08 (s, 9H).

¹³C-NMR(500 MHz, DMSO-d₆) δ ppm 157.3, 149.9, 144.8, 112.9, 110.5, 79.3, 73.7, 66.0, 17.5.

5 **Preparation R2am: 7-(3,4,5-trimethoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 3** starting from **Preparation R1b** and 5-iodo-1,2,3-trimethoxybenzene as reagents, **Preparation R2am** was obtained. HRMS calculated for C₁₅H₁₅N₃O₄: 301.1063; found 302.1138 [(M+H)⁺ form].

10 ¹H-NMR (500 MHz, MSM-d₆): δ (ppm) 12.07 (brs, 1 H), 7.95 (d, 1 H), 7.49 (d, 1 H), 6.99 (s, 2 H), 6.66 (d, 1 H), 3.82 (s, 6 H), 3.7 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d₆): δ (ppm) 144.5, 124.6, 103.2, 103, 60.6, 56.6.

Preparation R2an: 7-(3,5-dichlorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

15 Using **General Procedure 2** starting from **Preparation R1a** and 3,5-dichlorophenylboronic acid as reagents, **Preparation R2an** was obtained. HRMS calculated for C₁₂H₇Cl₂N₃O: 278.9966; found 280.0040 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d₆): δ (ppm) 12.03 (vbrs, 1 H), 8.03 (s, 1 H), 7.95 (d, 2 H), 7.64 (t, 1 H), 7.63 (d, 1 H), 6.71 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d₆): δ (ppm) 145.3, 126.7, 123.8, 122.7, 104.4

20 **Preparation R2ao: 7-(3-chloro-5-methoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 2** starting from **Preparation R1a** and 3-chloro-5-methoxyphenylboronic acid as reagents, **Preparation R2ao** was obtained. HRMS calculated for C₁₃H₁₀ClN₃O₂: 275.0461; found 276.0541 [(M+H)⁺ form].

25 ¹H-NMR (400 MHz, MSM-d₆): δ (ppm) 12.18 (s, 1 H), 8 (d, 1 H), 7.6 (d, 1 H), 7.51 (t, 1 H), 7.33 (t, 1 H), 7.08 (t, 1 H), 6.69 (d, 1 H), 3.85 (s, 3 H).

¹³C-NMR (100 MHz, MSM-d₆): δ (ppm) 161, 158.7, 147.5, 145, 139.7, 134.5, 124, 116.3, 112.7, 110.2, 109.4, 104, 56.4

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Preparation R2ap: 7-(3,5-dimethoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 2-(3,5-dimethoxy)-phenyl-4,4,5,5-tetramethyl-(1,3,2)-dioxaborolane as reagents, **Preparation R2ap** was obtained. HRMS calculated for C₁₄H₁₃N₃O₃: 271.0957; found 272.1030 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.11 (s, 1 H), 7.95 (d, 1 H), 7.52 (d, 1 H), 6.91 (d, 2 H), 6.66 (d, 1 H), 6.54 (t, 1 H), 3.8 (s, 6 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.5, 124.2, 103.5, 103.1, 98.9.

Preparation R2aq: 7-(3,4-dichlorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1b** and 3,4-dichlorophenylboronic acid as reagents, **Preparation R2aq** was obtained. HRMS calculated for C₁₂H₇Cl₂N₃O: 278.9966; found 280.003 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.21 (brs, 1 H), 8.15 (t, 1 H), 8.02 (brs, 1 H), 7.82 (d, 1 H), 7.82 (d, 1 H), 7.61 (d, 1 H), 6.72 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 145.1, 131.5, 125.9, 124.3, 123.8, 104.2.

Preparation R2ar: 7-(4-chloro-3-fluorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-chloro-3-fluoriodobenzene as reagents, **Preparation R2ar** was obtained. HRMS calculated for C₁₂H₇ClFN₃O: 263.0262; found 264.0339 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.21 (s, 1 H), 8.02 (d, 1 H), 7.97 (dd, 1 H), 7.77 (dd, 1 H), 7.72 (dd, 1 H), 7.6 (d, 1 H), 6.72 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 145.1, 131.5, 123.7, 121.5, 112.8, 104.2.

Preparation R2as: 7-(4-chloro-3-methoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-chloro-5-iodoanisole as reagents, **Preparation R2as** was obtained. HRMS calculated for C₁₃H₁₀ClN₃O₂: 275.0461; found 276.0537 [(M+H)⁺ form].

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¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.15 (brs, 1 H), 7.98 (brs, 1 H), 7.58 (d, 1 H), 7.57 (d, 1 H), 7.49 (d, 1 H), 7.36 (dd, 1 H), 6.7 (d, 1 H), 3.93 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 155.3, 147.4, 144.8, 137.7, 130.5, 124.2, 119.8, 117.3, 110, 109.4, 103.7, 56.9.

5 **Preparation R2at: 7-(3,4-dimethoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 2** starting from **Preparation R1b** and 3,4-dimethoxyphenylboronic acid pinacol ester as reagents, **Preparation R2at** was obtained. HRMS calculated for C₁₄H₁₃N₃O₃: 271.0957; found 272.103 [(M+H)⁺ form].

10 ¹H-NMR (500 MHz, MSM-d6): δ (ppm) 7.92 (d, 1 H), 7.43 (d, 1 H), 7.25 (d, 1 H), 7.19 (dd, 1 H), 7.08 (d, 1 H), 6.65 (d, 1 H), 3.8 (s, 6 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.5, 124.6, 116.9, 112.2, 109.3, 103.1, 56.3.

Preparation R2au: 4-{4-oxo-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-7-yl}benzonitrile

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodobenzonitrile as reagents, **Preparation R2au** was obtained. HRMS calculated for C₁₃H₈N₄O: 236,0698; found 237.0775 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.25 (brs, 1 H), 8.05 (m, 2 H), 8.03 (m, 2 H), 8.02 (brs, 1 H), 7.66 (d, 1 H), 6.75 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 147.6, 145.2, 141.5, 134, 124.6, 123.6, 119, 110.6, 109.4, 104.7.

20 **Preparation R2av: 7-[4-(trifluoromethyl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodobenzotrifluoride as reagents, **Preparation R2av** was obtained. HRMS calculated for C₁₃H₈F₃N₃O: 279,0619; found 280.0691 [(M+H)⁺ form].

25 ¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.23 (brs, 1 H), 8.02 (m, 2 H), 8.01 (d, 1 H), 7.92 (m, 2 H), 7.63 (d, 1 H), 6.74 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.6, 145.1, 126.9, 124.7, 123.8, 110.4, 104.5 ¹⁵N-NMR (50.6 MHz, MSM-d6): δ (ppm) 170.9.

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Preparation R2aw: 7-[4-(difluoromethyl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-(difluoromethyl)-4-iodobenzene as reagents, **Preparation R2aw** was obtained. HRMS calculated for $C_{13}H_9F_2N_3O$: 261.0714; found 262.0784 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.17 (brs, 1 H), 7.99 (d, 1 H), 7.91 (m, 2 H), 7.75 (m, 2 H), 7.58 (d, 1 H), 7.12 (t, 1 H), 6.72 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.9, 127.2, 124.7, 123.9, 115.1, 104.1.

Preparation R2ax: 7-[4-(hydroxymethyl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodobenzyl alcohol as reagents, **Preparation R2ax** was obtained. HRMS calculated for $C_{13}H_{11}N_3O_2$: 241.0851; found 242.0925 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.07 (brs, 1 H), 7.94 (s, 1 H), 7.66 (m, 2 H), 7.47 (m, 2 H), 7.45 (d, 1 H), 6.67 (d, 1 H), 5.31 (t, 1 H), 4.56 (d, 2 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.9, 147.4, 144.6, 142.2, 136.6, 127.6, 124.3, 124.2, 109.9, 103.5, 62.8.

Preparation R2ay: 7-(4-chlorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-chloro-4-iodobenzene as reagents, **Preparation R2ay** was obtained. HRMS calculated for $C_{12}H_8ClN_3O$: 245.0356; found 246.0427 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.15 (brs, 1 H), 7.97 (d, 1 H), 7.78 (dm, 1 H), 7.61 (dm, 1 H), 7.53 (d, 1 H), 6.7 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.3, 144.8, 136.7, 131.7, 129.6, 126.1, 123.9, 109.9, 103.9.

Preparation R2az: 7-[4-(dimethylamino)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

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Using **General Procedure 2** starting from **Preparation R1a** and 4-(dimethylamino)phenylboronic acid as reagents, **Preparation R2az** was obtained. HRMS calculated for $C_{14}H_{14}N_4O$: 254.1168; found 255.1243 $[(M+H)^+]$ form].

^1H -NMR (400 MHz, MSM-d6): δ (ppm) 11.98 (brs, 1 H), 7.89 (d, 1 H), 7.43 (m, 2 H), 7.33 (d, 1 H), 6.82 (m, 2 H), 6.61 (d, 1 H), 2.94 (s, 6 H).

^{13}C -NMR (100 MHz, MSM-d6): δ (ppm) 144.1, 125.6, 124.3, 112.7, 102.7, 40.6.

Preparation R2ba: 7-[4-(trifluoromethoxy)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-iodo-4-(trifluoromethoxy)benzene as reagents, **Preparation R2ba** was obtained. HRMS calculated for $C_{13}H_8F_3N_3O_2$: 295.0569; found 296.0648 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.15 (s, 1 H), 7.97 (d, 1 H), 7.86 (m, 2 H), 7.56 (m, 2 H), 7.54 (m, 1 H), 6.71 (d, 1 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 144.8, 126.4, 124.1, 122.5, 103.9.

Preparation R2bb: 7-[4-(benzyloxy)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-benzyloxyiodobenzene as reagents, **Preparation R2bb** was obtained. HRMS calculated for $C_{19}H_{15}N_3O_2$: 317.1164; found 318.1243 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.05 (brs, 1 H), 7.92 (d, 1 H), 7.59 (dm, 2 H), 7.48 (dm, 2 H), 7.41 (d, 1 H), 7.41 (tm, 2 H), 7.35 (tm, 1 H), 7.16 (dm, 2 H), 6.65 (d, 1 H), 5.18 (s, 2 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 157.6, 147.3, 144.4, 137.4, 131, 129, 128.4, 128.2, 126.1, 124.3, 115.7, 109.4, 103.1, 69.9.

Preparation R2bc: 7-(5-methylthiophen-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-iodo-5-methylthiophene as reagents, **Preparation R2bc** was obtained. HRMS calculated for $C_{11}H_9N_3OS$: 231.0466; found 232.0541 $[(M+H)^+]$ form].

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¹H-NMR (400 MHz, MSM-d6): δ (ppm) 12.17 (brs, 1 H), 7.99 (d, 1 H), 7.49 (d, 1 H), 7.14 (d, 1 H), 6.76 (dq, 1 H), 6.67 (d, 1 H), 2.46 (d, 3 H).

¹³C-NMR (100 MHz, MSM-d6): δ (ppm) 145, 124.2, 123.9, 119.4, 103.9, 15.4.

Preparation R2bd: 7-(5-chlorothiophen-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-chloro-5-iodothiophene as reagents, **Preparation R2bd** was obtained. HRMS calculated for C₁₀H₆N₃OSCl: 250.9920; found 252.0005 ((M+H)⁺ form].

¹H-NMR (500 MHz, dmso-d6) δ ppm 12.28 (brs, 1 H), 8.07 (d, 1 H), 7.67 (d, 1 H), 7.3 (d, 1 H), 7.13 (d, 1 H), 6.72 (d, 1 H).

¹³C-NMR (500 MHz, dmso-d6) δ ppm 158.4, 146.8, 145.6, 136.4, 125.5, 124.6, 123.3, 117.5, 109.3, 104.6 .

Preparation R2be: 7-(2,3-dihydro-1,4-benzodioxin-6-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 1,4-benzodioxane-6-boronic acid as reagents, **Preparation R2be** was obtained. HRMS calculated for C₁₄H₁₁N₃O₃: 269,0800; found 270.0881 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.05 (brs, 1 H), 7.92 (d, 1 H), 7.4 (d, 1 H), 7.22 (d, 1 H), 7.13 (dd, 1 H), 6.99 (d, 1 H), 6.63 (d, 1 H), 4.33-4.25 (m, 4 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.4, 124.3, 117.7, 117.6, 113.8, 103.2.

Preparation R2bf: 7-(2H-1,3-benzodioxol-5-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 3,4-methylenedioxyphenylboronic acid as reagents, **Preparation R2bf** was obtained. HRMS calculated for C₁₃H₉N₃O₃: 255,0644; found 256.0719 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.05 (brs, 1 H), 7.92 (d, 1 H), 7.4 (d, 1 H), 7.29 (d, 1 H), 7.12 (dd, 1 H), 7.05 (d, 1 H), 6.63 (d, 1 H), 6.11 (s, 2 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.5, 124.5, 118.2, 108.7, 106.5, 103.1, 102.2.

Preparation R2bg: 7-(naphthalen-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 2-naphthaleneboronic acid as reagents, **Preparation R2bg** was obtained. HRMS calculated for C₁₆H₁₁N₃O: 261.0902; found 262.0982 [(M+H)⁺ form].

5 ¹H-NMR (500 MHz, MSM-d₆): δ (ppm) 12.14 (s, 1 H), 8.25 (d, 1 H), 8.09 (d, 1 H), 8.01 (m, 1 H), 8.01 (m, 1 H), 8 (s, 1 H), 7.91 (dd, 1 H), 7.63 (d, 1 H), 7.6 (tm, 1 H), 7.57 (tm, 1 H), 6.74 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d₆): δ (ppm) 158.8, 147.6, 144.8, 135.4, 133.4, 132, 129.4, 128.4, 128.2, 127.4, 126.9, 124.4, 123.5, 122.3, 109.9, 103.8.

10 **Preparation R2bh: 7-[3-(trifluoromethyl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 3** starting from **Preparation R1b** and 3-iodobenzotrifluoride as reagents, **Preparation R2bh** was obtained. HRMS calculated for C₁₃H₈F₃N₃O: 279.0620; found 280.0699 [(M+H)⁺ form].

15 ¹H-NMR (500 MHz, MSM-d₆): δ (ppm) 12.19 (brs, 1 H), 8.18 (brs, 1 H), 8.07 (dm, 1 H), 8.02 (d, 1 H), 7.79 (t, 1 H), 7.77 (dm, 1 H), 7.65 (d, 1 H), 6.73 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d₆): δ (ppm) 145.1, 131.1, 128.3, 124, 123.9, 121, 104.1.

Preparation R2bi: 7-{3-[(4-methylpiperazin-1-yl)methyl]phenyl}-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

20 Using **General Procedure 2** starting from **Preparation R1b** and 3-(4-methyl-1-piperazinylmethyl)benzeneboronic acid pinacol ester as reagents, **Preparation R2bi** was obtained. HRMS calculated for C₁₈H₂₁N₅O: 323.1746; found 324.1828 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d₆): δ (ppm) 12.37/12.2/11.95 (brs, 3 H), 8.04 (brs, 1 H), 7.98 (s, 1 H), 7.91 (dm, 1 H), 7.67 (dm, 1 H), 7.63 (d, 1 H), 7.62 (t, 1 H), 6.72 (d, 1 H), 4.49 (brs, 2 H), 3.8-3.3 (brm, 8 H), 2.8 (brs, 3 H).

25 ¹³C-NMR (125 MHz, MSM-d₆): δ (ppm) 144.8, 130.3, 130, 127.3, 125.7, 124, 103.9, 58.7, 42.7.

Preparation R2bj: 7-[3-(hydroxymethyl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

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Using **General Procedure 3** starting from **Preparation R1b** and 3-iodobenzyl alcohol as reagents, **Preparation R2bj** was obtained. HRMS calculated for $C_{13}H_{11}N_3O_2$: 241.0851; found 242.0935 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.11 (brs, 1 H), 7.95 (d, 1 H), 7.64 (brt, 1 H), 7.55 (dm, 1 H), 7.48 (t, 1 H), 7.46 (d, 1 H), 7.35 (dm, 1 H), 6.68 (d, 1 H), 4.58 (s, 2 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 147.4, 144.6, 144.4, 137.7, 129.4, 125.4, 124.2, 123, 122.5, 109.7, 103.5, 62.9.

Preparation R2bk: 7-(3-chlorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-chloro-3-iodobenzene as reagents, **Preparation R2bk** was obtained. HRMS calculated for $C_{12}H_8ClN_3O$: 245.0356; found 246.0437 $[(M+H)^+]$ form].

^1H -NMR (400 MHz, MSM-d6): δ (ppm) 12.17 (brs, 1 H), 8 (d, 1 H), 7.92 (m, 1 H), 7.74 (dm, 1 H), 7.58 (d, 1 H), 7.57 (t, 1 H), 7.47 (dm, 1 H), 6.7 (d, 1 H).

^{13}C -NMR (100 MHz, MSM-d6): δ (ppm) 145, 131.3, 127.2, 124.1, 123.9, 122.9, 104.

Preparation R2bl: 7-(3-fluorophenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 1-fluoro-3-iodobenzene as reagents, **Preparation R2bl** was obtained. HRMS calculated for $C_{12}H_8N_3OF$: 229.0651; found 230.0729 $[(M+H)^+]$ form].

^1H -NMR (400 MHz, MSM-d6): δ (ppm) 12.17 (brs, 1 H), 7.99 (d, 1 H), 7.72 (dm, 1 H), 7.64 (m, 1 H), 7.58 (d, 1 H), 7.58 (m, 1 H), 7.25 (m, 1 H), 6.71 (d, 1 H).

^{13}C -NMR (100 MHz, MSM-d6): δ (ppm) 144.9, 131.4, 130.9, 123.9, 120.2, 114, 111.6.

^{19}F -NMR (376.5 MHz, MSM-d6): δ (ppm) -111.7.

Preparation R2bm: 7-[3-(dimethylamino)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 3-(*N,N*-dimethylamino)phenylboronic acid as reagents, **Preparation R2bm** was obtained. HRMS calculated for $C_{14}H_{14}N_4O$: 254.1168; found 255.1229 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.04 (brs, 1 H), 7.92 (d, 1 H), 7.45 (d, 1 H), 7.3 (t, 1 H), 6.94 (m, 1 H), 6.93 (dm, 1 H), 6.74 (dm, 1 H), 6.65 (d, 1 H), 2.95 (s, 6 H).

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¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 144.3, 129.9, 124.4, 112.4, 111.4, 108.6, 103.1, 40.5.

Preparation R2bn: 7-[3-(morpholin-4-yl)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

5 Using **General Procedure 2** starting from **Preparation R1a** and 3-(morpholino)phenylboronic acid as reagents, **Preparation R2bn** was obtained. ¹H-NMR (400 MHz, MSM-d6): δ (ppm) 12.05 (brs, 1 H), 7.93 (s, 1 H), 7.47 (d, J=3.53 Hz, 1 H), 7.36 (t, J=8.13 Hz, 1 H), 7.19 (t, J=2.20 Hz, 1 H), 7.11 (dd, J=1.27, 7.93 Hz, 1 H), 6.98 (dd, J=1.96, 8.49 Hz, 1 H), 6.65 (d, J=3.5 Hz, 1 H), 3.75 (t, J=4.61 Hz, 4 H), 3.18 (t, 10 J=4.61 Hz, 4 H).

