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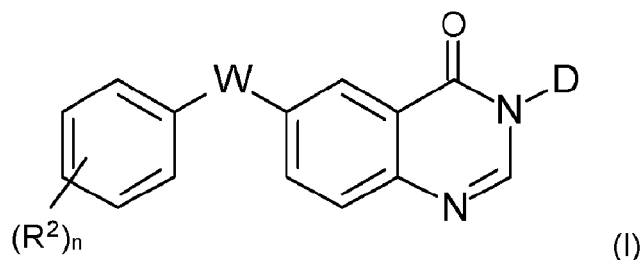
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(54) Title: QUINAZOLINONE DERIVATIVES USEFUL AS FGFR KINASE MODULATORS



(57) Abstract: The invention relates to new quinazolinone derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

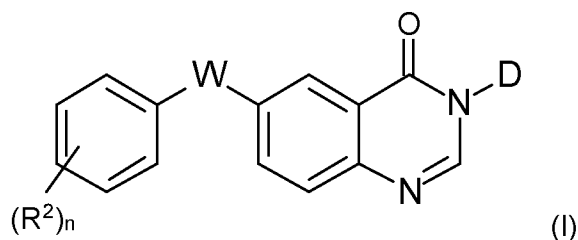
## QUINAZOLINONE DERIVATIVES USEFUL AS FGFR KINASE MODULATORS

### FIELD OF THE INVENTION

The invention relates to new quinazolinone derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

### SUMMARY OF THE INVENTION

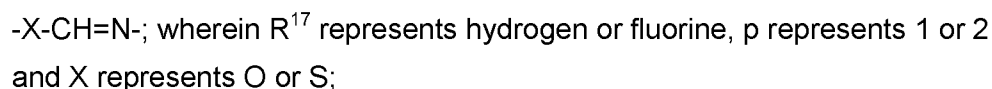
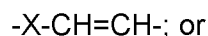
According to a first aspect of the invention there is provided compounds of formula (I):



including any tautomeric or stereochemically isomeric form thereof, wherein

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-;

each R<sup>2</sup> is independently selected from hydroxyl, halogen, cyano, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, hydroxyC<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkoxy, haloC<sub>1-4</sub>alkyl, haloC<sub>1-4</sub>alkoxy, hydroxyhaloC<sub>1-4</sub>alkyl, hydroxyhaloC<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, haloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl wherein each C<sub>1-4</sub>alkyl may optionally be substituted with one or two hydroxyl groups, hydroxyhaloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, R<sup>13</sup>, C<sub>1-4</sub>alkyl substituted with R<sup>13</sup>, C<sub>1-4</sub>alkyl substituted with -C(=O)-R<sup>13</sup>, C<sub>1-4</sub>alkoxy substituted with R<sup>13</sup>, C<sub>1-4</sub>alkoxy substituted with -C(=O)-R<sup>13</sup>, -C(=O)-R<sup>13</sup>, C<sub>1-4</sub>alkyl substituted with -NR<sup>7</sup>R<sup>8</sup>, C<sub>1-4</sub>alkyl substituted with -C(=O)-NR<sup>7</sup>R<sup>8</sup>, C<sub>1-4</sub>alkoxy substituted with -NR<sup>7</sup>R<sup>8</sup>, C<sub>1-4</sub>alkoxy substituted with -C(=O)-NR<sup>7</sup>R<sup>8</sup>, -NR<sup>7</sup>R<sup>8</sup> and -C(=O)-NR<sup>7</sup>R<sup>8</sup>; or when two R<sup>2</sup> groups are attached to adjacent carbon atoms they may be taken together to form a radical of formula:



D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

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R<sup>1</sup> represents hydrogen, halo, cyano, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>4</sup>R<sup>5</sup>, -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -C(=O)-C<sub>1-6</sub>alkyl-NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, -C(=O)-R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>6</sup>, hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -Si(CH<sub>3</sub>)<sub>3</sub>, C<sub>1-6</sub>alkyl substituted with -P(=O)(OH)<sub>2</sub> or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>;

20 R<sup>3a</sup> represents -NR<sup>10</sup>R<sup>11</sup>, hydroxyl, C<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxy substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, hydroxyC<sub>2-6</sub>alkenyl, hydroxyC<sub>2-6</sub>alkynyl, hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl-O-C(=O)-, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl-C(=O)-, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups or with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl substituted with C<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkynyl substituted with C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, C<sub>2-6</sub>alkenyl substituted with R<sup>9</sup>, C<sub>2-6</sub>alkynyl substituted with R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>2-6</sub>alkenyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>2-6</sub>alkynyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl,

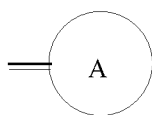
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$-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2-\text{haloC}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^{12}-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{haloC}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^{12}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{R}^{13}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OH})_2$  or  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OC}_{1-6}\text{alkyl})_2$ ;

$\text{R}^{3b}$  represents hydrogen or hydroxyl; provided that if  $\text{R}^{3a}$  represents  $-\text{NR}^{10}\text{R}^{11}$ , then  $\text{R}^{3b}$  represents hydrogen; or

$\text{R}^{3a}$  and  $\text{R}^{3b}$  are taken together to form  $=\text{O}$ , to form  $=\text{NR}^{10}$ , to form cyclopropyl together with the carbon atom to which they are attached, to form  $=\text{CH}-\text{C}_{0-4}$ alkyl substituted with



$\text{R}^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano,  $\text{C}_{1-4}$ alkyl, hydroxy $\text{C}_{1-4}$ alkyl,  $\text{H}_2\text{N}-\text{C}_{1-4}$ alkyl,  $(\text{C}_{1-4}\text{alkyl})\text{NH}-\text{C}_{1-4}$ alkyl,  $(\text{C}_{1-4}\text{alkyl})_2\text{N}-\text{C}_{1-4}$ alkyl,  $(\text{haloC}_{1-4}\text{alkyl})\text{NH}-\text{C}_{1-4}$ alkyl,  $\text{C}_{1-4}$ alkoxy $\text{C}_{1-4}$ alkyl,  $-\text{C}(=\text{O})-\text{NH}_2$ ,  $-\text{C}(=\text{O})-\text{NH}(\text{C}_{1-4}\text{alkyl})$ ,  $-\text{C}(=\text{O})-\text{N}(\text{C}_{1-4}\text{alkyl})_2$ ;

$\text{R}^{3c}$  represents hydrogen, hydroxyl,  $\text{C}_{1-6}$ alkoxy,  $\text{R}^9$ ,  $-\text{NR}^{10}\text{R}^{11}$ ,  $-\text{C}(=\text{O})-\text{NR}^{14}\text{R}^{15}$ , cyano,  $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl or  $-\text{CH}(\text{OH})-\text{C}_{1-6}$ alkyl;

$\text{R}^3$  represents hydroxyl,  $\text{C}_{1-6}$ alkoxy, hydroxy $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ alkoxy substituted with  $-\text{NR}^{10}\text{R}^{11}$ ,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkenyl,  $\text{C}_{2-6}$ alkynyl, halo $\text{C}_{1-6}$ alkyl optionally substituted with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, hydroxy $\text{C}_{1-6}$ alkyl optionally substituted with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, hydroxy $\text{C}_{2-6}$ alkenyl, hydroxy $\text{C}_{2-6}$ alkynyl, hydroxyhalo $\text{C}_{1-6}$ alkyl, cyano $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with carboxyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{O}-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl- $\text{O}-\text{C}(=\text{O})-$ ,  $\text{C}_{1-6}$ alkyl substituted with  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl- $\text{C}(=\text{O})-$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl wherein each  $\text{C}_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups or with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{2-6}$ alkenyl substituted with  $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ alkyl substituted with  $\text{R}^9$  and optionally substituted with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{R}^9$ ,  $\text{C}_{1-6}$ alkyl substituted with hydroxyl and  $\text{R}^9$ ,  $\text{C}_{2-6}$ alkenyl substituted with  $\text{R}^9$ ,  $\text{C}_{2-6}$ alkynyl substituted with  $\text{R}^9$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^{10}\text{R}^{11}$ ,  $\text{C}_{2-6}$ alkenyl substituted with  $-\text{NR}^{10}\text{R}^{11}$ ,  $\text{C}_{2-6}$ alkynyl substituted with  $-\text{NR}^{10}\text{R}^{11}$ ,  $\text{C}_{1-6}$ alkyl substituted with

- hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $-C_{1-6}$ alkyl- $C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}$ alkyl substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}$ alkyl substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;
- 10  $R^4$  and  $R^5$  each independently represent hydrogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^{14}R^{15}$ , hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ ,  $-C(=O)-NR^{14}R^{15}$ ,  $-C(=O)-O-C_{1-6}alkyl$ ,  $-C(=O)-R^{13}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$  or  $C_{1-6}alkyl$  substituted with  $R^{13}$ ;
- 15  $R^6$  represents  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S; said  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl, optionally and each independently being substituted by 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from cyano,  $C_{1-6}$ alkyl, cyano $C_{1-6}$ alkyl, hydroxyl, carboxyl, hydroxy $C_{1-6}$ alkyl, halogen, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl,  $C_{1-6}alkyl-O-C(=O)-$ ,  $-NR^{14}R^{15}$ ,  $-C(=O)-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-NR^{14}R^{15}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}alkyl$  or  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-NR^{14}R^{15}$ ;
- 20  $R^7$  and  $R^8$  each independently represent hydrogen,  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl or  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl;

R<sup>9</sup> represents C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl each optionally and each independently being substituted with 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from =O, C<sub>1-4</sub>alkyl, hydroxyl, carboxyl, hydroxyC<sub>1-4</sub>alkyl, cyano, cyanoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl-O-C(=O)-, C<sub>1-4</sub>alkyl substituted with C<sub>1-4</sub>alkyl-O-C(=O)-, C<sub>1-4</sub>alkyl-C(=O)-, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl wherein each C<sub>1-4</sub>alkyl may optionally be substituted with one or two hydroxyl groups, halogen, haloC<sub>1-4</sub>alkyl, hydroxyhaloC<sub>1-4</sub>alkyl, -NR<sup>14</sup>R<sup>15</sup>, -C(=O)-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-4</sub>alkyl substituted with -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-4</sub>alkyl substituted with -C(=O)-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-4</sub>alkoxy, -S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-4</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-4</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-4</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>13</sup>, -C(=O)-R<sup>13</sup>, C<sub>1-4</sub>alkyl substituted with R<sup>13</sup>, phenyl optionally substituted with R<sup>16</sup>, phenylC<sub>1-6</sub>alkyl wherein the phenyl is optionally substituted with R<sup>16</sup>, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with R<sup>16</sup>; or when two of the substituents of R<sup>9</sup> are attached to the same atom, they may be taken together to form a 4 to 7-membered saturated monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen, carboxyl, C<sub>1-6</sub>alkyl, cyanoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>14</sup>R<sup>15</sup>, haloC<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, -C(=O)-R<sup>6</sup>, -C(=O)-C<sub>1-6</sub>alkyl, -C(=O)-hydroxyC<sub>1-6</sub>alkyl, -C(=O)-haloC<sub>1-6</sub>alkyl, -C(=O)-hydroxyhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -Si(CH<sub>3</sub>)<sub>3</sub>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with carboxyl, or C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>12</sup> represents hydrogen or C<sub>1-4</sub>alkyl optionally substituted with C<sub>1-4</sub>alkoxy;

R<sup>13</sup> represents C<sub>3-8</sub>cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said C<sub>3-8</sub>cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, =O, cyano, -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, or -NR<sup>14</sup>R<sup>15</sup>;

R<sup>14</sup> and R<sup>15</sup> each independently represent hydrogen, or haloC<sub>1-4</sub>alkyl, or C<sub>1-4</sub>alkyl optionally substituted with a substituent selected from hydroxyl, C<sub>1-4</sub>alkoxy, amino or mono-or di(C<sub>1-4</sub>alkyl)amino;

R<sup>16</sup> represents hydroxyl, halogen, cyano, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, -NR<sup>14</sup>R<sup>15</sup> or -C(=O)NR<sup>14</sup>R<sup>15</sup>;

n independently represents an integer equal to 0, 1, 2, 3 or 4;

the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

WO2012/118492, WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO2004/030635, WO2008/141065, WO2011/026579, WO2011/028947, WO2007/003419, WO00/42026, WO2012/154760, WO2011/047129, WO2003/076416, WO2002/096873, WO2000/055153, EP548934, US4166117, WO2011/135376 and WO2012/073017 which each disclose a series of heterocyclyl derivatives.

## DETAILED DESCRIPTION OF THE INVENTION

Unless the context indicates otherwise, references to formula (I) in all sections of this document (including the uses, methods and other aspects of the invention) include references to all other sub-formula (e.g. Ia), sub-groups, preferences, embodiments and examples as defined herein.

The prefix "C<sub>x-y</sub>" (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C<sub>1-6</sub>alkyl group contains from 1 to 6 carbon atoms, a C<sub>3-6</sub>cycloalkyl group contains from 3 to 6 carbon atoms, a C<sub>1-4</sub>alkoxy group contains from 1 to 4 carbon atoms, and so on.

The term 'halo' or 'halogen' as used herein refers to a fluorine, chlorine, bromine or iodine atom.

The term 'C<sub>1-4</sub>alkyl', or 'C<sub>1-6</sub>alkyl' as used herein as a group or part of a group refers to a linear or branched saturated hydrocarbon group containing from 1 to 4 or 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl or hexyl and the like.

The term 'C<sub>2-4</sub>alkenyl' or 'C<sub>2-6</sub>alkenyl' as used herein as a group or part of a group refers to a linear or branched hydrocarbon group containing from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon double bond.

The term 'C<sub>2-4</sub>alkynyl' or 'C<sub>2-6</sub>alkynyl' as used herein as a group or part of a group refers to a linear or branched hydrocarbon group having from 2 to 4 or 2 to 6 carbon atoms and containing a carbon carbon triple bond.

The term 'C<sub>1-4</sub>alkoxy' or 'C<sub>1-6</sub>alkoxy' as used herein as a group or part of a group refers to an -O-C<sub>1-4</sub>alkyl group or an -O-C<sub>1-6</sub>alkyl group wherein C<sub>1-4</sub>alkyl and C<sub>1-6</sub>alkyl are as defined herein. Examples of such groups include methoxy, ethoxy, propoxy, butoxy, and the like.

The term 'C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl' or 'C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl' as used herein as a group or part of a group refers to a C<sub>1-4</sub>alkyl-O-C<sub>1-4</sub>alkyl group or a C<sub>1-6</sub>alkyl-O-C<sub>1-6</sub>alkyl group wherein C<sub>1-4</sub>alkyl and C<sub>1-6</sub>alkyl are as defined herein. Examples of such groups include methoxyethyl, ethoxyethyl, propoxymethyl, butoxypropyl, and the like.

The term 'C<sub>3-8</sub>cycloalkyl' as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl and the like.

The term 'C<sub>3-8</sub>cycloalkenyl' as used herein refers to a monocyclic hydrocarbon ring of 3 to 8 carbon atoms having a carbon carbon double bond.

The term 'hydroxyC<sub>1-4</sub>alkyl' or 'hydroxyC<sub>1-6</sub>alkyl' as used herein as a group or part of a group refers to a C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a hydroxyl group. The terms 'hydroxyC<sub>1-4</sub>alkyl' or

'hydroxyC<sub>1-6</sub>alkyl' therefore include monohydroxyC<sub>1-4</sub>alkyl, monohydroxyC<sub>1-6</sub>alkyl and also polyhydroxyC<sub>1-4</sub>alkyl and polyhydroxyC<sub>1-6</sub>alkyl. There may be one, two, three or more hydrogen atoms replaced with a hydroxyl group, so the hydroxyC<sub>1-4</sub>alkyl or hydroxyC<sub>1-6</sub>alkyl may have one, two, three or more hydroxyl groups. Examples of such groups include hydroxymethyl, hydroxyethyl, hydroxypropyl and the like.

The term 'haloC<sub>1-4</sub>alkyl' or 'haloC<sub>1-6</sub>alkyl' as used herein as a group or part of a group refers to a C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a halogen. The term 'haloC<sub>1-4</sub>alkyl' or 'haloC<sub>1-6</sub>alkyl' therefore include monohaloC<sub>1-4</sub>alkyl, monohaloC<sub>1-6</sub>alkyl and also polyhaloC<sub>1-4</sub>alkyl and polyhaloC<sub>1-6</sub>alkyl. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC<sub>1-4</sub>alkyl or haloC<sub>1-6</sub>alkyl may have one, two, three or more halogens. Examples of such groups include fluoroethyl, fluoromethyl, trifluoromethyl or trifluoroethyl and the like.

The term 'hydroxyhaloC<sub>1-4</sub>alkyl' or 'hydroxyhaloC<sub>1-6</sub>alkyl' as used herein as a group or part of a group refers to a C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group as defined herein wherein one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The term 'hydroxyhaloC<sub>1-4</sub>alkyl' or 'hydroxyhaloC<sub>1-6</sub>alkyl' therefore refers to a C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group wherein one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen.

The term 'hydroxyC<sub>1-4</sub>alkoxy' or 'hydroxyC<sub>1-6</sub>alkoxy' as used herein as a group or part of a group refers to an -O-C<sub>1-4</sub>alkyl group or an -O-C<sub>1-6</sub>alkyl group wherein the C<sub>1-4</sub>alkyl and C<sub>1-6</sub>alkyl group is as defined above and one or more than one hydrogen atom of the C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group is replaced with a hydroxyl group. The term 'hydroxyC<sub>1-4</sub>alkoxy' or 'hydroxyC<sub>1-6</sub>alkoxy' therefore include monohydroxyC<sub>1-4</sub>alkoxy, monohydroxyC<sub>1-6</sub>alkoxy and also polyhydroxyC<sub>1-4</sub>alkoxy and polyhydroxyC<sub>1-6</sub>alkoxy. There may be one, two, three or more hydrogen atoms replaced with a hydroxyl group so the hydroxyC<sub>1-4</sub>alkoxy or hydroxyC<sub>1-6</sub>alkoxy may have one, two, three or more hydroxyl groups. Examples of such groups include hydroxymethoxy, hydroxyethoxy, hydroxypropoxy and the like.

The term 'haloC<sub>1-4</sub>alkoxy' or 'haloC<sub>1-6</sub>alkoxy' as used herein as a group or part of a group refers to a -O-C<sub>1-4</sub>alkyl group or a -O-C<sub>1-6</sub>alkyl group as defined herein wherein one or

more than one hydrogen atom is replaced with a halogen. The terms 'haloC<sub>1-4</sub>alkoxy' or 'haloC<sub>1-6</sub>alkoxy' therefore include monohaloC<sub>1-4</sub>alkoxy, monohaloC<sub>1-6</sub>alkoxy and also polyhaloC<sub>1-4</sub>alkoxy and polyhaloC<sub>1-6</sub>alkoxy. There may be one, two, three or more hydrogen atoms replaced with a halogen, so the haloC<sub>1-4</sub>alkoxy or haloC<sub>1-6</sub>alkoxy may have one, two, three or more halogens. Examples of such groups include fluoroethyloxy, difluoromethoxy or trifluoromethoxy and the like.

The term 'hydroxyhaloC<sub>1-4</sub>alkoxy' as used herein as a group or part of a group refers to an -O-C<sub>1-4</sub>alkyl group wherein the C<sub>1-4</sub>alkyl group is as defined herein and wherein one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The term 'hydroxyhaloC<sub>1-4</sub>alkoxy' therefore refers to a -O-C<sub>1-4</sub>alkyl group wherein one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen.

The term 'haloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl' as used herein as a group or part of a group refers to a C<sub>1-4</sub>alkyl-O-C<sub>1-4</sub>alkyl group wherein C<sub>1-4</sub>alkyl is as defined herein and wherein in one or both of the C<sub>1-4</sub>alkyl groups one or more than one hydrogen atom is replaced with a halogen. The term 'haloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl' therefore refers to a C<sub>1-4</sub>alkyl-O-C<sub>1-4</sub>alkyl group wherein in one or both of the C<sub>1-4</sub>alkyl groups one, two, three or more hydrogen atoms are replaced with a halogen and wherein C<sub>1-4</sub>alkyl is as defined herein. Preferably, in one of the C<sub>1-4</sub>alkyl groups one or more than one hydrogen atom is replaced with a halogen. Preferably, haloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl means C<sub>1-4</sub>alkyl substituted with haloC<sub>1-4</sub>alkoxy.

The term 'hydroxyhaloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl' as used herein refers to a C<sub>1-4</sub>alkyl-O-C<sub>1-4</sub>alkyl group wherein C<sub>1-4</sub>alkyl is as defined herein and wherein in one or both of the C<sub>1-4</sub>alkyl groups one or more than one hydrogen atom is replaced with a hydroxyl group and one or more than one hydrogen atom is replaced with a halogen. The terms 'hydroxyhaloC<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl' therefore refers to a C<sub>1-4</sub>alkyl-O-C<sub>1-4</sub>alkyl group wherein in one or both of the C<sub>1-4</sub>alkyl groups one, two, three or more hydrogen atoms are replaced with a hydroxyl group and one, two, three or more hydrogen atoms are replaced with a halogen and wherein C<sub>1-4</sub>alkyl is as defined herein.

The term 'hydroxyC<sub>2-6</sub>alkenyl' as used herein refers to a C<sub>2-6</sub>alkenyl group wherein one or more than one hydrogen atom is replaced with a hydroxyl group and wherein C<sub>2-6</sub>alkenyl is as defined herein.

- 5 The term 'hydroxyC<sub>2-6</sub>alkynyl' as used herein refers to a C<sub>2-6</sub>alkynyl group wherein one or more than one hydrogen atom is replaced with a hydroxyl group and wherein C<sub>2-6</sub>alkynyl is as defined herein.

10 The term 'phenylC<sub>1-6</sub>alkyl' as used herein refers to a C<sub>1-6</sub>alkyl group as defined herein which is substituted with one phenyl group.

The term 'cyanoC<sub>1-4</sub>alkyl' or 'cyanoC<sub>1-6</sub>alkyl' as used herein refers to a C<sub>1-4</sub>alkyl or C<sub>1-6</sub>alkyl group as defined herein which is substituted with one cyano group.

- 15 The term "heterocyclyl" as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. Thus, for example, the term "heterocyclyl group" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated heterocyclyl ring systems. In general, unless the context indicates otherwise, such groups may be monocyclic or bicyclic and may
- 20 contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Reference to 4 to 7 ring members include 4, 5, 6 or 7 atoms in the ring and reference to 4 to 6 ring members include 4, 5, or 6 atoms in the ring. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7 and 8 ring members, more usually 3 to 7, and preferably 5, 6 or 7 ring members, more preferably 5 or 6 ring members. Examples of
- 25 bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members. Where reference is made herein to heterocyclyl groups, the heterocyclyl ring can, unless the context indicates otherwise, be optionally substituted (i.e. unsubstituted or substituted) by one or more substituents as discussed herein.
- 30 The heterocyclyl groups can be heteroaryl groups having from 5 to 12 ring members, more usually from 5 to 10 ring members. The term "heteroaryl" is used herein to denote a heterocyclyl group having aromatic character. The term "heteroaryl" embraces polycyclic (e.g. bicyclic) ring systems wherein one or more rings are non-aromatic, provided that at least one ring is aromatic. In such polycyclic systems, the group may
- 35 be attached by the aromatic ring, or by a non-aromatic ring.



Examples of heteroaryl groups are monocyclic and bicyclic groups containing from five to twelve ring members, and more usually from five to ten ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings, or two fused five membered rings. Each ring may contain up to about five heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of five membered heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole, furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, thiadiazole, isothiazole, pyrazole, triazole and tetrazole groups.

Examples of six membered heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine.

A bicyclic heteroaryl group may be, for example, a group selected from:

- a) a benzene ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms;
- b) a pyridine ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- c) a pyrimidine ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- d) a pyrrole ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- e) a pyrazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- f) an imidazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- g) an oxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;

- h) an isoxazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- i) a thiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- 5 j) an isothiazole ring fused to a 5- or 6-membered ring containing 0, 1 or 2 ring heteroatoms;
- k) a thiophene ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- l) a furan ring fused to a 5- or 6-membered ring containing 0, 1, 2 or 3 ring heteroatoms;
- 10 m) a cyclohexyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms; and
- n) a cyclopentyl ring fused to a 5- or 6-membered ring containing 1, 2 or 3 ring heteroatoms.

15 Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole (e.g. imidazo[2,1-b]thiazole) and imidazoimidazole (e.g. imidazo[1,2-a]imidazole).

20 Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, indolizine, indoline, isoindoline, purine (e.g., adenine, guanine), indazole, pyrazolopyrimidine (e.g. pyrazolo[1,5-a]pyrimidine),  
 25 triazolopyrimidine (e.g. [1,2,4]triazolo[1,5-a]pyrimidine), benzodioxole, imidazopyridine and pyrazolopyridine (e.g. pyrazolo[1,5-a]pyridine) groups.

Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman,  
 30 chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups.

Examples of polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include, tetrahydroisoquinoline, tetrahydroquinoline, dihydrobenzthiene,  
 35 dihydrobenzfuran, 2,3-dihydro-benzo[1,4]dioxine, benzo[1,3]dioxole, 4,5,6,7-

tetrahydrobenzofuran, tetrahydrotriazolopyrazine (e.g. 5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine), indoline and indane groups.

A nitrogen-containing heteroaryl ring must contain at least one ring nitrogen atom. Each ring may, in addition, contain up to about four other heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 3 heteroatoms, for example 1, 2 or 3, more usually up to 2 nitrogens, for example a single nitrogen. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five.

Examples of nitrogen-containing heteroaryl groups include, but are not limited to, pyridyl, pyrrolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, furazanyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), tetrazolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzoxazolyl, benzisoxazole, benzthiazolyl and benzisothiazole, indolyl, 3H-indolyl, isoindolyl, indoliziny, isoindoliny, purinyl (e.g., adenine [6-aminopurine], guanine [2-amino-6-hydroxypurine]), indazolyl, quinoliziny, benzoxazinyl, benzodiazinyl, pyridopyridinyl, quinoxaliny, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

Examples of nitrogen-containing polycyclic heteroaryl groups containing an aromatic ring and a non-aromatic ring include tetrahydroisoquinolinyl, tetrahydroquinolinyl, and indolinyl.

The term 'non-aromatic group', 'non-aromatic ring system' or 'non-aromatic ring' embraces, unless the context indicates otherwise, unsaturated ring systems without aromatic character, partially saturated and fully saturated heterocyclyl ring systems.

The terms "unsaturated" and "partially saturated" refer to rings wherein the ring structure(s) contains atoms sharing more than one valence bond i.e. the ring contains at least one multiple bond e.g. a C=C, C≡C or N=C bond. The term "fully saturated" refers to rings where there are no multiple bonds between ring atoms. Saturated heterocyclyl groups include piperidine, morpholine, thiomorpholine, piperazine. Partially saturated heterocyclyl groups include pyrazolines, for example 2-pyrazoline and 3-pyrazoline.

Examples of non-aromatic heterocyclyl groups are groups having from 3 to 12 ring members, more usually 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1, 2, 3 or 4 heteroatom ring members), usually selected from nitrogen, oxygen and sulphur. The heterocyclyl groups can contain, for example, cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic amide moieties (e.g. as in pyrrolidone), cyclic thioamides, cyclic thioesters, cyclic ureas (e.g. as in imidazolidin-2-one) cyclic ester moieties (e.g. as in butyrolactone), cyclic sulphones (e.g. as in sulpholane and sulpholene), cyclic sulfoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Particular examples include morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), piperidone, pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, azetidine, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydro pyranyl), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclyl groups include saturated groups such as piperidine, pyrrolidine, azetidine, morpholine, piperazine and N-alkyl piperazines.

In a nitrogen-containing non-aromatic heterocyclyl ring the ring must contain at least one ring nitrogen atom. The heterocyclic groups can contain, for example cyclic amine moieties (e.g. as in pyrrolidine), cyclic amides (such as a pyrrolidinone, piperidone or caprolactam), cyclic sulphonamides (such as an isothiazolidine 1,1-dioxide, [1,2]thiazinane 1,1-dioxide or [1,2]thiazepane 1,1-dioxide) and combinations thereof. Particular examples of nitrogen-containing non-aromatic heterocyclyl groups include aziridine, morpholine, thiomorpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, dihydrothiazole, imidazoline, imidazolidinone, oxazoline, thiazoline, 6H-1,2,5-thiadiazine, 2-pyrazoline, 3-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine.

The heterocyclyl groups can be polycyclic fused ring systems or bridged ring systems such as the oxa- and aza analogues of bicycloalkanes, tricycloalkanes (e.g.

adamantane and oxa-adamantane). For an explanation of the distinction between fused and bridged ring systems, see *Advanced Organic Chemistry*, by Jerry March, 4<sup>th</sup> Edition, Wiley Interscience, pages 131-133, 1992.

- 5 The heterocyclyl groups can each be unsubstituted or substituted by one or more substituent groups. For example, heterocyclyl groups can be unsubstituted or substituted by 1, 2, 3 or 4 substituents. Where the heterocyclyl group is monocyclic or bicyclic, typically it is unsubstituted or has 1, 2 or 3 substituents.
- 10 The term "carbocyclyl" as used herein shall, unless the context indicates otherwise, include both aromatic and non-aromatic ring systems. Thus, for example, the term "carbocyclyl group" includes within its scope aromatic, non-aromatic, unsaturated, partially saturated and fully saturated carbocyclyl ring systems. In general, unless the context indicates otherwise, such groups may be monocyclic or bicyclic and may
- 15 contain, for example, 3 to 12 ring members, more usually 5 to 10 ring members. Reference to 4 to 7 ring members include 4, 5, 6 or 7 atoms in the ring and reference to 4 to 6 ring members include 4, 5, or 6 atoms in the ring. Examples of monocyclic groups are groups containing 3, 4, 5, 6, 7 and 8 ring members, more usually 3 to 7, and preferably 5, 6 or 7 ring members, more preferably 5 or 6 ring members. Examples of
- 20 bicyclic groups are those containing 8, 9, 10, 11 and 12 ring members, and more usually 9 or 10 ring members. Where reference is made herein to carbocyclyl groups, the carbocyclyl ring can, unless the context indicates otherwise, be optionally substituted (i.e. unsubstituted or substituted) by one or more substituents as discussed herein.
- 25 The term 'carbocyclyl' comprises aryl, C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl.