Preparation R2bo: 7-[3-(trifluoromethoxy)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 3-(trifluoromethoxy)iodobenzene as reagents, **Preparation R2bo** was obtained. HRMS calculated for C₁₃H₈F₃N₃O₂: 295.0569; found 296.0651 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.91 (s, 1 H), 8 (s, 1 H), 7.87 (t, 1 H), 7.82 (ddd, 1 H), 7.68 (t, 1 H), 7.6 (d, 1 H), 7.41 (ddd, 1 H), 6.71 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 145.1, 131.5, 123.9, 123.2, 119.5, 117.1, 104.1.

Preparation R2bp: 7-(3-methoxyphenyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

20 Using **General Procedure 3** starting from **Preparation R1b** and 3-iodoanisole as reagents, **Preparation R2bp** was obtained. HRMS calculated for C₁₃H₁₁N₃O₂: 241.0851; found 242.0928 [(M+H)⁺ form].

¹H-NMR (400 MHz, MSM-d6): δ (ppm) 12.1 (brs, 1 H), 7.95 (d, 1 H), 7.51 (d, 1 H), 7.44 (t, 1 H), 7.31 (m, 1 H), 7.3 (m, 1 H), 6.98 (dm, 1 H), 6.67 (d, 1 H), 3.82 (s, 3 H).

25 ¹³C-NMR (100 MHz, MSM-d6): δ (ppm) 144.6, 130.4, 124.2, 116.7, 112.9, 110.5, 103.5.

Preparation R2bq: 7-[3-(benzyloxy)phenyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

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Using **General Procedure 3** starting from **Preparation R1b** and 1-benzyloxy-3-iodobenzene as reagents, **Preparation R2bq** was obtained. HRMS calculated for $C_{19}H_{15}N_3O_2$: 317.1164; found 318.1235 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.1 (brs, 1 H), 7.95 (d, 1 H), 7.51 (d, 1 H), 7.51-7.31 (m, 5 H), 7.44 (t, 1 H), 7.41 (m, 1 H), 7.32 (dm, 1 H), 7.05 (dm, 1 H), 6.68 (d, 1 H), 5.18 (s, 2 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 144.6, 130.5, 124.1, 116.8, 113.6, 111.4, 103.6, 70.

Preparation R2br: 7-(6-methylpyridin-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 2-iodo-6-methylpyridine as reagents, **Preparation R2br** was obtained. HRMS calculated for $C_{12}H_{10}N_4O$: 226.0855; found 227.0933 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12 (brs, 1 H), 8.25 (dm, 1 H), 8.05 (s, 1 H), 7.9 (t, 1 H), 7.88 (d, 1 H), 7.25 (dm, 1 H), 6.68 (d, 1 H), 2.52 (s, 3 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 144.9, 139.5, 122, 121.8, 113.8, 103.7, 24.4.

Preparation R2bs: 7-(6-methoxypyridin-2-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

The mixture of **Preparation R1a** (1.0 g, 6.51 mmol), 2-iodo-6-methoxy-pyridine (2.35 g, 9.77 mmol, 1.5 eq.), copper(I)-iodide (125 mg, 0.65 mmol, 0.1 eq.), potassium-phosphate tribasic (2.76 g, 13 mmol, 2 eq.), (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (74 mg, 0.65 mmol, 0.1 eq.) in PDO (50 ml) was stirred under inert atmosphere for 4 hours at 100 °C. The inorganics was filtered off and the filtrate was evaporated. The resulted residue was purified by flash chromatography (DCM).

The arylated product (920 mg, 3.5 mmol) and lithium-hydroxide monohydrate (1.48 g, 35 mmol) were stirred in the mixture of PDO (15 ml) and water (15 ml) at 110 °C for 24 hours. The residue was acidified by aq. HCl solution (1 N, 50 ml) and the resulted precipitate was filtered off and dried to give **Preparation R2bs**. HRMS calculated for $C_{12}H_{10}N_4O_2$: 242.0804; found 243.0884 $[(M+H)^+]$ form].

^1H -NMR (500 MHz, MSM-d6): δ (ppm) 12.21 (brs, 1 H), 8.08 (dd, 1 H), 8.03 (s, 1 H), 7.94 (d, 1 H), 7.9 (t, 1 H), 6.78 (dd, 1 H), 6.7 (d, 1 H), 3.94 (s, 3 H).

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¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 163.2, 158.5, 147.6, 147.4, 144.9, 141.9, 121.9, 111.2, 108.4, 108.4, 103.8, 53.9.

Preparation R2bt: 7-(naphthalen-1-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and 1-naphthaleneboronic acid as reagents, **Preparation R2bt** was obtained. HRMS calculated for C₁₆H₁₁N₃O: 261.0902; found 262.0984 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.04 (s, 1 H), 8.12 (d, 1 H), 8.09 (d, 1 H), 7.78 (d, 1 H), 7.67 (t, 1 H), 7.61 (dm, 1 H), 7.6 (t, 1 H), 7.51 (tm, 1 H), 7.39 (d, 1 H), 7.21 (t, 1 H), 6.77 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.9, 149.2, 144.6, 134.2, 134.1, 130.4, 129.5, 128.7, 127.8, 127.2, 126.4, 126.3, 126, 123, 108.7, 103.1

Preparation R2bu: 7-(pyridin-3-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and pyridine-3-boronic acid as reagents, **Preparation R2bu** was obtained. HRMS calculated for C₁₁H₈N₄O: 212.0698; found 213.0774 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.29 (s, 1 H), 8.55 (dd, 1 H), 8.47 (dd, 1 H), 8.06 (brs, 1 H), 8.03 (t, 1 H), 7.9 (d, 1 H), 7.4 (t, 1 H), 6.7 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 149.1, 145, 139.4, 122.5, 122, 116.9, 104.

¹⁵N-NMR (50.6 MHz, MSM-d6): δ (ppm) 171.2.

Preparation R2bv: 7-(pyridin-4-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 2** starting from **Preparation R1a** and pyridine-4-boronic acid pinacol ester as reagents, **Preparation R2bv** was obtained. HRMS calculated for C₁₁H₈N₄O: 212.0698; found 213.0773 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ ppm 12.31 (brs, 1 H), 8.69 (m, 2 H), 8.05 (s, 1 H), 7.99 (m, 2 H), 7.73 (d, 1 H), 6.76 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 151.3, 145.6, 122.8, 117.3, 105.

Preparation R2bw: 7-[1-(difluoromethyl)-1H-pyrazol-4-yl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

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Using **General Procedure 3** starting from **Preparation R1b** and 1-(difluoromethyl)-4-iodo-1*H*-pyrazole as reagents, **Preparation R2bw** was obtained. HRMS calculated for C₁₀H₇F₂N₅O: 251.0619; found 252.0682 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.88 (brs, 1 H), 8.83 (d, 1 H), 8.4 (d, 1 H), 8.03 (s, 1 H), 7.91 (t, 1 H), 7.58 (d, 1 H), 6.69 (d, 1 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 145.2, 136.2, 123.2, 121.3, 111, 104.

Preparation R2bx: 7-(1-methyl-1*H*-pyrazol-4-yl)-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one

Using **General Procedure 3** starting from **Preparation R1b** and 4-iodo-1-methyl-1*H*-pyrazole as reagents, **Preparation R2bx** was obtained. HRMS calculated for C₁₀H₉N₅O: 215.0807; found 216.0889 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 12.12 (brs, 1 H), 8.27 (s, 1 H), 7.96 (s, 1 H), 7.91 (d, 1 H), 7.42 (d, 1 H), 6.63 (d, 1 H), 3.89 (s, 3 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.6, 146.9, 144.7, 132.1, 124.3, 123.4, 121.4, 109, 103.4, 38.5.

Preparation R2by: 7-(propan-2-yl)-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and 2-iodopropane as reagents, **Preparation R2by** was obtained. HRMS calculated for C₉H₁₁N₃O: 177.0902; found 178.0979 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.83 (brs, 1 H), 7.87 (s, 1 H), 7.24 (d, 1 H), 6.47 (d, 1 H), 4.85 (sept., 1 H), 1.42 (d, 6 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.8, 146.8, 143.5, 120.7, 108.2, 102, 46.5, 23.

¹⁵N-NMR (50.6 MHz, MSM-d6): δ (ppm) 168.

Preparation R2ca: 7-cyclobutyl-3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and cyclobutyl bromide as reagents, **Preparation R2ca** was obtained. HRMS calculated for C₁₀H₁₁N₃O: 189.0902; found 190.0974 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.85 (brs, 1 H), 7.88 (brs, 1 H), 7.09 (d, 1 H), 6.44 (d, 1 H), 3.70 (m, 1 H)

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¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.7, 143.8, 125.1, 108.1, 101.7, 31.8.

Preparation R2cb: 7-(1-methylpiperidin-4-yl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 4** starting from **Preparation R1a** and 4-hydroxy-1-methylpiperidine as reagents, **Preparation R2cb** was obtained. HRMS calculated for C₁₂H₁₆N₄O: 232.1324; found 233.1405 [(M+H)⁺ form].

¹H-NMR (500 MHz, MSM-d6): δ (ppm) 11.82 (brs, 1 H), 7.86 (d, 1 H), 7.29 (d, 1 H), 6.46 (d, 1 H), 4.44 (m, 1 H), 2.89/2.05 (m, 4 H), 2.22 (s, 3 H), 2.02/1.82 (m, 4 H).

¹³C-NMR (125 MHz, MSM-d6): δ (ppm) 143.9, 121.2, 102.1, 55.1, 52.1, 46.1, 32.3.

10 **Preparation R2cc: 7-(2,2-difluoroethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 1** starting from **Preparation R1a** and 2-iodo-1,1-difluoroethane as reagents, **Preparation R2cc** was obtained. HRMS calculated for C₈H₇N₃OF₂: 199.0557; found 200.0634 ((M+H)⁺ form].

15 ¹H-NMR (400 MHz, DMSO-d6) δ ppm 11.99 (brs, 1 H), 7.93 (s, 1 H), 7.16 (d, 1 H), 6.53 (d, 1 H), 6.37 (tt, 1 H), 4.6 (td, 2 H).

¹³C-NMR (400 MHz, DMSO-d6) δ ppm 144.4, 124.8, 114.3, 102.5, 46.2 .

Preparation R2cd: 7-(2-fluoroethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and 1-fluoro-2-iodoethane as reagents, **Preparation R2cd** was obtained. HRMS calculated for C₈H₈NOF: 181.0651; found 182.0728 ((M+H)⁺ form].

¹H-NMR (400 MHz, dmso-d6) δ ppm 11.91 (brs, 1 H), 7.9 (s, 1 H), 7.17 (d, 1 H), 6.49 (d, 1 H), 4.74 (dt, 2 H), 4.43 (dt, 2 H).

¹³C-NMR (400 MHz, dmso-d6) δ ppm 144, 124.3, 102, 83.1, 45.1.

Preparation R2ce: 7-(2-hydroxyethyl)-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

25 Using **General Procedure 1** starting from **Preparation R1a** and 2-chloroethanol as reagents, **Preparation R2ce** was obtained. ¹H-NMR (400 MHz, MSM-d6): δ (ppm) 11.83 (brs, 1 H), 7.86 (d, J=2.4 Hz, 1 H), 7.12 (d, J=3.92 Hz, 1 H), 6.43 (d, J=3.14 Hz, 1 H), 4.92 (t, J=5.49 Hz, 1 H), 4.15 (t, J=6.28 Hz, 2 H), 3.68 (q, J=5.49 Hz, 2 H).

Preparation R2cg: 7-[(4-chlorophenyl)methyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one

Using **General Procedure 1** starting from **Preparation R1a** and 4-chlorobenzyl bromide as reagents, **Preparation R2cg** was obtained. HRMS calculated for $C_{13}H_{10}ClN_3O$:
5 259.0512; found 260.0583 $[(M+H)^+]$ form].

^1H -NMR (400 MHz, MSM-d6): δ (ppm) 11.93 (s, 1 H), 7.9 (s, 1 H), 7.39 (m, 2 H), 7.23 (m, 2 H), 7.22 (d, 1 H), 6.51 (d, 1 H), 5.34 (s, 2 H).

^{13}C -NMR (100 MHz, MSM-d6): δ (ppm) 158.7, 147.4, 144.2, 137.5, 132.5, 129.5, 129, 124.2, 108.3, 102.4, 47.5.

10 **Preparation R2ch: 7-[(3-chlorophenyl)methyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 1** starting from **Preparation R1a** and 3-chlorobenzyl bromide as reagents, **Preparation R2ch** was obtained. HRMS calculated for $C_{13}H_{10}ClN_3O$:
259.0512; found 260.0580 $[(M+H)^+]$ form].

15 ^1H -NMR (500 MHz, MSM-d6): δ (ppm) 11.94 (brs, 1 H), 7.92 (d, 1 H), 7.35 (m, 1 H), 7.35 (m, 1 H), 7.28 (t, 1 H), 7.25 (d, 1 H), 7.16 (dm, 1 H), 6.51 (d, 1 H), 5.35 (s, 2 H).

^{13}C -NMR (125 MHz, MSM-d6): δ (ppm) 158.7, 147.6, 144.3, 140.9, 133.6, 131.1, 128, 127.5, 126.4, 124.3, 108.4, 102.4, 47.5.

20 **Preparation R2ci: 7-[(2-chlorophenyl)methyl]-3H,4H,7H-pyrrolo[2,3-d]pyrimidin-4-one**

Using **General Procedure 1** starting from **Preparation R1a** and 2-chlorobenzyl bromide as reagents, **Preparation R2ci** was obtained. HRMS calculated for $C_{13}H_{10}ClN_3O$:
259.0512; found 260.0587 $[(M+H)^+]$ form].

25 ^1H -NMR (400 MHz, MSM-d6): δ (ppm) 11.95 (brs, 1 H), 7.89 (d, 1 H), 7.5 (dm, 1 H), 7.32 (m, 1 H), 7.26 (m, 1 H), 7.17 (d, 1 H), 6.72 (dm, 1 H), 6.55 (d, 1 H), 5.44 (s, 2 H).

^{13}C -NMR (100 MHz, MSM-d6): δ (ppm) 144.3, 129.8, 129.8, 128.8, 128.1, 124.5, 102.5, 46.

EXAMPLES

The following Examples illustrate the invention but do not limit it in any way.

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(7-methyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 1)**

5 Using **General Procedure 5** starting from **Preparation R2g** and **Preparation R1c** as reagents, **EXAMPLE 1** was obtained. HRMS calculated for C₃₀H₃₉N₅O₅: 549.2951; found 550.3021 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxothieno[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 2)**

10 Using **General Procedure 5** starting from 3*H*-thieno[2,3-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 2** was obtained. HRMS calculated for C₂₉H₃₆N₄O₅S: 552.2406; found 553.2479 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[(7-ethyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 3)**

15 Using **General Procedure 5** starting from **Preparation R2h** and **Preparation R1c** as reagents, **EXAMPLE 3** was obtained. HRMS calculated for C₃₁H₄₁N₅O₅: 563.3108; found 564.319 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-prop-2-ynyl-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 4)**

20 Using **General Procedure 5** starting from **Preparation R2i** and **Preparation R1c** as reagents, **EXAMPLE 4** was obtained. HRMS calculated for C₃₂H₃₉N₅O₅: 573.2951; found 574.3024 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[(7-cyclopropyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 5)**

25 Using **General Procedure 5** starting from **Preparation R2j** and **Preparation R1c** as reagents, **EXAMPLE 5** was obtained. HRMS calculated for C₃₂H₄₁N₅O₅: 575.3108; found 576.3189 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[(7-chloro-4-oxo-thieno[3,4-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 6)**

Using **General Procedure 5** starting from 7-chloro-3*H*-thieno[3,4-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 6** was obtained. HRMS calculated for C₂₉H₃₅ClN₄O₅S: 586.2017; found 609.1912 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-[(7-buta-2,3-dienyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 7)**

Using **General Procedure 5** starting from **Preparation R2k** and **Preparation R1c** as reagents, **EXAMPLE 7** was obtained. HRMS calculated for C₃₃H₄₁N₅O₅: 587.3108; found 588.318 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(cyclopropylmethyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 8)**

Using **General Procedure 5** starting from **Preparation R2l** and **Preparation R1c** as reagents, **EXAMPLE 8** was obtained. HRMS calculated for C₃₃H₄₃N₅O₅: 589.3264; found 590.3342 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(7-isobutyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 9)**

Using **General Procedure 5** starting from **Preparation R2m** and **Preparation R1c** as reagents, **EXAMPLE 9** was obtained. HRMS calculated for C₃₃H₄₅N₅O₅: 591.342; found 592.3501 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(9-methyl-4-oxo-pyrimido[4,5-*b*]indol-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 10)**

Using **General Procedure 5** starting from **Preparation R2n** and **Preparation R1c** as reagents, **EXAMPLE 10** was obtained. HRMS calculated for C₃₄H₄₁N₅O₅: 599.3108; found 600.3181 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(cyclobutylmethyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 11)**

5 Using **General Procedure 5** starting from **Preparation R2o** and **Preparation R1c** as reagents, **EXAMPLE 11** was obtained. HRMS calculated for C₃₄H₄₅N₅O₅: 603.342; found 604.3502 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(2-dimethylaminoethyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 12)**

10 Using **General Procedure 5** starting from **Preparation R2p** and **Preparation R1c** as reagents, **EXAMPLE 12** was obtained. HRMS calculated for C₃₃H₄₆N₆O₅: 606.353; found 607.36 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-phenyl-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 13)**

15 Using **General Procedure 5** starting from **Preparation R2q** and **Preparation R1c** as reagents, **EXAMPLE 13** was obtained. HRMS calculated for C₃₅H₄₁N₅O₅: 611.3108; found 612.3192 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-phenyl-5H-pyrrolo[3,2-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 14)**

20 Using **General Procedure 5** starting from 7-phenyl-3,5-dihydropyrrolo[3,2-d]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 14** was obtained. HRMS calculated for C₃₅H₄₁N₅O₅: 611.3108; found 612.3182 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(2-pyridyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 15)**

25 Using **General Procedure 5** starting from **Preparation R2b** and **Preparation R1c** as reagents, **EXAMPLE 15** was obtained. HRMS calculated for C₃₄H₄₀N₆O₅: 612.306; found 613.3132 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-1-phenyl-pyrazolo[3,4-d]pyrimidin-5-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 16)**

Using **General Procedure 5** starting from 1-phenyl-5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 16** was obtained. HRMS calculated for C₃₄H₄₀N₆O₅: 612.306; found 613.312 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(6-oxo-9-phenyl-purin-1-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 17)**

Using **General Procedure 5** starting from 9-phenyl-1*H*-purin-6-one and **Preparation R1c** as reagents, **EXAMPLE 17** was obtained. HRMS calculated for C₃₄H₄₀N₆O₅: 612.306; found 613.3142 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[(7-bromo-4-oxo-pyrrolo[2,1-*f*][1,2,4]triazin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 18)**

Using **General Procedure 5** starting from 7-bromo-3*H*-pyrrolo[2,1-*f*][1,2,4]triazin-4-one and **Preparation R1c** as reagents, **EXAMPLE 18** was obtained. HRMS calculated for C₂₉H₃₆BrN₅O₅: 613.19; found 612.1851 [(M-H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(7-oxo-3-phenyl-isoxazolo[4,5-*d*]pyrimidin-6-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 19)**

Using **General Procedure 5** starting from 3-phenyl-6*H*-isoxazolo[4,5-*d*]pyrimidin-7-one and **Preparation R1c** as reagents, **EXAMPLE 19** was obtained. HRMS calculated for C₃₄H₃₉N₅O₆: 613.29; found 636.2782 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-pyrimidin-2-yl-pyrrolo[2,3-*d*]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 20)**

Using **General Procedure 5** starting from **Preparation R2s** and **Preparation R1c** as reagents, **EXAMPLE 20** was obtained. HRMS calculated for C₃₃H₃₉N₇O₅: 613.3013; found 614.3102 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(7-oxo-3-phenyl-triazolo[4,5-d]pyrimidin-6-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 21)**

Using **General Procedure 5** starting from 3-phenyl-6*H*-triazolo[4,5-*d*]pyrimidin-7-one and **Preparation R1c** as reagents, **EXAMPLE 21** was obtained. HRMS calculated for C₃₃H₃₉N₇O₅: 613.3013; found 614.3095 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-({4-[(6,8-dimethyl-4-oxopyrimido[5,4-*b*]indolizin-3(4*H*)-yl)methyl]-4-hydroxypiperidin-1-yl}carbonyl)-3-phenylpiperidine-1-carboxylate (EXAMPLE 22)**

Using **General Procedure 5** starting from **Preparation R2t** and **Preparation R1c** as reagents, **EXAMPLE 22** was obtained. HRMS calculated for C₃₄H₄₂N₆O₅: 614.3217; found 615.3301 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(1-methylimidazol-4-yl)-4-oxo-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 23)**

Using **General Procedure 5** starting from **Preparation R2u** and **Preparation R1c** as reagents, **EXAMPLE 23** was obtained. HRMS calculated for C₃₃H₄₁N₇O₅: 615.3169; found 616.324 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(3-thienyl)pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 24)**

Using **General Procedure 5** starting from **Preparation R2v** and **Preparation R1c** as reagents, **EXAMPLE 24** was obtained. HRMS calculated for C₃₃H₃₉N₅O₅S: 617.2672; found 618.2736 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(2-thienyl)pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 25)**

Using **General Procedure 5** starting from **Preparation R2w** and **Preparation R1c** as reagents, **EXAMPLE 25** was obtained. HRMS calculated for C₃₃H₃₉N₅O₅S: 617.2672; found 618.2744 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 26)**

Using **General Procedure 5** starting from **Preparation R2x** and **Preparation R1c** as reagents, **EXAMPLE 26** was obtained. HRMS calculated for C₃₁H₃₈F₃N₅O₅: 617.2825; found 618.2912 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-thiazol-2-yl-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 27)**

Using **General Procedure 5** starting from **Preparation R2y** and **Preparation R1c** as reagents, **EXAMPLE 27** was obtained. HRMS calculated for C₃₂H₃₈N₆O₅S: 618.2625; found 641.251 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-[3-(dimethylamino)propyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 28)**

Using **General Procedure 5** starting from **Preparation R2z** and **Preparation R1c** as reagents, **EXAMPLE 28** was obtained. HRMS calculated for C₃₄H₄₈N₆O₅: 620.3686; found 621.3731 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(m-tolyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 29)**

Using **General Procedure 5** starting from **Preparation R2aa** and **Preparation R1c** as reagents, **EXAMPLE 29** was obtained. HRMS calculated for C₃₆H₄₃N₅O₅: 625.3264; found 626.3357 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(p-tolyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 30)**

Using **General Procedure 5** starting from **Preparation R2ab** and **Preparation R1c** as reagents, **EXAMPLE 30** was obtained. HRMS calculated for C₃₆H₄₃N₅O₅: 625.3264; found 626.3358 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-[(7-benzyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 31)**

Using **General Procedure 5** starting from **Preparation R2ac** and **Preparation R1c** as reagents, **EXAMPLE 31** was obtained. HRMS calculated for C₃₆H₄₃N₅O₅: 625.3264; found 626.3343 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(6-methyl-4-oxo-7-phenyl-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 32)**

Using **General Procedure 5** starting from **Preparation R2ad** and **Preparation R1c** as reagents, **EXAMPLE 32** was obtained. HRMS calculated for C₃₆H₄₃N₅O₅: 625.3264; found 626.3335 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(7-oxo-3-phenyl-isothiazolo[4,5-d]pyrimidin-6-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 33)**

Using **General Procedure 5** starting from 3-phenyl-6*H*-isothiazolo[4,5-*d*]pyrimidin-7-one and **Preparation R1c** as reagents, **EXAMPLE 33** was obtained. HRMS calculated for C₃₄H₃₉N₅O₅S: 629.2672; found 652.2559 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-fluorophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 34)**

Using **General Procedure 5** starting from **Preparation R2ae** and **Preparation R1c** as reagents, **EXAMPLE 34** was obtained. HRMS calculated for C₃₅H₄₀FN₅O₅: 629.3013; found 530.2568 [(M+H-Boc) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(3-fluorophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 35)**

Using **General Procedure 5** starting from **Preparation R2bl** and **Preparation R1c** as reagents, **EXAMPLE 35** was obtained. HRMS calculated for C₃₅H₄₀FN₅O₅: 629.3013; found 652.2909 [(M+Na) form].

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▪ **tert-butyl (3R,4R)-4-[4-[(7-bromo-4-oxo-thieno[3,2-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 36)**

Using **General Procedure 5** starting from 7-bromo-3*H*-thieno[3,2-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 36** was obtained. HRMS calculated for C₂₉H₃₅BrN₄O₅S: 630.1511; found 653.1419 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(5-methyl-2-thienyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 37)**

Using **General Procedure 5** starting from **Preparation R2bc** and **Preparation R1c** as reagents, **EXAMPLE 37** was obtained. HRMS calculated for C₃₄H₄₁N₅O₅S: 631.2828; found 654.2719 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(1-methyl-4-piperidyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 38)**

Using **General Procedure 5** starting from **Preparation R2cb** and **Preparation R1c** as reagents, **EXAMPLE 38** was obtained. HRMS calculated for C₃₅H₄₈N₆O₅: 632.3686; found 633.3766 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-cyanophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 39)**

Using **General Procedure 5** starting from **Preparation R2au** and **Preparation R1c** as reagents, **EXAMPLE 39** was obtained. HRMS calculated for C₃₆H₄₀N₆O₅: 636.306; found 637.3127 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(4-methoxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 40)**

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Using **General Procedure 5** starting from **Preparation R2c** and **Preparation R1c** as reagents, **EXAMPLE 40** was obtained. HRMS calculated for C₃₆H₄₃N₅O₆: 641.3214; found 642.3297 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(3-methoxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 41)**

Using **General Procedure 5** starting from **Preparation R2bp** and **Preparation R1c** as reagents, **EXAMPLE 41** was obtained. HRMS calculated for C₃₆H₄₃N₅O₆: 641.3214; found 642.3313 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-[4-(hydroxymethyl)phenyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 42)**

Using **General Procedure 5** starting from **Preparation R2ax** and **Preparation R1c** as reagents, **EXAMPLE 42** was obtained. HRMS calculated for C₃₆H₄₃N₅O₆: 641.3214; found 642.3288 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[6-(hydroxymethyl)-4-oxo-7-phenyl-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 43)**

Preparation R1b (10 g, 67.05 mmol, 1 eq.), iodobenzene (87.2 mmol, 1.3 eq.), CuI (1.28 g, 6.705 mmol, 0.1 eq.), DMEDA (1.45 ml, 13.4 mmol, 1.18 g, 0.2 eq.), anhydrous K₂CO₃ (12.05 g, 87.16 mmol, 1.3 eq.) was suspended in dry acetonitrile (50 ml), flushed with N₂ and stirred at 80 °C for 1.5 h. After the reaction completed, the mixture was diluted with water (200 ml) and cooled to r.t. The mixture was filtered, and washed with water (3 x 30 ml), aq. NH₃ solution (40 ml, 25%), water (3 x 50 ml), heptane (50 then 30 ml) and dried in vacuum.

A flame dried 3-necked round flask was charged with 5 ml dry THF under N₂ atmosphere. 420 µl (1.5 eq.) iPr₂NH was added via a syringe and the round flask was cooled to -78°C. 1.25 ml (1.5 eq.) *n*-BuLi was added via a syringe and stirred for 30 minutes. Then 4-methoxy-7-phenyl-pyrrolo[2,3-*d*]pyrimidine obtained in previous step (450 mg, 2 mmol,

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1 eq.) dissolved in 20 ml dry THF was added dropwise and stirred for 1 hour. Then methyl formate (360 mg, 3 eq.) was added dissolved in 10 ml dry THF. After the reaction was completed 40 ml sat. NH₄Cl was added and extracted with 3 x 40 ml EEO, dried, filtered and evaporated. Flash chromatography with Hexane:EEO gave (4-methoxy-7-phenyl-pyrrolo[2,3-*d*]pyrimidin-6-yl)methanol.

A part of the crude product (127 mg, 0.5 mmol) was dissolved in 2.5 ml PDO and cc. HCl (82 µL, 1 mmol, 2 eq.) was added. The solution was heated, stirred at 100 °C for 2 hours, and it was evaporated to give 6-(hydroxymethyl)-7-phenyl-3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one which was reacted according to **General Procedure 5** with **Preparation R1c** as reagents to give **EXAMPLE 43**. HRMS calculated for C₃₆H₄₃N₅O₆: 641.3214; found 642.3295 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[1-(4-methoxyphenyl)-4-oxo-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 44)**

Using **General Procedure 5** starting from 1-(4-methoxyphenyl)-5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 44** was obtained. HRMS calculated for C₃₅H₄₂N₆O₆: 642.3166; found 665.3057 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(6-methoxy-2-pyridyl)-4-oxo-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 45)**

Using **General Procedure 5** starting from **Preparation R2bs** and **Preparation R1c** as reagents, **EXAMPLE 45** was obtained. HRMS calculated for C₃₅H₄₂N₆O₆: 642.3166; found 643.3231 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-chlorophenyl)-4-oxo-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 46)**

Using **General Procedure 5** starting from **Preparation R2ay** and **Preparation R1c** as reagents, **EXAMPLE 46** was obtained. HRMS calculated for C₃₅H₄₀ClN₅O₅: 645.2718; found 646.2787 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(3-chlorophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 47)**

5 Using **General Procedure 5** starting from **Preparation R2bk** and **Preparation R1c** as reagents, **EXAMPLE 47** was obtained. HRMS calculated for $C_{35}H_{40}ClN_5O_5$: 645.2718; found 646.2821 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[(6-chloro-4-oxo-7-phenyl-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 48)**

10 Using **General Procedure 5** starting from **Preparation R2ai** and **Preparation R1c** as reagents, **EXAMPLE 48** was obtained. HRMS calculated for $C_{35}H_{40}ClN_5O_5$: 645.2718; found 646.2782 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(5-chloro-2-thienyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 49)**

15 Using **General Procedure 5** starting from **Preparation R2bd** and **Preparation R1c** as reagents, **EXAMPLE 49** was obtained. HRMS calculated for $C_{33}H_{38}ClN_5O_5S$: 651.2282; found 652.2348 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-[1-(difluoromethyl)pyrazol-4-yl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 50)**

20 Using **General Procedure 5** starting from **Preparation R2bw** and **Preparation R1c** as reagents, **EXAMPLE 50** was obtained. HRMS calculated for $C_{33}H_{39}F_2N_7O_5$: 651.2981; found 674.2867 [(M+Na) form].

25 ▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-dimethylaminophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 51)**

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Using **General Procedure 5** starting from **Preparation R2az** and **Preparation R1c** as reagents, **EXAMPLE 51** was obtained. HRMS calculated for $C_{37}H_{46}N_6O_5$: 654.353; found 655.3589 [(M+H) form].

5 ■ **tert-butyl (3R,4R)-4-[4-[[7-[3-(dimethylamino)phenyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 52)**

Using **General Procedure 5** starting from **Preparation R2bm** and **Preparation R1c** as reagents, **EXAMPLE 52** was obtained. HRMS calculated for $C_{37}H_{46}N_6O_5$: 654.353; found 655.3602 [(M+H) form].

10 ■ **tert-butyl (3R,4R)-4-[4-[[7-(1,3-benzodioxol-5-yl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 53)**

Using **General Procedure 5** starting from **Preparation R2bf** and **Preparation R1c** as reagents, **EXAMPLE 53** was obtained. HRMS calculated for $C_{36}H_{41}N_5O_7$: 655.3006; found 655.3006 [(M+H) form].

15 ■ **tert-butyl (3R,4R)-4-[4-[[7-[(2-chlorophenyl)methyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 54)**

Using **General Procedure 5** starting from **Preparation R2ci** and **Preparation R1c** as reagents, **EXAMPLE 54** was obtained. HRMS calculated for $C_{36}H_{42}N_5O_5Cl$: 659.2875; found 660.2949 [(M+H) form].

20 ■ **tert-butyl (3R,4R)-4-[4-[[7-[(3-chlorophenyl)methyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 55)**

25 Using **General Procedure 5** starting from **Preparation R2ch** and **Preparation R1c** as reagents, **EXAMPLE 55** was obtained. HRMS calculated for $C_{36}H_{42}ClN_5O_5$: 659.2875; found 660.2933 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-[[7-[(4-chlorophenyl)methyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 56)**

Using **General Procedure 5** starting from **Preparation R2cg** and **Preparation R1c** as reagents, **EXAMPLE 56** was obtained. HRMS calculated for $C_{36}H_{42}ClN_5O_5$: 659.2875; found 660.2949 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-fluoro-3-methoxy-phenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 57)**

Using **General Procedure 5** starting from **Preparation R2e** and **Preparation R1c** as reagents, **EXAMPLE 57** was obtained. HRMS calculated for $C_{36}H_{42}FN_5O_6$: 659.3119; found 660.3194 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-[4-(difluoromethyl)phenyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 58)**

Using **General Procedure 5** starting from **Preparation R2aw** and **Preparation R1c** as reagents, **EXAMPLE 58** was obtained. HRMS calculated for $C_{36}H_{41}F_2N_5O_5$: 661.3076; found 662.3141 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(1-naphthyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 59)**

Using **General Procedure 5** starting from **Preparation R2bt** and **Preparation R1c** as reagents, **EXAMPLE 59** was obtained. HRMS calculated for $C_{39}H_{43}N_5O_5$: 661.3264; found 662.3345 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(2-naphthyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 60)**

Using **General Procedure 5** starting from **Preparation R2bg** and **Preparation R1c** as reagents, **EXAMPLE 60** was obtained. HRMS calculated for $C_{35}H_{35}N_5O_5$: 661.3264; found 606.2715 [(M+H-C(CH₃)₃) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-chloro-3-fluoro-phenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 61)**

Using **General Procedure 5** starting from **Preparation R2ar** and **Preparation R1c** as reagents, **EXAMPLE 61** was obtained. HRMS calculated for C₃₅H₃₉ClFN₅O₅: 663.2624; found 564.218 [(M+H-Boc) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 62)**

Using **General Procedure 5** starting from 7-(2-trimethylsilylethoxymethyl)-3*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 62** was obtained. HRMS calculated for C₃₅H₅₁N₅O₆Si: 665.3609; found 666.3696 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 63)**

Using **General Procedure 5** starting from **Preparation R2be** and **Preparation R1c** as reagents, **EXAMPLE 63** was obtained. HRMS calculated for C₃₇H₄₃N₅O₇: 669.3162; found 670.3238 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxo-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 64)**

Using **General Procedure 5** starting from 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-5*H*-pyrazolo[3,4-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 64** was obtained. HRMS calculated for C₃₆H₄₂N₆O₇: 670.3115; found 693.3019 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(3,4-dimethoxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 65)**

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Using **General Procedure 5** starting from **Preparation R2at** and **Preparation R1c** as reagents, **EXAMPLE 65** was obtained. HRMS calculated for $C_{37}H_{45}N_5O_7$: 671.3319; found 672.3396 [(M+H) form].

5 ▪ **tert-butyl (3R,4R)-4-[4-[[7-(3,5-dimethoxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 66)**

Using **General Procedure 5** starting from **Preparation R2ap** and **Preparation R1c** as reagents, **EXAMPLE 66** was obtained. HRMS calculated for $C_{37}H_{45}N_5O_7$: 671.3319; found 672.3401 [(M+H) form].

10 ▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(6-iodo-7-methyl-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 67)**

Using **General Procedure 5** starting from **Preparation R2aj** and **Preparation R1c** as reagents, **EXAMPLE 67** was obtained. HRMS calculated for $C_{30}H_{38}IN_5O_5$: 675.1918; found 676.1994 [(M+H) form].

15 ▪ **tert-butyl (3R,4R)-4-[4-[[7-(3-chloro-5-methoxy-phenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 68)**

Using **General Procedure 5** starting from **Preparation R2ao** and **Preparation R1c** as reagents, **EXAMPLE 68** was obtained. HRMS calculated for $C_{36}H_{42}ClN_5O_6$: 675.2823; found 676.2891 [(M+H) form].

20 ▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-chloro-3-methoxy-phenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 69)**

Using **General Procedure 5** starting from **Preparation R2as** and **Preparation R1c** as reagents, **EXAMPLE 69** was obtained. HRMS calculated for $C_{36}H_{42}ClN_5O_6$: 675.2823; found 676.2885 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-[[7-(3,4-dichlorophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 70)**

Using **General Procedure 5** starting from **Preparation R2aq** and **Preparation R1c** as reagents, **EXAMPLE 70** was obtained. HRMS calculated for C₃₅H₃₉Cl₂N₅O₅: 679.2328; found 680.2399 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(3,5-dichlorophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 71)**

Using **General Procedure 5** starting from **Preparation R2an** and **Preparation R1c** as reagents, **EXAMPLE 71** was obtained. HRMS calculated for C₃₅H₃₉Cl₂N₅O₅: 679.2328; found 680.2399 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-[4-(trifluoromethyl)phenyl]pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 72)**

Using **General Procedure 5** starting from **Preparation R2av** and **Preparation R1c** as reagents, **EXAMPLE 72** was obtained. HRMS calculated for C₃₆H₄₀F₃N₅O₅: 679.2982; found 680.3068 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-[3-(trifluoromethyl)phenyl]pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 73)**

Using **General Procedure 5** starting from **Preparation R2bh** and **Preparation R1c** as reagents, **EXAMPLE 73** was obtained. HRMS calculated for C₃₆H₄₀F₃N₅O₅: 679.2982; found 702.2875 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[6-iodo-4-oxo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 74)**

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Using **General Procedure 5** starting from **Preparation R2al** and **Preparation R1c** as reagents, **EXAMPLE 74** was obtained. HRMS calculated for $C_{35}H_{50}IN_5O_6Si$: 791.2575; found 792.265 [(M+H) form].

5 ▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-[3-(trifluoromethoxy)phenyl]pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 75)**

Using **General Procedure 5** starting from **Preparation R2bo** and **Preparation R1c** as reagents, **EXAMPLE 75** was obtained. HRMS calculated for $C_{36}H_{40}F_3N_5O_6$: 695.2931; found 696.2997 [(M+H) form].

10 ▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-[4-(trifluoromethoxy)phenyl]pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 76)**

Using **General Procedure 5** starting from **Preparation R2ba** and **Preparation R1c** as reagents, **EXAMPLE 76** was obtained. HRMS calculated for $C_{36}H_{40}F_3N_5O_6$: 695.2931; found 696.3006 [(M+H) form].