The term 'aryl' as used herein refers to carbocyclyl aromatic groups including phenyl, naphthyl, indenyl, and tetrahydronaphthyl groups.

- 30 Whenever used hereinbefore or hereinafter that substituents can be selected each independently out of a list of numerous definitions, all possible combinations are intended which are chemically possible. Whenever used hereinbefore or hereinafter that a particular substituent is further substituted with two or more groups, such as for example hydroxyhaloC<sub>1-4</sub>alkyl, hydroxyhaloC<sub>1-4</sub>alkoxy, all possible combinations are
- 35 intended which are chemically possible.

In one embodiment, D represents an aromatic ring.

5 In one embodiment, D represents a 5 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

10 In one embodiment, D represents an aromatic 3 to 12, in particular an aromatic 5 to 12, ring membered monocyclic or bicyclic carbocyclyl or an aromatic 3 to 12, in particular an aromatic 5 to 12, ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

15 In one embodiment, D represents an aromatic 3 to 12 (e.g. 5 to 10) ring membered monocyclic or bicyclic carbocyclyl, wherein said carbocyclyl may be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

20 In one embodiment, D represents phenyl or naphthyl, wherein said phenyl or naphthyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

25 In one embodiment, D represents a 5 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

30 In one embodiment, D represents an aromatic 5 to 12 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl group may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

35 In one embodiment, D represents a 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

In one embodiment, D represents an aromatic 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said

heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

In one embodiment, D represents a 5 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

In one embodiment, D represents a 5 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

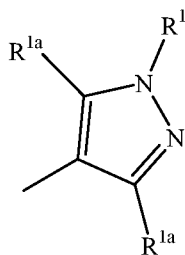
In one embodiment, D represents pyrazolyl (e.g. pyrazol-4yl), wherein said pyrazolyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

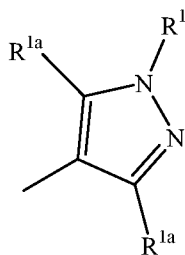
In one embodiment, D represents a 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

In one embodiment, D represents a 6 ring membered monocyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

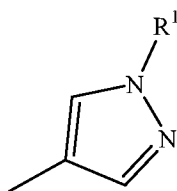
In one embodiment, D represents a 12 ring membered bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.


In one embodiment, D represents a 12 ring membered bicyclic aromatic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.



In one embodiment D represents  wherein  $R^1$  represents hydrogen,  $C_{1-6}$ alkyl,  $C_{2-4}$ alkenyl, hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl, cyano $C_{1-4}$ alkyl,

C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>6</sup>, hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -Si(CH<sub>3</sub>)<sub>3</sub>, C<sub>1-6</sub>alkyl substituted with -P(=O)(OH)<sub>2</sub> or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>; and each R<sup>1a</sup> is independently selected from hydrogen, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkyl substituted with amino or mono- or di(C<sub>1-4</sub>alkyl)amino or -NH(C<sub>3-8</sub>cycloalkyl), cyanoC<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, and C<sub>1-4</sub>alkyl substituted with one or more fluoro atoms. In one embodiment R<sup>1a</sup> is independently selected from hydrogen and C<sub>1-4</sub>alkyl. In one embodiment R<sup>1a</sup> is hydrogen.



In one embodiment, D represents  wherein R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>6</sup>, hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -Si(CH<sub>3</sub>)<sub>3</sub>, C<sub>1-6</sub>alkyl substituted with -P(=O)(OH)<sub>2</sub> or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>.

In one embodiment, D is other than pyrazolyl, in particular D is pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, tetrazolyl, oxazolyl, pyrimidinyl, thiadiazolyl, oxadiazolyl, said rings being optionally substituted. Said optional substituents may represent halo, cyano, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, -C(=O)-O-C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl



substituted with  $-NR^4R^5$ ,  $-C(=O)-NR^4R^5$ ,  $-C(=O)-C_{1-6}alkyl-NR^4R^5$ ,  $R^6$ ,  $C_{1-6}alkyl$  substituted with  $R^6$ .

In one embodiment, D is optionally substituted 4-pyrazolyl. In one embodiment, D is 4-pyrazolyl substituted at the 1 position with  $C_{1-6}alkyl$  for example methyl.

In one embodiment, D is 1-pyrazolyl or 2-pyrazolyl, both may optionally be substituted.

In one embodiment, D is optionally substituted pyrazolyl.

In one embodiment, D is other than pyrazolyl, in particular D is pyridinyl, phenyl, pyrrolyl, imidazolyl, triazolyl, pyrolopyridinyl, 1,3-benzodioxolyl, indolyl, thiazolyl, tetrazolyl, oxazolyl, pyrimidinyl, said rings being optionally substituted.

In one embodiment, D is optionally substituted phenyl.

In one embodiment, D is phenyl.

In one embodiment, D is phenyl or optionally substituted pyrazolyl.

In one embodiment, D is a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl is substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups.

In one embodiment, D is substituted phenyl or substituted pyrazolyl.

In one embodiment, D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl is substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups;  
 $R^1$  represents  $C_{1-4}alkyl$ .

In one embodiment, D is pyrazolyl or phenyl, each optionally substituted with  $C_{1-4}alkyl$ ; in particular D is pyrazolyl optionally substituted with  $C_{1-4}alkyl$ .

In one embodiment, D is pyrazolyl or phenyl, each optionally substituted with C<sub>1-4</sub>alkyl; W is -N(R<sup>3</sup>)- or -C(=O)-; R<sup>3</sup> is C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>.

- 5 In one embodiment, D is pyrazolyl or phenyl, each optionally substituted with C<sub>1-4</sub>alkyl; W is -N(R<sup>3</sup>)-; R<sup>3</sup> is C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>.

In one embodiment, D is pyrazolyl optionally substituted with C<sub>1-4</sub>alkyl; W is -N(R<sup>3</sup>)-; R<sup>3</sup> is C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>.

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In one embodiment, D is pyrazolyl substituted with C<sub>1-4</sub>alkyl; W is -N(R<sup>3</sup>)-; R<sup>3</sup> is C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>; R<sup>9</sup> is imidazolyl.

In one embodiment, D is pyrazolyl substituted with C<sub>1-4</sub>alkyl; W is -N(R<sup>3</sup>)-.

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In one embodiment, D represents a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups; W is -N(R<sup>3</sup>)-.

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In one embodiment R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>6</sup>, hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with -Si(CH<sub>3</sub>)<sub>3</sub>, C<sub>1-6</sub>alkyl substituted with -P(=O)(OH)<sub>2</sub> or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>.

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In one embodiment R<sup>1</sup> represents hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with -NR<sup>4</sup>R<sup>5</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>4</sup>R<sup>5</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -

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$S(=O)_2$ -C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NH-S(=O)_2$ -C<sub>1-6</sub>alkyl, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with  $-C(=O)-R^6$ , hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, or C<sub>1-6</sub>alkyl substituted with  $-Si(CH_3)_3$ .

- 5 In one embodiment R<sup>1</sup> represents hydrogen, halo, cyano, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy,  $-C(=O)-O-$  C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with  $-O-C(=O)-$  C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NR^4R^5$ ,  $-C(=O)-C_{1-6}alkyl-NR^4R^5$ , C<sub>1-6</sub>alkyl substituted with  $-C(=O)-$   
 10  $NR^4R^5$ ,  $-S(=O)_2$ -C<sub>1-6</sub>alkyl,  $-S(=O)_2$ -haloC<sub>1-6</sub>alkyl,  $-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with  $-NH-S(=O)_2$ -C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NH-S(=O)_2$ -haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NR^{12}-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>,  $-C(=O)-R^6$ ,  
 15 C<sub>1-6</sub>alkyl substituted with  $-C(=O)-R^6$ , hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl substituted with  $-Si(CH_3)_3$ , C<sub>1-6</sub>alkyl substituted with  $-P(=O)(OH)_2$  or C<sub>1-6</sub>alkyl substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ .

In one embodiment R<sup>1</sup> represents hydrogen.

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In one embodiment R<sup>1</sup> represents C<sub>1-6</sub>alkyl. In one embodiment R<sup>1</sup> represents methyl.

In one embodiment, R<sup>1</sup> is not C<sub>1-6</sub>alkyl substituted with R<sup>6</sup>.

- 25 In one embodiment R<sup>1</sup> represents hydrogen, halo, cyano, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy,  $-C(=O)-O-$  C<sub>1-6</sub>alkyl, C<sub>2-4</sub>alkenyl, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups,  $-NR^4R^5$ , C<sub>1-6</sub>alkyl substituted with  $-O-C(=O)-$  C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NR^4R^5$ ,  $-C(=O)-NR^4R^5$ ,  $-C(=O)-C_{1-6}alkyl-NR^4R^5$ , C<sub>1-6</sub>alkyl substituted  
 30 with  $-C(=O)-NR^4R^5$ ,  $-S(=O)_2$ -C<sub>1-6</sub>alkyl,  $-S(=O)_2$ -haloC<sub>1-6</sub>alkyl,  $-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with  $-NH-S(=O)_2$ -C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NH-S(=O)_2$ -haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  $-NR^{12}-S(=O)_2$ -NR<sup>14</sup>R<sup>15</sup>, R<sup>6</sup>,  $-C(=O)-R^6$ ,  
 35 C<sub>1-6</sub>alkyl substituted with  $-C(=O)-R^6$ , hydroxyC<sub>1-6</sub>alkyl substituted with R<sup>6</sup>, C<sub>1-6</sub>alkyl

substituted with  $-\text{Si}(\text{CH}_3)_3$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OH})_2$  or  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OC}_{1-6}\text{alkyl})_2$ .

In one embodiment  $\text{R}^1$  represents hydrogen, halo, cyano,  $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy,  $-\text{C}(=\text{O})-\text{O}-\text{C}_{1-6}$ alkyl,  $\text{C}_{2-4}$ alkenyl, hydroxy $\text{C}_{1-6}$ alkyl, halo $\text{C}_{1-6}$ alkyl, hydroxyhalo $\text{C}_{1-6}$ alkyl, cyano $\text{C}_{1-4}$ alkyl,  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl wherein each  $\text{C}_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^4\text{R}^5$ ,  $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl- $\text{NR}^4\text{R}^5$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{NR}^4\text{R}^5$ ,  $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $-\text{S}(=\text{O})_2$ -halo $\text{C}_{1-6}$ alkyl,  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2$ -halo $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2$ -halo $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^{12}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{R}^6$ ,  $-\text{C}(=\text{O})-\text{R}^6$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{R}^6$ , hydroxy $\text{C}_{1-6}$ alkyl substituted with  $\text{R}^6$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{Si}(\text{CH}_3)_3$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OH})_2$  or  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OC}_{1-6}\text{alkyl})_2$ .

In one embodiment each  $\text{R}^2$  is independently selected from hydroxyl, halogen, cyano,  $\text{C}_{1-4}$ alkyl,  $\text{C}_{2-4}$ alkenyl,  $\text{C}_{1-4}$ alkoxy, hydroxy $\text{C}_{1-4}$ alkyl, hydroxy $\text{C}_{1-4}$ alkoxy, halo $\text{C}_{1-4}$ alkyl, halo $\text{C}_{1-4}$ alkoxy,  $\text{C}_{1-4}$ alkoxy $\text{C}_{1-4}$ alkyl,  $\text{R}^{13}$ ,  $\text{C}_{1-4}$ alkoxy substituted with  $\text{R}^{13}$ ,  $-\text{C}(=\text{O})-\text{R}^{13}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $\text{NR}^7\text{R}^8$ ,  $\text{C}_{1-4}$ alkoxy substituted with  $\text{NR}^7\text{R}^8$ ,  $-\text{NR}^7\text{R}^8$  and  $-\text{C}(=\text{O})-\text{NR}^7\text{R}^8$ ; or when two  $\text{R}^2$  groups are attached to adjacent carbon atoms they may be taken together to form a radical of formula  $-\text{O}-(\text{C}(\text{R}^{17})_2)_p-\text{O}-$  wherein  $\text{R}^{17}$  represents hydrogen or fluorine and  $p$  represents 1 or 2.

In one embodiment each  $\text{R}^2$  is independently selected from hydroxyl, halogen, cyano,  $\text{C}_{1-4}$ alkyl,  $\text{C}_{2-4}$ alkenyl,  $\text{C}_{1-4}$ alkoxy, hydroxy $\text{C}_{1-4}$ alkyl, hydroxy $\text{C}_{1-4}$ alkoxy, halo $\text{C}_{1-4}$ alkoxy,  $\text{C}_{1-4}$ alkoxy $\text{C}_{1-4}$ alkyl,  $\text{R}^{13}$ ,  $\text{C}_{1-4}$ alkoxy substituted with  $\text{R}^{13}$ ,  $-\text{C}(=\text{O})-\text{R}^{13}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $\text{NR}^7\text{R}^8$ ,  $\text{C}_{1-4}$ alkoxy substituted with  $\text{NR}^7\text{R}^8$ ,  $-\text{NR}^7\text{R}^8$  or  $-\text{C}(=\text{O})-\text{NR}^7\text{R}^8$ .

In one embodiment one or more  $\text{R}^2$  represents  $\text{C}_{1-4}$ alkoxy, for example  $\text{CH}_3\text{O}-$ , or halo, for example fluoro.

In one embodiment one or more  $\text{R}^2$  represents  $\text{C}_{1-4}$ alkoxy, for example  $\text{CH}_3\text{O}-$ .

In one embodiment  $n$  is equal to 0. In one embodiment  $n$  is equal to 1. In one embodiment  $n$  is equal to 2. In one embodiment  $n$  is equal to 3. In one embodiment  $n$  is equal to 4.

5 In one embodiment,  $n$  is equal to 1, 2, 3 or 4.

In one embodiment,  $n$  is equal to 1, 2, 3 or 4, in particular 4, and at least one  $R^2$  represents  $C_{1-4}$ alkoxy, for example  $CH_3O-$ .

10 In one embodiment,  $n$  is equal to 2, 3 or 4.

In one embodiment,  $n$  is 4.

15 In one embodiment  $n$  is equal to 2 and one  $R^2$  is present at the 3-position and the other is present at the 5-position.

In one embodiment  $n$  is equal to 2 and one  $R^2$  is present at the 3-position and the other is present at the 5-position and each  $R^2$  represents  $C_{1-4}$ alkoxy, for example each  $R^2$  represents  $CH_3O-$ .

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In one embodiment  $n$  is equal to 3 and one  $R^2$  is present at the 2-position, one  $R^2$  is present at the 3-position and one  $R^2$  is present at the 5-position.

25 In one embodiment  $n$  is equal to 3 and one  $R^2$  is present at the 3-position and represents  $C_{1-4}$ alkoxy, for example  $CH_3O-$ ; one  $R^2$  is present at the 5-position and represents  $C_{1-4}$ alkoxy, for example  $CH_3O-$ ; one  $R^2$  is present at the 2-position and represents halogen, for example fluoro.

30 In one embodiment  $n$  is equal to 4 and one  $R^2$  is present at the 2-position, one  $R^2$  is present at the 3-position, one  $R^2$  is present at the 5-position and one  $R^2$  is present at the 6-position.

35 In one embodiment  $n$  is equal to 4 and one  $R^2$  is present at the 3-position and represents  $C_{1-4}$ alkoxy, for example  $CH_3O-$ ; one  $R^2$  is present at the 5-position and represents  $C_{1-4}$ alkoxy, for example  $CH_3O-$ ; one  $R^2$  is present at the 2-position and represents halogen,

for example fluoro, and one R<sup>2</sup> is present at the 6-position and represents halogen, for example fluoro.

In one embodiment, R<sup>3</sup> represents C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, hydroxyC<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl optionally substituted (e.g. substituted) with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups or with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, -C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, C<sub>2-6</sub>alkenyl substituted with R<sup>9</sup>, C<sub>2-6</sub>alkynyl substituted with R<sup>9</sup>, hydroxyC<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, R<sup>13</sup>, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl-C(=O)- or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>.

In one embodiment, R<sup>3</sup> represents C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl optionally substituted (e.g. substituted) with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups or with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, -C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, C<sub>2-6</sub>alkenyl

substituted with  $R^9$ , hydroxy $C_{1-6}$ alkoxy,  $C_{2-6}$ alkenyl,  $R^{13}$ ,  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $C(=O)-$  or  $C_{1-6}$ alkyl substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ .

In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  
 5 halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein  
 each  $C_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups,  $C_{1-6}$ alkyl  
 substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  
 hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $C_{1-6}$   
 10  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$   
 $C_{1-6}$ alkyl substituted with carboxyl,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl  
 substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  
 $C_{1-6}$ alkyl substituted with hydroxyl and  $R^9$ ,  $-C_{1-6}alkyl-C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}$ alkyl  
 substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-R^9$ ,  $C_{2-6}$ alkynyl  
 substituted with  $R^9$ , hydroxy $C_{1-6}$ alkoxy,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $R^{13}$  or  $C_{1-6}$ alkyl  
 15 substituted with  $C_{1-6}$ alkoxy $C_{1-6}alkyl-C(=O)-$ .

In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl  
 optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxyhalo $C_{1-6}$ alkyl, hydroxy $C_{2-6}$ alkynyl,  
 $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}$ alkoxy $C_{1-6}alkyl$  wherein each  $C_{1-6}$ alkyl  
 20 may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}$   
 $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ , cyano $C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  
 $C_{1-6}$ alkyl substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two  
 halo atoms and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl  
 substituted with  $C_{1-6}$ alkoxy $C_{1-6}alkyl-C(=O)-$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ ,  
 25  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with carboxyl,  $C_{1-6}$ alkyl  
 substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}$   
 $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $R^9$  and  
 substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $R^9$ ,  $-C_{1-6}alkyl-$   
 $C(R^{12})=N-O-R^{12}$ ,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}$ alkyl  
 30 substituted with  $-C(=O)-R^9$ ,  $C_{2-6}$ alkenyl substituted with  $R^9$ ,  $C_{2-6}$ alkynyl substituted with  
 $R^9$ ,  $C_{1-6}alkyloxyC_{1-6}alkyl$  wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or  
 two hydroxyl groups,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $R^{13}$ , or  $C_{1-6}$ alkyl substituted with  $-$   
 $P(=O)(OC_{1-6}alkyl)_2$ .

35 In one embodiment,  $R^3$  represents  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  
 halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}$ alkoxy $C_{1-6}alkyl$  wherein

each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>,  
 5 C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, -C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, C<sub>2-6</sub>alkynyl substituted with R<sup>9</sup>, hydroxyC<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl or R<sup>13</sup>.

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In one embodiment, R<sup>3</sup> represents C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with  
 15 hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, -C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, hydroxyC<sub>1-6</sub>alkoxy, C<sub>2-6</sub>alkenyl or R<sup>13</sup>.

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In one embodiment R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

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In one embodiment R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup> or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

In one embodiment R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

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In one embodiment R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>; R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl.



In one embodiment  $R^3$  represents hydroxy $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkynyl substituted with  $R^9$ , or  $C_{2-6}$ alkynyl.

- 5 In one embodiment  $R^3$  represents hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl, or  $C_{2-6}$ alkynyl.

- In one embodiment  $R^3$  represents hydroxy $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkynyl substituted with  $R^9$ , or  
10  $C_{2-6}$ alkynyl.

In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ .

- In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ ,  $R^9$   
15 represents an optionally substituted saturated or an aromatic 5 or 6 membered monocyclic heterocyclyl, for example optionally substituted isoxazolidinyl, pyrimidinyl, imidazolyl or pyrrolidinyl, in particular optionally substituted imidazolyl (e.g. imidazol-2-yl). In one embodiment, imidazolyl is substituted with  $-S(=O)_2-NR^{14}R^{15}$  (e.g.  $-S(=O)_2-N(CH_3)_2$ ). In one embodiment,  $R^9$  represents unsubstituted imidazolyl (e.g. imidazol-2-yl).  
20

- In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ ,  $R^9$  represents an optionally substituted aromatic 6 membered monocyclic heterocyclyl containing one or two nitrogen heteroatom, for example pyrimidinyl or pyridinyl.  
25

In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ ,  $R^9$  represents an optionally substituted 5 membered aromatic heterocycle, such as for example imidazolyl. Optional substituents may represent  $-S(=O)_2-NR^{14}R^{15}$ .

- 30 In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ ,  $R^9$  represents a substituted 5 membered aromatic heterocycle, such as for example imidazolyl.

- In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g.  $C_{1-4}$ alkyl) substituted with  $R^9$ ,  $R^9$   
35 represents an optionally substituted saturated 5 or 6 membered monocyclic heterocyclyl, for example optionally substituted isoxazolidinyl or pyrrolidinyl, in particular optionally

substituted pyrrolidinyl. In one embodiment the pyrrolidinyl is substituted with oxo. In one embodiment the pyrrolidinyl substituted with oxo is pyrrolidin-2-yl substituted with oxo.

5 In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g. methyl or n-propyl) substituted with  $R^9$ ,  $R^9$  represents  $C_{3-8}$ cycloalkyl, for example cyclopropyl.

10 In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl substituted with hydroxyl, halo and/or  $-NR^{10}R^{11}$ . In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl substituted with hydroxyl, halo or  $-NR^{10}R^{11}$ , wherein the  $C_{1-6}$ alkyl group is a straight chain alkyl group e.g. 2-ethyl, n-propyl. In a further embodiment  $R^3$  represents  $C_{1-6}$ alkyl substituted with hydroxyl or halo.

15 In one embodiment  $R^3$  represents hydroxy $C_{1-6}$ alkyl.  $R^3$  may represent  $-\text{CH}_2\text{CH}_2\text{OH}$  or  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$ .

In one embodiment  $R^3$  represents hydroxyhalo $C_{1-6}$ alkyl, for example  $R^3$  may represent  $-\text{CH}_2\text{CHOHCF}_3$ .

20 In one embodiment  $R^3$  represents halo $C_{1-6}$ alkyl, for example  $R^3$  may represent  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$ .

In one embodiment  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ .

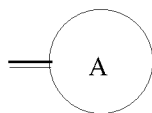
25 In one embodiment  $R^3$  represents  $C_{1-4}$ alkyl substituted with  $-NR^{10}R^{11}$ . In one embodiment  $R^3$  represents  $C_{1-4}$ alkyl substituted  $-NR^{10}R^{11}$ , wherein the  $C_{1-4}$ alkyl group is a straight chain alkyl group e.g. 2-ethyl, n-propyl. In one embodiment  $R^3$  represents  $C_{1-4}$ alkyl substituted with  $-NR^{10}R^{11}$ , wherein the  $C_{1-4}$ alkyl group is an ethylene group ( $-\text{CH}_2\text{CH}_2-$ ).

30 In one embodiment when  $R^3$  represents  $C_{1-6}$ alkyl (e.g. 2-ethyl, n-propyl) substituted with  $-NR^{10}R^{11}$ ;  $R^{10}$  and  $R^{11}$  are independently selected from hydrogen,  $C_{1-6}$ alkyl and halo $C_{1-6}$ alkyl (e.g. hydrogen, iso-propyl or  $-\text{CH}_2\text{CF}_3$ ).

35 In one embodiment,  $R^3$  is hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ , or  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ; in particular  $R^3$  is  $C_{1-6}$ alkyl substituted with  $R^9$ , or  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ; more in particular  $R^3$  is  $C_{1-6}$ alkyl substituted with  $R^9$ .

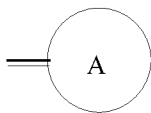
- In one embodiment  $R^{3a}$  represents  $-NR^{10}R^{11}$ , hydroxyl,  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups,  $C_{1-6}$ alkyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with carboxyl,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $R^9$ ,  $-C_{1-6}$ alkyl- $C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-R^9$ ,  $C_{2-6}$ alkynyl substituted with  $R^9$ , hydroxy $C_{1-6}$ alkoxy,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $R^{13}$  or  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $C(=O)-$ .
- 15 In one embodiment  $R^{3a}$  is  $-NR^{10}R^{11}$ , hydroxyl, hydroxy $C_{1-6}$ alkyl, cyano $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $-NR^{10}R^{11}$ , or  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ .
- 20 In one embodiment  $R^{3a}$  is hydroxyl,  $C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $R^9$ .
- In one embodiment  $R^{3a}$  is  $C_{1-6}$ alkyl substituted with  $R^9$ .
- 25 In one embodiment  $R^{3a}$  is  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl, for example  $-CH_2-C(=O)-O-CH_3$ .
- In one embodiment  $R^{3a}$  represents hydroxyl.
- 30 In one embodiment  $R^{3b}$  represents hydrogen.
- In one embodiment  $R^{3b}$  represents hydroxyl.
- In one embodiment  $R^{3a}$  represents hydroxyl and  $R^{3b}$  represents hydrogen.

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form =O, to form =NR<sup>10</sup>, to form cyclopropyl together with the carbon atom to which they are attached, to form =CH-C<sub>0</sub>.



<sub>4</sub>alkyl substituted with  $R^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, H<sub>2</sub>N-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>1-4</sub>alkyl, (haloC<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(=O)-NH<sub>2</sub>, -C(=O)-NH(C<sub>1-4</sub>alkyl), -C(=O)-N(C<sub>1-4</sub>alkyl)<sub>2</sub>.

10 In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form =O, to form cyclopropyl together with the carbon atom to which they are attached, to form =CH-C<sub>0-4</sub>alkyl



substituted with  $R^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond.

15

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form =O.

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form cyclopropyl together with the carbon atom to which they are attached.

20

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form =CH-C<sub>0-4</sub>alkyl substituted with  $R^{3c}$ , for example =CH-CH<sub>2</sub>-  $R^{3c}$  or =CH- $R^{3c}$ .

In one embodiment  $R^{3c}$  represents hydrogen.

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In one embodiment  $R^{3c}$  represents hydroxyl, C<sub>1-6</sub>alkoxy,  $R^9$ , -NR<sup>10</sup>R<sup>11</sup>, -C(=O)-NR<sup>14</sup>R<sup>15</sup>, cyano, -C(=O)-C<sub>1-6</sub>alkyl or -CH(OH)- C<sub>1-6</sub>alkyl.

In one embodiment  $R^{3c}$  represents hydroxyl, -C(=O)-NR<sup>14</sup>R<sup>15</sup>, -NR<sup>10</sup>R<sup>11</sup>, cyano, or

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-C(=O)-C<sub>1-6</sub>alkyl.

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form  $=CH-C_{0.4}alkyl$  (for example  $=CH-CH_2-$  or  $=CH-$ ) substituted with  $R^{3c}$  wherein  $R^{3c}$  represents hydroxyl or  $-C(=O)-NR^{14}R^{15}$ , for example  $-C(=O)NH(CH_3)$ .

- 5 In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form  $=CH-C_{1.4}alkyl$  in the Z configuration.

In one embodiment  $R^{3a}$  and  $R^{3b}$  are taken together to form  $=CH-C_{1.4}alkyl$  in the E configuration.

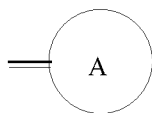
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- In one embodiment  $R^{3a}$  represents  $-NR^{10}R^{11}$ , hydroxyl,  $C_{1-6}alkoxy$ , hydroxy $C_{1-6}alkoxy$ ,  $C_{1-6}alkoxy$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$ ,  $C_{2-6}alkynyl$ , halo $C_{1-6}alkyl$  optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{1-6}alkyl$  optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{2-6}alkynyl$ , hydroxyhalo $C_{1-6}alkyl$ , cyano $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with carboxyl,  $C_{1-6}alkyl$  substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-O-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-O-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkoxyC_{1-6}alkyl$  wherein each  $C_{1-6}alkyl$  may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{2-6}alkynyl$  substituted with  $C_{1-6}alkoxy$ ,  $C_{1-6}alkyl$  substituted with  $R^9$  and optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-R^9$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $R^9$ ,  $C_{2-6}alkynyl$  substituted with  $R^9$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}alkynyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $-C_{1-6}alkyl-C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-S(=O)_2-haloC_{1-6}alkyl$ ,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}alkyl$  substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}alkyl$  substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;

$R^{3b}$  represents hydrogen or hydroxyl; provided that if  $R^{3a}$  represents  $-NR^{10}R^{11}$ , then  $R^{3b}$  represents hydrogen; or

$R^{3a}$  and  $R^{3b}$  are taken together to form  $=O$ , to form  $=NR^{10}$ , to form cyclopropyl together with the carbon atom to which they are attached, to form  $=CH-C_{0.4}alkyl$  substituted with

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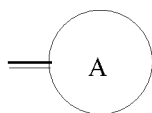


$R^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano,  $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkyl,  $H_2N-C_{1-4}$ alkyl,  $(C_{1-4}alkyl)NH-C_{1-4}alkyl$ ,  
 5  $(C_{1-4}alkyl)_2N-C_{1-4}alkyl$ ,  $(haloC_{1-4}alkyl)NH-C_{1-4}alkyl$ ,  $C_{1-4}alkoxyC_{1-4}alkyl$ ,  $-C(=O)-NH_2$ ,  
 $-C(=O)-NH(C_{1-4}alkyl)$ ,  $-C(=O)-N(C_{1-4}alkyl)_2$ .

In one embodiment  $R^{3a}$  represents  $-NR^{10}R^{11}$ , hydroxyl,  $C_{1-6}alkoxy$ , hydroxy $C_{1-6}alkoxy$ ,  $C_{1-6}alkoxy$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$ ,  $C_{2-6}alkenyl$ , halo $C_{1-6}alkyl$  optionally  
 10 substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{1-6}alkyl$  optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{2-6}alkenyl$ , hydroxyhalo $C_{1-6}alkyl$ , cyano $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with carboxyl,  $C_{1-6}alkyl$  substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-O-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-O-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  
 15  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkoxyC_{1-6}alkyl$  wherein each  $C_{1-6}alkyl$  may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{2-6}alkenyl$  substituted with  $C_{1-6}alkoxy$ ,  $C_{1-6}alkyl$  substituted with  $R^9$  and optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-R^9$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $R^9$ ,  $C_{2-6}alkenyl$  substituted with  $R^9$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}alkenyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $-C_{1-6}alkyl-C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-S(=O)_2-haloC_{1-6}alkyl$ ,  
 $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  
 25  $-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}alkyl$  substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}alkyl$  substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;

$R^{3b}$  represents hydrogen or hydroxyl; provided that if  $R^{3a}$  represents  $-NR^{10}R^{11}$ , then  $R^{3b}$   
 30 represents hydrogen; or

$R^{3a}$  and  $R^{3b}$  are taken together to form  $=O$ , to form  $=NR^{10}$ , to form cyclopropyl together with the carbon atom to which they are attached, to form  $=CH-C_{0-4}alkyl$  substituted with



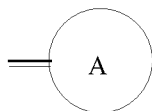
$R^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated

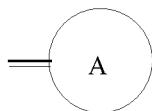
heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, H<sub>2</sub>N-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>1-4</sub>alkyl, (haloC<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(=O)-NH<sub>2</sub>,  
 5 -C(=O)-NH(C<sub>1-4</sub>alkyl), -C(=O)-N(C<sub>1-4</sub>alkyl)<sub>2</sub>.

In one embodiment R<sup>3a</sup> represents -NR<sup>10</sup>R<sup>11</sup>, hydroxyl, C<sub>1-6</sub>alkoxy, hydroxyC<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkoxy substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl,  
 10 hydroxyhaloC<sub>1-6</sub>alkyl, cyanoC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with carboxyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl-O-C(=O)-, C<sub>1-6</sub>alkyl substituted with C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl-C(=O)-, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups or with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -C(=O)-R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and R<sup>9</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with hydroxyl and -NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with one or two halogens and -NR<sup>10</sup>R<sup>11</sup>, -C<sub>1-6</sub>alkyl-C(R<sup>12</sup>)=N-O-R<sup>12</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>10</sup>R<sup>11</sup>, C<sub>1-6</sub>alkyl substituted with -O-C(=O)-NR<sup>10</sup>R<sup>11</sup>, -  
 20 S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>12</sup>-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>13</sup>, C<sub>1-6</sub>alkyl substituted with  
 25 -P(=O)(OH)<sub>2</sub> or C<sub>1-6</sub>alkyl substituted with -P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>;

R<sup>3b</sup> represents hydrogen or hydroxyl; provided that if R<sup>3a</sup> represents -NR<sup>10</sup>R<sup>11</sup>, then R<sup>3b</sup> represents hydrogen; or

R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O, to form =NR<sup>10</sup>, to form cyclopropyl together with the carbon atom to which they are attached, to form =CH-C<sub>0-4</sub>alkyl substituted with



30 R<sup>3c</sup>, or to form  wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, H<sub>2</sub>N-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl,

(C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>1-4</sub>alkyl, (haloC<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(=O)-NH<sub>2</sub>,  
-C(=O)-NH(C<sub>1-4</sub>alkyl), -C(=O)-N(C<sub>1-4</sub>alkyl)<sub>2</sub>.

In one embodiment, R<sup>3a</sup> is not alkenyl or substituted alkenyl.

5

In one embodiment, R<sup>3a</sup> is not alkynyl or substituted alkynyl.

In one embodiment, R<sup>3a</sup> is not alkenyl, substituted alkenyl, alkynyl or substituted alkynyl.

10 In one embodiment, R<sup>9</sup> is selected from:

an optionally substituted C<sub>3-8</sub>cycloalkyl,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl,

an optionally substituted saturated 6 membered monocyclic heterocyclyl,

a saturated or an aromatic 3, 4, 5 or 6 membered monocyclic heterocyclyl containing

15 one or two oxygen heteroatoms,

an optionally substituted 4 membered heterocyclyl containing one oxygen heteroatom,

an optionally substituted aromatic 6 membered monocyclic heterocycle containing one

or two nitrogen heteroatoms,

a partially saturated 6 membered monocyclic heterocyclyl containing one nitrogen

20 heteroatom which may optionally be substituted,

an optionally substituted saturated 4 membered monocyclic heterocyclyl containing one  
nitrogen heteroatom,

a saturated 5 membered monocyclic heterocyclyl containing one nitrogen heteroatom,

a saturated 6 membered monocyclic heterocyclyl containing one nitrogen heteroatom,

25 a bicyclic heterocyclyl containing a benzene ring fused to a 5- or 6-membered ring  
containing 1, 2 or 3 ring heteroatoms,

a 4, 5 or 6 membered monocyclic saturated heterocycle substituted with two

substituents which are attached to the same atom and which are taken together to form  
a 4 to 7-membered saturated monocyclic heterocyclyl containing at least one

30 heteroatom selected from N, O or S,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing one  
sulphur heteroatom,

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing one  
sulphur and one nitrogen heteroatom,

35 a saturated 6 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

an aromatic 5 membered monocyclic heterocyclyl containing four nitrogen heteroatoms,



an aromatic 5 membered monocyclic heterocyclyl containing one oxygen and two nitrogen heteroatoms, .

an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

5 an optionally substituted aromatic 5 membered monocyclic heterocyclyl containing three nitrogen heteroatoms,

a saturated 5 membered monocyclic heterocyclyl containing one nitrogen and one oxygen heteroatom,

10 a saturated 6 membered monocyclic heterocyclyl containing one nitrogen and one sulphur heteroatom,

a saturated 7 membered monocyclic heterocyclyl containing two nitrogen heteroatoms,

a saturated 7 membered monocyclic heterocyclyl containing one nitrogen and one oxygen heteroatom, and

phenyl or naphthyl, in particular phenyl.

15

In one embodiment,  $R^9$  represents an optionally substituted 5 membered aromatic or saturated heterocycle, such as for example imidazolyl, pyrrolidinyl, isoxazolidinyl.

Optional substituents may represent =O, a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said

20 heterocyclyl is optionally substituted with  $R^{16}$ ; or  $-S(=O)_2-NR^{14}R^{15}$ .

In one embodiment,  $R^9$  represents  $C_{3-6}$ cycloalkyl, such as for example cyclopropyl, a 3 membered saturated heterocyclyl, such as for example oxiranyl, an optionally

25 optionally substituted 5 membered saturated heterocycle, such as for example pyrrolidinonyl, an optionally substituted 6 membered aromatic or saturated heterocycle, such as for

example pyridyl, pyrimidinyl, pyrazinyl, piperazinyl, or morpholinyl, an optionally substituted bicyclic heterocycle, such as for example 1H-isoindol-1,3-dione. Optional

substituents may represent =O,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyl substituted with  $-NR^{14}R^{15}$ , hydroxy $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl-C(=O)-.

30

In one embodiment,  $R^9$  represents an optionally substituted 5 membered aromatic heterocycle, such as for example imidazolyl, or an optionally substituted 6 membered aromatic heterocycle, such as for example pyridyl, pyrimidinyl or pyrazinyl. Optional substituents may represent  $C_{1-4}$ alkoxy or  $-S(=O)_2-NR^{14}R^{15}$ .

35

In one embodiment,  $R^9$  represents an optionally substituted 5 membered aromatic heterocycle, such as for example imidazolyl. Optional substituents may represent  $-S(=O)_2-NR^{14}R^{15}$ .

- 5 In one embodiment,  $R^9$  represents an optionally substituted 6 membered aromatic heterocycle, such as for example pyridinyl or pyrimidinyl. Optional substituents may represent  $C_{1-4}$ alkoxy.

- 10 In one embodiment,  $R^9$  represents an optionally substituted 5 membered aromatic or saturated heterocycle, such as for example imidazolyl, pyrrolidinyl, oxazolidinyl. Optional substituents may represent  $=O$ , a 5 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with  $R^{16}$ ; or  $-S(=O)_2-NR^{14}R^{15}$ .

- 15 In one embodiment,  $R^9$  represents  $C_{3-6}$ cycloalkyl, such as for example cyclopropyl, a 3 membered saturated heterocyclyl, such as for example oxiranyl, an optionally substituted 5 membered saturated heterocycle, such as for example pyrrolidinonyl, an optionally substituted 6 membered aromatic or saturated heterocycle, such as for example pyridyl, pyrimidinyl, pyrazinyl, piperazinyl, or morpholinyl, an optionally substituted bicyclic heterocycle, such as for example 1H-isoindol-1,3-dione. Optional substituents may represent  $=O$ ,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkyl substituted with  $-NR^{14}R^{15}$ , hydroxy $C_{1-4}$ alkyl, or  $C_{1-4}$ alkyl- $C(=O)-$ .
- 20

- 25 In one embodiment,  $R^9$  is imidazolyl, in particular 2-imidazolyl, optionally substituted with  $-S(=O)_2-NR^{14}R^{15}$ ; in particular  $R^9$  is imidazolyl, in particular 2-imidazolyl.

In one embodiment  $R^{10}$  represents hydrogen or  $C_{1-6}$ alkyl.

- 30 In one embodiment  $R^{10}$  is hydrogen.

- In one embodiment  $R^{11}$  represents hydrogen,  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $-C(=O)-C_{1-6}$ alkyl,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ , hydroxy $C_{1-6}$ alkyl,  $-C(=O)-$ hydroxyhalo $C_{1-6}$ alkyl,  $-C(=O)-R^6$ , cyano $C_{1-6}$ alkyl,  $R^6$ ,  $-C(=O)-R^6$ ,  $C_{1-6}$ alkyl substituted with  $R^6$ ,  $-C(=O)-$ halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-Si(CH_3)_3$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{14}R^{15}$ ,  $C_{1-6}$ alkoxy, hydroxyhalo $C_{1-6}$ alkyl, carboxyl, or  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl.
- 35

In one embodiment  $R^{10}$  and  $R^{11}$  represent hydrogen or  $C_{1-6}$ alkyl.

In one embodiment,  $R^6$  represents a 6-membered monocyclic saturated heterocyclyl which is optionally substituted. For example piperazinyl or morpholinyl or tetrahydropyranyl, optionally substituted with halogen,  $C_{1-6}$ alkyl, or  $C_{1-6}$ alkyl-O-C(=O)-.

In one embodiment,  $R^6$  represents a 6-membered monocyclic aromatic heterocyclyl which is optionally substituted. For example pyridinyl, optionally substituted with halogen,  $C_{1-6}$ alkyl, or  $C_{1-6}$ alkyl-O-C(=O)-.

In one embodiment  $R^6$  represents an optionally substituted saturated 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, such as for example tetrahydropyran.

In one embodiment,  $R^6$  represents  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkenyl, 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S; said  $C_{3-8}$ cycloalkyl,  $C_{3-8}$ cycloalkenyl, 4 to 7-membered monocyclic heterocyclyl, optionally and each independently being substituted by 1, 2, 3, 4 or 5 substituents, each substituent independently being selected from cyano,  $C_{1-6}$ alkyl, cyano $C_{1-6}$ alkyl, hydroxyl, carboxyl, hydroxy $C_{1-6}$ alkyl, halogen, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl-O-C(=O)-,  $-NR^{14}R^{15}$ ,  $-C(=O)-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{14}R^{15}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2-NR^{14}R^{15}$ .

In one embodiment,  $R^{12}$  represents hydrogen or  $C_{1-4}$ alkyl optionally substituted with  $C_{1-4}$ alkyloxy.

In one embodiment,  $R^{13}$  represents a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N or O.

In one embodiment,  $R^{14}$  and  $R^{15}$  each independently represent hydrogen or  $C_{1-4}$ alkyl.

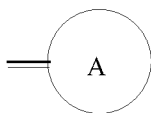
In one embodiment, W is  $-N(R^3)-$ .

In one embodiment, W is  $-C(R^{3a}R^{3b})-$ .

5 In one embodiment, W is  $-C(=O)-$ .

In one embodiment, W is  $-N(R^3)-$  or  $-C(R^{3a}R^{3b})-$  wherein  $R^{3a}$  and  $R^{3b}$  are not taken together to form  $=O$ .

- 10 In one embodiment, W is  $-N(R^3)-$  or  $-C(R^{3a}R^{3b})-$  wherein  $R^{3a}$  represents  $-NR^{10}R^{11}$ , hydroxyl,  $C_{1-6}$ alkoxy, hydroxy $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, halo $C_{1-6}$ alkyl optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl, hydroxy $C_{2-6}$ alkenyl, hydroxy $C_{2-6}$ alkynyl, hydroxyhalo $C_{1-6}$ alkyl, cyano $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with
- 15 carboxyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $O-C(=O)-$ ,  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $C(=O)-$ ,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl substituted with  $C_{1-6}$ alkoxy,  $C_{2-6}$ alkynyl substituted with  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkyl substituted with  $R^9$  and optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-R^9$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $R^9$ ,  $C_{2-6}$ alkenyl substituted with  $R^9$ ,  $C_{2-6}$ alkynyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkenyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkynyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with
- 25 hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $-C_{1-6}$ alkyl- $C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}$ alkyl substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}$ alkyl substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;
- 30  $R^{3b}$  represents hydrogen or hydroxyl; provided that if  $R^{3a}$  represents  $-NR^{10}R^{11}$ , then  $R^{3b}$  represents hydrogen; or
- 35  $R^{3a}$  and  $R^{3b}$  are taken together to form  $=NR^{10}$ , to form cyclopropyl together with the carbon atom to which they are attached, to form  $=CH-C_{0-4}alkyl$  substituted with  $R^{3c}$ , or to



form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano, C<sub>1-4</sub>alkyl, hydroxyC<sub>1-4</sub>alkyl, H<sub>2</sub>N-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, (C<sub>1-4</sub>alkyl)<sub>2</sub>N-C<sub>1-4</sub>alkyl, (haloC<sub>1-4</sub>alkyl)NH-C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(=O)-NH<sub>2</sub>, -C(=O)-NH(C<sub>1-4</sub>alkyl), -C(=O)-N(C<sub>1-4</sub>alkyl)<sub>2</sub>.

In one embodiment, W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)- wherein R<sup>3a</sup> and R<sup>3b</sup> are not taken together.

In one embodiment, W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-; R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>.

In one embodiment, W is -N(R<sup>3</sup>)-, D is a 5 or 6 membered monocyclic aromatic carbocyclyl or heterocyclyl, wherein said carbocyclyl or heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups; n is 2 or 4; R<sup>2</sup> is C<sub>1-6</sub>alkyloxy or halo; R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

In one embodiment, W is -N(R<sup>3</sup>)-, D is phenyl, or pyrazolyl substituted with C<sub>1-6</sub>alkyl; n is 2 or 4; R<sup>2</sup> is C<sub>1-6</sub>alkyloxy or halo; R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

In one embodiment, W is -N(R<sup>3</sup>)-, D is a 5 or 6 membered monocyclic aromatic carbocyclyl or heterocyclyl, wherein said carbocyclyl or heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups; n is 2, 3 or 4; R<sup>2</sup> is C<sub>1-6</sub>alkyloxy or halo; R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>; R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl.

In one embodiment, W is -N(R<sup>3</sup>)-, D is phenyl, or pyrazolyl substituted with C<sub>1-6</sub>alkyl; n is 2, 3 or 4; R<sup>2</sup> is C<sub>1-6</sub>alkyloxy or halo; R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>, or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>; R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl.

In one embodiment, W is  $-N(R^3)-$ , D is a 5 or 6 membered monocyclic aromatic carbocyclyl or heterocyclyl, wherein said carbocyclyl or heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups, in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl, more in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl, and n is 2 or 4; even more in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2 or 4,  $R^2$  is  $C_{1-6}$ alkyloxy or halo; even further in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy or halo, and said  $R^2$  is placed in position 2,3, 5 or 6; even further in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2;  $R^2$  is  $C_{1-6}$ alkyloxy and said  $R^2$  is placed in position 3 or 5; and  $R^3$  is hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $R^9$ .

In one embodiment, W is  $-C(R^{3a}R^{3b})-$ , D is a 5 or 6 membered monocyclic aromatic carbocyclyl or heterocyclyl, wherein said carbocyclyl or heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy or halo;  $R^3$  is hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $R^9$ .

In one embodiment, W is  $-C(R^{3a}R^{3b})-$ , D is phenyl, or pyrazolyl substituted with  $C_{1-6}$ alkyl; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy or halo;  $R^3$  is hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $R^9$ .

In one embodiment, W is  $-C(R^{3a}R^{3b})-$ , D is a 5 or 6 membered monocyclic aromatic carbocyclyl or heterocyclyl, wherein said carbocyclyl or heterocyclyl may optionally be substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups; in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl, more in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl, and n is 2 or 4; even more in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy or halo; even further in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy and said  $R^2$  is placed in position 2,3, 5 or 6; even further in particular D is phenyl, or pyrazolyl optionally substituted with  $C_{1-6}$ alkyl; n is 2 or 4;  $R^2$  is  $C_{1-6}$ alkyloxy and said  $R^2$  is placed in position 2,3, 5 or 6; and  $R^3$  is hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $R^9$ .

In one embodiment, n represents an integer equal to 2 or 4;  $R^2$  represents  $C_{1-4}$ alkoxy or halogen, for example  $CH_3O-$  or fluoro;  $R^3$  represents hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl substituted with  $R^9$ , D represents pyrazolyl, in particular pyrazol-4-yl substituted with  $C_{1-6}$ alkyl; W is  $-N(R^3)-$ .

In one embodiment,

D is pyrazolyl or phenyl, each optionally substituted with C<sub>1-4</sub>alkyl;

W is -N(R<sup>3</sup>)- or -C(=O)-;

5 R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or

C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> is imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl.

10

In one embodiment,

D is pyrazolyl or phenyl, each optionally substituted with C<sub>1-4</sub>alkyl;

W is -N(R<sup>3</sup>)-;

R<sup>3</sup> is hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or

15 C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> is imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl.

20 In one embodiment,

W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S,

25 wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or

C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

30 R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one

heteroatom selected from N, O or S, said 5 membered monocyclic heterocyclyl

optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

35 n independently represents an integer equal to 1, 2, 3 or 4.

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered

- 5 monocyclic heterocyclyl containing at least one N-atom, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one R<sup>1</sup> group;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyc<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or

C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

- 10 R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one N-atom, said 5 membered monocyclic heterocyclyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

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In one embodiment,

W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is fluoro, chloro or methoxy;

D represents phenyl or pyrazolyl substituted with methyl on the NH-group;

- 20 R<sup>1</sup> represents methyl;

R<sup>3</sup> represents hydroxyethyl, methyl substituted with R<sup>9</sup>, or

ethyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> represents imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen, ethyl or isopropyl;

- 25 R<sup>14</sup> and R<sup>15</sup> represent methyl;

n independently represents an integer equal to 1, 2, 3 or 4.

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-;

- 30 each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

- 35 R<sup>1</sup> represents C<sub>1-6</sub>alkyl;



R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> represents a 3 to 12 membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said 3 to 12 membered monocyclic or bicyclic heterocyclyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> each represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl or -C(=O)-O-C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or

C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O or =CH-C<sub>0-4</sub>alkyl substituted with R<sup>3c</sup>;

R<sup>3c</sup> is cyano;

R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said 5 membered monocyclic heterocyclyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N or O, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one R<sup>1</sup> group;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl or -C(=O)-O-C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or  
C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O or =CH-C<sub>0-4</sub>alkyl substituted with R<sup>3c</sup>;

5 R<sup>3c</sup> is cyano;

R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one N-atom,  
said 5 membered monocyclic heterocyclyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

10 n independently represents an integer equal to 1, 2, 3 or 4.

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is fluoro, chloro or methoxy;

15 D represents phenyl, pyridinyl, piperidinyl, tetrahydro-2H-pyranyl, pyrimidinyl or  
pyrazolyl, wherein pyrazolyl or piperidinyl are optionally substituted with methyl or tert-  
butoxycarbonyl on the NH-group;

R<sup>3</sup> represents 2-hydroxyethyl, 3-hydroxypropyl, -(CH<sub>2</sub>)<sub>2</sub>-NR<sup>10</sup>R<sup>11</sup>, -(CH<sub>2</sub>)<sub>3</sub>-NR<sup>10</sup>R<sup>11</sup>, or  
methyl substituted with R<sup>9</sup>;

20 R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O or =CH-CN;

R<sup>9</sup> represents imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen, methyl, ethyl or isopropyl;

R<sup>14</sup> and R<sup>15</sup> represent methyl;

n independently represents an integer equal to 1, 2, 3 or 4.

25

In one embodiment,

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-; in particular W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

30 D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12  
ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom  
selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be  
optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl or -C(=O)-O-C<sub>1-6</sub>alkyl;

35 R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl  
substituted with R<sup>9</sup> and optionally substituted with -O-C(=O)-C<sub>1-6</sub>alkyl, or C<sub>1-6</sub>alkyl  
substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O or =CH-C<sub>0-4</sub>alkyl substituted with R<sup>3c</sup>;

R<sup>3c</sup> is cyano;

R<sup>9</sup> represents a 3 to 12 membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said 3 to 12 membered monocyclic or bicyclic

5 heterocyclyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> each represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

10 In one embodiment,

W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is fluoro or methoxy;

D represents piperidinyl or tetrahydro-2H-pyranyl, in particular 4-piperidinyl or tetrahydro-2H-pyran-4-yl ;

15 R<sup>3</sup> represents C<sub>1-4</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen, methyl, ethyl or isopropyl;

n independently represents an integer equal to 3 or 4.

In one embodiment,

20 W is -N(R<sup>3</sup>)-;

each R<sup>2</sup> is fluoro or methoxy;

D represents piperidinyl, tetrahydro-2H-pyranyl, or pyrazolyl, wherein pyrazolyl or piperidinyl are optionally substituted with methyl on the NH-group;

R<sup>3</sup> represents -(CH<sub>2</sub>)<sub>2</sub>-NR<sup>10</sup>R<sup>11</sup>, -(CH<sub>2</sub>)<sub>3</sub>-NR<sup>10</sup>R<sup>11</sup>, or methyl substituted with R<sup>9</sup>;

25 R<sup>9</sup> represents imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen, methyl, ethyl or isopropyl;

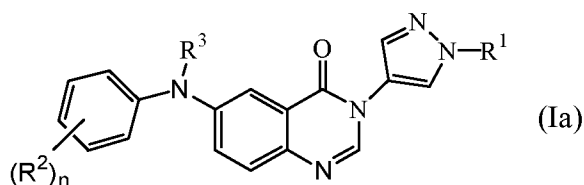
R<sup>14</sup> and R<sup>15</sup> represent methyl;

n independently represents an integer equal to 3 or 4.

30 In one embodiment, R<sup>3</sup> represents hydroxyC<sub>2-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or C<sub>2-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>.

In one embodiment the compound of formula (I) is a compound of formula (Ia)

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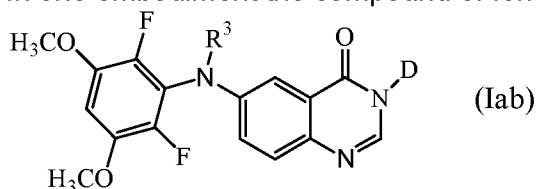


including any tautomeric or stereochemically isomeric form thereof;

wherein  $n$ ,  $R^1$ ,  $R^2$  and  $R^3$  are as defined herein;

the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment the compound of formula (I) is a compound of formula (Ia)

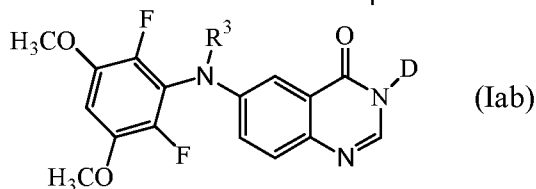


including any tautomeric or stereochemically isomeric form thereof;

10 wherein  $R^3$  and  $D$  are as defined herein;

the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment the compound of formula (I) is a compound of formula (Ia)



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including any tautomeric or stereochemically isomeric form thereof;

wherein  $R^3$  represents ethyl substituted with  $-NR^{10}R^{11}$ ;

$R^{10}$  and  $R^{11}$  each independently represent hydrogen, ethyl or isopropyl;

$D$  represents pyrazolyl substituted with methyl;

20 the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment,  $D$  represents phenyl, 3-pyridinyl, 4-pyridinyl, 4-piperidinyl,

tetrahydro-2H-pyran-4-yl, 5-pyrimidinyl or pyrazol-4-yl, wherein pyrazol-4-yl or 4-

25 piperidinyl are optionally substituted with methyl or tert-butoxycarbonyl on the NH-group.

In one embodiment, D represents a non-aromatic 5 or 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups.

5

In one embodiment, D represents a non-aromatic 6 ring membered monocyclic heterocyclyl containing at least one heteroatom selected from N or O, wherein said heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3) R<sup>1</sup> groups; in particular D is unsubstituted.

10

In another embodiment, D represents piperidinyl or tetrahydro-2H-pyranyl, in particular 4-piperidinyl or tetrahydro-2H-pyran-4-yl.

In one embodiment the compound of formula (I) is a compound of formula (Ia),

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including any tautomeric or stereochemically isomeric form thereof; wherein:

R<sup>1</sup> represents C<sub>1-6</sub>alkyl;

R<sup>2</sup> represents C<sub>1-4</sub>alkoxy, for example CH<sub>3</sub>O-, or halo, for example fluoro;

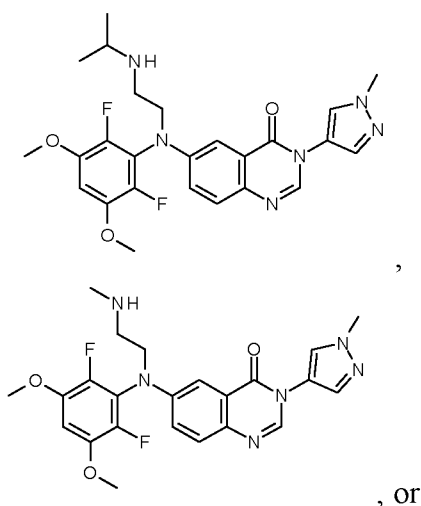
n = 2 or 4; and

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>;

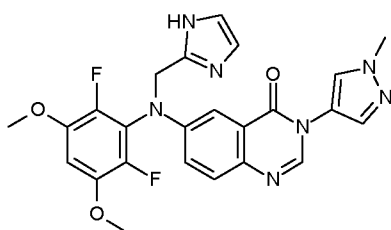
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the *N*-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates thereof.

In one embodiment, the compound of formula (I) is any one of the following compounds

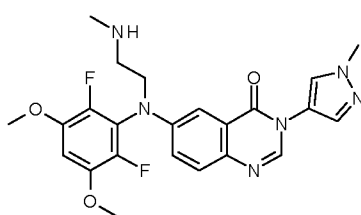
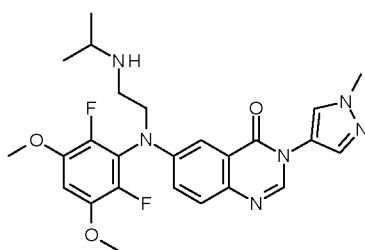


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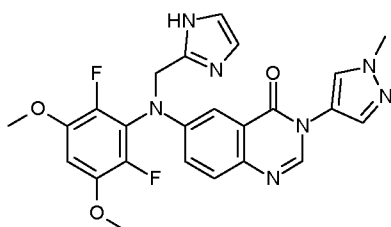


a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof; in particular a pharmaceutically acceptable salt thereof or a solvate thereof.

In one embodiment, the compound of formula (I) is any one of the following compounds

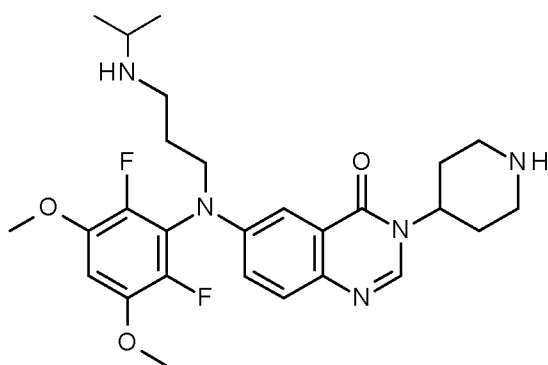


, or



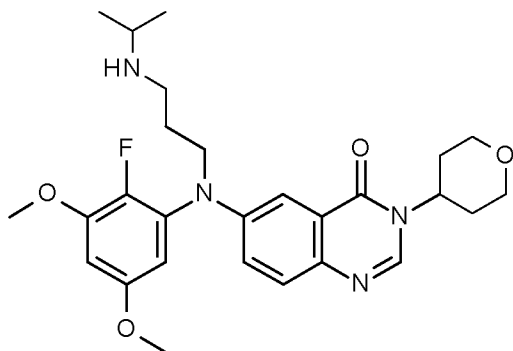
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In one embodiment, the compound of formula (I) is any one of the following compounds



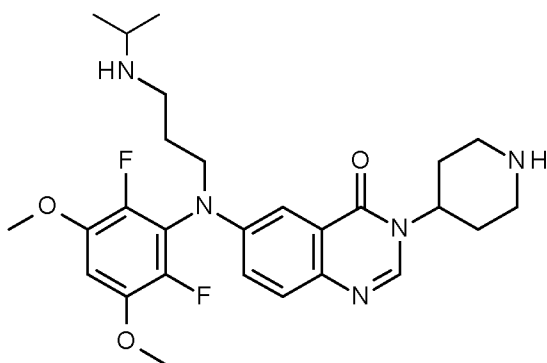
, or

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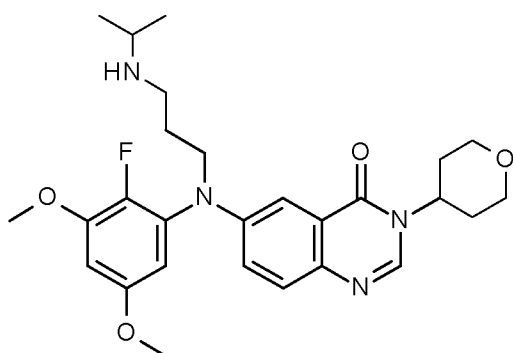


a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof; in particular a pharmaceutically acceptable salt thereof or a solvate thereof.