15 ▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-(3-morpholinophenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 77)**

Using **General Procedure 5** starting from **Preparation R2bn** and **Preparation R1c** as reagents, **EXAMPLE 77** was obtained. HRMS calculated for $C_{39}H_{48}N_6O_6$: 696.3635; found 697.3708 [(M+H) form].

20 ▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[4-oxo-7-(3,4,5-trimethoxyphenyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 78)**

25 Using **General Procedure 5** starting from **Preparation R2am** and **Preparation R1c** as reagents, **EXAMPLE 78** was obtained. HRMS calculated for $C_{38}H_{47}N_5O_8$: 701.3425; found 702.3487 [(M+H) form].

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▪ **tert-butyl (3R,4R)-4-[4-[[7-(4-benzyloxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 79)**

Using **General Procedure 5** starting from **Preparation R2bb** and **Preparation R1c** as reagents, **EXAMPLE 79** was obtained. HRMS calculated for C₄₂H₄₇N₅O₆: 717.3527; found 718.3603 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[7-(3-benzyloxyphenyl)-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 80)**

Using **General Procedure 5** starting from **Preparation R2bq** and **Preparation R1c** as reagents, **EXAMPLE 80** was obtained. HRMS calculated for C₄₂H₄₇N₅O₆: 717.3527; found 740.3423 [(M+Na) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[[7-[3-[(4-methylpiperazin-1-yl)methyl]phenyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-3-yl]methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 81)**

Using **General Procedure 5** starting from **Preparation R2bi** and **Preparation R1c** as reagents, **EXAMPLE 81** was obtained. HRMS calculated for C₄₁H₅₃N₇O₅: 723.4108; found 724.4175 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-[[6-cyano-4-oxo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-3-yl]methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 82)**

EXAMPLE 74 was dissolved in PDO and copper cyanide (4.2 eq), tetraethylammonium cyanide (1.05 eq.), Pd₂(dba)₃ (0.1 eq.), and 1,1'-bis(diphenylphosphino)ferrocene (0.4 eq.) were added. The mixture was heated and stirred at 110 °C till the reaction was completed.

The residue was purified by flash chromatography in DCM-MeOH gradient to give **EXAMPLE 82**. HRMS calculated for C₃₆H₅₀N₆O₆Si: 690.3561; found 691.3637 [(M+H) form].

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▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 83)**

Using **General Procedure 5** starting from 3*H*,4*H*,7*H*-pyrrolo[2,3-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 83** as HCl salt. HRMS calculated for C₂₄H₂₉N₅O₃: 435.2271; found 436.2345 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-methyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 84)**

Using **General Procedure 6** starting from **EXAMPLE 1** as reagent, **EXAMPLE 84** was obtained as HCl salt. HRMS calculated for C₂₅H₃₁N₅O₃: 449.2427; found 450.2517 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]thieno[2,3-d]pyrimidin-4-one (EXAMPLE 85)**

Using **General Procedure 6** starting from **EXAMPLE 2** as reagent, **EXAMPLE 85** was obtained as HCl salt. HRMS calculated for C₂₄H₂₈N₄O₃S: 452.1882; found 453.1933 [(M+H) form].

▪ **7-ethyl-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 86)**

Using **General Procedure 6** starting from **EXAMPLE 3** as reagent, **EXAMPLE 86** was obtained as HCl salt. HRMS calculated for C₂₆H₃₃N₅O₃: 463.2583; found 464.2654 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-prop-2-ynyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 87)**

Using **General Procedure 6** starting from **EXAMPLE 4** as reagent, **EXAMPLE 87** was obtained as HCl salt. HRMS calculated for C₂₇H₃₁N₅O₃: 473.2427; found 474.2502 [(M+H) form].

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▪ **7-cyclopropyl-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 88)**

Using **General Procedure 6** starting from **EXAMPLE 5** as reagent, **EXAMPLE 88** was obtained as HCl salt. HRMS calculated for $C_{27}H_{33}N_5O_3$: 475.2583; found 476.2668 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-isopropyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 89)**

Using **General Procedure 5** starting from **Preparation R2by** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 89** as HCl salt. HRMS calculated for $C_{27}H_{35}N_5O_3$: 477.274; found 478.2819 [(M+H) form].

▪ **7-(2-hydroxyethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 90)**

Using **General Procedure 5** starting from **Preparation R2ce** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 90** as HCl salt. HRMS calculated for $C_{26}H_{33}N_5O_4$: 479.2533; found (NMR available form).

▪ **7-(2-fluoroethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 91)**

Using **General Procedure 5** starting from **Preparation R2cd** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 91** as HCl salt. HRMS calculated for $C_{26}H_{32}N_5O_3F$: 481.2489; found 482.2555 [(M+H) form].

▪ **7-chloro-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]thieno[3,4-d]pyrimidin-4-one (EXAMPLE 92)**

Using **General Procedure 6** starting from **EXAMPLE 6** as reagent, **EXAMPLE 92** was obtained as HCl salt. HRMS calculated for $C_{24}H_{27}ClN_4O_3S$: 486.1492; found 487.1544 [(M+H) form].

▪ **7-buta-2,3-dienyl-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 93)**

Using **General Procedure 6** starting from **EXAMPLE 7** as reagents, **EXAMPLE 93** was obtained as HCl salt. HRMS calculated for C₂₈H₃₃N₅O₃: 487.2583; found 488.2657 [(M+H) form].

▪ **7-cyclobutyl-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 94)**

Using **General Procedure 5** starting from **Preparation R2ca** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 94** as HCl salt. HRMS calculated for C₂₈H₃₅N₅O₃: 489.274; found 490.2796 [(M+H) form].

▪ **7-(cyclopropylmethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 95)**

Using **General Procedure 6** starting from **EXAMPLE 8** as reagent, **EXAMPLE 95** was obtained as HCl salt. HRMS calculated for C₂₈H₃₅N₅O₃: 489.274; found 490.2817 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-isobutyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 96)**

Using **General Procedure 6** starting from **EXAMPLE 9** as reagent, **EXAMPLE 96** was obtained as HCl salt. HRMS calculated for C₂₈H₃₇N₅O₃: 491.2896; found 492.2963 [(M+H) form].

▪ **7-(2,2-difluoroethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 97)**

Using **General Procedure 5** starting from **Preparation R2cc** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 97** as HCl salt. HRMS calculated for C₂₆H₃₁N₅O₃F₂: 499.2395; found 500.2485 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-9-methyl-pyrimido[4,5-b]indol-4-one (EXAMPLE 98)**

Using **General Procedure 6** starting from **EXAMPLE 10** as reagent, **EXAMPLE 98** was obtained as HCl salt. HRMS calculated for $C_{29}H_{33}N_5O_3$: 499.2583; found 500.2677 [(M+H) form].

▪ **7-(cyclobutylmethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 99)**

Using **General Procedure 6** starting from **EXAMPLE 11** as reagent, **EXAMPLE 99** was obtained as HCl salt. HRMS calculated for $C_{29}H_{37}N_5O_3$: 503.2896; found 504.2957 [(M+H) form].

▪ **7-(2-dimethylaminoethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 100)**

Using **General Procedure 6** starting from **EXAMPLE 12** as reagent, **EXAMPLE 100** was obtained as HCl salt. HRMS calculated for $C_{28}H_{38}N_6O_3$: 506.3005; found 254.1581 [(M+2H) $^{2+}$ form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 101)**

Using **General Procedure 6** starting from **EXAMPLE 13** as reagent, **EXAMPLE 101** was obtained as HCl salt. HRMS calculated for $C_{30}H_{33}N_5O_3$: 511.2583; found 512.2648 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-5H-pyrrolo[3,2-d]pyrimidin-4-one (EXAMPLE 102)**

Using **General Procedure 6** starting from **EXAMPLE 14** as reagents, **EXAMPLE 102** was obtained as HCl salt. HRMS calculated for $C_{30}H_{33}N_5O_3$: 511.2583; found 512.2647 [(M+H) form].

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▪ **5-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-1-phenyl-pyrazolo[3,4-d]pyrimidin-4-one (EXAMPLE 103)**

Using **General Procedure 6** starting from **EXAMPLE 16** as reagent, **EXAMPLE 103** was obtained as HCl salt. HRMS calculated for $C_{29}H_{32}N_6O_3$: 512.2536; found 513.2623 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-pyridyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 104)**

Using **General Procedure 6** starting from **EXAMPLE 15** as reagent, **EXAMPLE 104** was obtained as HCl salt. HRMS calculated for $C_{29}H_{32}N_6O_3$: 512.2536; found 257.134 [(M+2H) $^{2+}$ form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(3-pyridyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 105)**

Using **General Procedure 5** starting from **Preparation R2bu** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 105** as HCl salt. HRMS calculated for $C_{29}H_{32}N_6O_3$: 512.2536; found 513.261 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(4-pyridyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 106)**

Using **General Procedure 5** starting from **Preparation R2bv** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 106** as HCl salt. HRMS calculated for $C_{29}H_{32}N_6O_3$: 512.2536; found 513.2609 [(M+H) form].

▪ **1-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-9-phenyl-purin-6-one (EXAMPLE 107)**

Using **General Procedure 6** starting from **EXAMPLE 17** as reagent, **EXAMPLE 107** was obtained as HCl salt. HRMS calculated for $C_{29}H_{32}N_6O_3$: 512.2536; found 513.2616 [(M+H) form].

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▪ **7-bromo-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,1-f][1,2,4]triazin-4-one (EXAMPLE 108)**

Using **General Procedure 6** starting from **EXAMPLE 18** as reagent, **EXAMPLE 108** was obtained as HCl salt. HRMS calculated for $C_{24}H_{28}BrN_5O_3$: 513.1376; found 514.1462 [(M+H) form].

▪ **6-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-3-phenyl-isoxazolo[4,5-d]pyrimidin-7-one (EXAMPLE 109)**

Using **General Procedure 6** starting from **EXAMPLE 19** as reagent, **EXAMPLE 109** was obtained as HCl salt. HRMS calculated for $C_{29}H_{31}N_5O_4$: 513.2376; found 514.2451 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-pyrimidin-2-yl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 110)**

Using **General Procedure 6** starting from **EXAMPLE 20** as reagent, **EXAMPLE 110** was obtained as HCl salt. HRMS calculated for $C_{28}H_{31}N_7O_3$: 513.2488; found 257.6326 [(M+2H)²⁺ form].

▪ **6-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-3-phenyl-triazolo[4,5-d]pyrimidin-7-one (EXAMPLE 111)**

Using **General Procedure 6** starting from **EXAMPLE 21** as reagent, **EXAMPLE 111** was obtained as HCl salt. HRMS calculated for $C_{28}H_{31}N_7O_3$: 513.2488; found 514.2576 [(M+H) form].

▪ **3-[(4-hydroxy-1-{[(3R,4R)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-6,8-dimethylpyrimido[5,4-b]indolizin-4(3H)-one (EXAMPLE 112)**

Using **General Procedure 6** starting from **EXAMPLE 22** as reagent, **EXAMPLE 112** was obtained as HCl salt. HRMS calculated for $C_{29}H_{34}N_6O_3$: 514.2692; found 515.2757 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(1-methylimidazol-4-yl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 113)**

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Using **General Procedure 6** starting from **EXAMPLE 23** as reagent, **EXAMPLE 113** was obtained as HCl salt. HRMS calculated for $C_{28}H_{33}N_7O_3$: 515.2645; found 516.2728 [(M+H) form].

5 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(1-methylpyrazol-4-yl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 114)**

Using **General Procedure 5** starting from **Preparation R2bx** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 114** as HCl salt. HRMS calculated for $C_{28}H_{33}N_7O_3$: 515.2645; found 516.2716 [(M+H) form].

10 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-thienyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 115)**

Using **General Procedure 6** starting from **EXAMPLE 25** as reagent, **EXAMPLE 115** was obtained as HCl salt. HRMS calculated for $C_{28}H_{31}N_5O_3S$: 517.2148; found 518.2231 [(M+H) form].

15 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(3-thienyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 116)**

Using **General Procedure 6** starting from **EXAMPLE 24** as reagent, **EXAMPLE 116** was obtained as HCl salt. HRMS calculated for $C_{28}H_{31}N_5O_3S$: 517.2148; found 518.2233 [(M+H) form].

20 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenyl-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl]-4-piperidyl]methyl]-7H-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 117)**

EXAMPLE 62 (610 mg, 0.92 mmol) was dissolved in 12 ml DCM, then TFA (211 μ l, 2.73 mmol, 3 eq.) and formic acid (399 μ l, 10.6 mmol, 11.5 eq.) were added. The mixture was stirred at r.t. for 118 hours, then potassium carbonate (2.22g 16.1 mmol) was added.
25 The solution was extrated with DCM (2x70 ml) and organic phase was dried ($MgSO_4$) and evaporated.

112 mg (0.2 mmol) of crude 3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-4-one product

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was solved in 2 ml dry THF, then triethyl amine (42 μ l, 0.3 mmol, 1.5 eq.) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (32 μ l, 0.22 mol, 1.2 eq.) were added. The mixture was stirred at r.t. for 141 hours, then 5 ml water was added. The solution was extracted with DCM (2x10 ml) and organic phase was dried (MgSO₄) and evaporated

5 The obtained 3-[[4-hydroxy-1-[(3*R*,4*R*)-3-phenyl-1-(2,2,2-trifluoroethyl)piperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-*d*]pyrimidin-4-one was solved in 270 μ l dry THF, and tetrabutylammonium fluoride (270 μ l, 1M in THF, 0.27 mmol) and molecular sieves were added and stirred at 75 °C for 20 hours, then the molecular sieves was filtered off and the residue was purified by preparative HPLC in
10 25mM NH₄HCO₃-acetonitrile gradient method, to give **EXAMPLE 117**. HRMS calculated for C₂₆H₃₀F₃N₅O₃: 517.2301; found 518.2361 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3*R*,4*R*)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2,2,2-trifluoroethyl)pyrrolo[2,3-*d*]pyrimidin-4-one (EXAMPLE 118)**

Using **General Procedure 6** starting from **EXAMPLE 26** as reagent, **EXAMPLE 118** was
15 obtained as HCl salt. HRMS calculated for C₂₆H₃₀F₃N₅O₃: 517.2301; found 518.2386 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3*R*,4*R*)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-thiazol-2-yl-pyrrolo[2,3-*d*]pyrimidin-4-one (EXAMPLE 119)**

Using **General Procedure 6** starting from **EXAMPLE 27** as reagent, **EXAMPLE 119** was
20 obtained as HCl salt. HRMS calculated for C₂₇H₃₀N₆O₃S: 518.21; found 519.2181 [(M+H) form].

▪ **7-[3-(dimethylamino)propyl]-3-[[4-hydroxy-1-[(3*R*,4*R*)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-*d*]pyrimidin-4-one (EXAMPLE 120)**

Using **General Procedure 6** starting from **EXAMPLE 28** as reagent, **EXAMPLE 120** was
25 obtained as HCl salt. HRMS calculated for C₂₉H₄₀N₆O₃: 520.3162; found 261.1666 [(M+2H)₂⁺ form].

▪ **3-[[4-hydroxy-1-[(3*R*,4*R*)-1-methyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-*d*]pyrimidin-4-one (EXAMPLE 121)**

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Using **General Procedure 7** starting from **EXAMPLE 101** and methyl iodide as reagents, **EXAMPLE 121** was obtained as HCl salt. HRMS calculated for $C_{31}H_{35}N_5O_3$: 525.274; found 526.2802 [(M+H) form].

5 ■ **7-benzyl-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 122)**

Using **General Procedure 6** starting from **EXAMPLE 31** as reagent, **EXAMPLE 122** was obtained as HCl salt. HRMS calculated for $C_{31}H_{35}N_5O_3$: 525.274; found 526.2822 [(M+H) form].

10 ■ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(p-tolyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 123)**

Using **General Procedure 6** starting from **EXAMPLE 30** as reagent, **EXAMPLE 123** was obtained as HCl salt. HRMS calculated for $C_{31}H_{35}N_5O_3$: 525.274; found 526.2816 [(M+H) form].

15 ■ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(m-tolyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 124)**

Using **General Procedure 6** starting from **EXAMPLE 29** as reagent, **EXAMPLE 124** was obtained as HCl salt. HRMS calculated for $C_{31}H_{35}N_5O_3$: 525.274; found 526.2825 [(M+H) form].

20 ■ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-6-methyl-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 125)**

Using **General Procedure 6** starting from **EXAMPLE 32** as reagent, **EXAMPLE 125** was obtained as HCl salt. HRMS calculated for $C_{31}H_{35}N_5O_3$: 525.274; found 526.2827 [(M+H) form].

25 ■ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(6-methyl-2-pyridyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 126)**

Using **General Procedure 5** starting from **Preparation R2br** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General**

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Procedure 6, to give **EXAMPLE 126** as HCl salt. HRMS calculated for $C_{30}H_{34}N_6O_3$: 526.2692; found 527.2764 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxo-7-phenyl-thieno[3,4-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 127)**

5 **EXAMPLE 6** (370 mg, 0.63 mmol) was dissolved in 2 ml THF and 2 ml water, then phenyl boronic acid (308 mg, 2.52 mmol, 4 eq.), AtaPhos*PdCl₂ (8.6 mg, 0.012 mmol, 0.2 eq.), cesium carbonate (617 mg, 1.89 mmol, 3 eq.) were added. The mixture was heated and stirred in Anton Paar microwave reactor for 1 hour at 100 °C. The residue was purified by preparative HPLC in 5mM NH₄HCO₃-MeCN gradient method, to give **EXAMPLE 127**.
10 HRMS calculated for $C_{35}H_{40}N_4O_5S$: 628.2719; found 629.2788 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl)methyl]-7-(6-oxo-1H-pyridin-2-yl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 128)**

Using **General Procedure 6** starting from **EXAMPLE 45** as reagents, **EXAMPLE 128** was obtained. HRMS calculated for $C_{29}H_{32}N_6O_4$: 528.2485; found 529.2567 [(M+H) form].

15 ▪ **6-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl)methyl]-3-phenyl-isothiazolo[4,5-d]pyrimidin-7-one (EXAMPLE 129)**

Using **General Procedure 6** starting from **EXAMPLE 33** as reagent, **EXAMPLE 129** was obtained. HRMS calculated for $C_{29}H_{31}N_5O_3S$: 529.2148; found 530.2223 [(M+H) form].

20 ▪ **7-(4-fluorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl)methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 130)**

Using **General Procedure 6** starting from **EXAMPLE 34** as reagent, **EXAMPLE 130** was obtained. HRMS calculated for $C_{30}H_{30}FN_5O_3$: 529.2489; found 530.2584 [(M+H) form].

▪ **7-(3-fluorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl)methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 131)**

25 Using **General Procedure 6** starting from **EXAMPLE 35** as reagents, **EXAMPLE 131** was obtained. HRMS calculated for $C_{30}H_{32}FN_5O_3$: 529.2489; found 530.2571 [(M+H) form].

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▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(5-methyl-2-thienyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 132)**

Using **General Procedure 6** starting from **EXAMPLE 37** as reagent, **EXAMPLE 132** was obtained. HRMS calculated for $C_{29}H_{33}N_5O_3S$: 531.2304; found 532.2361 [(M+H) form].

5 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(1-methyl-4-piperidyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 133)**

Using **General Procedure 6** starting from **EXAMPLE 38** as reagent, **EXAMPLE 133** was obtained. HRMS calculated for $C_{30}H_{40}N_6O_3$: 532.3162; found 267.1658 [(M+2H) $^{2+}$ form].