- 5 In one embodiment, the compound of formula (I) is any one of the following compounds



, or



- 10 For the avoidance of doubt, it is to be understood that each general and specific preference, embodiment and example for one substituent may be combined, whenever possible, with each general and specific preference, embodiment and example for one or more, preferably, all other substituents as defined herein and that all such embodiments are embraced by this application.

**Methods for the Preparation of Compounds of Formula (I)**

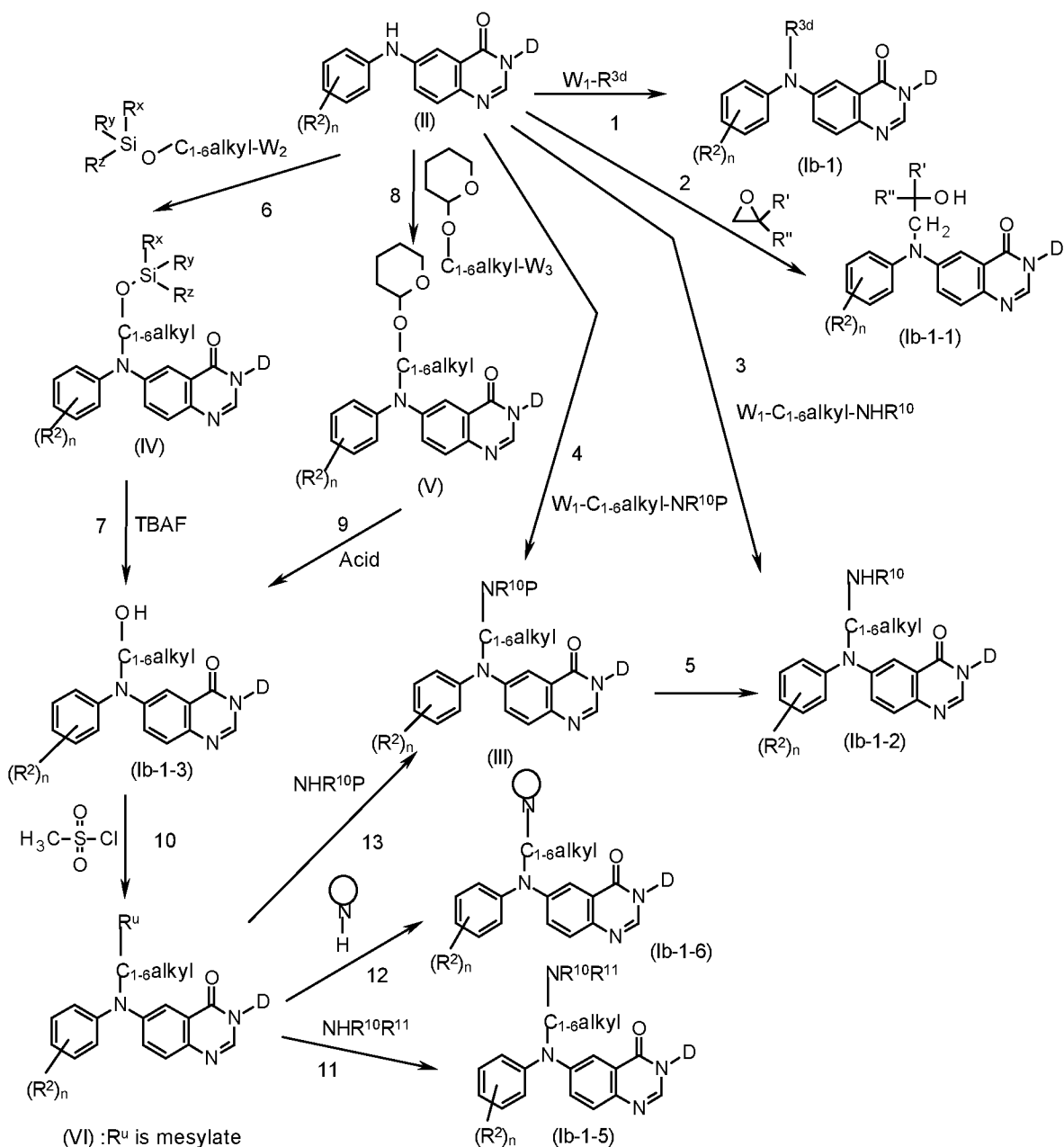
In this section, as in all other sections of this application unless the context indicates otherwise, references to formula (I) also include all other sub-groups and examples thereof as defined herein.

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In general, compounds of formula (I) wherein W is  $-N(R^3)-$ , said compounds being represented by formula (Ib), can be prepared according to the following reaction Scheme 1.



Scheme 1



In Scheme 1, the following reaction conditions apply:

- 5 1: in the presence of a suitable base, such as for example sodium hydride or  $Cs_2CO_3$ , and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide, tetrahydrofuran or acetonitrile and wherein  $W_1$  represents a suitable leaving group, such as for example halo, e.g. bromo, chloro and the like, or  $-O-S(=O)_2-CH_3$ , and  $R^{3d}$  represents optionally substituted  $C_{1-6}$ alkyl, such as for example  $-CH_2-C_3H_5$ ;

2: in the presence of a suitable base, such as for example sodium hydride,  $\text{Cs}_2\text{CO}_3$ , or potassium hydroxide, and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide or acetonitrile and wherein  $\text{R}'$  represents optionally substituted  $\text{C}_{1-4}$ alkyl and  $\text{R}''$  represents hydrogen or optionally substituted  $\text{C}_{1-4}$ alkyl;

3: in the presence of a suitable phase transfer reagent such as for example tetrabutylammonium bromide, a suitable base such as for example potassium hydroxide, and a suitable solvent such as for example 2-methyltetrahydrofuran and water. When, an intermediate of formula (II) is reacting with an intermediate of formula  $\text{W}_1\text{-C}_{1-6}\text{alkyl-Ncycle}$ ; the following conditions can be applied: a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide.

4: in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, e.g. N,N-dimethylformamide or N,N-dimethylacetamide, and wherein wherein P represents a suitable protective group, such as for example  $\text{-C(=O)-O-C(CH}_3)_3$ ;

5: in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, and a suitable solvent, such as for example dichloromethane or an alcohol, e.g. methanol;

6: in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide or tetrahydrofuran, and wherein  $\text{W}_2$  represents a suitable leaving group, such as for example halo, e.g. bromo and wherein  $\text{R}^x$  and  $\text{R}^y$  represent  $\text{C}_{1-4}$ alkyl, and  $\text{R}^z$  represent  $\text{C}_{1-4}$ alkyl or phenyl, for instance  $\text{R}^x$  and  $\text{R}^y$  represent  $\text{CH}_3$  and  $\text{R}^z$  represents  $\text{C(CH}_3)_3$  or phenyl;

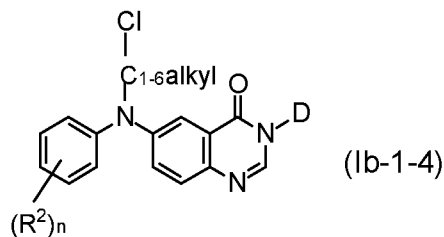
7: in the presence of a suitable solvent, such as for example tetrahydrofuran. This type of reaction can also be performed in the presence of a suitable acid, such as for example acetic acid or HCl, and a suitable solvent, such as for example dioxane;

8: in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide and wherein  $\text{W}_3$  represents a suitable leaving group, such as for example halo, e.g. bromo and the like;

9: in the presence of a suitable acid, such as for example HCl, and a suitable solvent, such as for example an alcohol, e.g. methanol or isopropanol;

10: in the presence of a suitable base, such as for example triethylamine or diisopropylethanamine, and a suitable solvent, such as for example dichloromethane or tetrahydrofuran.

During this reaction also a compound of formula (Ib-1-4) can be formed:



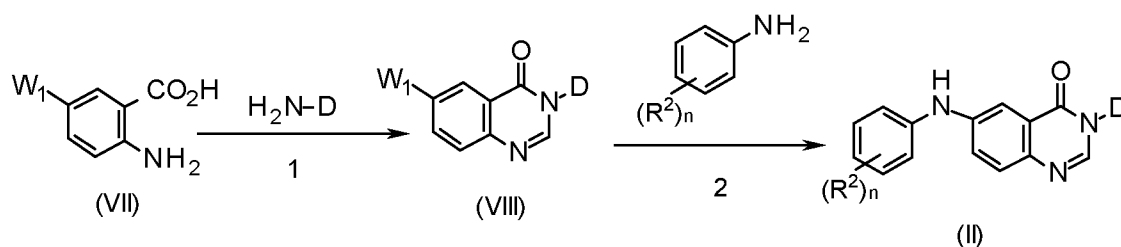
11: optionally in the presence of a suitable base, such as for example triethylamine,  $K_2CO_3$ ,  $Na_2CO_3$  or sodium hydride, and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran, dioxane, N,N-dimethylformamide, 1-methyl-pyrrolidinone. This type of reaction can also be performed with a suitable salt of  $NHR^{10}R^{11}$ , e.g. HCl salt of  $NHR^{10}R^{11}$ , or may be performed in the presence of potassium iodide. In this way compounds wherein  $R^3$  represents iodo $C_{1-6}$ alkyl can be obtained.

12: in the presence of a suitable solvent, such as for example acetonitrile, 1-methyl-2-pyrrolidinone, optionally in the presence of potassium iodide or a suitable base, such as for example  $Na_2CO_3$ ,  $K_2CO_3$  or triethylamine. This reaction can also be performed with a suitable salt of  $H-N$  (where N is a suitable nitrogen containing ring (unsubstituted or substituted) within the definition of  $R^9$ ),

13: in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example dimethylacetamide and wherein P represents a suitable protective group, such as for example  $-C(=O)-O-C(CH_3)_3$ .

Intermediates of formula (II) used in the above Scheme 1 can be prepared according to the following reaction Scheme 2.

Scheme 2

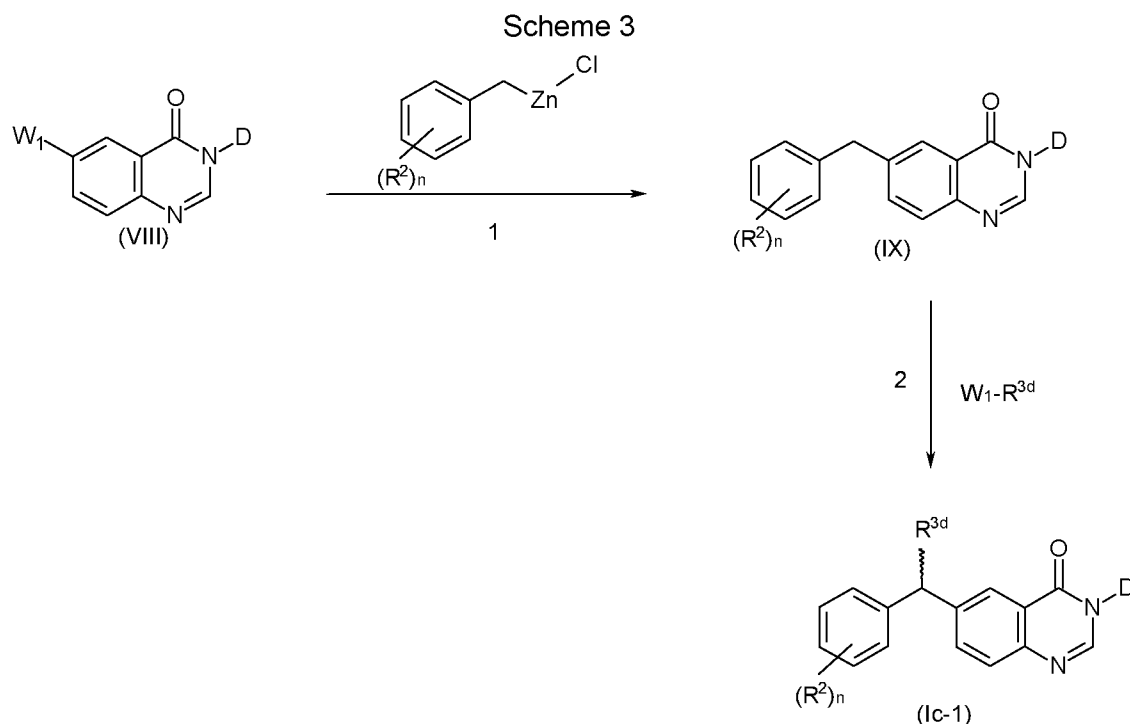


In Scheme 2 where  $W_1$  represents a suitable leaving group such as for example halo, e.g. bromo, chloro and the like, the following reaction conditions apply:

1: in the presence of triethyl orthoformate in a suitable solvent such as for example toluene;

2: in the presence of a suitable catalyst, such as for example chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II), a suitable base, such as for example cesium carbonate, in a suitable solvent, such as for example toluene; or in the presence of a suitable catalyst such as for example tris(dibenzylideneacetone)dipalladium(0) (Pd<sub>2</sub>dba<sub>3</sub>) in the presence of a suitable ligand, such as for example [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine] (BINAP), and a suitable base, such as for example cesium carbonate, in a suitable solvent, such as for example dioxane.

- 10 In general, compounds of formula (I) wherein W is -C(R<sup>3a</sup> R<sup>3b</sup>)-, said compounds being represented by formula (Ic-1), can be prepared according to the following reaction Scheme 3.



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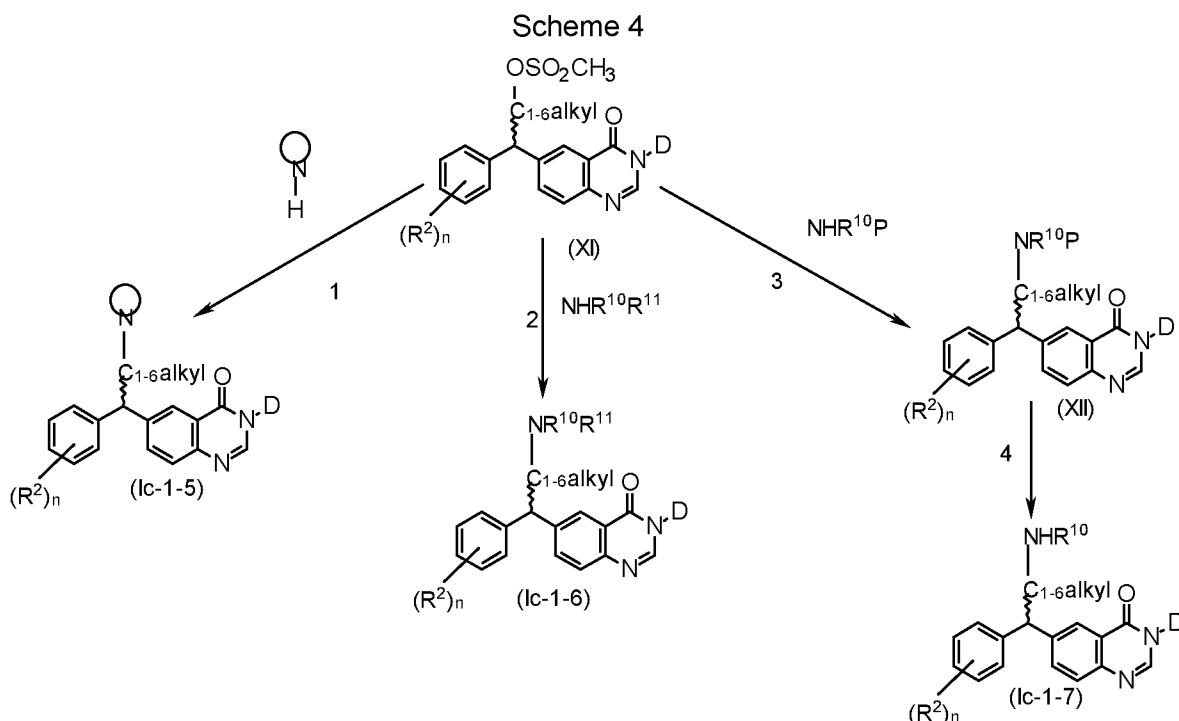
In Scheme 3, where W<sub>1</sub> represents a suitable leaving group such as for example halo, e.g. bromo, chloro and the like, the following reaction conditions apply:

- 1: in the presence of a suitable catalyst such as for example [1,1'-bis(diphenylphosphino)-κP]ferrocene]dichloropalladium (PdCl<sub>2</sub>dppf), and a suitable solvent such as for example tetrahydrofuran (THF);
- 2: in the presence of a suitable base, such as for example butyl lithium, and a suitable solvent, such as for example THF, and R<sup>3d</sup> represents optionally substituted C<sub>1-6</sub>alkyl.
- This reaction can also be performed with a protected form of the reactant, namely W<sub>1</sub>-

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$R^{3d}$ -P wherein P is a suitable protective group, such as for example a *tert*-butyldimethylsilyl group followed by a suitable deprotection reaction, such as in the presence of a suitable desilylating reagent such as for example tetrabutylammonium fluoride, in a suitable solvent such as for example tetrahydrofuran or such as in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid (TFA), and a suitable solvent, such as for example an alcohol, e.g. methanol, or dichloromethane.

Compounds of formula (I) wherein W is  $-C(R^{3a}R^{3b})-$ , said compounds being represented by formula (Ic-1), can also be prepared according to the following reaction Scheme 4.



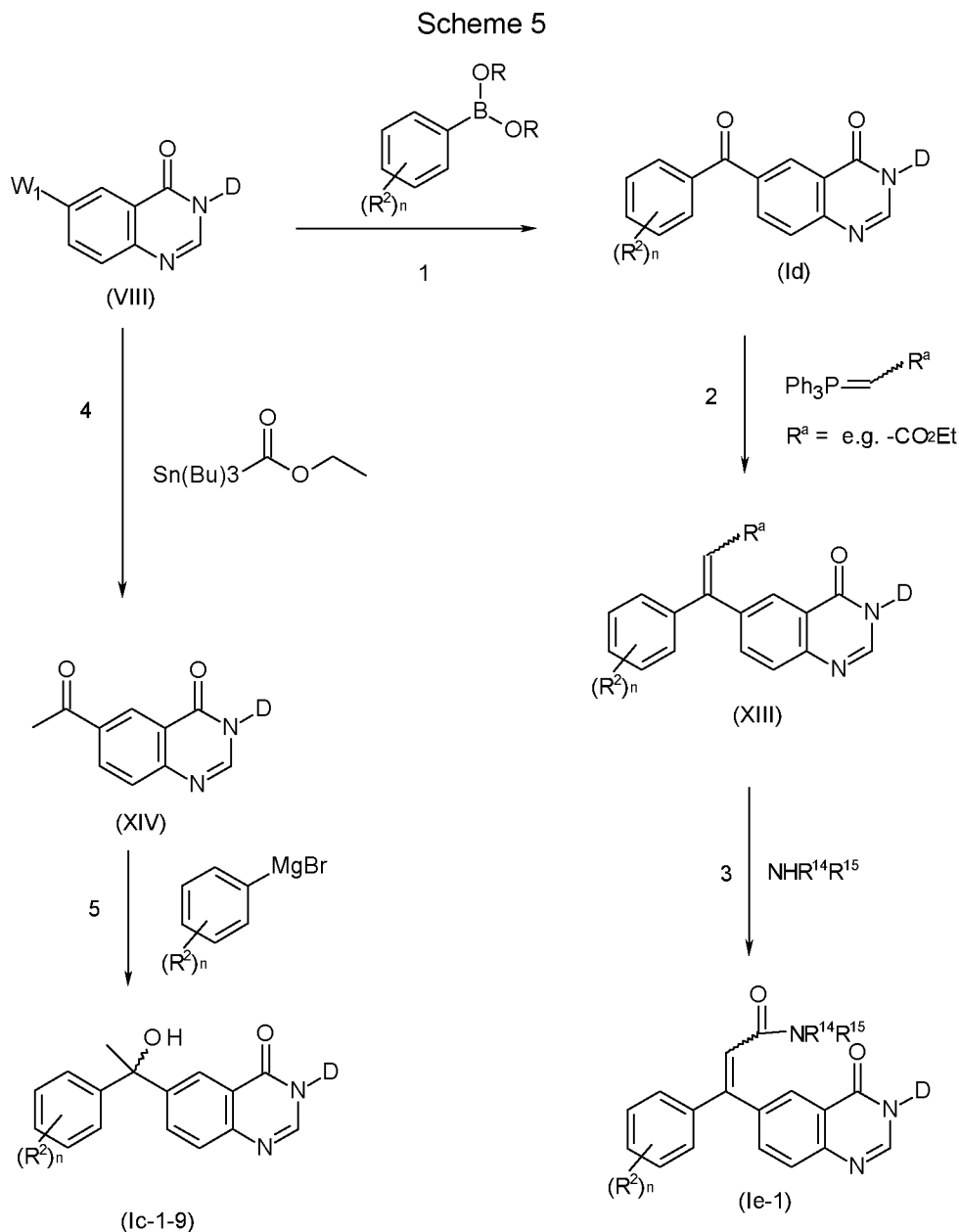
In Scheme 4, the following reaction conditions apply:

1,2,3: optionally in the presence of a suitable base, such as for example triethylamine, isopropylamine, potassium carbonate, sodium carbonate or sodium hydride, and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran, N,N-dimethylformamide, a suitable alcohol, e.g. 1-butanol and the like, and wherein P represents a suitable protective group, such as for example  $-C(=O)-OC(CH_3)_3$ ;

Step 1 can also be performed with a suitable salt of  $H-N$  (where N is a nitrogen-containing ring) which is a suitable nitrogen containing ring (unsubstituted or substituted) within the definition of  $R^9$ .

4: in the presence of a suitable acid, such as for example HCl or TFA, and a suitable solvent, such as for example dichloromethane or an alcohol, e.g. methanol.

Compounds of formula (I) wherein W is  $-C(R^{3a} R^{3b})-$ , said compounds being represented by formula (Ic-1), (Id) or (Ie), can be prepared according to the following reaction Scheme 5.



In Scheme 5, the following reaction conditions apply:

- 10 1: in the presence of carbon monoxide, a suitable palladium catalyst, such as for example palladium(II) acetate ( $Pd(OAc)_2$ ), a suitable ligand, such as for example

tricyclohexylphosphine, a suitable base, such as for example triethylamine in a suitable solvent, such as for example toluene

2: in a suitable solvent such as for example toluene

3: in the presence of a suitable lewis acid, such as for example trimethylaluminum, and

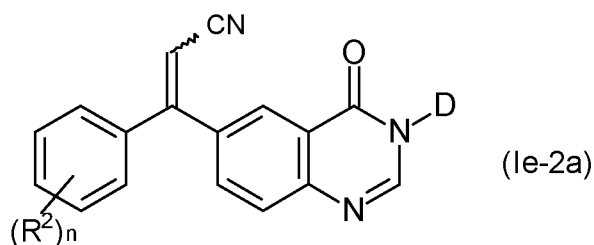
5 a suitable solvent, such as for example toluene;

4: in the presence of a suitable catalyst, such as for example

tetrakis(triphenylphosphine)palladium ( $\text{Pd}(\text{PPh}_3)_4$ ), a suitable solvent, such as for example toluene and a suitable acid such as hydrogen chloride

5: in the presence of a suitable solvent, such as for example tetrahydrofuran.

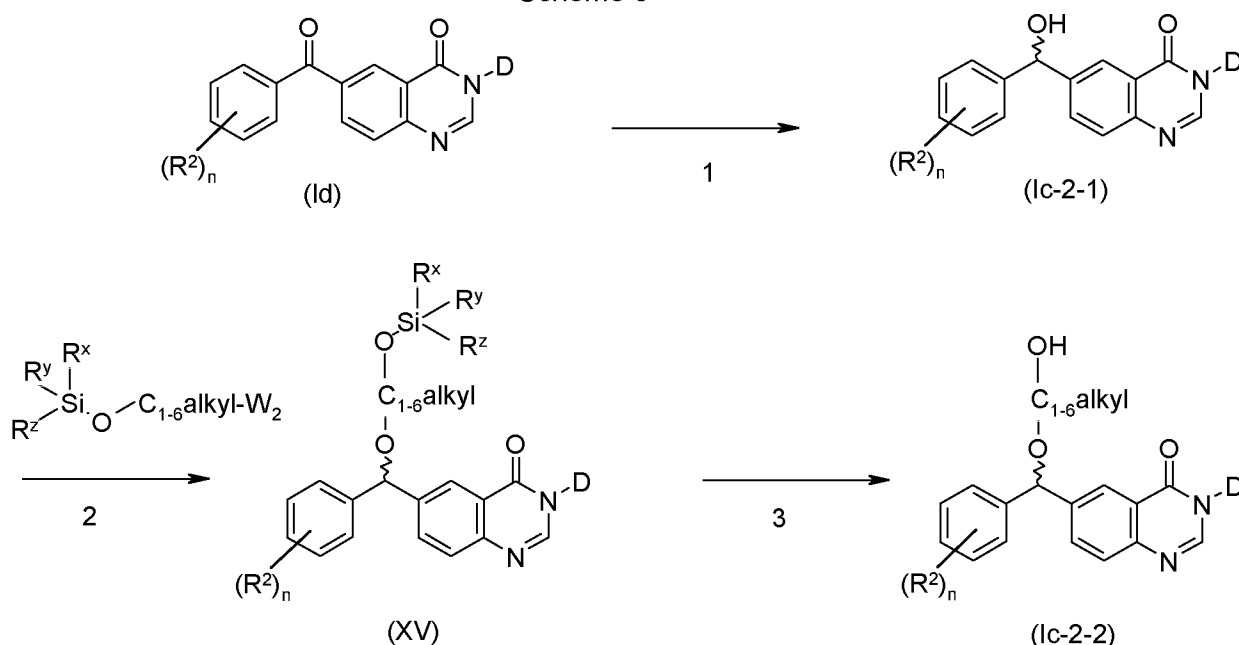
10 A compound of formula (Ie-2a)



can be prepared by an analogous reaction protocol as used for the synthesis of an intermediate of formula (XIII).

15 Compounds of formula (I) wherein W is  $-\text{C}(\text{R}^{3a}\text{R}^{3b})-$ , said compounds being represented by formula (Ic-2) can be prepared according to the following reaction Scheme 6.

Scheme 6



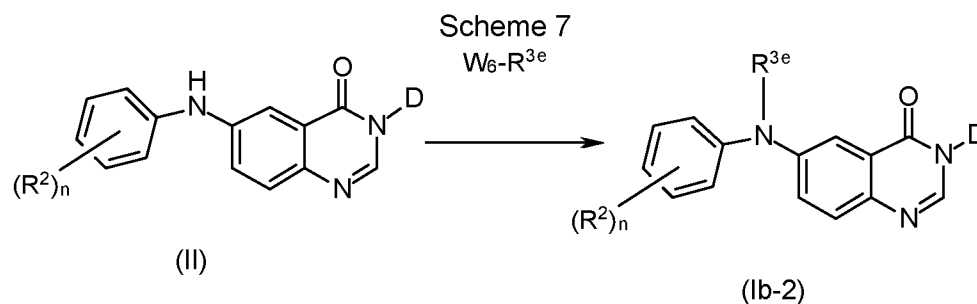
In Scheme 6, the following reaction conditions apply:

- 1: in the presence of a suitable reducing agent, such as for example sodium borohydride and in the presence of a suitable solvent, such as for example methanol;
- 2: in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide, and wherein R<sup>x</sup> and R<sup>y</sup> represents C<sub>1-4</sub>alkyl, and wherein R<sup>z</sup> represents C<sub>1-4</sub>alkyl or phenyl, for instance R<sup>x</sup> and R<sup>y</sup> represent CH<sub>3</sub> and R<sup>z</sup> represents C(CH<sub>3</sub>)<sub>3</sub> or phenyl, and wherein W<sub>2</sub> represents a suitable leaving group, such as for example halo, e.g. bromo;
- 3: in the presence of a suitable acid, such as for example TFA, and a suitable solvent, such as for example tetrahydrofuran. This reaction can also be performed with tetrabutyl ammonium fluoride in the presence of a suitable solvent such as for example tetrahydrofuran.

Compounds of formula (Ib) wherein R<sup>3</sup> represents optionally substituted C<sub>2-6</sub>alkynyl, said compounds being represented by formula (Ib-2), can be prepared according to reaction Scheme 7.