10 ▪ **4-[3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-4-oxo-pyrrolo[2,3-d]pyrimidin-7-yl]benzonitrile (EXAMPLE 134)**

Using **General Procedure 6** starting from **EXAMPLE 39** as reagent, **EXAMPLE 134** was obtained. HRMS calculated for $C_{31}H_{32}N_6O_3$: 536.2536; found 537.2599 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(4-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 135)**

15 Using **General Procedure 6** starting from **EXAMPLE 40** as reagents, **EXAMPLE 135** was obtained. HRMS calculated for $C_{31}H_{35}N_5O_4$: 541.2689; found 542.2784 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(3-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 136)**

20 Using **General Procedure 6** starting from **EXAMPLE 41** as reagents, **EXAMPLE 136** was obtained. HRMS calculated for $C_{31}H_{35}N_5O_4$: 541.2689; found 542.2777 [(M+H) form].

▪ **7-[4-(hydroxymethyl)phenyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 137)**

Using **General Procedure 6** starting from **EXAMPLE 42** as reagents, **EXAMPLE 137** was obtained. HRMS calculated for $C_{31}H_{35}N_5O_4$: 541.2689; found 542.2787 [(M+H) form].

25 ▪ **7-[3-(hydroxymethyl)phenyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 138)**

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Using **General Procedure 5** starting from **Preparation R2bj** and **Preparation R1c** as reagents, the resulted Boc-protected crude product was reacted using **General Procedure 6**, to give **EXAMPLE 138**. HRMS calculated for $C_{31}H_{35}N_5O_4$: 541.2689; found 542.2769 [(M+H) form].

5 ▪ **6-(hydroxymethyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 139)**

Using **General Procedure 6** starting from **EXAMPLE 43** as reagent, **EXAMPLE 139** was obtained. HRMS calculated for $C_{31}H_{35}N_5O_4$: 541.2689; found 542.2763 [(M+H) form].

10 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(6-methoxy-2-pyridyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 140)**

Using **General Procedure 6** starting from **EXAMPLE 45** as reagent, **EXAMPLE 140** was obtained. HRMS calculated for $C_{30}H_{34}N_6O_4$: 542.2642; found 543.2698 [(M+H) form].

15 ▪ **7-(4-fluorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-1-methyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 141)**

Using **General Procedure 7** starting from **EXAMPLE 130** and methyl iodide as reagents, **EXAMPLE 141** was obtained. HRMS calculated for $C_{31}H_{34}N_5O_3F$: 543.2646; found 544.2721 [(M+H) form].

20 ▪ **7-(3-chlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 142)**

Using **General Procedure 6** starting from **EXAMPLE 47** as reagent, **EXAMPLE 142** was obtained. HRMS calculated for $C_{30}H_{32}ClN_5O_3$: 545.2194; found 546.2248 [(M+H) form].

25 ▪ **7-(4-chlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 143)**

Using **General Procedure 6** starting from **EXAMPLE 46** as reagent, **EXAMPLE 143** was obtained. HRMS calculated for $C_{30}H_{32}ClN_5O_3$: 545.2194; found 546.2262 [(M+H) form].

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▪ **6-chloro-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 144)**

Using **General Procedure 6** starting from **EXAMPLE 48** as reagent, **EXAMPLE 144** was obtained. HRMS calculated for $C_{30}H_{32}ClN_5O_3$: 545.2194; found 546.2277 [(M+H) form].

5 ▪ **7-(5-chloro-2-thienyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 145)**

Using **General Procedure 6** starting from **EXAMPLE 49** as reagent, **EXAMPLE 145** was obtained. HRMS calculated for $C_{28}H_{30}ClN_5O_3S$: 551.1758; found 552.1844 [(M+H) form].

10 ▪ **7-[1-(difluoromethyl)pyrazol-4-yl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 146)**

Using **General Procedure 6** starting from **EXAMPLE 50** as reagent, **EXAMPLE 146** was obtained. HRMS calculated for $C_{28}H_{31}F_2N_7O_3$: 551.2457; found 552.254 [(M+H) form].

▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 147)**

15 Using **General Procedure 8** starting from **EXAMPLE 101** and acetic acid as reagents, **EXAMPLE 147** was obtained. HRMS calculated for $C_{32}H_{35}N_5O_4$: 553.2689; found 554.2757 [(M+H) form].

▪ **7-(4-dimethylaminophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 148)**

20 Using **General Procedure 6** starting from **EXAMPLE 51** as reagent, **EXAMPLE 148** was obtained. HRMS calculated for $C_{32}H_{38}N_6O_3$: 554.3005; found 555.3076 [(M+H) form].

▪ **7-[3-(dimethylamino)phenyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 149)**

25 Using **General Procedure 6** starting from **EXAMPLE 52** as reagent, **EXAMPLE 149** was obtained. HRMS calculated for $C_{32}H_{38}N_6O_3$: 554.3005; found 555.3086 [(M+H) form].

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▪ **7-(1,3-benzodioxol-5-yl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 150)**

Using **General Procedure 6** starting from **EXAMPLE 53** as reagent, **EXAMPLE 150** was obtained. HRMS calculated for $C_{31}H_{33}N_5O_5$: 555.2482; found 556.2556 [(M+H) form].

5 ▪ **3-[[4-hydroxy-1-[(3R,4R)-1-methyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]-7-(4-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 151)**

Using **General Procedure 7** starting from **EXAMPLE 135** and methyl iodide as reagents, **EXAMPLE 151** was obtained. HRMS calculated for $C_{32}H_{37}N_5O_4$: 555.2845; found 556.2922 [(M+H) form].

10 ▪ **7-(3-chlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-1-methyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 152)**

Using **General Procedure 7** starting from **EXAMPLE 142** and methyl iodide as reagents, **EXAMPLE 152** was obtained. HRMS calculated for $C_{31}H_{34}N_5O_3Cl$: 559.235; found 560.2425 [(M+H) form].

15 ▪ **7-(4-chlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-1-methyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 153)**

Using **General Procedure 7** starting from **EXAMPLE 143** and methyl iodide as reagents, **EXAMPLE 153** was obtained. HRMS calculated for $C_{31}H_{34}N_5O_3Cl$: 559.235; found 560.2423 [(M+H) form].

20 ▪ **7-[(4-chlorophenyl)methyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 154)**

Using **General Procedure 6** starting from **EXAMPLE 56** as reagent, **EXAMPLE 154** was obtained. HRMS calculated for $C_{31}H_{34}ClN_5O_3$: 559.235; found 560.2418 [(M+H) form].

25 ▪ **7-[(3-chlorophenyl)methyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 155)**

Using **General Procedure 6** starting from **EXAMPLE 55** as reagent, **EXAMPLE 155** was obtained. HRMS calculated for $C_{31}H_{34}ClN_5O_3$: 559.235; found 560.2432 [(M+H) form].

▪ **7-[(2-chlorophenyl)methyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 156)**

Using **General Procedure 6** starting from **EXAMPLE 54** as reagent, **EXAMPLE 156** was obtained. HRMS calculated for $C_{31}H_{34}ClN_5O_3$: 559.235; found 560.2429 [(M+H) form].

5 ▪ **7-(4-fluoro-3-methoxy-phenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 157)**

Using **General Procedure 6** starting from **EXAMPLE 57** as reagent, **EXAMPLE 157** was obtained. HRMS calculated for $C_{31}H_{34}FN_5O_4$: 559.2595; found 560.2638 [(M+H) form].

10 ▪ **7-[4-(difluoromethyl)phenyl]-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 158)**

Using **General Procedure 6** starting from **EXAMPLE 58** as reagent, **EXAMPLE 158** was obtained. HRMS calculated for $C_{31}H_{33}F_2N_5O_3$: 561.2551; found 562.2636 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-naphthyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 159)**

15 Using **General Procedure 6** starting from **EXAMPLE 60** as reagent, **EXAMPLE 159** was obtained. HRMS calculated for $C_{34}H_{35}N_5O_3$: 561.274; found 562.2831 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(1-naphthyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 160)**

20 Using **General Procedure 6** starting from **EXAMPLE 59** as reagent, **EXAMPLE 160** was obtained. HRMS calculated for $C_{34}H_{35}N_5O_3$: 561.274; found 562.2827 [(M+H) form].

▪ **7-(4-chloro-3-fluoro-phenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 161)**

Using **General Procedure 6** starting from **EXAMPLE 61** as reagent, **EXAMPLE 161** was obtained. HRMS calculated for $C_{30}H_{31}N_5O_3FCl$: 563.21; found 564.2181 [(M+H) form].

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▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 162)**

EXAMPLE 62 (1.6 g, 2.4 mmol) was dissolved in 30 ml DCM, then TFA (3 ml) and formic acid (550 µl, 7.2 mmol, 3 eq.) were added. The mixture was stirred at r.t. for 4 days, then potassium carbonate (15 g, 108 mmol) was added. The solution was extracted with DCM and organic phase was dried (MgSO₄) and evaporated to give **EXAMPLE 162**. HRMS calculated for C₃₀H₄₃N₅O₄Si: 565.3084; found 566.3138 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-1-isobutyl-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 163)**

Using **General Procedure 7** starting from **EXAMPLE 101** and 1-bromo-2-methyl-propane as reagents, **EXAMPLE 163** was obtained. HRMS calculated for C₃₄H₄₁N₅O₃: 567.3209; found 568.328 [(M+H) form].

▪ **7-(2,3-dihydro-1,4-benzodioxin-6-yl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 164)**

Using **General Procedure 6** starting from **EXAMPLE 63** as reagent, **EXAMPLE 164** was obtained. HRMS calculated for C₃₂H₃₅N₅O₅: 569.2638; found 570.2709 [(M+H) form].

▪ **1-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrazolo[3,4-d]pyrimidin-4-one (EXAMPLE 165)**

Using **General Procedure 6** starting from **EXAMPLE 64** as reagent, **EXAMPLE 165** was obtained. HRMS calculated for C₃₁H₃₄N₆O₅: 570.2591; found 571.2663 [(M+H) form].

▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-(4-fluorophenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 166)**

Using **General Procedure 8** starting from **EXAMPLE 130** and acetic acid as reagents, **EXAMPLE 166** was obtained. HRMS calculated for C₃₂H₃₄FN₅O₄: 571.2595; found 572.2679 [(M+H) form].

▪ **7-(3,5-dimethoxyphenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 167)**

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Using **General Procedure 6** starting from **EXAMPLE 66** as reagent, **EXAMPLE 167** was obtained. HRMS calculated for $C_{32}H_{37}N_5O_5$: 571.2795; found 572.2881 [(M+H) form].

▪ **7-(3,4-dimethoxyphenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 168)**

5 Using **General Procedure 6** starting from **EXAMPLE 65** as reagent, **EXAMPLE 168** was obtained. HRMS calculated for $C_{32}H_{37}N_5O_5$: 571.2795; found 572.2892 [(M+H) form].

▪ **5-[[1-[(3R,4R)-1,1-dimethyl-3-phenyl-piperidin-1-ium-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-1-(4-methoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-one (EXAMPLE 169)**

10 Using **General Procedure 7** starting from **EXAMPLE 135** and methyl iodide as reagents, **EXAMPLE 169** was obtained. HRMS calculated for $C_{32}H_{39}N_6O_4$: 571.3027; found 571.3038 [(M+) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-6-iodo-7-methyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 170)**

15 Using **General Procedure 6** starting from **EXAMPLE 67** as reagent, **EXAMPLE 170** was obtained. HRMS calculated for $C_{25}H_{30}IN_5O_3$: 575.1393; found 576.1455 [(M+H) form].

▪ **7-(3-chloro-5-methoxy-phenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 171)**

20 Using **General Procedure 6** starting from **EXAMPLE 68** as reagent, **EXAMPLE 171** was obtained. HRMS calculated for $C_{31}H_{34}ClN_5O_4$: 575.2299; found 576.2382 [(M+H) form].

▪ **7-(4-chloro-3-methoxy-phenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 172)**

Using **General Procedure 6** starting from **EXAMPLE 69** as reagents, **EXAMPLE 172** was obtained. HRMS calculated for $C_{31}H_{34}ClN_5O_4$: 575.2299; found 576.2382 [(M+H) form].

25 ▪ **7-(3,5-dichlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 173)**

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Using **General Procedure 6** starting from **EXAMPLE 71** as reagent, **EXAMPLE 173** was obtained. HRMS calculated for $C_{30}H_{31}N_5O_3Cl_2$: 579.1804; found 580.1891 [(M+H) form].

▪ **7-(3,4-dichlorophenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 174)**

5 Using **General Procedure 6** starting from **EXAMPLE 70** as reagent, **EXAMPLE 174** was obtained. HRMS calculated for $C_{30}H_{31}Cl_2N_5O_3$: 579.1804; found 580.187 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-[4-(trifluoromethyl)phenyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 175)**

10 Using **General Procedure 6** starting from **EXAMPLE 72** as reagent, **EXAMPLE 175** was obtained. HRMS calculated for $C_{31}H_{32}N_5O_3F_3$: 579.2457; found 580.2529 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-[3-(trifluoromethyl)phenyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 176)**

Using **General Procedure 6** starting from **EXAMPLE 73** as reagent, **EXAMPLE 176** was obtained. HRMS calculated for $C_{31}H_{32}F_3N_5O_3$: 579.2457; found 580.2509 [(M+H) form].

15 ▪ **3-[[4-hydroxy-1-[(3R,4R)-1-(2-methylpropanoyl)-3-phenyl-piperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 177)**

Using **General Procedure 8** starting from **EXAMPLE 101** and 2-methylpropanoic acid as reagents, **EXAMPLE 177** was obtained. HRMS calculated for $C_{34}H_{39}N_5O_4$: 581.3002; found 582.3072 [(M+H) form].

20 ▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-(4-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 178)**

Using **General Procedure 8** starting from **EXAMPLE 135** and acetic acid as reagents, **EXAMPLE 178** was obtained. HRMS calculated for $C_{33}H_{37}N_5O_5$: 583.2795; found 584.2868 [(M+H) form].

25 ▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-(3-methoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 179)**

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Using **General Procedure 8** starting from **EXAMPLE 136** and acetic acid as reagents, **EXAMPLE 179** was obtained. HRMS calculated for $C_{33}H_{37}N_5O_5$: 583.2795; found 584.2863 [(M+H) form].

▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-(3-chlorophenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 180)**

Using **General Procedure 8** starting from **EXAMPLE 142** and acetic acid as reagents, **EXAMPLE 180** was obtained. HRMS calculated for $C_{32}H_{34}ClN_5O_4$: 587.2299; found 588.238 [(M+H) form].

▪ **3-[[1-[(3R,4R)-1-acetyl-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-(4-chlorophenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 181)**

Using **General Procedure 8** starting from **EXAMPLE 143** and acetic acid as reagents, **EXAMPLE 181** was obtained. HRMS calculated for $C_{32}H_{34}ClN_5O_4$: 587.2299; found 588.2366 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-[4-(trifluoromethoxy)phenyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 182)**

Using **General Procedure 6** starting from **EXAMPLE 76** as reagent, **EXAMPLE 182** was obtained. HRMS calculated for $C_{31}H_{32}N_5O_4F_3$: 595.2407; found 596.2494 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-[3-(trifluoromethoxy)phenyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 183)**

Using **General Procedure 6** starting from **EXAMPLE 75** as reagent, **EXAMPLE 183** was obtained. HRMS calculated for $C_{31}H_{32}N_5O_4F_3$: 595.2407; found 596.2491 [(M+H) form].

▪ **3-[[1-[(3R,4R)-1-(2,2-dimethylpropanoyl)-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 184)**

Using **General Procedure 8** starting from **EXAMPLE 101** and 2,2-dimethylpropanoic acid as reagents, **EXAMPLE 184** was obtained. HRMS calculated for $C_{35}H_{41}N_5O_4$: 595.3159; found 596.3221 [(M+H) form].

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▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(3-morpholinophenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 185)**

Using **General Procedure 6** starting from **EXAMPLE 77** as reagent, **EXAMPLE 185** was obtained. HRMS calculated for $C_{34}H_{40}N_6O_4$: 596.3111; found 597.3187 [(M+H) form].

5 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-(3,4,5-trimethoxyphenyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 186)**

Using **General Procedure 6** starting from **EXAMPLE 78** as reagent, **EXAMPLE 186** was obtained. HRMS calculated for $C_{33}H_{39}N_5O_6$: 601.29; found 602.296 [(M+H) form].

10 ▪ **3-[[1-[(3R,4R)-1-(3,3-dimethylbutanoyl)-3-phenyl-piperidine-4-carbonyl]-4-hydroxy-4-piperidyl]methyl]-7-phenyl-pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 187)**

Using **General Procedure 8** starting from **EXAMPLE 101** and 3,3-dimethylbutanoic acid as reagents, **EXAMPLE 187** was obtained. HRMS calculated for $C_{36}H_{43}N_5O_4$: 609.3315; found 610.3384 [(M+H) form].

15 ▪ **7-(4-benzyloxyphenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 188)**

Using **General Procedure 6** starting from **EXAMPLE 79** as reagent, **EXAMPLE 188** was obtained. HRMS calculated for $C_{37}H_{39}N_5O_4$: 617.3002; found 618.3083 [(M+H) form].

20 ▪ **7-(3-benzyloxyphenyl)-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 189)**

Using **General Procedure 6** starting from **EXAMPLE 80** as reagent, **EXAMPLE 189** was obtained. HRMS calculated for $C_{37}H_{39}N_5O_4$: 617.3002; found 618.3051 [(M+H) form].

25 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-[3-[(4-methylpiperazin-1-yl)methyl]phenyl]pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 190)**

Using **General Procedure 6** starting from **EXAMPLE 81** as reagent, **EXAMPLE 190** was obtained. HRMS calculated for $C_{36}H_{45}N_7O_3$: 623.3584; found 624.3656 [(M+H) form].

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▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-7-phenyl-thieno[3,4-d]pyrimidin-4-one (EXAMPLE 191)**

Using **General Procedure 6** starting from **EXAMPLE 127** as reagent, **EXAMPLE 191** was obtained. HRMS calculated for $C_{30}H_{32}N_4O_3S$: 528.2195; found 529.2265 [(M+H) form].

5 ▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-6-iodo-7-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-d]pyrimidin-4-one (EXAMPLE 192)**

EXAMPLE 74 (647 mg, 0.82 mmol) was dissolved in 13 ml DCM, then TFA (188 μ l, 2.46 mmol, 3 eq.) and formic acid (356 μ l, 9.43 mmol, 11.5 eq.) were added. The mixture was stirred at r.t. for 214 hours, then potassium carbonate (1.99 g, 14.3 mmol) was added. The solution was extrated with DCM (2x70 ml) and organic phase ($MgSO_4$) was dried and evaporated to give **EXAMPLE 192**. HRMS calculated for $C_{30}H_{42}IN_5O_4Si$: 691.2051; found 692.2155 [(M+H) form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(4-oxopyrido[3,2-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 193)**

15 Using **General Procedure 5** starting from 3*H*-pyrido[3,2-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 193** was obtained. HRMS calculated for $C_{30}H_{37}N_5O_5$: 547.2795; found 548.2870 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrido[3,2-d]pyrimidin-4-one (EXAMPLE 194)**

20 Using **General Procedure 6** starting from **EXAMPLE 193** as reagent, **EXAMPLE 194** was obtained as HCl salt. HRMS calculated for $C_{25}H_{29}N_5O_3$: 447.227; found 448.2365 [(M+H)⁺ form].

▪ **tert-butyl (3R,4R)-4-[4-[(6-chloro-4-oxo-pyrido[3,2-d]pyrimidin-3-yl)methyl]-4-hydroxy-piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 195)**

25 Using **General Procedure 5** starting from 6-chloro-3*H*-pyrido[3,2-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 195** was obtained. HRMS calculated for $C_{30}H_{36}ClN_5O_5$: 581.2405; found 604.2239 [(M+Na) form].

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▪ **6-chloro-3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]pyrido[3,2-d]pyrimidin-4-one (EXAMPLE 196)**

Using **General Procedure 6** starting from **EXAMPLE 195** as reagent, **EXAMPLE 196** was obtained as HCl salt. HRMS calculated for C₂₅H₂₈ClN₅O₃: 481.1881; found 482.1949 [(M+H)⁺ form].

▪ **tert-butyl (3R,4R)-4-[4-hydroxy-4-[(6-methoxy-4-oxo-pyrido[3,2-d]pyrimidin-3-yl)methyl]piperidine-1-carbonyl]-3-phenyl-piperidine-1-carboxylate (EXAMPLE 197)**

Using **General Procedure 5** starting from 6-methoxy-3*H*-pyrido[3,2-*d*]pyrimidin-4-one and **Preparation R1c** as reagents, **EXAMPLE 197** was obtained. HRMS calculated for C₃₁H₃₉N₅O₆: 577.29; found 578.2976 [(M+H) form].

▪ **3-[[4-hydroxy-1-[(3R,4R)-3-phenylpiperidine-4-carbonyl]-4-piperidyl]methyl]-6-methoxy-pyrido[3,2-d]pyrimidin-4-one (EXAMPLE 198)**

Using **General Procedure 6** starting from **EXAMPLE 197** as reagent, **EXAMPLE 198** was obtained as HCl salt. HRMS calculated for C₂₆H₃₁N₅O₄: 477.2376; found 478.2458 [(M+H)⁺ form].

PHARMACOLOGICAL STUDY

EXAMPLE A: Evaluation of the inhibition of USP7 by the Fluorescence Intensity (FLINT) readings

USP7 activity was measured using Rhodamine-110 c-terminal labelled Ubiquitin as a
5 substrate (*Viva Biosciences*). Incubation with USP7 results in the release of
Rhodamine-110 leading to an increase in fluorescence which can be used in the continuous
measurement of USP7 activity.

The USP7 reactions were performed in a 50 μ L volume, in 384 well black solid low
binding plates (Corning #3575). The reaction buffer consisted of 100 mM Bicine pH 8.0,
10 0.01 % TritonX100, 1 mM TCEP, and 10 % DMSO.

0.25 nM His-His-USP7 (aa208-560, [C315A]) was incubated with compound (final
concentration 10 % DMSO) for 60 minutes at 30 °C. The reaction was then initiated by the
addition of 500 nM Ubiquitin-Rhodamine-110 substrate and the plate read every 3 minutes
for 21 minutes to measure the release of Rhodamine-110. Fluorescence Intensity (FLINT)
15 readings were measured using a Biomek Neo plate reader (Ex.485 nm, Em.535 nm).

The inhibition of increasing doses of compound was expressed as a percentage reduction in
kinetic rate compared to the kinetic rates established between 'DMSO only' and 'total
inhibition' controls (no USP7). The inhibitory concentrations that gave a 50 % reduction in
kinetic rate (IC_{50}) were determined, from 11-point dose response curves, in XL-Fit using a
20 4-Parameter Logistic Model (Sigmoidal Dose-Response Model).

The results presented in Table 1 below show that compounds of the invention inhibit
interaction between USP7 protein and the fluorescent peptide described hereinbefore.

EXAMPLE B: *In vitro* cytotoxicity

The cytotoxicity studies were carried out on the MM1S multiple myeloma tumour cell line. The cells are distributed onto microplates and exposed to the test compounds for 96 hours. The cell viability is then quantified by a colorimetric assay, the Microculture Tetrazolium Assay (Cancer Res., 1987, 47, 939-942).

5 The results are expressed in IC₅₀ (the concentration of compound that inhibits cell viability by 50%) and are presented in Table 1 below.

The results show that the compounds of the invention are cytotoxic.

Table 1: IC₅₀ of USP7 inhibition and of cytotoxicity for MM1S cells

EXAMPLE	IC ₅₀ (M) USP7 FLINT	IC ₅₀ (M) MTT MM1S	EXAMPLE	IC ₅₀ (M) USP7 FLINT	IC ₅₀ (M) MTT MM1S
2	1.28E-07	ND	147	4.06E-07	ND
15	2.74E-07	ND	151	5.24E-08	ND
40	4.99E-08	3.15E-08	152	6.48E-08	ND
44	6.15E-08	ND	153	4.86E-08	7.47E-08
57	7.02E-08	ND	157	3.93E-08	ND
64	6.87E-08	ND	163	1.08E-07	ND
101	3.16E-08	2.72E-07	165	1.96E-08	3.00E-07
103	5.29E-08	ND	166	1.02E-07	ND
104	3.94E-07	ND	169	8.60E-07	ND
117	1.20E-06	ND	177	1.03E-07	ND
121	1.40E-07	ND	178	9.61E-08	ND
130	3.77E-08	ND	179	8.84E-08	ND
135	2.87E-08	1.35E-07	180	8.90E-08	ND
136	4.86E-08	ND	181	7.42E-08	ND
141	7.48E-08	ND	184	8.30E-08	ND
142	5.67E-08	ND	187	8.85E-08	ND
143	4.12E-08	ND			

ND: not determined

EXAMPLE C: Anti-tumor activity *in vivo*

The anti-tumour activity of the compounds of the invention is evaluated in a xenograft model of multiple myeloma and/or acute lymphoblastic leukaemia cells.

Human tumour cells are grafted subcutaneously into immunosuppressed mice.

- 5 When the tumour volume (TV) reaches about 200 mm³, the mice are treated *per os* with the various compounds once a day for 5 days on/2 days off during 3 weeks. The tumour mass is measured twice weekly from the start of treatment.

The compounds of the invention display anti-tumour activities represented by the TGI (tumor growth inhibition) at the end of the treatment period. The TGI is defined as follows:

$$10 \quad \text{TGI} = \left(1 - \frac{\text{Median (DTV at Dx in treated group)}}{\text{Median (DTV at Dx in control group)}} \right) \times 100 ,$$

with:

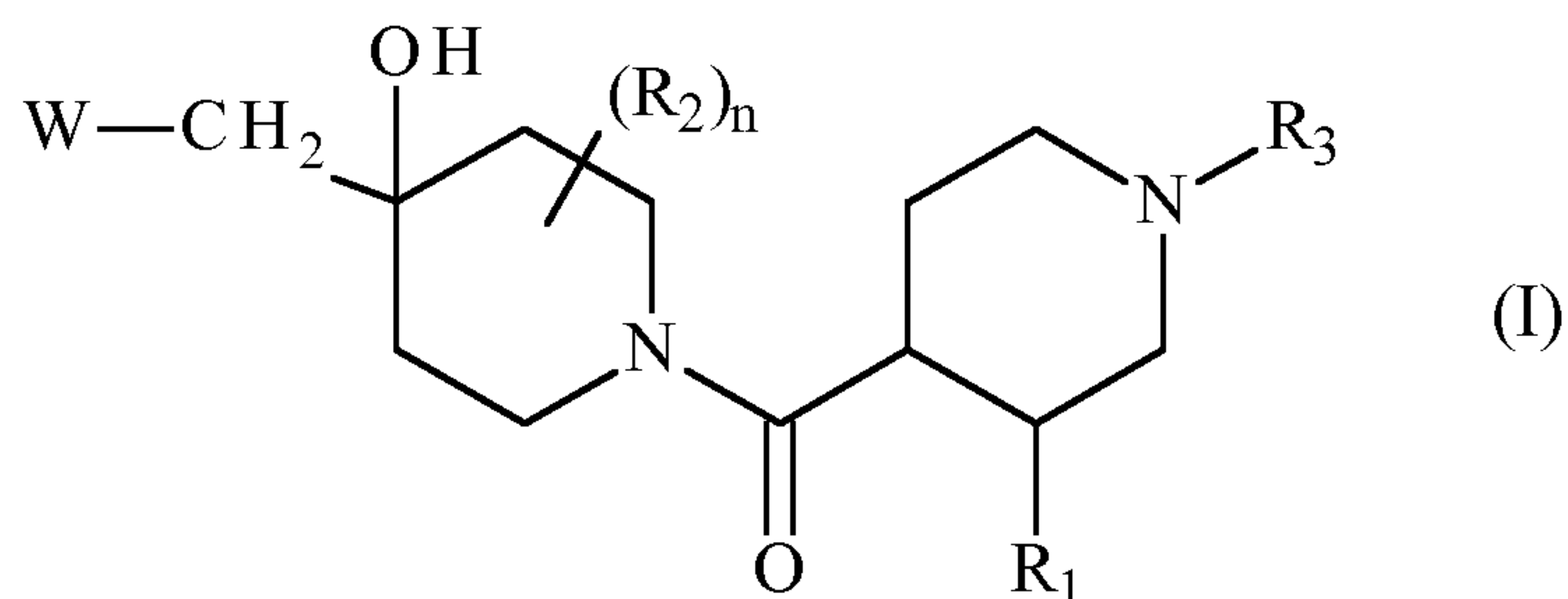
DTV (delta tumoral volume) at Dx = (TV at Dx) – (TV at randomization for each animal).

EXAMPLE D: Pharmaceutical composition: Tablets

	1000 tablets containing a dose of 5 mg of a compound selected from Examples 1 to 198.....	5 g
15	Wheat starch	20 g
	Maize starch.....	20 g
	Lactose	30 g
	Magnesium stearate	2 g
	Silica.....	1 g
20	Hydroxypropylcellulose	2 g

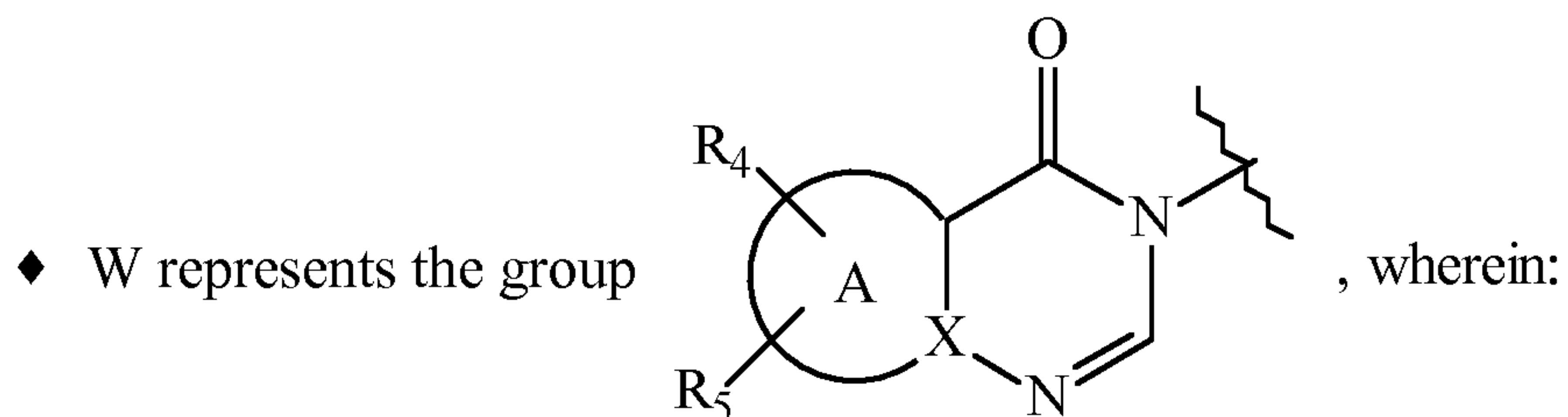
CLAIMS

1. Compound of formula (I):



wherein:

- 5
- ◆ R_1 represents an aryl group or a heteroaryl group,
 - ◆ R_2 represents a hydrogen atom or a halogen atom,
 - ◆ R_3 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group, a linear or branched halo (C_1-C_6) alkyl, a $-C(O)-R_8$ group, a $-C(O)-OR_8$ group,
 - ◆ n is an integer equal to 0, 1 or 2,



- 10
- A represents a heteroaryl ring,
 - X represents a carbon atom or a nitrogen atom,
 - R_4 represents a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6) alkyl group, a linear or branched (C_2-C_6) alkenyl group, a linear or branched (C_2-C_6) alkynyl group, a $-Y_1-NR_6R_7$ group, a $-Y_1-OR_6$ group, a linear or branched halo (C_1-C_6) alkyl group, an oxo group, a $-Y_1-Cy_1$ group, a $-Cy_1-R_7$ group, a $-Cy_1-OR_7$ group, or a $-Y_1-NR_6-C(O)-R_7$ group,
 - R_5 represents a hydrogen atom, a halogen atom, a linear or branched (C_1-C_6) alkyl group, a cyano group, or a $-hydroxy(C_1-C_6)$ alkyl group,
 - R_6 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group, or a $-Y_2-Si[(C_1-C_4)alkyl]_3$ group,
- 15
- 20

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- R₇ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, or a -Y₂-Cy₂ group,
- Y₁ and Y₂ independently of one another represent a bond or a linear or branched (C₁-C₄)alkylene group,

- 5
- ♦ R₈ represents a hydrogen atom, or a linear or branched (C₁-C₆)alkyl group,
 - ♦ Cy₁ and Cy₂ independently of one another, represent a cycloalkyl group, a heterocycloalkyl group, an aryl group, or a heteroaryl group,

it being understood that:

- “aryl” means a phenyl, naphthyl, or indanyl group,
- 10 - “heteroaryl” means any mono- or fused bi-cyclic group composed of from 5 to 10 ring members, having at least one aromatic moiety and containing from 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen,
- “cycloalkyl” means any mono- or fused bi-cyclic non-aromatic carbocyclic group containing from 3 to 7 ring members,
- 15 - “heterocycloalkyl” means any non-aromatic mono- or fused bi-cyclic group containing from 3 to 10 ring members, and containing from 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen,

it being possible for the aryl, heteroaryl, cycloalkyl and heterocycloalkyl groups so defined to be substituted by from 1 to 4 groups selected from linear or branched (C₁-C₆)alkyl, linear or branched (C₂-C₆)alkenyl, linear or branched (C₂-C₆)alkynyl, linear or branched halo(C₁-C₆)alkyl, -Y₁-OR', -Y₁-NR'R'', -Y₁-S(O)_m-R', oxo (or N-oxide where appropriate), nitro, cyano, -C(O)-R', -C(O)-OR', -O-C(O)-R', -C(O)-NR'R'', -Y₁-NR'-C(O)-R'', -Y₁-NR'-C(O)-OR'', halogen, cyclopropyl, and pyridinyl which can be substituted by a linear or branched (C₁-C₆)alkyl group,

- 20
- 25
- it being understood that R' and R'' independently of one another represent a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₁-C₆)alkoxy group, a linear or branched halo(C₁-C₆)alkyl, a linear or branched hydroxy(C₁-C₆)alkyl group, a linear or branched (C₁-C₆)alkoxy(C₁-C₆)alkyl group, a phenyl group, a cyclopropylmethyl group,

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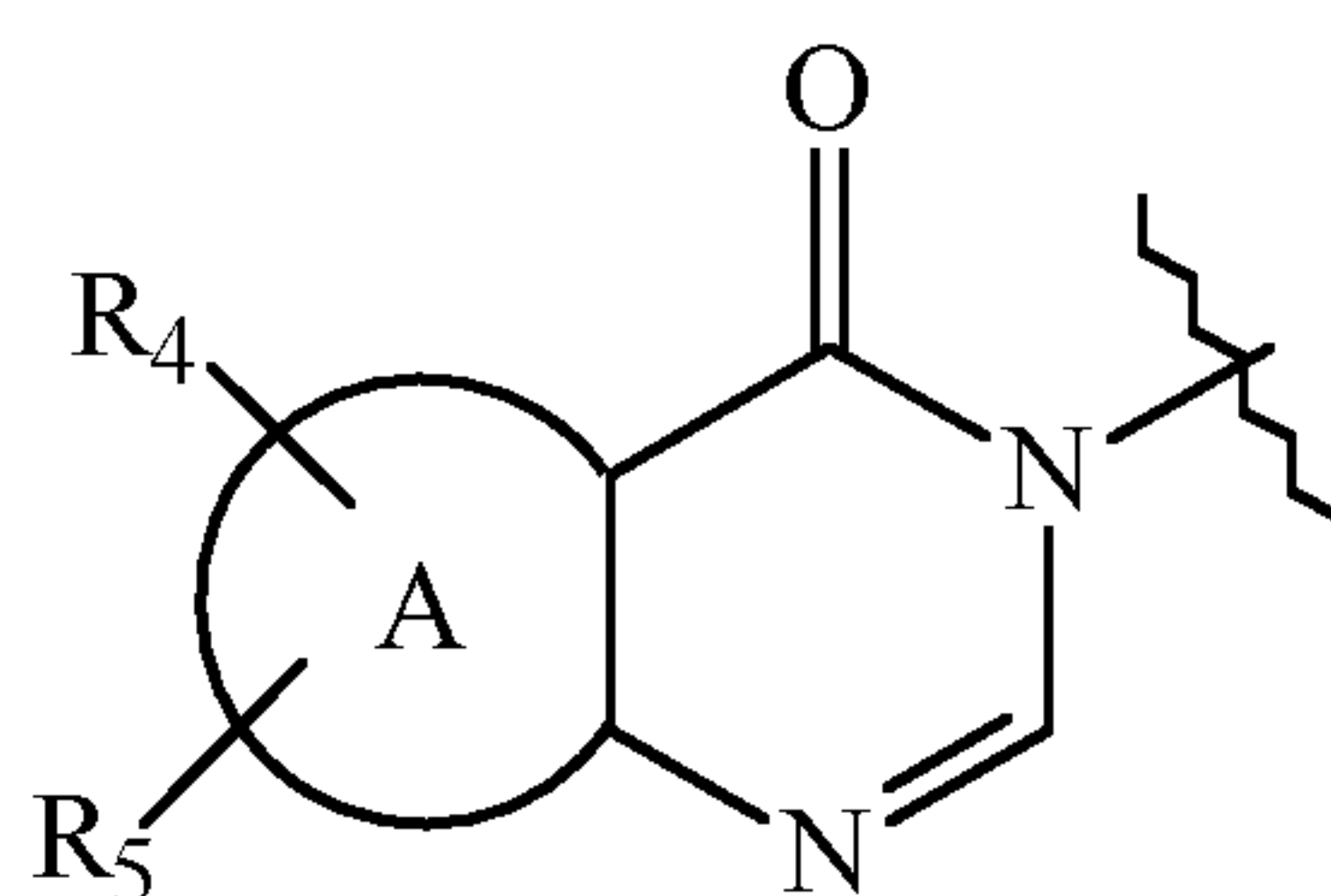
a tetrahydropyranyl group,

or the substituents of the pair (R', R'') form together with the nitrogen atom carrying them a non-aromatic ring composed of from 5 to 7 ring members, which may contain in addition to the nitrogen a second heteroatom selected from oxygen and nitrogen, it being understood that the nitrogen in question may be substituted by from 1 to 2 groups representing a hydrogen atom, or a linear or branched (C₁-C₆)alkyl group,