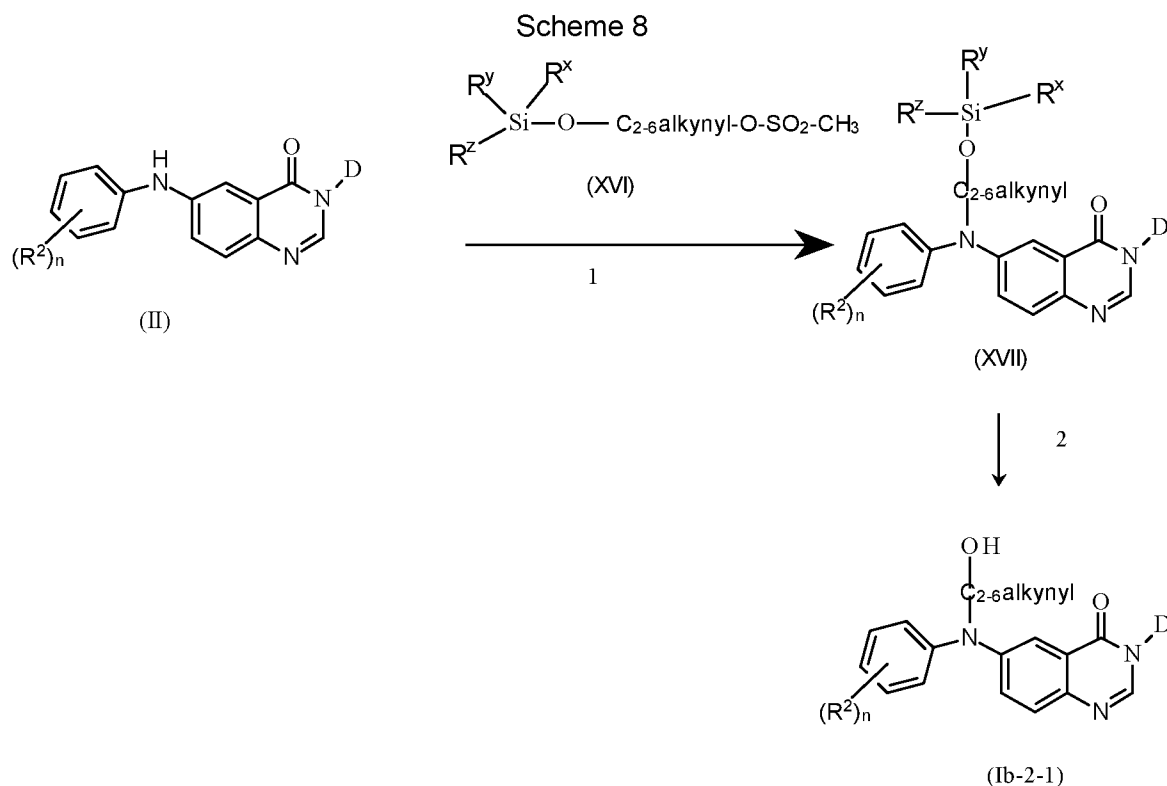
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In Scheme 7, the following reaction conditions apply:

in the presence of a suitable base, such as for example NaH, and a suitable solvent,  
 5 such as for example N,N-dimethylformamide and wherein R<sup>3e</sup> represents optionally  
 substituted C<sub>2-6</sub>alkynyl and W<sub>6</sub> represents a suitable leaving group such as for example  
 halo, e.g. chloro, or -O-S(=O)<sub>2</sub>-CH<sub>3</sub>, The intermediate W<sub>6</sub>-R<sup>3e</sup> wherein W<sub>6</sub> represents  
 -O-S(=O)<sub>2</sub>-CH<sub>3</sub>, can be prepared by reacting the corresponding alcohol derivative with  
 10 triethylamine or 4-dimethylaminopyridine, and a suitable solvent, such as for example  
 dichloromethane.

Compounds of formula (Ib-2), wherein R<sup>3e</sup> represents C<sub>2-6</sub>alkynyl substituted with  
 hydroxyl, said compounds being represented by formula (Ib-2-1), can be prepared  
 15 according to the following reaction Scheme 8.



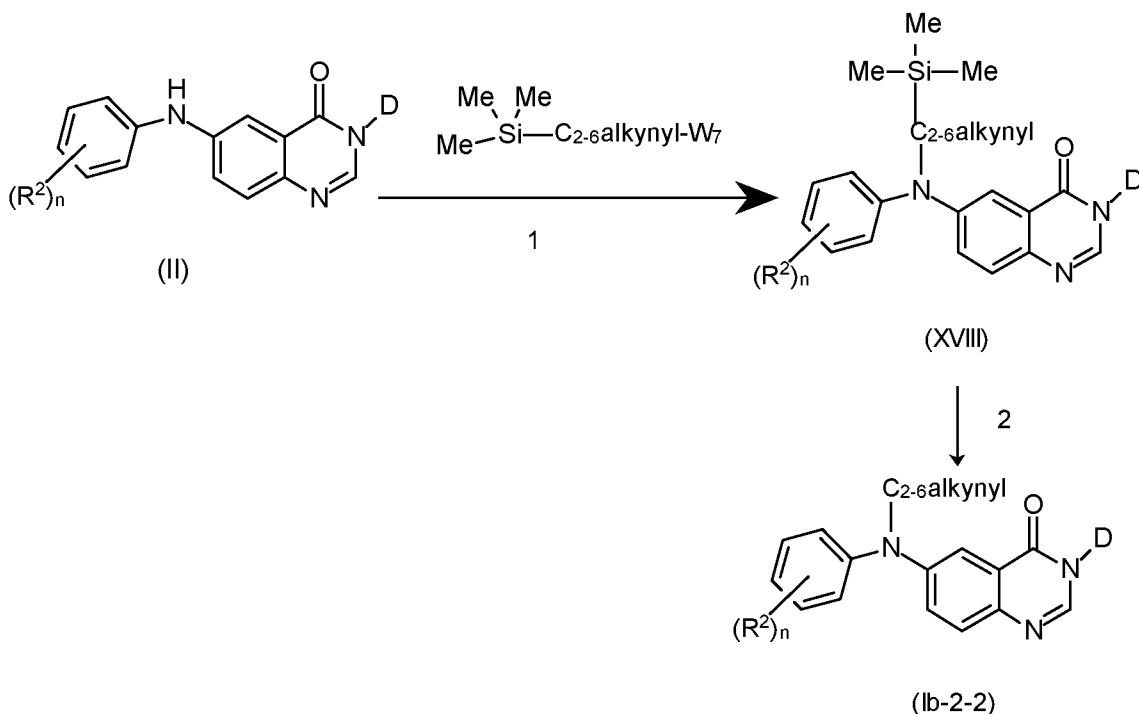
In Scheme 8, the following reaction conditions apply:

- 5 1: in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide, and where R<sup>x</sup>, R<sup>y</sup> and R<sup>z</sup> are as defined hereinabove;
  - 2: in the presence of a suitable acid, such as for example trifluoroacetic acid, and a suitable solvent, such as for example tetrahydrofuran. This reaction can also be
  - 10 performed with tetrabutyl ammonium fluoride in the presence of a suitable solvent such as for example tetrahydrofuran.
- Alternatively, instead of an intermediate of formula (XVI), halo-C<sub>2-6</sub>alkynyl-O-Si(R<sup>x</sup>)(R<sup>y</sup>)(R<sup>z</sup>) can also be used.

- 15 Compounds of formula (Ib-2), wherein R<sup>3e</sup> represents C<sub>2-6</sub>alkynyl, said compounds being represented by formula (Ib-2-2), can be prepared according to the following reaction Scheme 9.

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Scheme 9

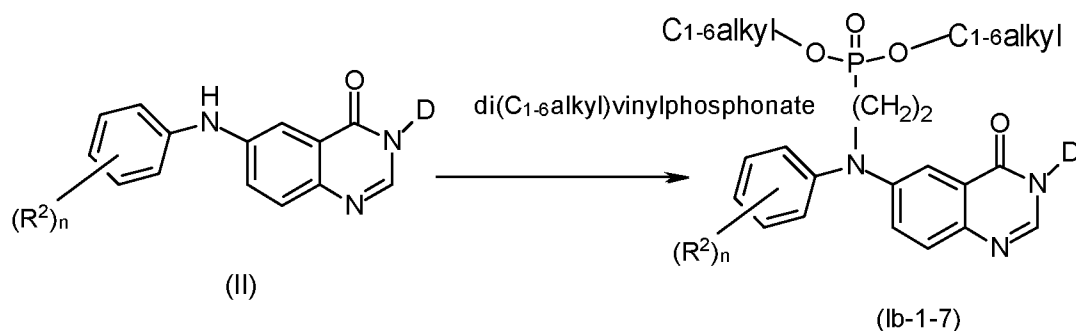


In Scheme 9, the following reaction conditions apply:

- 1: in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide, and wherein W<sub>7</sub> is a suitable leaving group, such as for example halogen;
- 2: in the presence of a suitable base, such as for example K<sub>2</sub>CO<sub>3</sub>, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like.

Compounds of formula (Ib), wherein R<sup>3</sup> represents ethyl substituted with –P(=O)(OC<sub>1-6</sub>alkyl)<sub>2</sub>, said compounds being represented by formula (Ib-1-7), can be prepared according to the following reaction Scheme 10.

Scheme 10



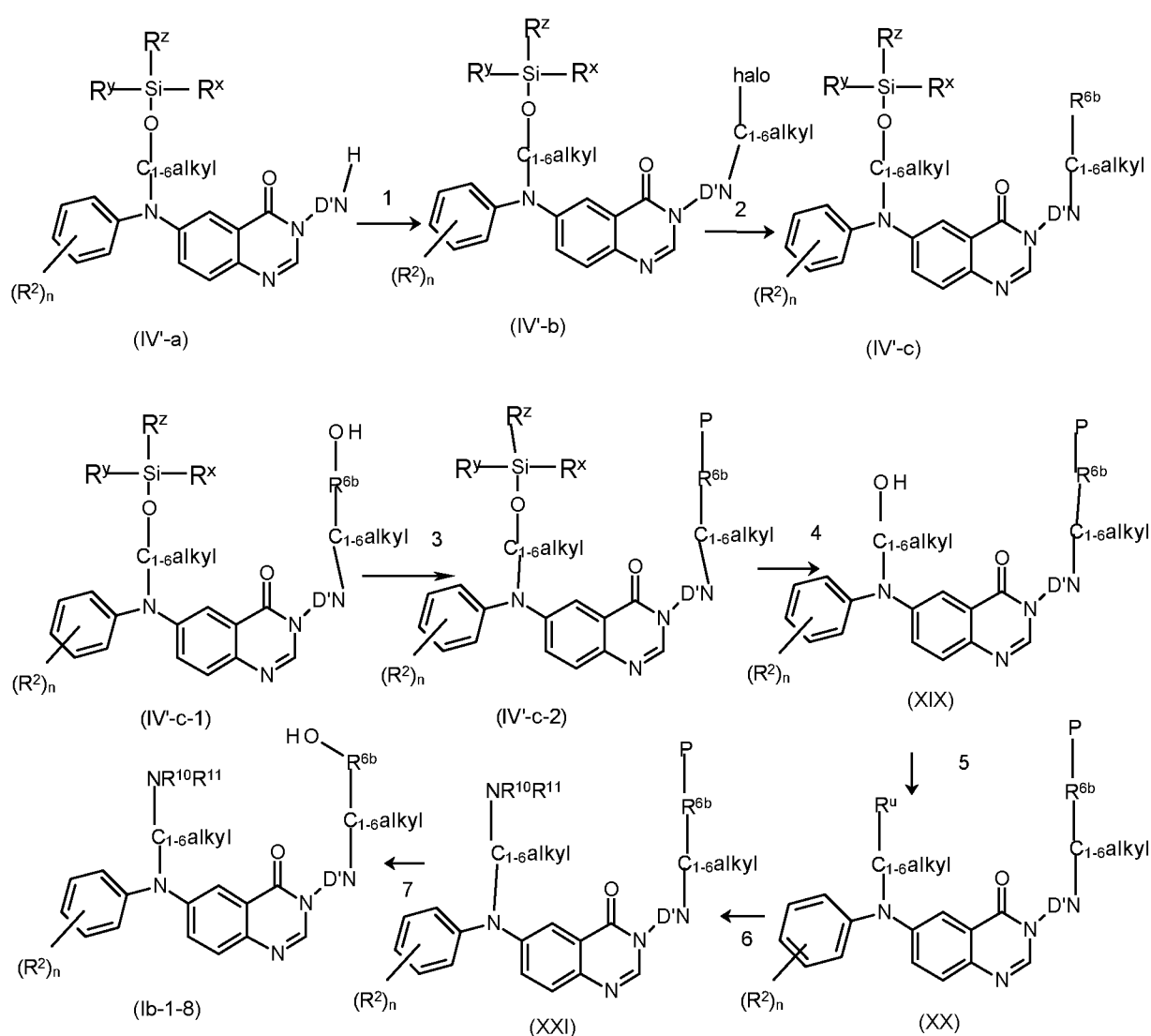
In Scheme 10, the following reaction conditions apply:

in the presence of a suitable catalyst, such as for example tri-N-butylphosphine, and a suitable solvent, such as for example acetonitrile.

Intermediates of formula (IV') wherein D is a ring moiety containing a nitrogen atom, as represented in Scheme 11, can be further reacted according to the following reaction

- 5 Scheme 11. In Scheme 11, R<sup>6b</sup> is defined as a 4 to 7-membered monocyclic heterocyclyl which is attached to the remainder of the molecule via a N-atom, and which optionally contains at least one additional heteroatom selected from N, O or S.

Scheme 11



In Scheme 11, the D'N moiety represents a -D moiety wherein the D ring moiety contains a nitrogen atom, the following reaction conditions apply:

1: by reaction with  $W_8$ -C<sub>1-6</sub>alkyl-halo wherein  $W_8$  represents a suitable leaving group, such as for example halo, e.g. chloro, in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example N,N-dimethylformamide;

2: by reaction with  $R^{6b}$  in the presence of a suitable base, such as for example  $K_2CO_3$ , and a suitable solvent, such as for example acetonitrile;

3: when in an intermediate of formula (IV'-c) the  $R^{6b}$  carries a hydroxyl group as in an intermediate of formula (IV'-c-1), then said hydroxyl group can be protected by a suitable protective group P, such as for example  $-O-C(=O)-C_{1-6}$ alkyl, by reaction with C<sub>1-6</sub>alkyl-C(=O)- $W_9$  wherein  $W_9$  represents a suitable leaving group, such as for example halo,

e.g. chloro, in the presence of a suitable base, such as for example triethylamine, 4-dimethylaminopyridine, and a suitable solvent, such as for example dichloromethane;

4: by reaction with tetrabutylammonium fluoride (TBAF) in the presence of a suitable solvent, such as for example tetrahydrofuran;

5: by reaction with methane sulfonyl chloride in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane, and wherein  $R^u$  represents  $-SO_2CH_3$ ;

6: by reaction with an intermediate of formula  $NHR^{10}R^{11}$  in a suitable solvent, such as for example acetonitrile;

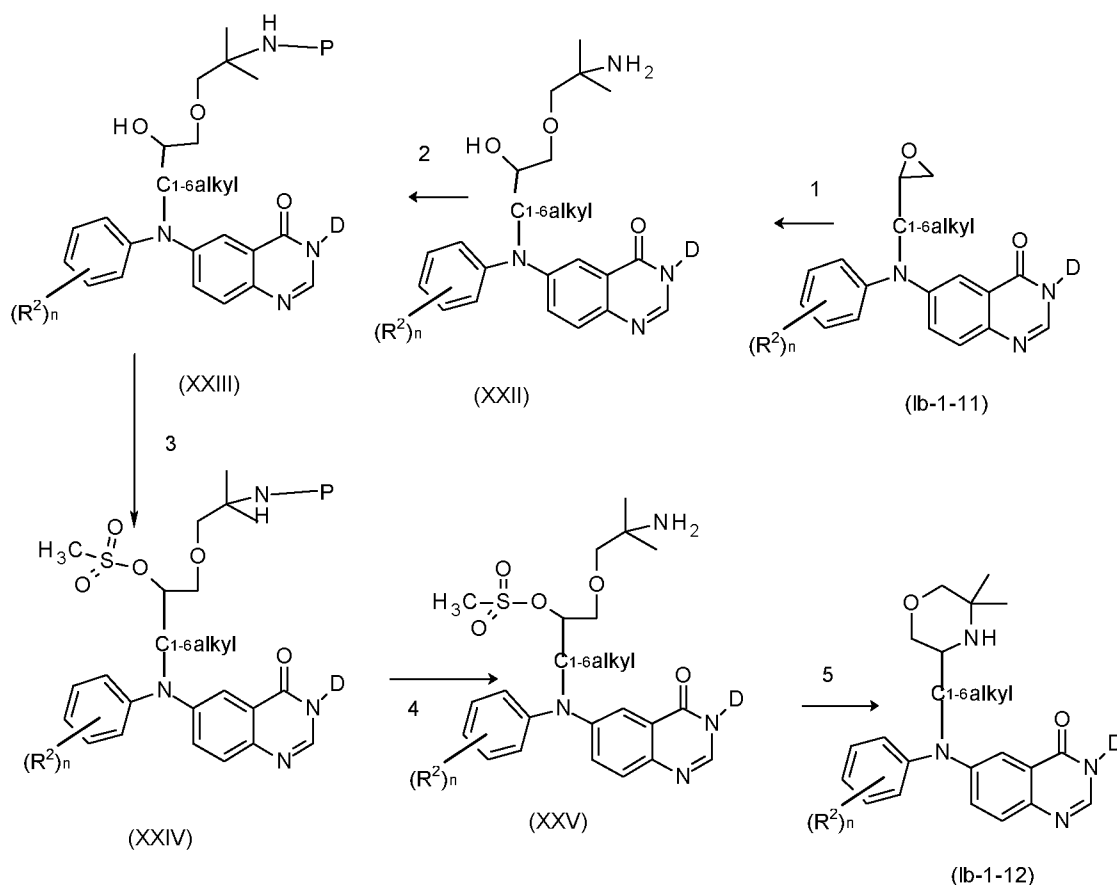
7: in the presence of a suitable base, such as for example  $K_2CO_3$ , and a suitable solvent, such as for example an alcohol, e.g. methanol and the like. It is considered to be within the knowledge of the person skilled in the art to recognize for which other D ring moieties the described reactions also apply.

Intermediates of formula (IV') and (XX) can also be reacted to prepare compounds of the present invention according to the reaction schemes as presented in Scheme 1. It is considered to be within the knowledge of the skilled person to recognize in which condition and for which definitions of  $R^1$  on the D ring moiety a protective group may be appropriate for the reactions to be carried out. For instance, a hydroxyl group within the definition of  $R^1$  may be protected with a tert. butyldimethylsilyl moiety; a NH group within the definition of  $R^1$  may be protected with a  $-C(=O)-O-C(CH_3)_3$  group.

It is also considered to be within the knowledge of the skilled person to recognize appropriate deprotection reactions.

Compounds of formula (Ib) wherein  $R^3$  is C<sub>1-6</sub>alkyl substituted with 3,3-dimethylmorpholine can be prepared according to the below reaction Scheme 12.

Scheme 12

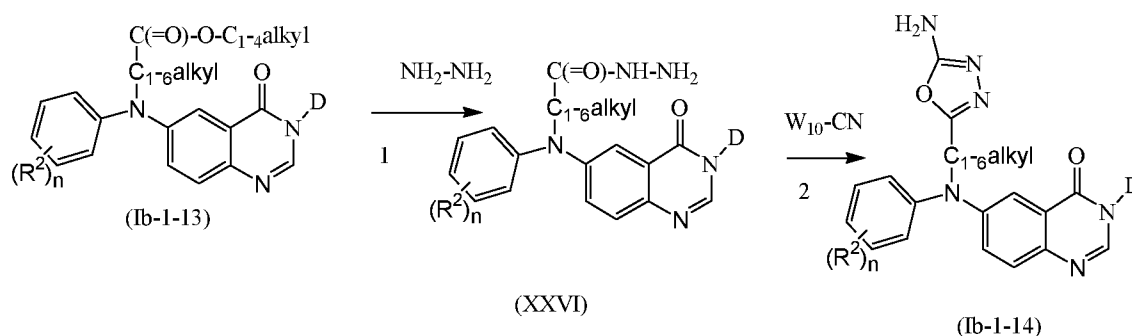


In Scheme 12, the following reaction conditions apply:

- 5 1: reaction with 2-amino-2-methyl-1-propanol in the presence of a suitable base, such as for example NaH and in the presence of a suitable solvent, such as for example *N,N*-dimethylformamide;
- 2: reaction with for instance di-tert-butyl dicarbonate in the presence of a suitable solvent, such as for example dioxane, and a suitable base, such as for example NaHCO<sub>3</sub>, and wherein P is a suitable protecting group P, such as for example –C(=O)–O–C(CH<sub>3</sub>)<sub>3</sub>;
- 10 3: reaction with methanesulfonyl chloride in the presence of a suitable solvent, such as for example dichloromethane, and a suitable base, such as for example triethylamine;
- 4: reaction with a suitable acid, such as for example trifluoroacetic acid, in the presence of a suitable solvent, such as for example dichloromethane;
- 15 5: in the presence of a suitable base, such as for example *N,N*-diisopropylethylamine and triethylamine, and a suitable solvent, such as for example an alcohol, e.g. methanol.

Compounds of formula (Ib) wherein R<sup>3</sup> is C<sub>1-6</sub>alkyl substituted with 5-amino-1,3,4-oxadiazolyl can be prepared according to the below reaction Scheme 13.

Scheme 13

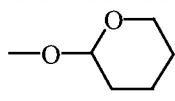


In Scheme 13, the following reaction conditions apply:

- 1: in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol;
- 2: in the presence of a suitable base, such as for example NaHCO<sub>3</sub>, and a suitable solvent, such as for example water or dioxane, and wherein W<sub>10</sub> represents a suitable leaving group, such as for example halo, e.g. bromo.

It is considered to be within the knowledge of the person skilled in the art to recognize in which condition and on which part of the molecule a protective group may be appropriate. For instance, protective group on the R<sup>1</sup> substituent or on the D moiety, or protective group on the R<sup>3</sup> substituent or on the R<sup>2</sup> substituent or combinations thereof.

The skilled person is also considered to be able to recognize the most feasible

protective group, such as for example -C(=O)-O-C<sub>1-4</sub>alkyl or  or

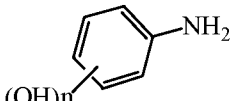
O-Si(CH<sub>3</sub>)<sub>2</sub>(C(CH<sub>3</sub>)<sub>3</sub>) or -CH<sub>2</sub>-O-CH<sub>2</sub>CH<sub>2</sub>-O-CH<sub>3</sub>. The skilled person is also considered to be able to recognize the most feasible deprotection reaction conditions, such as for example suitable acids, e.g. trifluoroacetic acid, hydrochloric acid, or suitable salts, such as for example tetrabutylammonium fluoride (TBAF).

The skilled person is also considered to be able to recognize that when R<sup>1</sup> represents C(=O)-morpholinyl, said R<sup>1</sup> can be prepared from -C(=O)-NH-CH<sub>2</sub>-CH<sub>2</sub>-O-CH<sub>2</sub>-CH<sub>2</sub>-O-SO<sub>2</sub>-4-methylphenyl, in the presence of sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide. Or that when R<sup>1</sup> represents -NH-C(=O)-morpholinyl, said R<sup>1</sup> can be prepared from -NH-C(=O)-O-C(CH<sub>3</sub>)<sub>3</sub> in the presence of morpholine, and a suitable solvent, such as for example 1-methyl-2-pyrrolidinone. Or that

when  $R^1$  represents hydroxyl $C_{1-6}$ alkyl, e.g.  $-CH_2-CH_2-OH$ , said  $R^1$  can be prepared from the corresponding alkoxy carbonyl intermediate, e.g.  $-CH_2-C(=O)-O-CH_2-CH_3$ , in the presence of Dibal-H 1M in hexane, and a suitable solvent, such as for example tetrahydrofuran.

5

The present invention also comprises deuterated compounds. These deuterated compounds may be prepared by using the appropriate deuterated intermediates during

the synthesis process. For instance the below intermediate  can be

converted into the below intermediate  by reaction with

10 iodomethane-D3 in the presence of a suitable base, such as for example cesium carbonate, and a suitable solvent, such as for example acetonitrile.

The compounds of formula (I) may also be converted into each other via art-known reactions or functional group transformations.

15 For instance, compounds of formula (I) wherein  $R^1$  represents tetrahydropyranyl can be converted into a compound of formula (I) wherein  $R^1$  represents hydrogen, by reaction with a suitable acid, such as for example HCl or trifluoroacetic acid, in the presence of a suitable solvent, such as for example dichloromethane, dioxane, or an alcohol, e.g. methanol, isopropanol and the like.

20 Compounds of formula (I) wherein  $R^1$  or  $R^3$  represent monohaloalkyl, can be converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with a ring moiety as defined hereinabove and linked to the  $C_{1-6}$ alkyl moiety by the nitrogen atom, by reaction with a suitable ring moiety optionally in the presence of a suitable base, such as for example triethylamine or  $K_2CO_3$  or sodium hydride, and optionally in  
25 the presence of a suitable solvent, such as for example acetonitrile, N,N-dimethylformamide or 1-methyl-2-pyrrolidinone.

Compounds of formula (I) wherein  $R^1$  or  $R^3$  represents  $C_{1-6}$ alkyl-OH, can be converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl-F by reaction with diethylaminosulfur trifluoride in the presence of a suitable solvent, such as for example  
30 dichloromethane and in the presence of catalytic amounts of an alcohol, such as for example ethanol. Likewise, a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with  $R^6$  or  $R^9$  wherein said  $R^6$  or  $R^9$  is substituted with OH, can be



converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with  $R^6$  or  $R^9$  wherein said  $R^6$  or  $R^9$  is substituted with F, by reaction with diethylaminosulfur trifluoride in the presence of a suitable solvent, such as for example dichloromethane.

- 5 Compounds of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with  $R^6$  or  $R^9$  wherein said  $R^6$  or  $R^9$  is substituted with  $-C(=O)-O-C_{1-6}$ alkyl, can be converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with  $R^6$  or  $R^9$  wherein said  $R^6$  or  $R^9$  is substituted with  $-CH_2-OH$ , by reaction with a suitable reducing agent such as for example  $LiAlH_4$ , in the presence of a suitable solvent, such as for  
10 example tetrahydrofuran.

Compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with 1,3-dioxo-2H-isoindol-2-yl, can be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with amino, by reaction with hydrazine monohydrate in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol.

- 15 Compounds of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with amino, can be converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2-C_{1-6}$ alkyl, by reaction with  $Cl-S(=O)_2-C_{1-6}$ alkyl in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dichloromethane.

- 20 Compounds of formula (I) wherein  $R^1$  or  $R^3$  represents  $C_{1-6}$ alkyl substituted with halo, can be converted into a compound of formula (I) wherein  $R^1$  or  $R^3$  represent  $C_{1-6}$ alkyl substituted with  $NR^4R^5$  or  $NR^{10}R^{11}$ , by reaction with  $NHR^4R^5$  or  $NHR^{10}R^{11}$ , either using such amino in large excess or in the presence of a suitable base, such as for example  $K_2CO_3$ , and a suitable solvent, such as for example acetonitrile, N,N-dimethylacetamide  
25 or 1-methyl-pyrrolidinone.


Compounds of formula (I) wherein  $R^1$  represents hydrogen, can be converted into a compound of formula (I) wherein  $R^1$  represents polyhalo $C_{1-6}$ alkyl or polyhydroxy $C_{1-6}$ alkyl or  $C_{1-6}$ alkyl or  $-S(=O)_2-NR^{14}R^{15}$  or  $-S(=O)_2-C_{1-6}$ alkyl, by reaction with polyhalo $C_{1-6}$ alkyl-W or polyhydroxy $C_{1-6}$ alkyl-W or  $C_{1-6}$ alkyl-W or  $W-S(=O)_2-NR^{14}R^{15}$  or  $W-S(=O)_2-C_{1-6}$ alkyl, wherein W represents a suitable leaving group, such as for example halo, e.g. bromo  
30 and the like, in the presence of a suitable base, such as for example sodium hydride or  $K_2CO_3$  or triethylamine or 4-dimethylamino-pyridine or diisopropylamine, and a suitable solvent, such as for example N,N-dimethylformamide or acetonitrile or dichloromethane.

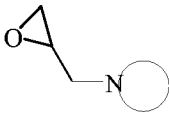

- Compounds of formula (I) wherein  $R^1$  represents hydrogen can also be converted into a  
35 compound of formula (I) wherein  $R^1$  represents  $C_{1-6}$ alkyl-OH, by reaction with  $W-C_{1-6}$ alkyl-O-Si(CH<sub>3</sub>)<sub>2</sub>(C(CH<sub>3</sub>)<sub>3</sub>) in the presence of a suitable base, such as for example

sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide. The skilled person will realize that this step is followed by reaction with a suitable acid, such as for example trifluoroacetic acid, in a suitable solvent, such as for example tetrahydrofuran, or by reaction with tetrabutyl ammonium fluoride in the presence of a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $R^1$  represents hydrogen, can also be converted into compound of formula (I) wherein  $R^1$  represents ethyl substituted with  $-S(=O)_2-C_{1-6}alkyl$ , by reaction with  $C_{1-6}alkyl$ -vinylsulfone, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example an alcohol, e.g. methanol or by reaction with  $C_{1-6}alkyl$ -2-bromoethylsulfone in the presence of a suitable deprotonating agent, such as for example NaH, and a suitable solvent, such as for example dimethylformamide.

Compounds of formula (I) wherein  $R^1$  represents hydrogen can also be converted into a

compound of formula (I) wherein  $R^1$  represents  $-CH_2-CHOH-CH_2-N$  , by reaction

with  in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide, wherein  $-N$   represents a suitable nitrogen containing ring within the definition of  $R^6$ .

Compounds of formula (I) wherein  $R^1$  represents  $C_{1-6}alkyl$  substituted with  $R^6$  wherein said  $R^6$  is substituted with  $-C(=O)-O-C_{1-6}alkyl$  or  $-S(=O)_2-NR^{14}R^{15}$  or wherein  $R^3$  represents  $C_{1-6}alkyl$  substituted with  $R^9$  wherein said  $R^9$  is substituted with  $-C(=O)-O-C_{1-6}alkyl$  or  $-S(=O)_2-NR^{14}R^{15}$ , can be converted into a compound of formula (I) wherein the  $R^6$  or  $R^9$  is unsubstituted, by reaction with a suitable acid, such as for example HCl and a suitable solvent, such as for example dioxane, acetonitrile or an alcohol, e.g.

isopropylalcohol.

Compounds of formula (I) wherein  $R^1$  represents  $C_{1-6}alkyl$  substituted with  $R^6$  wherein said  $R^6$  is a ring moiety comprising a nitrogen atom which is substituted with  $-CH_2-OH$  or wherein  $R^3$  represents  $C_{1-6}alkyl$  substituted with  $R^9$  wherein said  $R^9$  is a ring moiety comprising a nitrogen atom which is substituted with  $-CH_2-OH$ , can be converted into a compound of formula (I) wherein the  $R^6$  or  $R^9$  is unsubstituted, by reaction with sodium hydroxide, in the presence of a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $R^1$  represents  $C_{1-6}alkyl$  substituted with  $R^6$  or  $R^3$  represents  $C_{1-6}alkyl$  substituted with  $R^9$ , wherein said  $R^6$  or said  $R^9$  is unsubstituted, can

be converted into a compound of formula (I) wherein said R<sup>6</sup> or said R<sup>9</sup> is substituted with C<sub>1-6</sub>alkyl, by reaction with W-C<sub>1-6</sub>alkyl wherein W is as defined above, in the presence of a suitable base. Such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.

- 5 Compounds of formula (I) wherein R<sup>1</sup> or R<sup>3</sup> represent hydroxyC<sub>1-6</sub>alkyl, can be converted into the corresponding carbonyl compound, by reaction with Dess-Martin-periodinane, in the presence of a suitable solvent, such as for example dichloromethane.

- 10 Compounds of formula (I) wherein R<sup>1</sup> represents C<sub>1-6</sub>alkyl substituted with R<sup>6</sup> or R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, wherein said R<sup>6</sup> or said R<sup>9</sup> is substituted with C<sub>1-6</sub>alkyl-halo, can be converted into a compound of formula (I) wherein said R<sup>6</sup> or said R<sup>9</sup> is substituted with C<sub>1-6</sub>alkyl-CN, by reaction with sodium cyanide, in the presence of a suitable solvent, such as for example water or an alcohol, e.g. ethanol.

- 15 Compounds of formula (I) wherein R<sup>1</sup> represents C<sub>1-6</sub>alkyl substituted with R<sup>6</sup> wherein said R<sup>6</sup> is unsubstituted or wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with R<sup>9</sup> wherein said R<sup>9</sup> is unsubstituted, can be converted into a compound of formula (I) wherein R<sup>6</sup> or R<sup>9</sup> is substituted with -CH<sub>3</sub> or -CH(CH<sub>3</sub>)<sub>2</sub>, by reaction with formaldehyde or acetone and NaBH<sub>3</sub>CN, in the presence of a suitable solvent, such as for example tetrahydrofuran or an alcohol, e.g. methanol.

- 20 Compounds of formula (I) wherein R<sup>1</sup> contains a R<sup>6</sup> substituent substituted with OH or wherein R<sup>3</sup> contains a R<sup>9</sup> substituent substituted with OH, can be converted into a compound of formula (I) wherein the R<sup>6</sup> or R<sup>9</sup> substituent is substituted with C<sub>1-6</sub>alkyloxy, by reaction with W-C<sub>1-6</sub>alkyl, in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide.


- 25 Compounds of formula (I) wherein R<sup>1</sup> contains a R<sup>6</sup> substituent substituted with C<sub>1-6</sub>alkyloxy or wherein R<sup>3</sup> contains a R<sup>9</sup> substituent substituted with C<sub>1-6</sub>alkyloxy, can be converted into a compound of formula (I) wherein the R<sup>6</sup> or R<sup>9</sup> substituent is substituted with -OH by reaction with a suitable acid, such as for example hydrochloric acid.


- 30 Compounds of formula (I) wherein R<sup>1</sup> contains a R<sup>6</sup> substituent substituted with halo or wherein R<sup>3</sup> contains a R<sup>9</sup> substituent substituted with halo can be converted into a compound of formula (I) wherein the R<sup>6</sup> or R<sup>9</sup> substituent is substituted with -NR<sup>14</sup>R<sup>15</sup> by reaction with NHR<sup>14</sup>R<sup>15</sup> in a suitable solvent, such as for example 1-methyl-pyrrolidinone.

- 35 Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with -C(=O)-O-C<sub>1-6</sub>alkyl, can be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with COOH, by reaction with LiOH in the presence of a suitable solvent, such as for example tetrahydrofuran. Said compounds of formula (I) wherein R<sup>3</sup>

represents C<sub>1-6</sub>alkyl substituted with COOH, can be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with –C(=O)-NH<sub>2</sub> or –C(=O)-NHCH<sub>3</sub> or –C(=O)NR<sup>10</sup>R<sup>11</sup>, by reaction with NH(Si(CH<sub>3</sub>)<sub>3</sub>)<sub>2</sub> or MeNH<sub>3</sub><sup>+</sup>Cl<sup>-</sup> or NHR<sup>10</sup>R<sup>11</sup> in the presence of suitable peptide coupling reagents such as for example 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl and 1-hydroxybenzotriazole, a suitable base, such as for example triethylamine and a suitable solvent such as for example dichloromethane or N,N-dimethylformamide.

Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with –C(=O)-O-C<sub>1-6</sub>alkyl, can also be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with 4,5-dihydro-imidazol-2-yl, by reaction under N<sub>2</sub> with ethylenediamine and trimethylaluminium in the presence of a suitable solvent, such as for example toluene and heptane. Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with COOH, can also be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with –C(=O)-N(CH<sub>3</sub>)(OCH<sub>3</sub>) by reaction with dimethylhydroxylamine, in the presence of carbonyldiimidazole and a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with , can be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with 2 OH's, by reaction with a suitable acid, such as for example trifluoroacetic acid, and a suitable solvent, such as for example dioxane or water. These compounds of

formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with , can also be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with OH and NR<sup>10</sup>R<sup>11</sup>, by reaction with NH<sub>2</sub>R<sup>10</sup>R<sup>11</sup> optionally in salt form, such as for example NHR<sup>10</sup>R<sup>11</sup><sup>+</sup>Cl<sup>-</sup>, optionally in the presence of a suitable base, such as for example sodium hydride or Na<sub>2</sub>CO<sub>3</sub> or triethylamine, a suitable additive such as for example KI, and in the presence of a suitable solvent, such as for example N,N-dimethylformamide or an alcohol, e.g. 1-butanol or ethanol.

Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-3</sub>alkyl substituted with –C(=O)-O-C<sub>1-6</sub>alkyl, can be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-3</sub>alkyl substituted with –C(CH<sub>3</sub>)<sub>2</sub>-OH, by reaction with iodomethane and Mg powder, in the presence of a suitable solvent, such as for example diethylether or tetrahydrofuran.

Compounds of formula (I) wherein R<sup>3</sup> represents C<sub>1-5</sub>alkyl substituted with –C(=O)-O-C<sub>1-6</sub>alkyl, can be converted into a compound of formula (I) wherein R<sup>3</sup> represents C<sub>1-6</sub>alkyl substituted with –OH, by reaction with a suitable reducing agent such as for example LiAlH<sub>4</sub>, in a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $R^3$  represents  $C_{1-5}$ alkyl substituted with  $-OH$ , can be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-5}$ alkyl substituted with  $-O-C(=O)-C_{1-6}$ alkyl by reaction with  $Cl-C(=O)-C_{1-6}$ alkyl in the presence of a suitable base, such as for example NaH, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $R^3$  represents  $-CH_2-CH=CH_2$ , can be converted into a compound of formula (I) wherein  $R^3$  represents  $-CH_2-CHOH-CH_2-OH$ , by reaction with potassium permanganate, and a suitable solvent, such as for example acetone or water.

Compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-4}$ alkyl, can be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-C(C_{1-4}alkyl)=N-OH$ , by reaction with hydroxylamine, in the presence of a suitable base, such as for example pyridine, and a suitable solvent, such as for example an alcohol, e.g. ethanol.

Compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $NH_2$ , can be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-NH-C(=O)-R^6$  or with  $-NH-C(=O)-C_{1-6}$ alkyl or with  $-NH-C(=O)-polyhydroxyC_{1-6}alkyl$  or with  $-NH-C(=O)-polyhaloC_{1-6}alkyl$  or with  $-NH-C(=O)-polyhydroxypolyhaloC_{1-6}alkyl$ , by reaction with the corresponding COOH analogue, e.g.  $R^6-COOH$  or  $CF_3-C(CH_3)(OH)-$

COOH and the like, in the presence of suitable peptide coupling reagents such as 1-hydroxy-benzotriazole and 1-(3-dimethylamino)propylcarbodiimide optionally in the presence of a suitable base, such as for example triethylamine. Said compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $NH_2$ , can also be converted

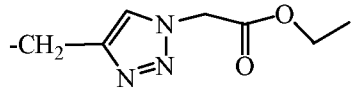
into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $NH-C(=O)-CF_3$ , by reaction with trifluoroacetic anhydride, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example tetrahydrofuran. Said compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl

substituted with  $NH_2$ , can also be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with  $-NH-polyhaloC_{1-6}alkyl$ , e.g.  $-NH-CH_2-CH_2-F$ , by

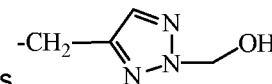
reaction with  $polyhaloC_{1-6}alkyl-W$ , with W as defined above, e.g. iodo-2-fluoroethane, in the presence of a suitable base, such as for example  $K_2CO_3$ , and a suitable solvent, such as for example N,N-dimethylformamide or dioxane.

Compounds of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with cyano, can be converted into a compound of formula (I) wherein  $R^3$  represents  $C_{1-6}$ alkyl substituted with tetrazolyl by reaction with sodium azide, and  $NH_4^+Cl^-$  in the presence of a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein  $R^3$  represents  $-\text{CH}_2-\text{C}\equiv\text{CH}$ , can be converted into a

compound of formula (I) wherein  $R^3$  represents , by reaction with ethyl azidoacetate in the presence of CuI and a suitable base, such as for example diisopropylamine, and a suitable solvent, such as for example tetrahydrofuran.

- 5 Compounds of formula (I) wherein  $R^3$  represents  $-\text{CH}_2-\text{C}\equiv\text{CH}$ , can be converted into a

compound of formula (I) wherein  $R^3$  represents  by reaction with sodium azide and formaldehyde, in the presence of a suitable catalyst, such as for example  $\text{CuSO}_4$  and sodium L ascorbate, a suitable acid, such as for example acetic acid, and a suitable solvent, such as for example dioxane.

- 10 Compounds of formula (I) wherein  $R^3$  represent  $\text{C}_{2-6}$ alkynyl, can be converted into a compound of formula (I) wherein  $R^3$  represents  $\text{C}_{2-6}$ alkynyl substituted with  $R^9$ , by reaction with  $\text{W}-R^9$  wherein W is as defined above, in the presence of a suitable catalyst, such as for example dichlorobis(triphenylphosphine)palladium, a suitable co-catalyst such as CuI, a suitable base, such as for example triethylamine, and a suitable solvent, such as for example dimethylsulfoxide.

Compounds of formula (I) wherein  $R^3$  comprises  $R^9$  substituted with halo, can be converted into a compound of formula (I) wherein  $R^3$  comprises  $R^9$  substituted with  $-\text{NR}^{14}\text{R}^{15}$  by reaction with  $\text{NHR}^{14}\text{R}^{15}$  in the presence of a suitable solvent, such as for example 1-methyl-2-pyrrolidinone.

- 20 Compounds of formula (I) wherein  $R^3$  comprises  $\text{C}_{2-6}$ alkynyl, can be hydrogenated into a compound of formula (I) wherein  $R^3$  comprises  $\text{C}_{2-6}$ alkyl in the presence of a suitable catalyst, such as for example palladium on charcoal, and a suitable solvent, such as for example ethylacetate.

- 25 Compounds of formula (I) wherein  $R^3$  comprises  $\text{C}_{2-6}$ alkynyl, can be hydrogenated into a compound of formula (I) wherein  $R^3$  comprises  $\text{C}_{2-6}$ alkenyl in the presence of a suitable catalyst, such as for example Lindlar catalyst, and a suitable solvent, such as for example ethylacetate.

- 30 Compounds of formula (I) wherein  $R^3$  represents  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OC}_{1-6}\text{alkyl})_2$  can be converted into a compound of formula (I) wherein  $R^3$  represents  $\text{C}_{1-6}$ alkyl substituted with  $-\text{P}(=\text{O})(\text{OH})_2$  by reaction with bromotrimethylsilane in the presence of a suitable solvent, such as for example dichloromethane.

Compounds of formula (I) wherein the  $R^9$  substituent is substituted with  $=\text{O}$ , can be converted into the corresponding reduced  $R^9$  substituent by reaction with a suitable

reducing agent, such as for example  $\text{NaBH}_4$  in a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $\text{R}^3$  comprises  $-\text{NHR}^{10}$  can be converted into a compound of formula (I) wherein  $\text{R}^3$  comprises  $-\text{NR}^{10}-(\text{C}=\text{O})$ -optionally substituted  $\text{C}_{1-6}$ alkyl,

5  $\text{C}_{1-6}$ alkyl, by reaction with the corresponding  $\text{W}-(\text{C}=\text{O})$ -optionally substituted  $\text{C}_{1-6}$ alkyl wherein W represents a suitable leaving group, such as for example halo, e.g. chloro and the like, in the presence of a suitable base, such as for example triethylamine, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein  $\text{R}^3$  represents  $\text{C}_{1-6}$ alkyl substituted with  $\text{NR}^{10}(\text{benzyl})$  can be converted into a compound of formula (I) wherein  $\text{R}^3$  represents  $\text{C}_{1-6}$ alkyl substituted with  $\text{NHR}^{10}$ , by reaction with 1-chloroethylchloroformate in the presence of a suitable solvent, such as for example dichloromethane

Compounds of formula (I) wherein  $\text{R}^1$  represents unsubstituted piperidine, can be converted into a compound of formula (I) wherein  $\text{R}^1$  represents 1-methyl-piperidine, by reaction with iodomethane in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein  $\text{R}^1$  represents hydrogen can be converted into a compound of formula (I) wherein  $\text{R}^1$  represents optionally substituted  $\text{C}_{1-6}$ alkyl, by reaction with optionally substituted  $\text{C}_{1-6}$ alkyl-W wherein W represents a suitable leaving group, such as for example halo, e.g. bromo and the like, in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example acetonitrile.

Compounds of formula (I) wherein  $\text{R}^2$  represents halo, e.g. bromo, can be converted into a compound of formula (I) wherein  $\text{R}^2$  represents cyano, by reaction with zinc cyanide, in the presence of a suitable catalyst, such as for example  $\text{Pd}_2(\text{dba})_3$  and a suitable ligand, such as for example 1,1-bis(diphenylphosphino)ferrocene, in the presence of a suitable solvent, such as for example N,N-dimethylformamide.

Said  $\text{R}^2$  substituent being cyano can be converted into  $-\text{CH}_2-\text{NH}_2$  by hydrogenation in the presence of  $\text{NH}_3$  and Nickel.

Compounds of formula (I) wherein  $\text{R}^2$  represents  $-\text{OCH}_3$  can be converted into a compounds of formula (I) wherein  $\text{R}^2$  represents  $-\text{OH}$  by reaction with boron tribromide in the presence of a suitable solvent, such as for example dichloromethane.

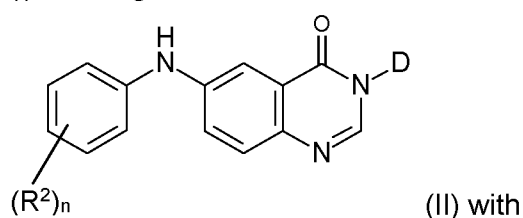
Compounds of formula (I) wherein  $\text{R}^2$  represents  $-\text{OH}$  can be converted into a compounds of formula (I) wherein  $\text{R}^2$  represents  $-\text{OCH}_3$  by reaction with methyl iodine in the presence of a suitable base, such as for example potassium carbonate, and a suitable solvent, such as for example N,N-dimethylformamide.

Compounds of formula (I) wherein  $R^2$  represents hydrogen, can be converted into a compound of formula (I) wherein  $R^2$  represents  $-\text{CHOH}-\text{CF}_3$  by reaction with trifluoroacetaldehyde methyl hemiketal.

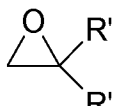
- 5 It is understood to be within the knowledge of the skilled man to recognize the above conversion reactions also applicable to the  $R^{3a}$  substituent.

A further aspect of the invention is a process for the preparation of a compound of formula (I) as defined herein, which process comprises:

- 10 (i) reacting an intermediate of formula

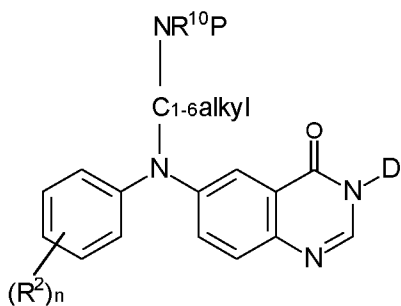


- (a)  $W_1-R^{3d}$  in the presence of a suitable base, such as for example sodium hydride or  $\text{Cs}_2\text{CO}_3$ , and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide, tetrahydrofuran or acetonitrile and wherein  $W_1$  represents a suitable leaving group, such as for example halo, e.g. bromo, chloro and the like, or  $-\text{O}-\text{S}(=\text{O})_2-\text{CH}_3$ , and  $R^{3d}$  represents optionally substituted  $\text{C}_{1-6}$ alkyl, such as for example  $-\text{CH}_2-\text{C}_3\text{H}_5$ ;
- 15 or



- (b) in the presence of a suitable base, such as for example sodium hydride,  $\text{Cs}_2\text{CO}_3$ , or potassium hydroxide, and a suitable solvent, such as for example N,N-dimethylformamide, N,N-dimethylacetamide or acetonitrile and wherein  $R'$  represents optionally substituted  $\text{C}_{1-4}$ alkyl and  $R''$  represents hydrogen or optionally substituted  $\text{C}_{1-4}$ alkyl; or
- (c)  $W_1-\text{C}_{1-6}\text{alkyl}-\text{NHR}^{10}$  in the presence of a suitable phase transfer reagent such as for example tetrabutylammonium bromide, a suitable base such as for example potassium hydroxide, and a suitable solvent such as for example 2-methyltetrahydrofuran and water;
- 25 (d)  $W_1-\text{C}_{1-6}\text{alkyl}-\text{Ncycle}$  in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example N,N-dimethylformamide or N,N-dimethylacetamide;
- 30 (ii) deprotecting an intermediate of formula

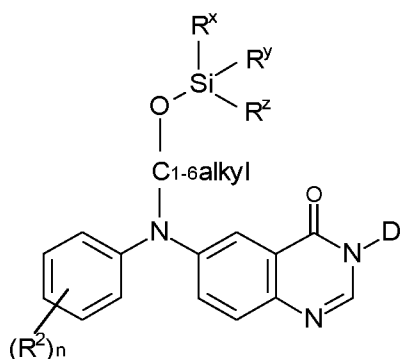




(III) in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, and a suitable solvent, such as for example dichloromethane or an alcohol, e.g. methanol;

(iii) reacting an intermediate of formula

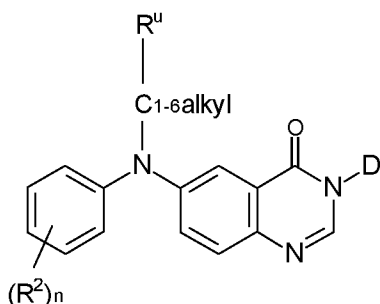
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(IV) wherein  $R^x$  and  $R^y$  represent  $C_{1-4}$ alkyl, and  $R^z$  represent  $C_{1-4}$ alkyl or phenyl, for instance  $R^x$  and  $R^y$  represent  $CH_3$  and  $R^z$  represents  $C(CH_3)_3$  or phenyl, with tetrabutylammonium fluoride (TBAF) in the presence of a suitable solvent, such as for example tetrahydrofuran. This type of reaction can also be performed in the presence of a suitable acid, such as for example acetic acid or HCl, and a suitable solvent, such as for example tetrahydrofurane or methanol

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(iv) reacting an intermediate of formula



(VI) wherein  $R^u$  is mesylate with

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(a)  $NHR^{10}R^{11}$  optionally in the presence of a suitable base, such as for example triethylamine,  $K_2CO_3$ ,  $Na_2CO_3$  or sodium hydride, and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran, dioxane, N,N-dimethylformamide or 1-methyl-pyrrolidinone. This type of reaction can also be performed with a suitable salt of  $NHR^{10}R^{11}$ , e.g. HCl salt of  $NHR^{10}R^{11}$ , or may be performed in the presence of

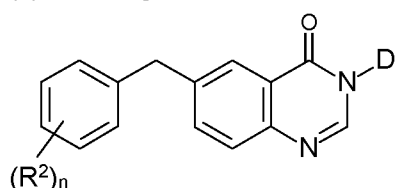
potassium iodide. In this way compounds wherein  $R^3$  represents iodoC<sub>1-6</sub>alkyl can be obtained; or



(b)  $\text{H}-\text{N}$  in the presence of a suitable solvent, such as for example acetonitrile or 1-methyl-2-pyrrolidinone, optionally in the presence of potassium iodide or a suitable base, such as for example  $\text{Na}_2\text{CO}_3$ ,  $\text{K}_2\text{CO}_3$  or triethylamine. This reaction can also be performed with a suitable salt of the suitable nitrogen containing ring within the definition of  $R^9$  ( $\text{H}-\text{N}$  represents a suitable nitrogen containing ring (unsubstituted or substituted) within the definition of  $R^9$ ); or

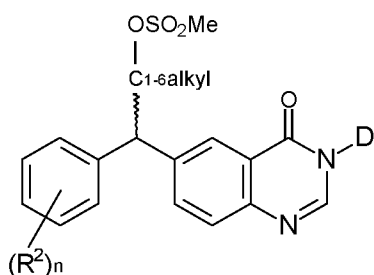
(c)  $\text{NHR}^{10}\text{P}$  in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example dimethylacetamide and wherein P represents a suitable protective group, such as for example  $-\text{C}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)_3$ , followed by a suitable deprotection reaction;

(v) reacting an intermediate of formula



(IX) with  $W_1-R^{3d}$  in the presence of a suitable base, such as for example butyl lithium, and a suitable solvent, such as for example tetrahydrofuran, and wherein  $W_1$  represents a suitable leaving group, such as for example halo, e.g. bromo and the like, and  $R^{3d}$  represents optionally substituted C<sub>1-6</sub>alkyl. This reaction can also be performed with a protected form of the reactant, namely  $W_1-R^{3d}-P$  wherein P is a suitable protective group, such as for example *tert*-butyldimethylsilyl group followed by a suitable deprotection reaction, such as in the presence of a suitable desilylating reagent such as for example tetrabutylammonium fluoride, in a suitable solvent such as for example tetrahydrofuran or in the presence of a suitable acid, such as for example HCl or trifluoroacetic acid, and a suitable solvent, such as for example an alcohol, e.g. methanol, or dichloromethane;

(vi) reacting an intermediate of formula



(XI) with

(a)  $\text{NHR}^{10}\text{R}^{11}$  optionally in the presence of a suitable base, such as for example triethylamine, potassium carbonate, sodium carbonate or sodium hydride, and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran,

5 N,N-dimethylformamide; or



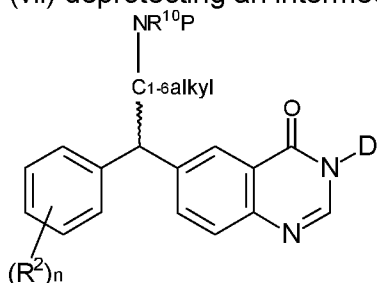
(b)  $\text{H}-\text{N}$  (where N is in a ring) optionally in the presence of a suitable base, such as for example triethylamine, potassium carbonate, sodium carbonate or sodium hydride, and optionally a suitable solvent, such as for example acetonitrile, tetrahydrofuran, N,N-dimethylformamide. This reaction can also be performed with a suitable salt of

10  $\text{H}-\text{N}$  (where N is in a ring) which is a suitable nitrogen containing ring (unsubstituted or substituted) within the definition of  $\text{R}^9$ ; or

(c)  $\text{NHR}^{10}\text{P}$ : in the presence of a suitable base, such as for example sodium hydride, and a suitable solvent, such as for example dimethylacetamide and wherein P represents a suitable protective group, such as for example  $-\text{C}(=\text{O})-\text{O}-\text{C}(\text{CH}_3)_3$ , followed

15 by a suitable deprotection reaction;

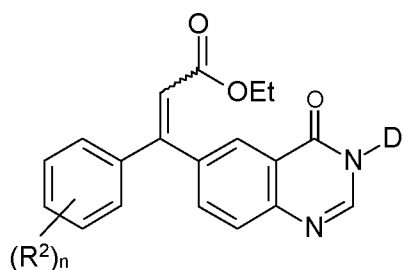
(vii) deprotecting an intermediate of formula



(XII) in the presence of a suitable acid, such as for

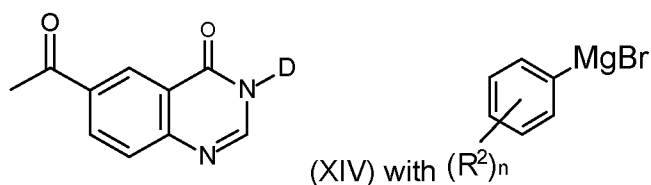
example HCl or trifluoroacetic acid, and a suitable solvent, such as for example dichloromethane or an alcohol, e.g. methanol;

20 (viii) reacting an intermediate of formula (XIII) wherein  $\text{R}^a$  is defined as  $-\text{CO}_2\text{Et}$ , said intermediates being represented by formula (XIII-a)



(XIII-a) with  $\text{NHR}^{14}\text{R}^{15}$  in the presence of a suitable Lewis acid, such as for example trimethylaluminum, and a suitable solvent, such as for example toluene;

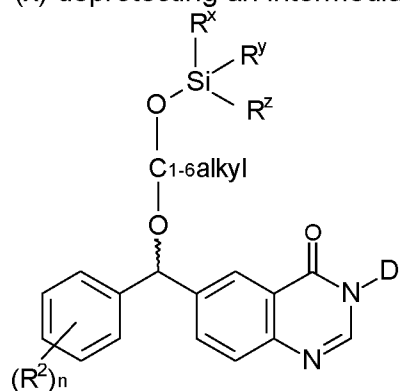
(ix) reacting an intermediate of formula



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solvent, such as for example tetrahydrofuran;

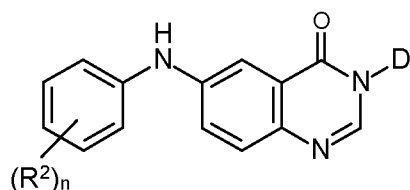
(x) deprotecting an intermediate of formula



(XV) in the presence of a suitable desilylating reagent such as for example tetrabutylammonium fluoride, and in the presence of a suitable solvent, such as for example tetrahydrofuran;

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(xi) reacting an intermediate of formula

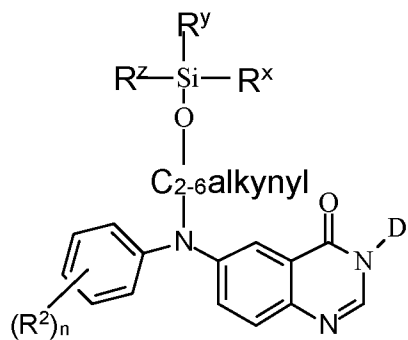


(II) with  $\text{W}_6\text{-R}^{3e}$  wherein  $\text{R}^{3e}$  represents optionally substituted  $\text{C}_{2-6}$ alkynyl and  $\text{W}_6$  represents a suitable leaving group such as for example halo, e.g. chloro, or  $-\text{O-S(=O)}_2\text{-CH}_3$ , in the presence of a suitable base, such as for

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example NaH, and a suitable solvent, such as for example N,N-dimethylformamide;

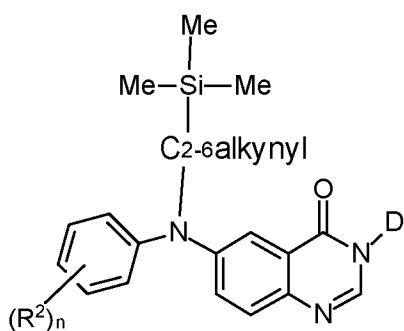
(xii) reacting an intermediate of formula



(XVII) with a suitable acid, such as for example

trifluoroacetic acid, in the presence of a suitable solvent, such as for example tetrahydrofuran. This reaction can also be performed with tetrabutyl ammonium fluoride in the presence of a suitable solvent such as for example tetrahydrofuran;

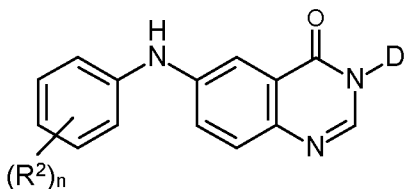
5 (xiii) reacting an intermediate of formula



(XVIII) in the presence of a suitable base, such as for

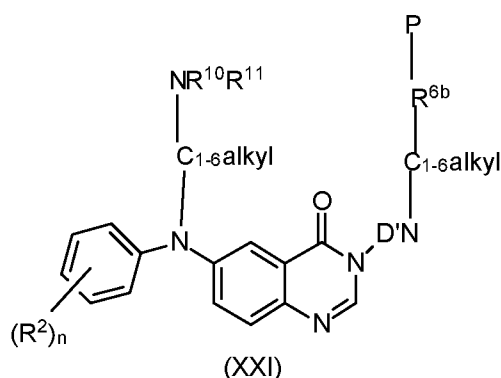
example K<sub>2</sub>CO<sub>3</sub>, and a suitable solvent, such as for example an alcohol, e.g. methanol and the like;

(xiv) reacting an intermediate of formula



10 (II) with di(C<sub>1-6</sub>alkyl)vinylphosphonate in the presence of a suitable catalyst, such as for example tri-N-butylphosphine, and a suitable solvent, such as for example acetonitrile;

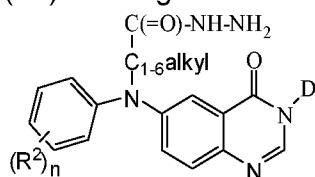
(xv) deprotecting an intermediate of formula



(XXI) wherein the D'N moiety represents a –D moiety wherein the D ring moiety contains a nitrogen atom, and P is a suitable protective group, such as for example –O-C(=O)-C<sub>1-6</sub>alkyl, in the presence of a suitable base, such as for example K<sub>2</sub>CO<sub>3</sub>, and a suitable solvent, such as for example an alcohol, e.g.