and it being understood that m is an integer equal to 0, 1 and 2,

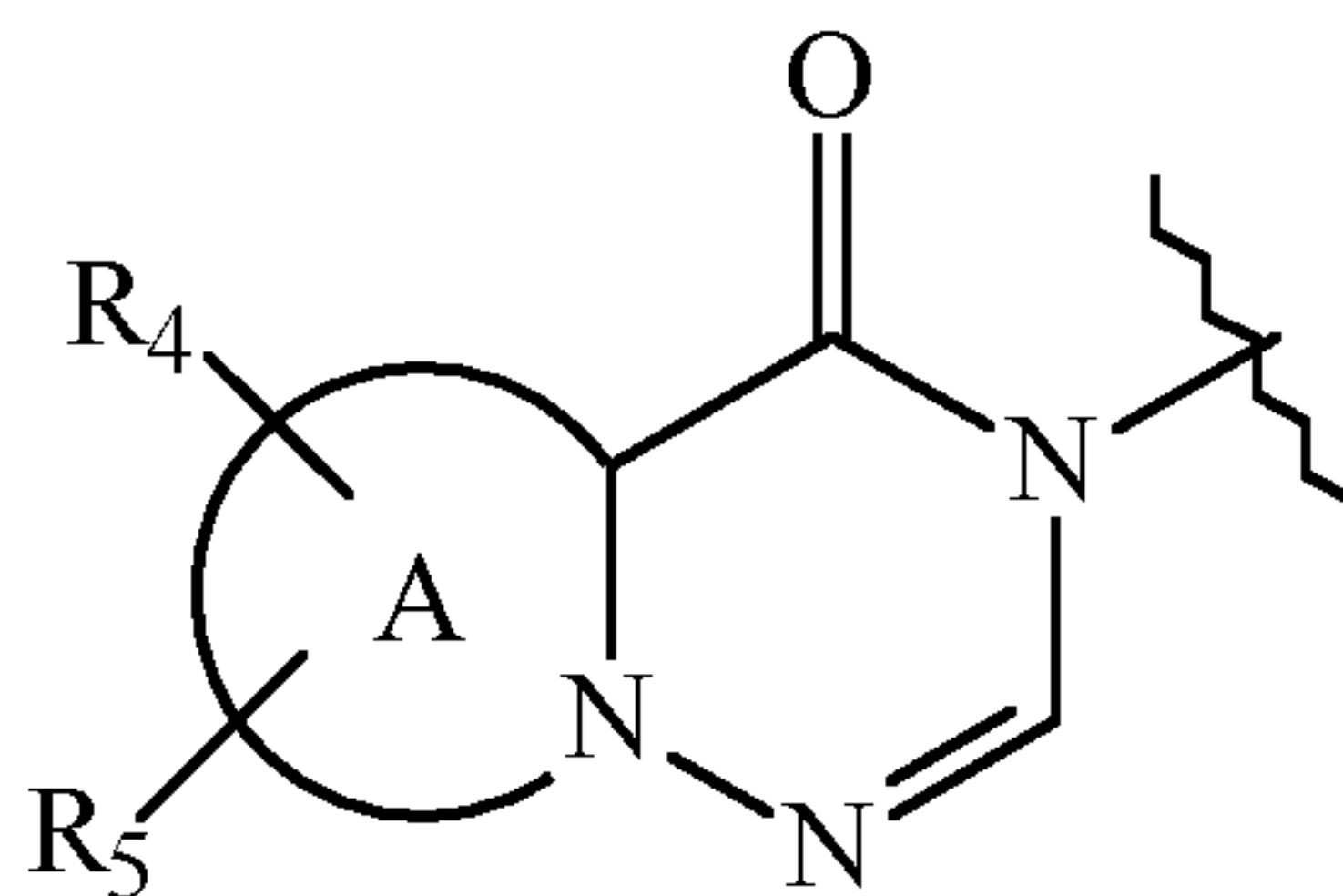
their enantiomers, diastereoisomers, and addition salts thereof with a pharmaceutically acceptable acid or base.

2. Compounds according to claim 1, wherein W represents the group



wherein R₄, R₅ and A are as defined in claim 1.

3. Compounds according to claim 1, wherein W represents the group



wherein R₄, R₅ and A are as defined in claim 1.

4. Compounds according to claim 1, wherein R₁ represents a phenyl group.

5. Compounds according to claim 1, wherein R₂ represents a hydrogen atom.

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6. Compounds according to claim 1, wherein R₃ represents a hydrogen atom, a methyl group, a -CH₂-CH(CH₃)₂ group, a -CH₂-CF₃ group, a -C(O)-CH₃ group, a -C(O)-CH(CH₃)₂ group, a -C(O)-CH₂-C(CH₃)₃ group, or a -C(O)-OC(CH₃)₃ group.
7. Compounds according to claim 1, wherein R₄ represents a hydrogen atom, a linear or branched (C₁-C₆)alkyl group, a linear or branched (C₂-C₆)alkenyl group, a linear or branched (C₂-C₆)alkynyl group, a -Y₁-NR₆R₇ group, a -Y₁-OR₆ group, a linear or branched halo(C₁-C₆)alkyl group, a -Y₁-Cy₁ group, a -Cy₁-R₇ group, or a -Cy₁-OR₇ group.
8. Compound according to claim 1, wherein R₅ represents a hydrogen atom, an iodine atom, a chlorine atom, a methyl group or a -CH₂-OH group.
9. Compounds according to claim 1, wherein R₆ represents a hydrogen atom, a methyl group, or a -(CH₂)₂-Si(CH₃)₃ group.
10. Compounds according to claim 1, wherein R₇ represents a hydrogen atom, a methyl group, or a -CH₂-Cy₂ group.
11. Compounds according to claim 1, which are:
 - *tert*-butyl (3*S*,4*S*)-4-({4-hydroxy-4-[(4-oxothieno[2,3-*d*]pyrimidin-3(4*H*)-yl)methyl]piperidin-1-yl}carbonyl)-3-phenylpiperidine-1-carboxylate;
 - *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[4-oxo-7-(pyridin-2-yl)-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl}piperidin-1-yl)carbonyl]-3-phenylpiperidine-1-carboxylate;
 - *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[7-(4-methoxyphenyl)-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl]methyl}piperidin-1-yl)carbonyl]-3-phenylpiperidine-1-carboxylate;
 - *tert*-butyl (3*R*,4*R*)-4-[(4-hydroxy-4-{[1-(4-methoxyphenyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl}piperidin-1-yl)carbonyl]-3-phenylpiperidine-1-carboxylate;

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- *tert*-butyl (3*R*,4*R*)-4-[(4-{[7-(4-fluoro-3-methoxyphenyl)-4-oxo-4,7-dihydro-3*H*-pyrrolo[2,3-*d*]pyrimidin-3-yl)methyl}-4-hydroxypiperidin-1-yl)carbonyl]-3-phenylpiperidine-1-carboxylate;

- *tert*-butyl (3*R*,4*R*)-4-[(4-{[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl)methyl}-4-hydroxypiperidin-1-yl)carbonyl]-3-phenylpiperidine-1-carboxylate;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 5-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-1-phenyl-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(pyridin-2-yl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenyl-1-(2,2,2-trifluoroethyl)piperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 7-(4-fluorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(3-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 7-(4-fluorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 7-(3-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 7-(4-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

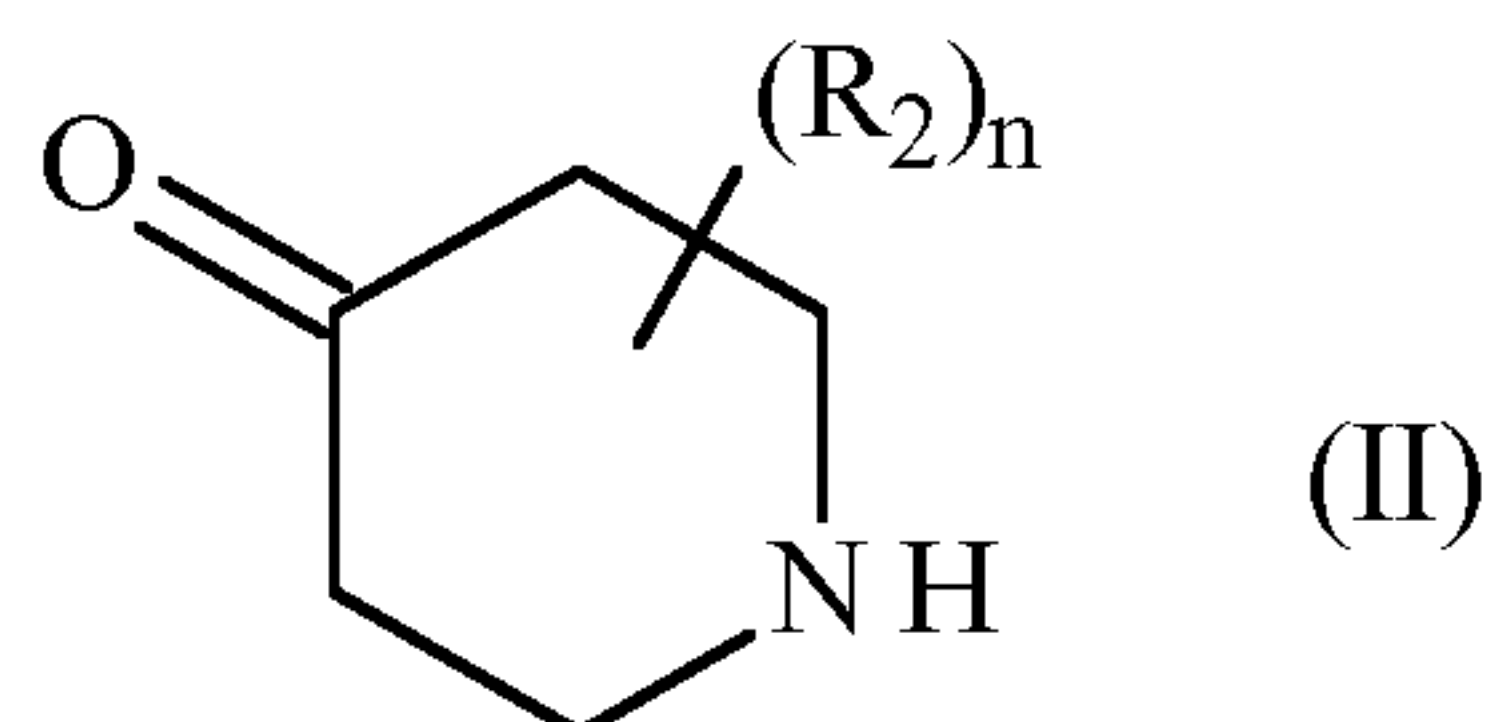
- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;

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- 7-(3-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 7-(4-chlorophenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-methyl-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 5 - 7-(4-fluoro-3-methoxyphenyl)-3-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-(2-methylpropyl)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-[(4-hydroxy-1-{[(3*R*,4*R*)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-1,5-dihydro-4*H*-pyrazolo[3,4-*d*]pyrimidin-4-one;
- 10 - 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-fluorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- (3*R*,4*R*)-4-[(4-hydroxy-4-{[1-(4-methoxyphenyl)-4-oxo-1,4-dihydro-5*H*-pyrazolo[3,4-*d*]pyrimidin-5-yl]methyl}piperidin-1-yl)carbonyl]-1,1-dimethyl-3-phenylpiperidinium;
- 15 - 3-[(4-hydroxy-1-{[(3*R*,4*R*)-1-(2-methylpropanoyl)-3-phenylpiperidin-4-yl]carbonyl}piperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 20 - 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(3-methoxyphenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(3-chlorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-acetyl-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-(4-chlorophenyl)-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 25 - 3-[(1-{[(3*R*,4*R*)-1-(2,2-dimethylpropanoyl)-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one;
- 3-[(1-{[(3*R*,4*R*)-1-(3,3-dimethylbutanoyl)-3-phenylpiperidin-4-yl]carbonyl}-4-hydroxypiperidin-4-yl)methyl]-7-phenyl-3,7-dihydro-4*H*-pyrrolo[2,3-*d*]pyrimidin-4-one.
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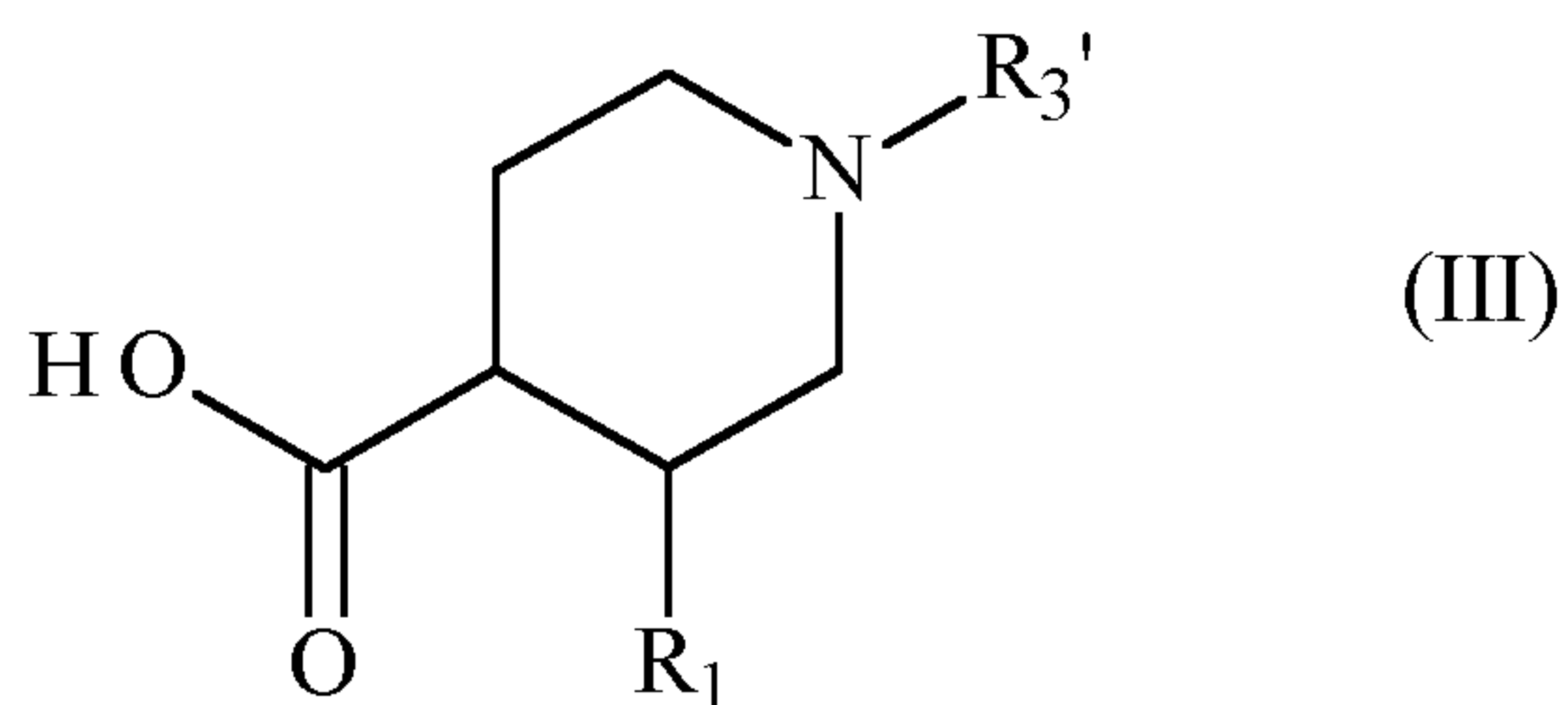
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12. Process for the preparation of a compound of formula (I) according to claim 1, characterised in that there is used as starting material the compound of formula (II):



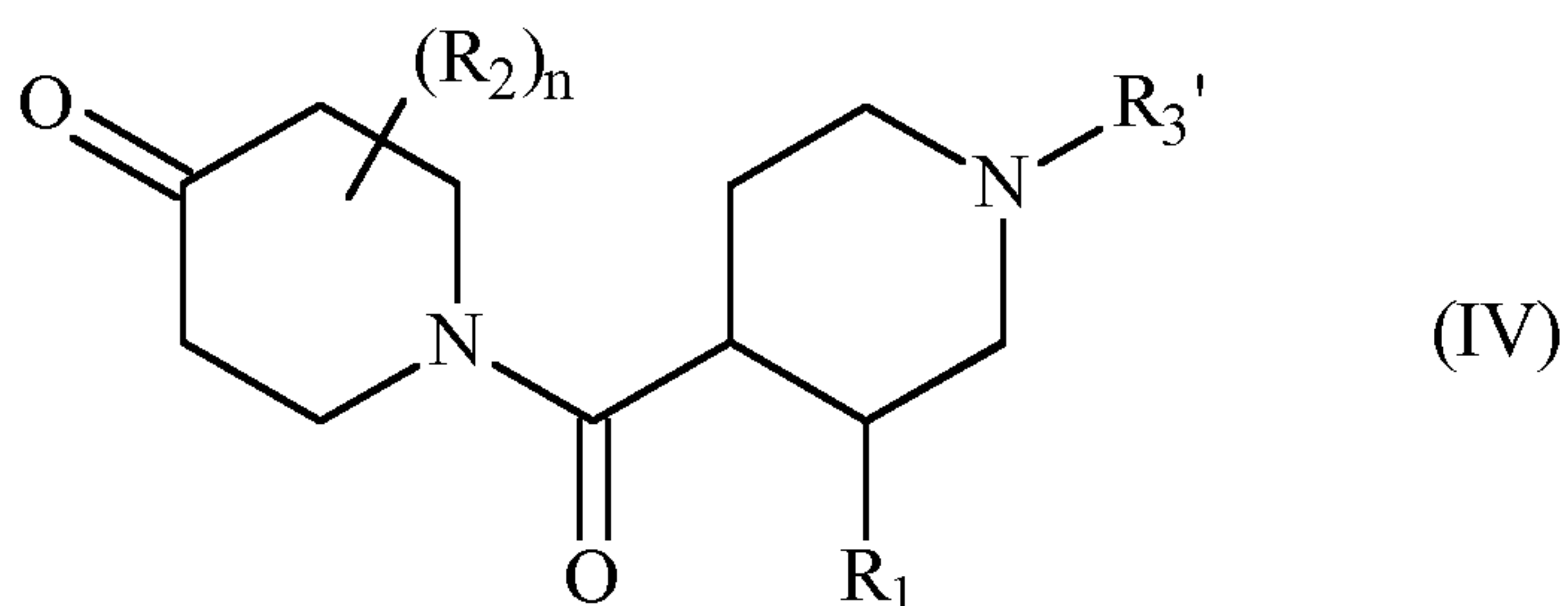
wherein R_2 and n are as defined for formula (I),

- 5 which is subjected to coupling with a compound of formula (III):



wherein R_1 is as defined for formula (I), and R_3' represents a $-C(O)-OR_8$ group wherein R_8 is as defined for formula (I),

to yield the compound of formula (IV):