5 methanol and the like;

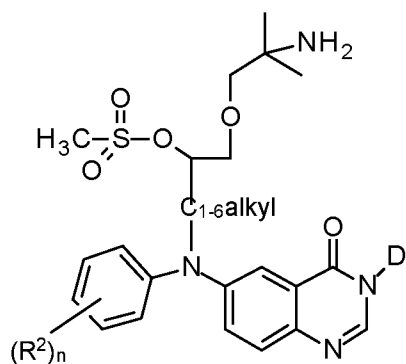
(xvi) reacting an intermediate of formula



(XXVI) with W<sub>10</sub>-CN wherein W<sub>10</sub> represents a suitable leaving group, such as for example halo, e.g. bromo, in the presence of a suitable base, such as for example

10 NaHCO<sub>3</sub>, and a suitable solvent, such as for example water or dioxane;

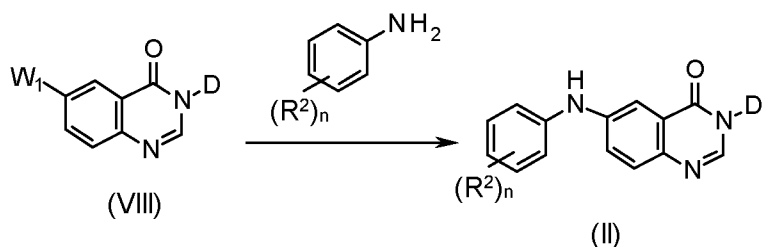
(xvii) reacting an intermediate of formula



(XXV) with a suitable base, such as for example *N,N*-diisopropylethylamine and triethylamine, in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol;

15 wherein the variables are as defined herein; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

A further embodiment is a process for synthesis of a compound of formula (II) wherein:



an intermediate of formula (VIII) is reacted with  $(R^2)_4-NH_2$  in the presence of a suitable catalyst, such as for example chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II), a suitable base, such as for example cesium carbonate in a suitable solvent, such as for example toluene.

#### Pharmaceutically Acceptable Salts, Solvates or Derivatives thereof

In this section, as in all other sections of this application, unless the context indicates otherwise, references to formula (I) include references to all other sub-groups, preferences, embodiments and examples thereof as defined herein.

Unless otherwise specified, a reference to a particular compound also includes ionic forms, salts, solvates, isomers, tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof, for example, as discussed below; preferably, the ionic forms, or salts or tautomers or isomers or N-oxides or solvates thereof; and more preferably, the ionic forms, or salts or tautomers or solvates or protected forms thereof, even more preferably the salts or tautomers or solvates thereof. Many compounds of the formula (I) can exist in the form of salts, for example acid addition salts or, in certain cases salts of organic and inorganic bases such as carboxylate, sulphonate and phosphate salts. All such salts are within the scope of this invention, and references to compounds of the formula (I) include the salt forms of the compounds. It will be appreciated that references to "derivatives" include references to ionic forms, salts, solvates, isomers, tautomers, N-oxides, esters, prodrugs, isotopes and protected forms thereof.

According to one aspect of the invention there is provided a compound as defined herein or a salt, tautomer, N-oxide or solvate thereof. According to a further aspect of the invention there is provided a compound as defined herein or a salt or solvate

thereof. References to compounds of the formula (I) and sub-groups thereof as defined herein include within their scope the salts or solvates or tautomers or N-oxides of the compounds.

- 5 The salt forms of the compounds of the invention are typically pharmaceutically acceptable salts, and examples of pharmaceutically acceptable salts are discussed in Berge *et al.* (1977) "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19. However, salts that are not pharmaceutically acceptable may also be prepared as intermediate forms which may then be converted into pharmaceutically acceptable salts.
- 10 Such non-pharmaceutically acceptable salts forms, which may be useful, for example, in the purification or separation of the compounds of the invention, also form part of the invention.

The salts of the present invention can be synthesized from the parent compound that

15 contains a basic or acidic moiety by conventional chemical methods such as methods described in *Pharmaceutical Salts: Properties, Selection, and Use*, P. Heinrich Stahl (Editor), Camille G. Wermuth (Editor), ISBN: 3-90639-026-8, Hardcover, 388 pages, August 2002. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with the appropriate base or acid in water or in an organic

20 solvent, or in a mixture of the two; generally, nonaqueous media such as ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are used. The compounds of the invention may exist as mono- or di-salts depending upon the pKa of the acid from which the salt is formed.

- 25 Acid addition salts may be formed with a wide variety of acids, both inorganic and organic. Examples of acid addition salts include salts formed with an acid selected from the group consisting of acetic, 2,2-dichloroacetic, adipic, alginic, ascorbic (e.g. L-ascorbic), L-aspartic, benzenesulphonic, benzoic, 4-acetamidobenzoic, butanoic, (+) camphoric, camphor-sulphonic, (+)-(1S)-camphor-10-sulphonic, capric, caproic,
- 30 caprylic, cinnamic, citric, cyclamic, dodecylsulphuric, ethane-1,2-disulphonic, ethanesulphonic, 2-hydroxyethanesulphonic, formic, fumaric, galactaric, gentisic, glucoheptonic, D-gluconic, glucuronic (e.g. D-glucuronic), glutamic (e.g. L-glutamic),  $\alpha$ -oxoglutaric, glycolic, hippuric, hydrobromic, hydrochloric, hydriodic, isethionic, lactic (e.g. (+)-L-lactic, ( $\pm$ )-DL-lactic), lactobionic, maleic, malic, (-)-L-malic, malonic,
- 35 ( $\pm$ )-DL-mandelic, methanesulphonic, naphthalenesulphonic (e.g. naphthalene-2-sulphonic), naphthalene-1,5-disulphonic, 1-hydroxy-2-naphthoic, nicotinic, nitric, oleic,



orotic, oxalic, palmitic, pantoic, phosphoric, propionic, L-pyroglutamic, pyruvic, salicylic, 4-amino-salicylic, sebacic, stearic, succinic, sulphuric, tannic, (+)-L-tartaric, thiocyanic, toluenesulphonic (e.g. *p*-toluenesulphonic), undecylenic and valeric acids, as well as acylated amino acids and cation exchange resins.

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One particular group of salts consists of salts formed from acetic, hydrochloric, hydriodic, phosphoric, nitric, sulphuric, citric, lactic, succinic, maleic, malic, isethionic, fumaric, benzenesulphonic, toluenesulphonic, methanesulphonic (mesylate), ethanesulphonic, naphthalenesulphonic, valeric, acetic, propanoic, butanoic, malonic, glucuronic and lactobionic acids. Another group of acid addition salts includes salts formed from acetic, adipic, ascorbic, aspartic, citric, DL-Lactic, fumaric, gluconic, glucuronic, hippuric, hydrochloric, glutamic, DL-malic, methanesulphonic, sebacic, stearic, succinic and tartaric acids.

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If the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO<sup>-</sup>), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na<sup>+</sup> and K<sup>+</sup>, alkaline earth metal cations such as Ca<sup>2+</sup> and Mg<sup>2+</sup>, and other cations such as Al<sup>3+</sup>. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH<sub>4</sub><sup>+</sup>) and substituted ammonium ions (e.g., NH<sub>3</sub>R<sup>+</sup>, NH<sub>2</sub>R<sub>2</sub><sup>+</sup>, NHR<sub>3</sub><sup>+</sup>, NR<sub>4</sub><sup>+</sup>).

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Examples of some suitable substituted ammonium ions are those derived from:

ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH<sub>3</sub>)<sub>4</sub><sup>+</sup>.

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Where the compounds of the formula (I) contain an amine function, these may form quaternary ammonium salts, for example by reaction with an alkylating agent according to methods well known to the skilled person. Such quaternary ammonium compounds are within the scope of formula (I). Compounds of the formula (I) containing an amine function may also form N-oxides. A reference herein to a compound of the formula (I) that contains an amine function also includes the N-oxide. Where a compound contains several amine functions, one or more than one nitrogen atom may be oxidised to form an N-oxide. Particular examples of N-oxides are the N-oxides of a tertiary amine or a

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nitrogen atom of a nitrogen-containing heterocycle. N-Oxides can be formed by treatment of the corresponding amine with an oxidizing agent such as hydrogen peroxide or a per-acid (e.g. a peroxy-carboxylic acid), see for example *Advanced Organic Chemistry*, by Jerry March, 4<sup>th</sup> Edition, Wiley Interscience, pages. More particularly, N-oxides can be made by the procedure of L. W. Deady (*Syn. Comm.* (1977), 7, 509-514) in which the amine compound is reacted with *m*-chloroperoxybenzoic acid (MCPBA), for example, in an inert solvent such as dichloromethane.

- 10 The compounds of the invention may form solvates, for example with water (i.e., hydrates) or common organic solvents. As used herein, the term "solvate" means a physical association of the compounds of the present invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of
- 15 isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The term "solvate" is intended to encompass both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include compounds of the invention in combination with water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid or ethanolamine and the like. The
- 20 compounds of the invention may exert their biological effects whilst they are in solution.

Solvates are well known in pharmaceutical chemistry. They can be important to the processes for the preparation of a substance (e.g. in relation to their purification, the storage of the substance (e.g. its stability) and the ease of handling of the substance

25 and are often formed as part of the isolation or purification stages of a chemical synthesis. A person skilled in the art can determine by means of standard and long used techniques whether a hydrate or other solvate has formed by the isolation conditions or purification conditions used to prepare a given compound. Examples of such techniques include thermogravimetric analysis (TGA), differential scanning

30 calorimetry (DSC), X-ray crystallography (e.g. single crystal X-ray crystallography or X-ray powder diffraction) and Solid State NMR (SS-NMR, also known as Magic Angle Spinning NMR or MAS-NMR). Such techniques are as much a part of the standard analytical toolkit of the skilled chemist as NMR, IR, HPLC and MS. Alternatively the skilled person can deliberately form a solvate using crystallisation conditions that include

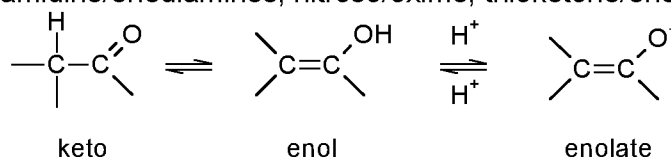
35 an amount of the solvent required for the particular solvate. Thereafter the standard methods described above, can be used to establish whether solvates had formed. Also

encompassed by formula (I) are any complexes (e.g. inclusion complexes or clathrates with compounds such as cyclodextrins, or complexes with metals) of the compounds.

Furthermore, the compounds of the present invention may have one or more polymorph (crystalline) or amorphous forms and as such are intended to be included in the scope of the invention.

Compounds of the formula (I) may exist in a number of different geometric isomeric, and tautomeric forms and references to compounds of the formula (I) include all such forms.


For the avoidance of doubt, where a compound can exist in one of several geometric isomeric or tautomeric forms and only one is specifically described or shown, all others are nevertheless embraced by formula (I). Other examples of tautomeric forms include, for example, keto-, enol-, and enolate-forms, as in, for example, the following tautomeric pairs: keto/enol (illustrated below), imine/enamine, amide/imino alcohol, amidine/enediamines, nitroso/oxime, thioketone/enethiol, and nitro/aci-nitro.



Where compounds of the formula (I) contain one or more chiral centres, and can exist in the form of two or more optical isomers, references to compounds of the formula (I) include all optical isomeric forms thereof (e.g. enantiomers, epimers and

diastereoisomers), either as individual optical isomers, or mixtures (e.g. racemic mixtures) of two or more optical isomers, unless the context requires otherwise. The optical isomers may be characterised and identified by their optical activity (i.e. as + and – isomers, or *d* and *l* isomers) or they may be characterised in terms of their absolute stereochemistry using the “R and S” nomenclature developed by Cahn, Ingold and Prelog, see *Advanced Organic Chemistry* by Jerry March, 4<sup>th</sup> Edition, John Wiley & Sons, New York, 1992, pages 109-114, and see also Cahn, Ingold & Prelog (1966) *Angew. Chem. Int. Ed. Engl.*, **5**, 385-415. Optical isomers can be separated by a number of techniques including chiral chromatography (chromatography on a chiral support) and such techniques are well known to the person skilled in the art. As an alternative to chiral chromatography, optical isomers can be separated by forming diastereoisomeric salts with chiral acids such as (+)-tartaric acid, (-)-pyroglutamic acid, (-)-di-toluoyl-L-tartaric acid, (+)-mandelic acid, (-)-malic acid, and (-)-camphorsulphonic, separating the diastereoisomers by preferential crystallisation, and then dissociating the salts to give the individual enantiomer of the free base.

Where compounds of the formula (I) exist as two or more optical isomeric forms, one enantiomer in a pair of enantiomers may exhibit advantages over the other enantiomer, for example, in terms of biological activity. Thus, in certain circumstances, it may be desirable to use as a therapeutic agent only one of a pair of enantiomers, or only one of a plurality of diastereoisomers. Accordingly, the invention provides compositions containing a compound of the formula (I) having one or more chiral centres, wherein at least 55% (e.g. at least 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95%) of the compound of the formula (I) is present as a single optical isomer (e.g. enantiomer or diastereoisomer). In one general embodiment, 99% or more (e.g. substantially all) of the total amount of the compound of the formula (I) may be present as a single optical isomer (e.g. enantiomer or diastereoisomer). When a specific isomeric form is identified (e.g. S configuration, or E isomer), this means that said isomeric form is substantially free of the other isomer(s), i.e. said isomeric form is present in at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99% or more (e.g. substantially all) of the total amount of the compound of the invention.

Hereinbefore or hereinafter, some compounds include the following bond . This indicates that the compound is a single stereoisomer with unknown configuration or a mixture of stereoisomers.

The compounds of the invention include compounds with one or more isotopic substitutions, and a reference to a particular element includes within its scope all isotopes of the element. For example, a reference to hydrogen includes within its scope  $^1\text{H}$ ,  $^2\text{H}$  (D), and  $^3\text{H}$  (T). Similarly, references to carbon and oxygen include within their scope respectively  $^{12}\text{C}$ ,  $^{13}\text{C}$  and  $^{14}\text{C}$  and  $^{16}\text{O}$  and  $^{18}\text{O}$ . The isotopes may be radioactive or non-radioactive. In one embodiment of the invention, the compounds contain no radioactive isotopes. Such compounds are preferred for therapeutic use. In another embodiment, however, the compound may contain one or more radioisotopes. Compounds containing such radioisotopes may be useful in a diagnostic context.

Esters such as carboxylic acid esters and acyloxy esters of the compounds of formula (I) bearing a carboxylic acid group or a hydroxyl group are also embraced by formula (I). In one embodiment of the invention, formula (I) includes within its scope esters of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group. In another embodiment of the invention, formula (I) does not include within its scope esters

of compounds of the formula (I) bearing a carboxylic acid group or a hydroxyl group.

Examples of esters are compounds containing the group  $-C(=O)OR$ , wherein R is an ester substituent, for example, a  $C_{1-6}$  alkyl group, a heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-6}$  alkyl group. Particular examples of ester groups include, but are not limited to,  $-C(=O)OCH_3$ ,  $-C(=O)OCH_2CH_3$ ,  $-C(=O)OC(CH_3)_3$ , and  $-C(=O)OPh$ .

Examples of acyloxy (reverse ester) groups are represented by  $-OC(=O)R$ , wherein R is an acyloxy substituent, for example, a  $C_{1-7}$  alkyl group, a  $C_{3-20}$  heterocyclyl group, or a  $C_{5-20}$  aryl group, preferably a  $C_{1-7}$  alkyl group. Particular examples of acyloxy groups include, but are not limited to,  $-OC(=O)CH_3$  (acetoxy),  $-OC(=O)CH_2CH_3$ ,  $-OC(=O)C(CH_3)_3$ ,  $-OC(=O)Ph$ , and  $-OC(=O)CH_2Ph$ .

For example, some prodrugs are esters of the active compound (e.g., a physiologically acceptable metabolically labile ester). By "prodrugs" is meant for example any compound that is converted *in vivo* into a biologically active compound of the formula (I).

During metabolism, the ester group  $-C(=O)OR$  is cleaved to yield the active drug. Such esters may be formed by esterification, for example, of any of the carboxylic acid groups  $-C(=O)OH$  in the parent compound, with, where appropriate, prior protection of any other reactive groups present in the parent compound, followed by deprotection if required.

Examples of such metabolically labile esters include those of the formula  $-C(=O)OR$  wherein R is:  $C_{1-6}$ alkyl (e.g., -Me, -Et, -nPr, -iPr, -nBu, -sBu, -iBu, -tBu);  $C_{1-6}$ aminoalkyl [e.g., aminoethyl; 2-(N,N-diethylamino)ethyl; 2-(4-morpholino)ethyl]; and acyloxy- $C_{1-7}$ alkyl [e.g., acyloxymethyl; acyloxyethyl; pivaloyloxymethyl; acetoxymethyl; 1-acetoxyethyl; 1-(1-methoxy-1-methyl)ethyl-carbonyloxyethyl; 1-(benzoyloxy)ethyl; isopropoxy-carbonyloxymethyl; 1-isopropoxy-carbonyloxyethyl; cyclohexyl-carbonyloxymethyl; 1-cyclohexyl-carbonyloxyethyl; cyclohexyloxy-carbonyloxymethyl; 1-cyclohexyloxy-carbonyloxyethyl; (4-tetrahydropyranyloxy) carbonyloxymethyl; 1-(4-tetrahydropyranyloxy)carbonyloxyethyl; (4-tetrahydropyranyl)carbonyloxymethyl; and 1-(4-tetrahydropyranyl)carbonyloxyethyl]. Also, some prodrugs are activated enzymatically to yield the active compound, or a compound which, upon further chemical reaction, yields the active compound (for example, as in antigen-directed enzyme pro-drug therapy (ADEPT), gene-directed enzyme pro-drug therapy (GDEPT) and ligand-directed enzyme pro-drug therapy (LIDEPT) etc.). For example, the prodrug may be a sugar derivative or other glycoside conjugate, or may be an amino acid ester derivative.

**Protein Tyrosine Kinases (PTK)**

The compounds of the invention described herein inhibit or modulate the activity of certain tyrosine kinases, and thus the compounds will be useful in the treatment or prophylaxis, in particular the treatment, of disease states or conditions mediated by those tyrosine kinases, in particular FGFR.

FGFR

The fibroblast growth factor (FGF) family of protein tyrosine kinase (PTK) receptors regulates a diverse array of physiologic functions including mitogenesis, wound healing, cell differentiation and angiogenesis, and development. Both normal and malignant cell growth as well as proliferation are affected by changes in local concentration of FGFs, extracellular signalling molecules which act as autocrine as well as paracrine factors. Autocrine FGF signalling may be particularly important in the progression of steroid hormone-dependent cancers to a hormone independent state. FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype. Furthermore, a number of oncogenes are homologues of genes encoding growth factor receptors, and there is a potential for aberrant activation of FGF-dependent signalling in human pancreatic cancer (Knights et al., Pharmacology and Therapeutics 2010 125:1 (105-117); Korc M. et al Current Cancer Drug Targets 2009 9:5 (639-651)).

The two prototypic members are acidic fibroblast growth factor (aFGF or FGF1) and basic fibroblast growth factor (bFGF or FGF2), and to date, at least twenty distinct FGF family members have been identified. The cellular response to FGFs is transmitted via four types of high affinity transmembrane protein tyrosine-kinase fibroblast growth factor receptors (FGFR) numbered 1 to 4 (FGFR1 to FGFR4).

Disruption of the FGFR1 pathway should affect tumor cell proliferation since this kinase is activated in many tumor types in addition to proliferating endothelial cells. The over-expression and activation of FGFR1 in tumor-associated vasculature has suggested a role for these molecules in tumor angiogenesis.

A recent study has shown a link between FGFR1 expression and tumorigenicity in Classic Lobular Carcinomas (CLC). CLCs account for 10-15% of all breast cancers and, in general, lack p53 and Her2 expression whilst retaining expression of the oestrogen receptor. A gene amplification of 8p12-p11.2 was demonstrated in ~50% of CLC cases

and this was shown to be linked with an increased expression of FGFR1. Preliminary studies with siRNA directed against FGFR1, or a small molecule inhibitor of the receptor, showed cell lines harbouring this amplification to be particularly sensitive to inhibition of this signalling pathway. Rhabdomyosarcoma (RMS) is the most common  
5 pediatric soft tissue sarcoma likely results from abnormal proliferation and differentiation during skeletal myogenesis. FGFR1 is over-expressed in primary rhabdomyosarcoma tumors and is associated with hypomethylation of a 5' CpG island and abnormal expression of the AKT1, NOG, and BMP4 genes. FGFR1 has also been linked to squamous lung cancer, colorectal cancer, glioblastoma, astrocytomas, prostate cancer,  
10 small cell lung cancer, melanoma, head and neck cancer, thyroid cancer, uterine cancer.

Fibroblast growth factor receptor 2 has high affinity for the acidic and/or basic fibroblast growth factors, as well as the keratinocyte growth factor ligands. Fibroblast growth  
15 factor receptor 2 also propagates the potent osteogenic effects of FGFs during osteoblast growth and differentiation. Mutations in fibroblast growth factor receptor 2, leading to complex functional alterations, were shown to induce abnormal ossification of cranial sutures (craniosynostosis), implying a major role of FGFR signalling in intramembranous bone formation. For example, in Apert (AP) syndrome, characterized  
20 by premature cranial suture ossification, most cases are associated with point mutations engendering gain-of-function in fibroblast growth factor receptor 2. In addition, mutation screening in patients with syndromic craniosynostoses indicates that a number of recurrent *FGFR2* mutations accounts for severe forms of Pfeiffer syndrome. Particular mutations of FGFR2 include W290C, D321A, Y340C, C342R, C342S, C342W, N549H,  
25 K641R in FGFR2.

Several severe abnormalities in human skeletal development, including Apert, Crouzon, Jackson-Weiss, Beare-Stevenson cutis gyrata, and Pfeiffer syndromes are associated with the occurrence of mutations in fibroblast growth factor receptor 2. Most, if not all,  
30 cases of Pfeiffer Syndrome (PS) are also caused by de novo mutation of the fibroblast growth factor receptor 2 gene, and it was recently shown that mutations in fibroblast growth factor receptor 2 break one of the cardinal rules governing ligand specificity. Namely, two mutant splice forms of fibroblast growth factor receptor, FGFR2c and FGFR2b, have acquired the ability to bind to and be activated by atypical FGF ligands.  
35 This loss of ligand specificity leads to aberrant signalling and suggests that the severe

phenotypes of these disease syndromes result from ectopic ligand-dependent activation of fibroblast growth factor receptor 2.

Genetic aberrations of the FGFR3 receptor tyrosine kinase such as chromosomal  
5 translocations or point mutations result in ectopically expressed or deregulated,  
constitutively active, FGFR3 receptors. Such abnormalities are linked to a subset of  
multiple myelomas and in bladder, hepatocellular, oral squamous cell carcinoma and  
cervical carcinomas. Accordingly, FGFR3 inhibitors would be useful in the treatment of  
multiple myeloma, bladder and cervical carcinomas. FGFR3 is also over-expressed in  
10 bladder cancer, in particular invasive bladder cancer. FGFR3 is frequently activated by  
mutation in urothelial carcinoma (UC). Increased expression was associated with  
mutation (85% of mutant tumors showed high-level expression) but also 42% of tumors  
with no detectable mutation showed over-expression, including many muscle-invasive  
tumors. FGFR3 is also linked to endometrial and thyroid cancer.

15 Over expression of FGFR4 has been linked to poor prognosis in both prostate and  
thyroid carcinomas. In addition a germline polymorphism (Gly388Arg) is associated with  
increased incidence of lung, breast, colon, liver (HCC) and prostate cancers. In addition,  
a truncated form of FGFR4 (including the kinase domain) has also been found to be  
20 present in 40% of pituitary tumours but not present in normal tissue. FGFR4  
overexpression has been observed in liver, colon and lung tumours. FGFR4 has been  
implicated in colorectal and liver cancer where expression of its ligand FGF19 is  
frequently elevated. FGFR4 is also linked to astrocytomas, rhabdomyosarcoma.

25 Fibrotic conditions are a major medical problem resulting from abnormal or excessive  
deposition of fibrous tissue. This occurs in many diseases, including liver cirrhosis,  
glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, as well as  
the natural process of wound healing. The mechanisms of pathological fibrosis are not  
fully understood but are thought to result from the actions of various cytokines (including  
30 tumor necrosis factor (TNF), fibroblast growth factors (FGF's), platelet derived growth  
factor (PDGF) and transforming growth factor beta. (TGF $\beta$ ) involved in the proliferation  
of fibroblasts and the deposition of extracellular matrix proteins (including collagen and  
fibronectin). This results in alteration of tissue structure and function and subsequent  
pathology.



A number of preclinical studies have demonstrated the up-regulation of fibroblast growth factors in preclinical models of lung fibrosis. TGF $\beta$ 1 and PDGF have been reported to be involved in the fibrogenic process and further published work suggests the elevation of FGF's and consequent increase in fibroblast proliferation, may be in response to elevated TGF $\beta$ 1. The potential therapeutic benefit of targeting the fibrotic mechanism in conditions such as idiopathic pulmonary fibrosis (IPF) is suggested by the reported clinical effect of the anti-fibrotic agent pirfenidone. Idiopathic pulmonary fibrosis (also referred to as Cryptogenic fibrosing alveolitis) is a progressive condition involving scarring of the lung. Gradually, the air sacs of the lungs become replaced by fibrotic tissue, which becomes thicker, causing an irreversible loss of the tissue's ability to transfer oxygen into the bloodstream. The symptoms of the condition include shortness of breath, chronic dry coughing, fatigue, chest pain and loss of appetite resulting in rapid weight loss. The condition is extremely serious with approximately 50% mortality after 5 years.

As such, the compounds which inhibit FGFR will be useful in providing a means of preventing the growth or inducing apoptosis in tumours, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In particular tumours with activating mutants of receptor tyrosine kinases or upregulation of receptor tyrosine kinases may be particularly sensitive to the inhibitors. Patients with activating mutants of any of the isoforms of the specific RTKs discussed herein may also find treatment with RTK inhibitors particularly beneficial.

#### Vascular Endothelial Growth Factor (VEGFR)

Chronic proliferative diseases are often accompanied by profound angiogenesis, which can contribute to or maintain an inflammatory and/or proliferative state, or which leads to tissue destruction through the invasive proliferation of blood vessels.

Angiogenesis is generally used to describe the development of new or replacement blood vessels, or neovascularisation. It is a necessary and physiological normal process by which vasculature is established in the embryo. Angiogenesis does not occur, in general, in most normal adult tissues, exceptions being sites of ovulation, menses and wound healing. Many diseases, however, are characterized by persistent and unregulated angiogenesis. For instance, in arthritis, new capillary blood vessels invade the joint and destroy cartilage. In diabetes (and in many different eye diseases), new

vessels invade the macula or retina or other ocular structures, and may cause blindness. The process of atherosclerosis has been linked to angiogenesis. Tumor growth and metastasis have been found to be angiogenesis-dependent.

5 The recognition of the involvement of angiogenesis in major diseases has been accompanied by research to identify and develop inhibitors of angiogenesis. These inhibitors are generally classified in response to discrete targets in the angiogenesis cascade, such as activation of endothelial cells by an angiogenic signal; synthesis and release of degradative enzymes; endothelial cell migration; proliferation of endothelial  
10 cells; and formation of capillary tubules. Therefore, angiogenesis occurs in many stages and attempts are underway to discover and develop compounds that work to block angiogenesis at these various stages.

There are publications that teach that inhibitors of angiogenesis, working by diverse  
15 mechanisms, are beneficial in diseases such as cancer and metastasis, ocular diseases, arthritis and hemangioma.

Vascular endothelial growth factor (VEGF), a polypeptide, is mitogenic for endothelial cells *in vitro* and stimulates angiogenic responses *in vivo*. VEGF has also been linked to  
20 inappropriate angiogenesis. VEGFR(s) are protein tyrosine kinases (PTKs). PTKs catalyze the phosphorylation of specific tyrosine residues in proteins involved in cell function thus regulating cell growth, survival and differentiation.

Three PTK receptors for VEGF have been identified: VEGFR-1 (Flt-1) ; VEGFR-2 (Flk-1  
25 or KDR) and VEGFR-3 (Flt-4). These receptors are involved in angiogenesis and participate in signal transduction. Of particular interest is VEGFR-2, which is a transmembrane receptor PTK expressed primarily in endothelial cells. Activation of VEGFR-2 by VEGF is a critical step in the signal transduction pathway that initiates tumour angiogenesis. VEGF expression may be constitutive to tumour cells and can  
30 also be upregulated in response to certain stimuli. One such stimuli is hypoxia, where VEGF expression is upregulated in both tumour and associated host tissues. The VEGF ligand activates VEGFR-2 by binding with its extracellular VEGF binding site. This leads to receptor dimerization of VEGFRs and autophosphorylation of tyrosine residues at the intracellular kinase domain of VEGFR- 2. The kinase domain operates to transfer a  
35 phosphate from ATP to the tyrosine residues, thus providing binding sites for signalling proteins downstream of VEGFR-2 leading ultimately to initiation of angiogenesis.

Inhibition at the kinase domain binding site of VEGFR-2 would block phosphorylation of tyrosine residues and serve to disrupt initiation of angiogenesis.

5 Angiogenesis is a physiologic process of new blood vessel formation mediated by various cytokines called angiogenic factors. Although its potential pathophysiologic role in solid tumors has been extensively studied for more than 3 decades, enhancement of angiogenesis in chronic lymphocytic leukemia (CLL) and other malignant hematological disorders has been recognized more recently. An increased level of angiogenesis has  
10 been documented by various experimental methods both in bone marrow and lymph nodes of patients with CLL. Although the role of angiogenesis in the pathophysiology of this disease remains to be fully elucidated, experimental data suggest that several angiogenic factors play a role in the disease progression. Biologic markers of angiogenesis were also shown to be of prognostic relevance in CLL. This indicates that  
15 VEGFR inhibitors may also be of benefit for patients with leukemia's such as CLL.