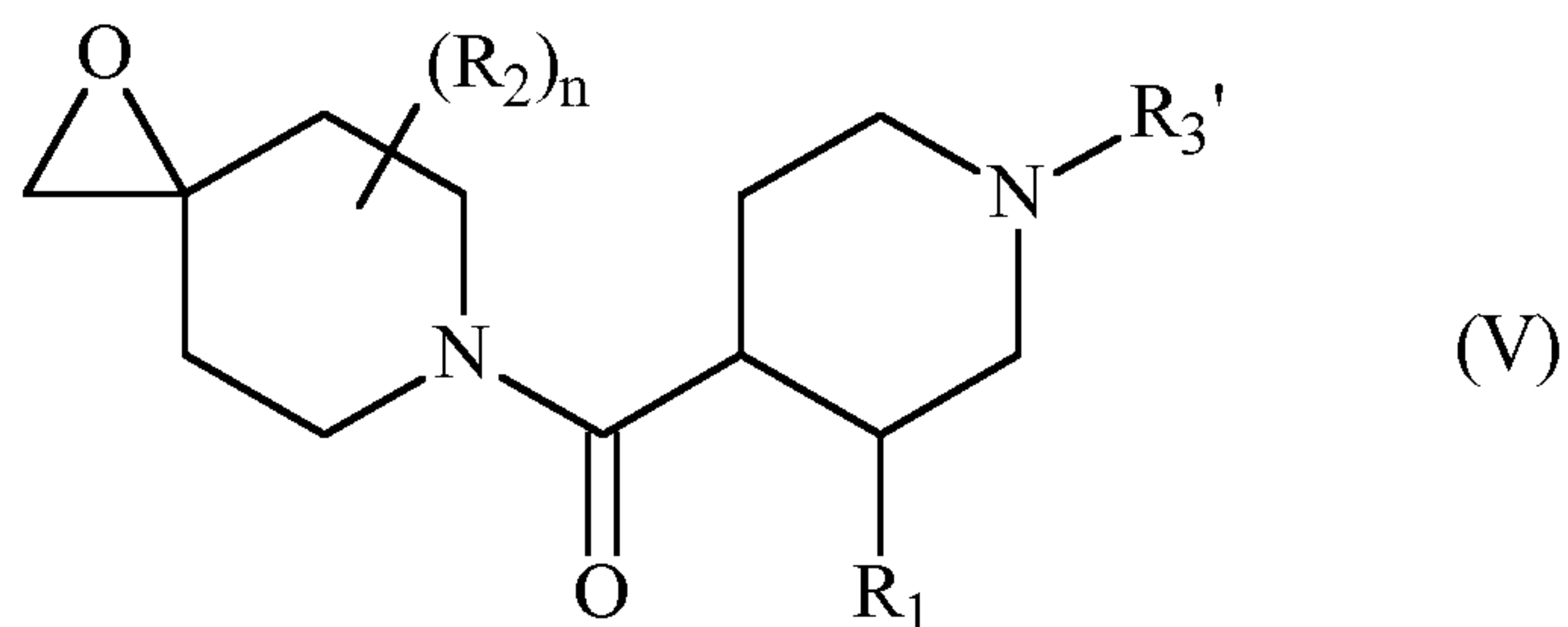


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wherein R_1 , R_2 , R_3' and n are as defined hereinbefore,

compound of formula (IV) which is further converted to an epoxide compound of formula (V):

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wherein R_1 , R_2 , R_3' and n are as defined hereinbefore,

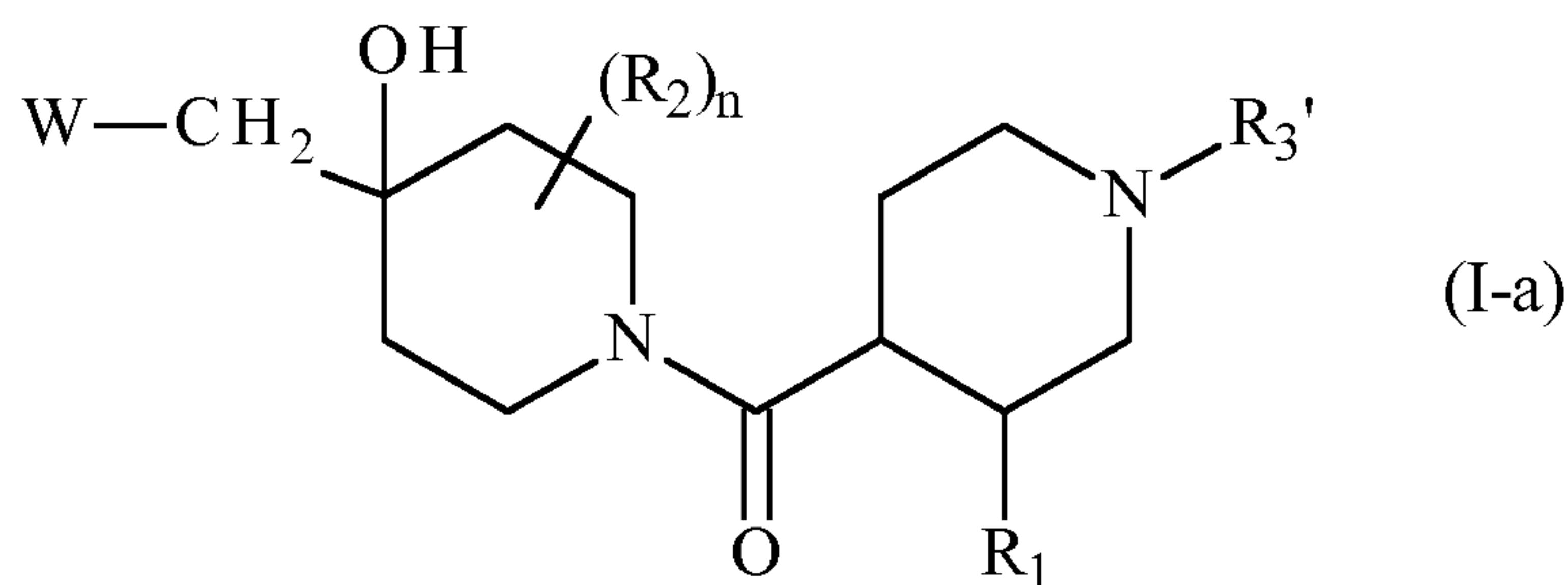
compound of formula (V) which is further subjected to coupling with compound of formula (VI):



5

wherein W is as defined for formula (I),

to yield the compound of formula (I-a), a particular case of the compounds of formula (I):



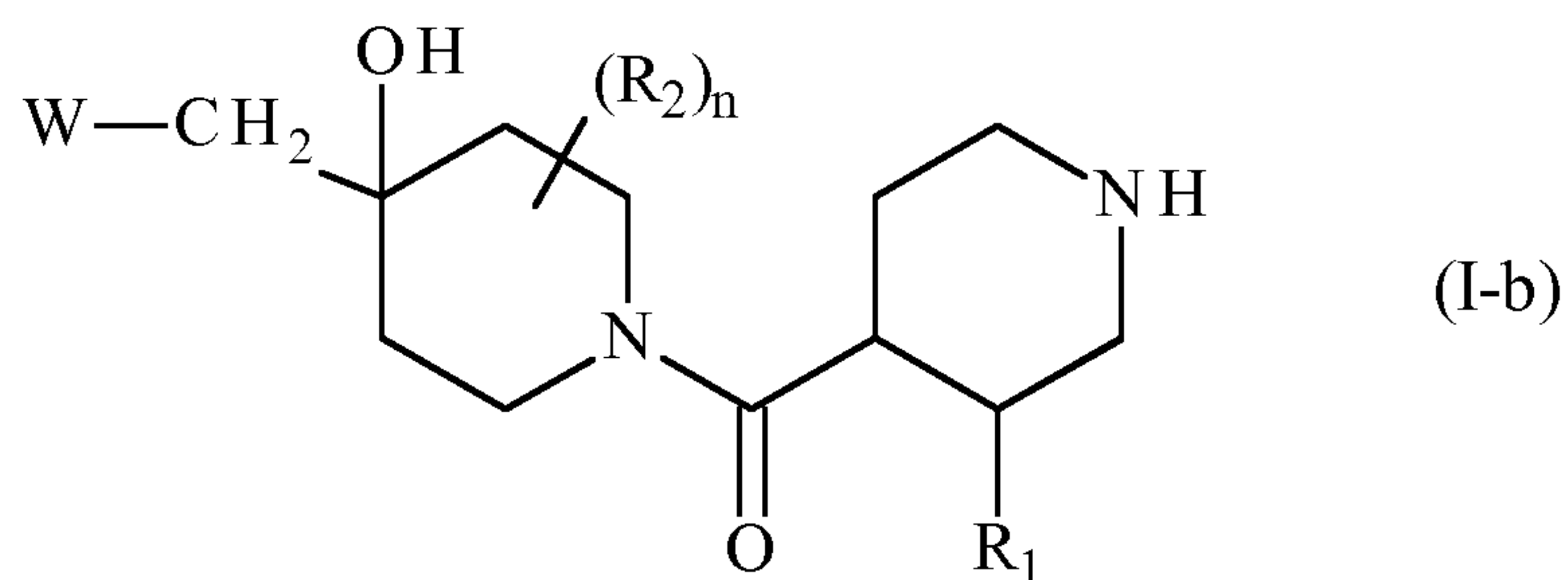
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wherein R_1 , R_2 , R_3' , n and W are as defined hereinbefore,

which compound of formula (I/a) may then, if required, be subjected to a reaction removing the R_3' group,

to yield the compound of formula (I-b), a particular case of the compounds of formula (I):

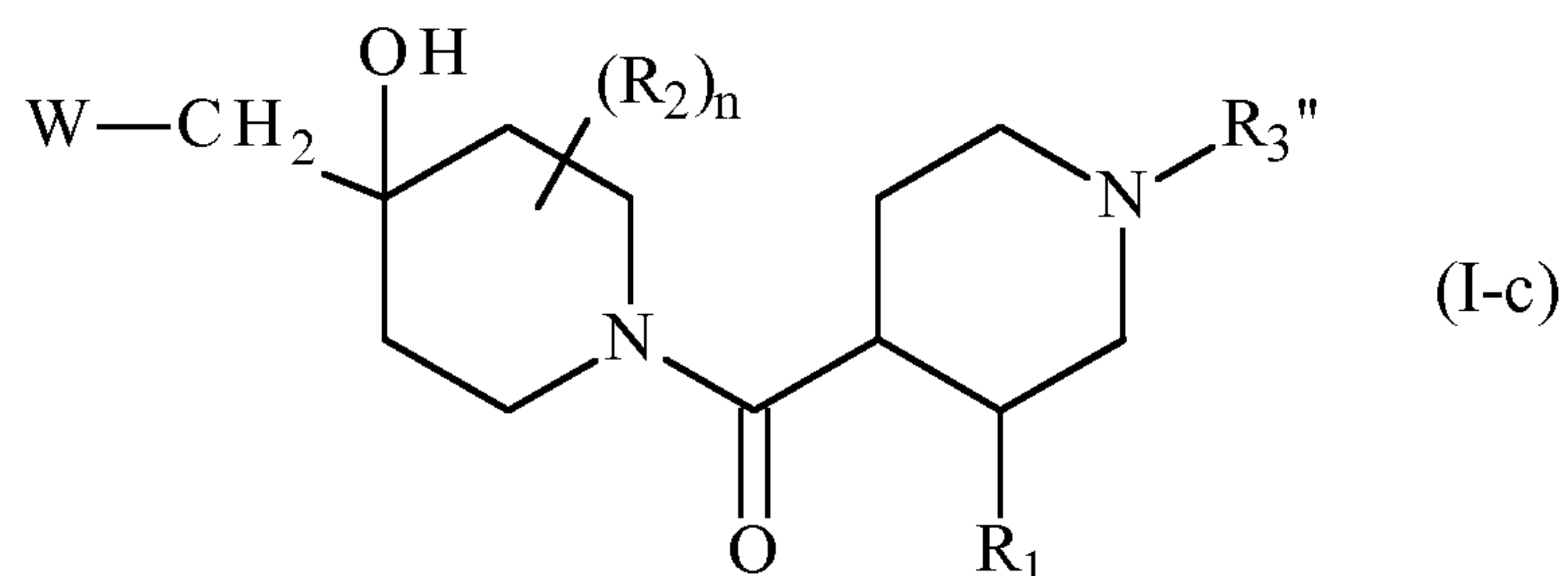
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wherein R_1 , R_2 , n and W are as defined hereinbefore,

which compound of formula (I/b) may then, if required, be subjected to a coupling reaction with compound of formula $R_3''\text{-Cl}$ wherein R_3'' represents a linear or branched ($C_1\text{-}C_6$)alkyl group, a linear or branched halo($C_1\text{-}C_6$)alkyl, or a $\text{-C(O)-}R_8$ group wherein R_8 is as defined for formula (I),

to yield the compound of formula (I-c), a particular case of the compounds of formula (I):



wherein R_1 , R_2 , R_3'' , n and W are as defined hereinbefore,

which compounds of formulae (I/a) to (I/c), which constitute the totality of the compounds of formula (I), may then be purified according to a conventional separation technique, which is converted, if desired, into its addition salts with a pharmaceutically acceptable acid or base and which is optionally separated into its isomers according to a conventional separation technique,

it being understood that at any moment considered appropriate during the course of the process described above, some groups (hydroxy, amino...) of the starting reagents or of the synthesis intermediates can be protected, subsequently deprotected and functionalized, as required by the synthesis.

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13. Pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 11 or an addition salt thereof with a pharmaceutically acceptable acid or base in combination with one or more pharmaceutically acceptable excipients.
- 5 14. Pharmaceutical composition according to claim 13 for use as pro-apoptotic and/or anti-proliferative agents.
15. Pharmaceutical composition according to claim 14 for use in the treatment of cancers and of auto-immune and immune system diseases.
- 10 16. Pharmaceutical composition according to claim 15 for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukemia, cancer of the colon, esophagus and liver, lymphoblastic leukemia, acute myeloid leukemia, lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer, pancreatic cancer and small-cell lung cancer.
- 15 17. Use of a pharmaceutical composition according to claim 13 in the manufacture of medicaments for use as pro-apoptotic and/or anti-proliferative agents.
18. Use of a pharmaceutical composition according to claim 13 in the manufacture of medicaments for use in the treatment of cancers and of auto-immune and immune system diseases.
- 20 19. Use of a pharmaceutical composition according to claim 13 in the manufacture of medicaments for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukemia, cancer of the colon, esophagus and liver, lymphoblastic leukemia, acute myeloid leukemia, lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer, pancreatic cancer and small-cell lung cancer.
20. Compound of formula (I) according to any one of claims 1 to 11 , or an addition salt

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thereof with a pharmaceutically acceptable acid or base, for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukemia, cancer of the colon, esophagus and liver, lymphoblastic leukemia, acute myeloid leukemia, lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer, pancreatic cancer and small-cell lung cancer.

21. Use of a compound of formula (I) according to any one of claims 1 to 11 or an addition salt thereof with a pharmaceutically acceptable acid or base, in the manufacture of medicaments for use in the treatment of cancers of the bladder, brain, breast and uterus, chronic lymphoid leukemia, cancer of the colon, esophagus and liver, lymphoblastic leukemia, acute myeloid leukemia, lymphomas, melanomas, malignant haemopathies, myelomas, ovarian cancer, non-small-cell lung cancer, prostate cancer, pancreatic cancer and small-cell lung cancer.

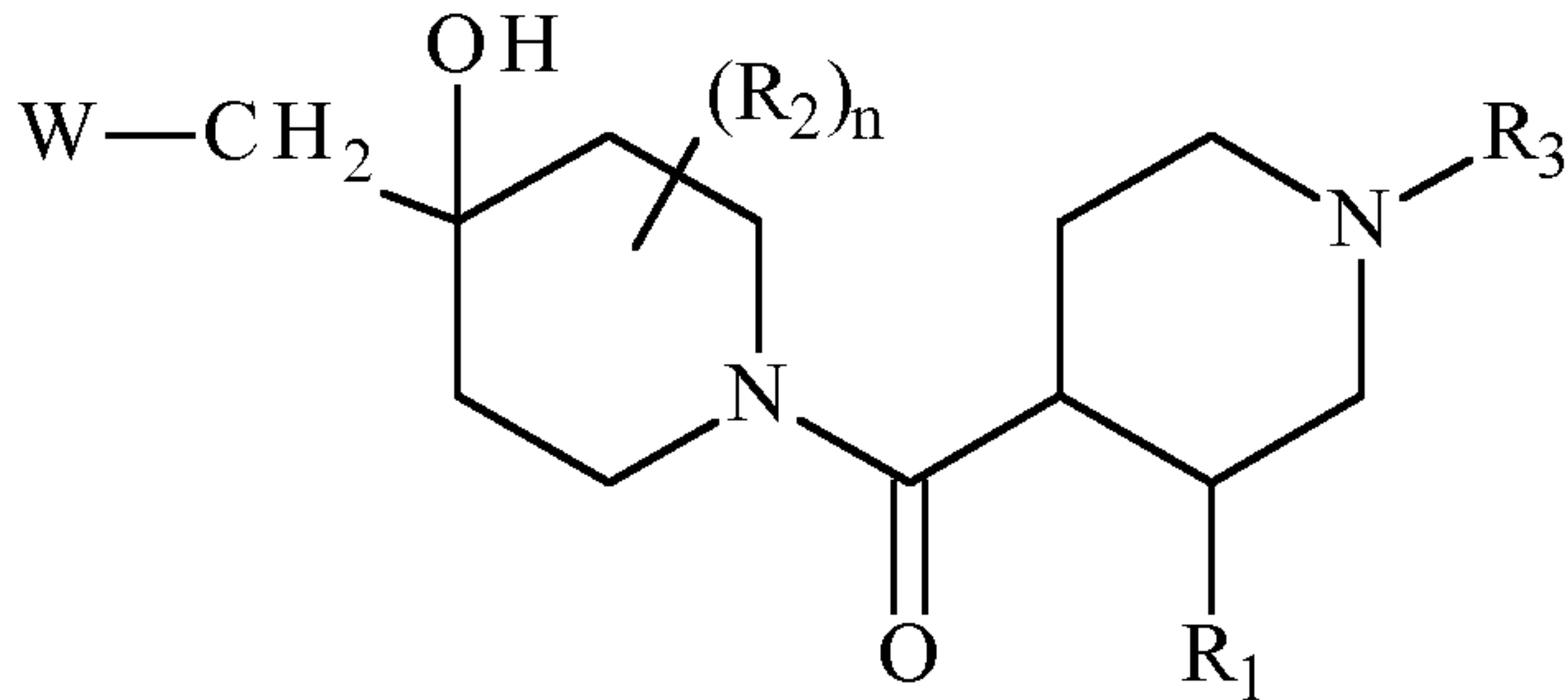
22. Combination of a compound of formula (I) according to any one of claims 1 to 11 with anti-cancer agents selected from genotoxic agents, mitotic poisons, anti-metabolites, proteasome inhibitors, kinase inhibitors, protein-protein interaction inhibitors, immunomodulators, E3 ligase inhibitors, chimeric antigen receptor T-cell therapy and antibodies.

23. Pharmaceutical composition comprising a combination according to claim 22 in combination with one or more pharmaceutically acceptable excipients.

24. Combination according to claim 22 for use in the treatment of cancers.

25. Use of a combination according to claim 22 in the manufacture of medicaments for use in the treatment of cancers.

26. Compound of formula (I) according to any one of claims 1 to 11 for use in the treatment of cancers requiring radiotherapy.



(I)