In order for a tumour mass to get beyond a critical size, it must develop an associated vasculature. It has been proposed that targeting a tumor vasculature would limit tumor expansion and could be a useful cancer therapy. Observations of tumor growth have  
20 indicated that small tumour masses can persist in a tissue without any tumour-specific vasculature. The growth arrest of nonvascularized tumors has been attributed to the effects of hypoxia at the center of the tumor. More recently, a variety of proangiogenic and antiangiogenic factors have been identified and have led to the concept of the "angiogenic switch," a process in which disruption of the normal ratio of angiogenic  
25 stimuli and inhibitors in a tumor mass allows for autonomous vascularization. The angiogenic switch appears to be governed by the same genetic alterations that drive malignant conversion: the activation of oncogenes and the loss of tumour suppressor genes. Several growth factors act as positive regulators of angiogenesis. Foremost among these are vascular endothelial growth factor (VEGF), basic fibroblast growth  
30 factor (bFGF), and angiogenin. Proteins such as thrombospondin (Tsp-1), angiostatin, and endostatin function as negative regulators of angiogenesis.

Inhibition of VEGFR2 but not VEGFR1 markedly disrupts angiogenic switching, persistent angiogenesis, and initial tumor growth in a mouse model. In late-stage  
35 tumors, phenotypic resistance to VEGFR2 blockade emerged, as tumors regrew during treatment after an initial period of growth suppression. This resistance to VEGF

blockade involves reactivation of tumour angiogenesis, independent of VEGF and associated with hypoxia-mediated induction of other proangiogenic factors, including members of the FGF family. These other proangiogenic signals are functionally implicated in the revascularization and regrowth of tumours in the evasion phase, as  
5 FGF blockade impairs progression in the face of VEGF inhibition.

There is evidence for normalization of glioblastoma blood vessels in patients treated with a pan-VEGF receptor tyrosine kinase inhibitor, AZD2171, in a phase 2 study. MRI determination of vessel normalization in combination with circulating biomarkers  
10 provides for an effective means to assess response to antiangiogenic agents.

#### PDGFR

A malignant tumour is the product of uncontrolled cell proliferation. Cell growth is controlled by a delicate balance between growth-promoting and growth-inhibiting  
15 factors. In normal tissue the production and activity of these factors results in differentiated cells growing in a controlled and regulated manner that maintains the normal integrity and functioning of the organ. The malignant cell has evaded this control; the natural balance is disturbed (via a variety of mechanisms) and unregulated, aberrant cell growth occurs. A growth factor of importance in tumour development is the platelet-  
20 derived growth factor (PDGF) that comprises a family of peptide growth factors that signal through cell surface tyrosine kinase receptors (PDGFR) and stimulate various cellular functions including growth, proliferation, and differentiation.

#### Advantages of a selective inhibitor

25 Development of FGFR kinase inhibitors with a differentiated selectivity profile provides a new opportunity to use these targeted agents in patient sub-groups whose disease is driven by FGFR deregulation. Compounds that exhibit reduced inhibitory action on additional kinases, particularly VEGFR2 and PDGFR-beta, offer the opportunity to have a differentiated side-effect or toxicity profile and as such allow for a more effective  
30 treatment of these indications. Inhibitors of VEGFR2 and PDGFR-beta are associated with toxicities such as hypertension or oedema respectively. In the case of VEGFR2 inhibitors this hypertensive effect is often dose limiting, may be contraindicated in certain patient populations and requires clinical management.

**Biological Activity and Therapeutic Uses**

The compounds of the invention, and subgroups thereof, have fibroblast growth factor receptor (FGFR) inhibiting or modulating activity and/or vascular endothelial growth factor receptor (VEGFR) inhibiting or modulating activity, and/or platelet derived growth factor receptor (PDGFR) inhibiting or modulating activity, and which will be useful in preventing or treating disease states or conditions described herein. In addition the compounds of the invention, and subgroups thereof, will be useful in preventing or treating diseases or condition mediated by the kinases. References to the preventing or prophylaxis or treatment of a disease state or condition such as cancer include within their scope alleviating or reducing the incidence of cancer.

As used herein, the term "modulation", as applied to the activity of a kinase, is intended to define a change in the level of biological activity of the protein kinase. Thus, modulation encompasses physiological changes which effect an increase or decrease in the relevant protein kinase activity. In the latter case, the modulation may be described as "inhibition". The modulation may arise directly or indirectly, and may be mediated by any mechanism and at any physiological level, including for example at the level of gene expression (including for example transcription, translation and/or post-translational modification), at the level of expression of genes encoding regulatory elements which act directly or indirectly on the levels of kinase activity. Thus, modulation may imply elevated/suppressed expression or over- or under-expression of a kinase, including gene amplification (i.e. multiple gene copies) and/or increased or decreased expression by a transcriptional effect, as well as hyper- (or hypo-)activity and (de)activation of the protein kinase(s) (including (de)activation) by mutation(s). The terms "modulated", "modulating" and "modulate" are to be interpreted accordingly.

As used herein, the term "mediated", as used e.g. in conjunction with a kinase as described herein (and applied for example to various physiological processes, diseases, states, conditions, therapies, treatments or interventions) is intended to operate limitatively so that the various processes, diseases, states, conditions, treatments and interventions to which the term is applied are those in which the kinase plays a biological role. In cases where the term is applied to a disease, state or condition, the biological role played by a kinase may be direct or indirect and may be necessary and/or sufficient for the manifestation of the symptoms of the disease, state or condition (or its aetiology or progression). Thus, kinase activity (and in particular aberrant levels of kinase activity, e.g. kinase over-expression) need not necessarily be the proximal cause of the disease,

state or condition: rather, it is contemplated that the kinase mediated diseases, states or conditions include those having multifactorial aetiologies and complex progressions in which the kinase in question is only partially involved. In cases where the term is applied to treatment, prophylaxis or intervention, the role played by the kinase may be direct or indirect and may be necessary and/or sufficient for the operation of the treatment, prophylaxis or outcome of the intervention. Thus, a disease state or condition mediated by a kinase includes the development of resistance to any particular cancer drug or treatment.

- Thus, for example, the compounds of the invention may be useful in alleviating or reducing the incidence of cancer.

More particularly, the compounds of the formulae (I) and sub-groups thereof are inhibitors of FGFRs. For example, compounds of the invention have activity against FGFR1, FGFR2, FGFR3, and/or FGFR4, and in particular FGFRs selected from FGFR1, FGFR2 and FGFR3; or in particular the compounds of formula (I) and sub-groups thereof are inhibitors of FGFR4.

Preferred compounds are compounds that inhibit one or more FGFR selected from FGFR1, FGFR2, FGFR3, and FGFR4. Preferred compounds of the invention are those having  $IC_{50}$  values of less than 0.1  $\mu$ M.

Compounds of the invention also have activity against VEGFR.

In addition many of the compounds of the invention exhibit selectivity for the FGFR 1, 2, and/or 3, and/or 4 compared to VEGFR (in particular VEGFR2) and/or PDGFR and such compounds represent one preferred embodiment of the invention. In particular, the compounds exhibit selectivity over VEGFR2. For example, many compounds of the invention have  $IC_{50}$  values against FGFR1, 2 and/or 3 and/or 4 that are between a tenth and a hundredth of the  $IC_{50}$  against VEGFR (in particular VEGFR2) and/or PDGFR B. In particular preferred compounds of the invention have at least 10 times greater activity against or inhibition of FGFR in particular FGFR1, FGFR2, FGFR3 and/or FGFR4 than VEGFR2. More preferably the compounds of the invention have at least 100 times greater activity against or inhibition of FGFR in particular FGFR1, FGFR2, FGFR3 and/or FGFR4 than VEGFR2. This can be determined using the methods described herein.

As a consequence of their activity in modulating or inhibiting FGFR, and/or VEGFR kinases, the compounds will be useful in providing a means of preventing the growth or inducing apoptosis of neoplasias, particularly by inhibiting angiogenesis. It is therefore anticipated that the compounds will prove useful in treating or preventing proliferative disorders such as cancers. In addition, the compounds of the invention could be useful in the treatment of diseases in which there is a disorder of proliferation, apoptosis or differentiation.

In particular tumours with activating mutants of VEGFR or upregulation of VEGFR and patients with elevated levels of serum lactate dehydrogenase may be particularly sensitive to the compounds of the invention. Patients with activating mutants of any of the isoforms of the specific RTKs discussed herein may also find treatment with the compounds of the invention particularly beneficial. For example, VEGFR overexpression in acute leukemia cells where the clonal progenitor may express VEGFR. Also, particular tumours with activating mutants or upregulation or overexpression of any of the isoforms of FGFR such as FGFR1, FGFR2 or FGFR3 or FGFR4 may be particularly sensitive to the compounds of the invention and thus patients as discussed herein with such particular tumours may also find treatment with the compounds of the invention particularly beneficial. It may be preferred that the treatment is related to or directed at a mutated form of one of the receptor tyrosine kinases, such as discussed herein. Diagnosis of tumours with such mutations could be performed using techniques known to a person skilled in the art and as described herein such as RTPCR and FISH.

Examples of cancers which may be treated (or inhibited) include, but are not limited to, a carcinoma, for example a carcinoma of the bladder, breast, colon (e.g. colorectal carcinomas such as colon adenocarcinoma and colon adenoma), kidney, urothelial, uterus, epidermis, liver, lung (for example adenocarcinoma, small cell lung cancer and non-small cell lung carcinomas, squamous lung cancer), oesophagus, head and neck, gall bladder, ovary, pancreas (e.g. exocrine pancreatic carcinoma), stomach, gastrointestinal (also known as gastric) cancer (e.g. gastrointestinal stromal tumours), cervix, endometrium, thyroid, prostate, or skin (for example squamous cell carcinoma or dermatofibrosarcoma protuberans); pituitary cancer, a hematopoietic tumour of lymphoid lineage, for example leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, B-cell lymphoma (e.g. diffuse large B-cell lymphoma), T-cell lymphoma,

Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma, or Burkett's lymphoma; a hematopoietic tumour of myeloid lineage, for example leukemias, acute and chronic myelogenous leukemias, chronic myelomonocytic leukemia (CMML), myeloproliferative disorder, myeloproliferative syndrome, myelodysplastic syndrome, or  
5 promyelocytic leukemia; multiple myeloma; thyroid follicular cancer; hepatocellular cancer, a tumour of mesenchymal origin (e.g. Ewing's sarcoma), for example fibrosarcoma or rhabdomyosarcoma; a tumour of the central or peripheral nervous system, for example astrocytoma, neuroblastoma, glioma (such as glioblastoma multiforme) or schwannoma; melanoma; seminoma; teratocarcinoma; osteosarcoma;  
10 xeroderma pigmentosum; keratocanthoma; thyroid follicular cancer; or Kaposi's sarcoma. In particular, squamous lung cancer, breast cancer, colorectal cancer, glioblastoma, astrocytomas, prostate cancer, small cell lung cancer, melanoma, head and neck cancer, thyroid cancer, uterine cancer, gastric cancer, hepatocellular cancer, cervix cancer, multiple myeloma, bladder cancer, endometrial cancer, urothelial cancer,  
15 colon cancer, rhabdomyosarcoma, pituitary gland cancer.

Certain cancers are resistant to treatment with particular drugs. This can be due to the type of the tumour or can arise due to treatment with the compound. In this regard, references to multiple myeloma includes bortezomib sensitive multiple myeloma or  
20 refractory multiple myeloma. Similarly, references to chronic myelogenous leukemia includes imatinib sensitive chronic myelogenous leukemia and refractory chronic myelogenous leukemia. Chronic myelogenous leukemia is also known as chronic myeloid leukemia, chronic granulocytic leukemia or CML. Likewise, acute myelogenous leukemia, is also called acute myeloblastic leukemia, acute granulocytic leukemia, acute  
25 nonlymphocytic leukaemia or AML.

The compounds of the invention can also be used in the treatment of hematopoietic diseases of abnormal cell proliferation whether pre-malignant or stable such as myeloproliferative diseases. Myeloproliferative diseases ("MPD"s) are a group of  
30 diseases of the bone marrow in which excess cells are produced. They are related to, and may evolve into, myelodysplastic syndrome. Myeloproliferative diseases include polycythemia vera, essential thrombocythemia and primary myelofibrosis. A further haematological disorder is hypereosinophilic syndrome. T-cell lymphoproliferative diseases include those derived from natural Killer cells.



In addition the compounds of the invention can be used to gastrointestinal (also known as gastric) cancer e.g. gastrointestinal stromal tumours. Gastrointestinal cancer refers to malignant conditions of the gastrointestinal tract, including the esophagus, stomach, liver, biliary system, pancreas, bowels, and anus.

5

Thus, in the pharmaceutical compositions, uses or methods of this invention for treating a disease or condition comprising abnormal cell growth, the disease or condition comprising abnormal cell growth in one embodiment is a cancer.

10 Particular subsets of cancers include multiple myeloma, bladder, cervical, prostate and thyroid carcinomas, lung, breast, and colon cancers.

A further subset of cancers includes multiple myeloma, bladder, hepatocellular, oral squamous cell carcinoma and cervical carcinomas.

15

The compound of the invention, having FGFR such as FGFR1 inhibitory activity, may be particularly useful in the treatment or prevention of breast cancer in particular Classic Lobular Carcinomas (CLC).

20 As the compounds of the invention have FGFR4 activity they will also be useful in the treatment of prostate or pituitary cancers, or they will be useful in the treatment of breast cancer, lung cancer, prostate cancer, liver cancer (HCC) or lung cancer.

25 In particular the compounds of the invention as FGFR inhibitors, are useful in the treatment of multiple myeloma, myeloproliferative disorders, endometrial cancer, prostate cancer, bladder cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, and oral squamous cell carcinoma.

30 Further subsets of cancer are multiple myeloma, endometrial cancer, bladder cancer, cervical cancer, prostate cancer, lung cancer, breast cancer, colorectal cancer and thyroid carcinomas.

35 In particular the compounds of the invention are useful in the treatment of multiple myeloma (in particular multiple myeloma with t(4;14) translocation or overexpressing FGFR3), prostate cancer (hormone refractory prostate carcinomas), endometrial cancer

(in particular endometrial tumours with activating mutations in FGFR2) and breast cancer (in particular lobular breast cancer).

In particular, the compounds of the invention have activity against tumours with FGFR3-TACC3 translocation, in particular bladder or brain tumours with FGFR3-TACC3 translocation.

In particular the compounds are useful in the treatment of lobular carcinomas such as CLC (Classic lobular carcinoma).

As the compounds have activity against FGFR3 they will be useful in the treatment of multiple myeloma and bladder cancer.

In particular the compounds are useful for the treatment of t(4;14) translocation positive multiple myeloma.

In one embodiment the compounds may be useful for the treatment of sarcoma. In one embodiment the compounds may be useful for the treatment of lung cancer, e.g. squamous cell carcinoma.

As the compounds have activity against FGFR2 they will be useful in the treatment of endometrial, ovarian, gastric, hepatocellular, uterine, cervix and colorectal cancers. FGFR2 is also overexpressed in epithelial ovarian cancer, therefore the compounds of the invention may be specifically useful in treating ovarian cancer such as epithelial ovarian cancer.

In one embodiment, the compounds may be useful for the treatment of lung cancer, in particular NSCLC, squamous cell carcinoma, liver cancer, kidney cancer, breast cancer, colon cancer, colorectal cancer, prostate cancer.

Compounds of the invention may also be useful in the treatment of tumours pre-treated with VEGFR2 inhibitor or VEGFR2 antibody (e.g. Avastin).

In particular the compounds of the invention may be useful in the treatment of VEGFR2-resistant tumours. VEGFR2 inhibitors and antibodies are used in the treatment of

thyroid and renal cell carcinomas, therefore the compounds of the invention may be useful in the treatment of VEGFR2-resistant thyroid and renal cell carcinomas.

The cancers may be cancers which are sensitive to inhibition of any one or more FGFRs selected from FGFR1, FGFR2, FGFR3, FGFR4, for example, one or more FGFRs selected from FGFR1, FGFR2 or FGFR3.

Whether or not a particular cancer is one which is sensitive to inhibition of FGFR or VEGFR signalling may be determined by means of a cell growth assay as set out below or by a method as set out in the section headed "Methods of Diagnosis".

The compounds of the invention, and in particular those compounds having FGFR, or VEGFR inhibitory activity, may be particularly useful in the treatment or prevention of cancers of a type associated with or characterised by the presence of elevated levels of FGFR, or VEGFR, for example the cancers referred to in this context in the introductory section of this application.

The compounds of the present invention may be useful for the treatment of the adult population. The compounds of the present invention may be useful for the treatment of the pediatric population.

It has been discovered that some FGFR inhibitors can be used in combination with other anticancer agents. For example, it may be beneficial to combine an inhibitor that induces apoptosis with another agent which acts via a different mechanism to regulate cell growth thus treating two of the characteristic features of cancer development. Examples of such combinations are set out below.

The compounds of the invention may be useful in treating other conditions which result from disorders in proliferation such as type II or non-insulin dependent diabetes mellitus, autoimmune diseases, head trauma, stroke, epilepsy, neurodegenerative diseases such as Alzheimer's, motor neurone disease, progressive supranuclear palsy, corticobasal degeneration and Pick's disease for example autoimmune diseases and neurodegenerative diseases.

One sub-group of disease states and conditions that the compounds of the invention may be useful consists of inflammatory diseases, cardiovascular diseases and wound healing.

- 5 FGFR, and VEGFR are also known to play a role in apoptosis, angiogenesis, proliferation, differentiation and transcription and therefore the compounds of the invention could also be useful in the treatment of the following diseases other than cancer; chronic inflammatory diseases, for example systemic lupus erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory  
10 bowel disease, autoimmune diabetes mellitus, Eczema hypersensitivity reactions, asthma, COPD, rhinitis, and upper respiratory tract disease; cardiovascular diseases for example cardiac hypertrophy, restenosis, atherosclerosis; neurodegenerative disorders, for example Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar  
15 degeneration; glomerulonephritis; myelodysplastic syndromes, ischemic injury associated myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, haematological diseases, for example, chronic anemia and aplastic anemia; degenerative diseases of the musculoskeletal system, for example, osteoporosis and arthritis, aspirin-sensitive  
20 rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

In addition, mutations of FGFR2 are associated with several severe abnormalities in human skeletal development and thus the compounds of invention could be useful in the treatment of abnormalities in human skeletal development, including abnormal  
25 ossification of cranial sutures (craniosynostosis), Apert (AP) syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, and Pfeiffer syndrome.

The compound of the invention, having FGFR such as FGFR2 or FGFR3 inhibitory  
30 activity, may be particularly useful in the treatment or prevention of the skeletal diseases. Particular skeletal diseases are achondroplasia or thanatophoric dwarfism (also known as thanatophoric dysplasia).

The compound of the invention, having FGFR such as FGFR1, FGFR2 or FGFR3  
35 inhibitory activity, may be particularly useful in the treatment or prevention in pathologies in which progressive fibrosis is a symptom. Fibrotic conditions in which the

compounds of the inventions may be useful in the treatment of include diseases exhibiting abnormal or excessive deposition of fibrous tissue for example in liver cirrhosis, glomerulonephritis, pulmonary fibrosis, systemic fibrosis, rheumatoid arthritis, as well as the natural process of wound healing. In particular the compounds of the inventions may also be useful in the treatment of lung fibrosis in particular in idiopathic pulmonary fibrosis.

The over-expression and activation of FGFR and VEGFR in tumor- associated vasculature has also suggested a role for compounds of the invention in preventing and disrupting initiation of tumor angiogenesis. In particular the compounds of the invention may be useful in the treatment of cancer, metastasis, leukemia's such as CLL, ocular diseases such as age-related macular degeneration in particular wet form of age-related macular degeneration, ischemic proliferative retinopathies such as retinopathy of prematurity (ROP) and diabetic retinopathy, rheumatoid arthritis and hemangioma.

The activity of the compounds of the invention as inhibitors of FGFR1-4, VEGFR and/or PDGFR A/B can be measured using the assays set forth in the examples below and the level of activity exhibited by a given compound can be defined in terms of the  $IC_{50}$  value. Preferred compounds of the present invention are compounds having an  $IC_{50}$  value of less than 1  $\mu$ M, more preferably less than 0.1  $\mu$ M.

The invention provides compounds that have FGFR inhibiting or modulating activity, and which may be useful in preventing or treating disease states or conditions mediated by FGFR kinases.

In one embodiment, there is provided a compound as defined herein for use in therapy, for use as a medicine. In a further embodiment, there is provided a compound as defined herein for use in the prophylaxis or treatment, in particular in the treatment, of a disease state or condition mediated by a FGFR kinase.

Thus, for example, the compounds of the invention may be useful in alleviating or reducing the incidence of cancer. Therefore, in a further embodiment, there is provided a compound as defined herein for use in the prophylaxis or treatment, in particular the treatment, of cancer. In one embodiment, the compound as defined herein is for use in the prophylaxis or treatment of FGFR-dependent cancer. In one embodiment, the

compound as defined herein is for use in the prophylaxis or treatment of cancer mediated by FGFR kinases.

Accordingly, the invention provides *inter alia*:

- 5       – A method for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.
- A method for the prophylaxis or treatment of a disease state or condition as described herein, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.
- 10      – A method for the prophylaxis or treatment of cancer, which method comprises administering to a subject in need thereof a compound of the formula (I) as defined herein.
- A method for alleviating or reducing the incidence of a disease state or condition mediated by a FGFR kinase, which method comprises administering to a subject  
15      in need thereof a compound of the formula (I) as defined herein.
- A method of inhibiting a FGFR kinase, which method comprises contacting the kinase with a kinase-inhibiting compound of the formula (I) as defined herein.
- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase using a compound of the formula (I) as defined  
20      herein.
- A compound of formula (I) as defined herein for use as a modulator of a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase.
- A compound of formula (I) as defined herein for use in the prophylaxis or treatment of cancer, in particular the treatment of cancer.
- 25      – A compound of formula (I) as defined herein for use as a modulator (e.g. inhibitor) of FGFR.
- The use of a compound of formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase, the compound having the formula (I) as defined  
30      herein.
- The use of a compound of formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as described herein.
- The use of a compound of formula (I) as defined herein for the manufacture of a  
35      medicament for the prophylaxis or treatment, in particular the treatment, of cancer.

- The use of a compound of formula (I) as defined herein for the manufacture of a medicament for modulating (e.g. inhibiting) the activity of FGFR.
- Use of a compound of formula (I) as defined herein in the manufacture of a medicament for modulating a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase.
- The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for prophylaxis or treatment of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4).
- The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of a cancer, the cancer being one which is characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4).
- The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing a genetic aberrations of FGFR3 kinase.
- The use of a compound of the formula (I) as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer in a patient who has been diagnosed as forming part of a sub-population possessing a genetic aberrations of FGFR3 kinase.
- A method for the prophylaxis or treatment of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4), the method comprising administering a compound of the formula (I) as defined herein.
- A method for alleviating or reducing the incidence of a disease or condition characterised by up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4), the method comprising administering a compound of the formula (I) as defined herein.
- A method for the prophylaxis or treatment of (or alleviating or reducing the incidence of) cancer in a patient suffering from or suspected of suffering from cancer; which method comprises (i) subjecting a patient to a diagnostic test to determine whether the patient possesses a genetic aberrations of FGFR3 gene; and (ii) where the patient does possess the said variant, thereafter administering to the patient a compound of the formula (I) as defined herein having FGFR3 kinase inhibiting activity.

- A method for the prophylaxis or treatment of (or alleviating or reducing the incidence of) a disease state or condition characterised by up-regulation of an FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4); which method comprises (i) subjecting a patient to a diagnostic test to detect a marker characteristic of up-regulation of a FGFR kinase (e.g. FGFR1 or FGFR2 or FGFR3 or FGFR4) and (ii) where the diagnostic test is indicative of up-regulation of a FGFR kinase, thereafter administering to the patient a compound of the formula (I) as defined herein having FGFR kinase inhibiting activity.

10 In one embodiment, the disease mediated by FGFR kinases is a oncology related disease (e.g. cancer). In one embodiment, the disease mediated by FGFR kinases is a non-oncology related disease (e.g. any disease disclosed herein excluding cancer). In one embodiment the disease mediated by FGFR kinases is a condition described herein. In one embodiment the disease mediated by FGFR kinases is a skeletal condition described herein. Particular abnormalities in human skeletal development, include abnormal ossification of cranial sutures (craniosynostosis), Apert (AP) syndrome, Crouzon syndrome, Jackson-Weiss syndrome, Beare-Stevenson cutis gyrate syndrome, Pfeiffer syndrome, achondroplasia and thanatophoric dwarfism (also known as thanatophoric dysplasia).

## 20 **Mutated Kinases**

Drug resistant kinase mutations can arise in patient populations treated with kinase inhibitors. These occur, in part, in the regions of the protein that bind to or interact with the particular inhibitor used in therapy. Such mutations reduce or increase the capacity of the inhibitor to bind to and inhibit the kinase in question. This can occur at any of the amino acid residues which interact with the inhibitor or are important for supporting the binding of said inhibitor to the target. An inhibitor that binds to a target kinase without requiring the interaction with the mutated amino acid residue will likely be unaffected by the mutation and will remain an effective inhibitor of the enzyme.

30 A study in gastric cancer patient samples showed the presence of two mutations in FGFR2, Ser167Pro in exon IIIa and a splice site mutation 940-2A-G in exon IIIc. These mutations are identical to the germline activating mutations that cause craniosynostosis syndromes and were observed in 13% of primary gastric cancer tissues studied. In addition activating mutations in FGFR3 were observed in 5% of the patient samples



tested and overexpression of FGFRs has been correlated with a poor prognosis in this patient group.

In addition there are chromosomal translocations or point mutations that have been  
5 observed in FGFR which give rise to gain-of-function, over-expressed, or constitutively active biological states.

The compounds of the invention would therefore find particular application in relation to cancers which express a mutated molecular target such as FGFR. Diagnosis of  
10 tumours with such mutations could be performed using techniques known to a person skilled in the art and as described herein such as RTPCR and FISH.

It has been suggested that mutations of a conserved threonine residue at the ATP binding site of FGFR would result in inhibitor resistance. The amino acid valine 561 has  
15 been mutated to a methionine in FGFR1 which corresponds to previously reported mutations found in Abl (T315) and EGFR (T766) that have been shown to confer resistance to selective inhibitors. Assay data for FGFR1 V561M showed that this mutation conferred resistance to a tyrosine kinase inhibitor compared to that of the wild type.

## 20 **Methods of Diagnosis**

Prior to administration of a compound of the formula (I), a patient may be screened to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against FGFR, and/or VEGFR.

25 For example, a biological sample taken from a patient may be analysed to determine whether a condition or disease, such as cancer, that the patient is or may be suffering from is one which is characterised by a genetic abnormality or abnormal protein expression which leads to up-regulation of the levels or activity of FGFR, and/or VEGFR  
30 or to sensitisation of a pathway to normal FGFR, and/or VEGFR activity, or to upregulation of these growth factor signalling pathways such as growth factor ligand levels or growth factor ligand activity or to upregulation of a biochemical pathway downstream of FGFR, and/or VEGFR activation.

Examples of such abnormalities that result in activation or sensitisation of the FGFR, and/or VEGFR signal include loss of, or inhibition of apoptotic pathways, up-regulation of the receptors or ligands, or presence of mutant variants of the receptors or ligands e.g. PTK variants. Tumours with mutants of FGFR1, FGFR2 or FGFR3 or FGFR4 or up-regulation, in particular over-expression of FGFR1, or gain-of-function mutants of FGFR2 or FGFR3 may be particularly sensitive to FGFR inhibitors.

For example, point mutations engendering gain-of-function in FGFR2 have been identified in a number of conditions. In particular activating mutations in FGFR2 have been identified in 10% of endometrial tumours.

In addition, genetic aberrations of the FGFR3 receptor tyrosine kinase such as chromosomal translocations or point mutations resulting in ectopically expressed or deregulated, constitutively active, FGFR3 receptors have been identified and are linked to a subset of multiple myelomas, bladder and cervical carcinomas. A particular mutation T674I of the PDGF receptor has been identified in imatinib-treated patients. In addition, a gene amplification of 8p12-p11.2 was demonstrated in ~50% of lobular breast cancer (CLC) cases and this was shown to be linked with an increased expression of FGFR1. Preliminary studies with siRNA directed against FGFR1, or a small molecule inhibitor of the receptor, showed cell lines harbouring this amplification to be particularly sensitive to inhibition of this signalling pathway.

Alternatively, a biological sample taken from a patient may be analysed for loss of a negative regulator or suppressor of FGFR or VEGFR. In the present context, the term "loss" embraces the deletion of a gene encoding the regulator or suppressor, the truncation of the gene (for example by mutation), the truncation of the transcribed product of the gene, or the inactivation of the transcribed product (e.g. by point mutation) or sequestration by another gene product.

The term up-regulation includes elevated expression or over-expression, including gene amplification (i.e. multiple gene copies) and increased expression by a transcriptional effect, and hyperactivity and activation, including activation by mutations. Thus, the patient may be subjected to a diagnostic test to detect a marker characteristic of up-regulation of FGFR, and/or VEGFR. The term diagnosis includes screening. By marker we include genetic markers including, for example, the measurement of DNA composition to identify mutations of FGFR, and/or VEGFR. The term marker also

includes markers which are characteristic of up regulation of FGFR and/or VEGFR, including enzyme activity, enzyme levels, enzyme state (e.g. phosphorylated or not) and mRNA levels of the aforementioned proteins.

5 The diagnostic tests and screens are typically conducted on a biological sample selected from tumour biopsy samples, blood samples (isolation and enrichment of shed tumour cells), stool biopsies, sputum, chromosome analysis, pleural fluid, peritoneal fluid, buccal spears, biopsy or urine.

Methods of identification and analysis of mutations and up-regulation of proteins are  
10 known to a person skilled in the art. Screening methods could include, but are not limited to, standard methods such as reverse-transcriptase polymerase chain reaction (RT-PCR) or in-situ hybridization such as fluorescence in situ hybridization (FISH).

Identification of an individual carrying a mutation in FGFR, and /or VEGFR may mean  
15 that the patient would be particularly suitable for treatment with a FGFR, and /or VEGFR inhibitor. Tumours may preferentially be screened for presence of a FGFR, and /or VEGFR variant prior to treatment. The screening process will typically involve direct sequencing, oligonucleotide microarray analysis, or a mutant specific antibody. In addition, diagnosis of tumours with such mutations could be performed using techniques  
20 known to a person skilled in the art and as described herein such as RT-PCR and FISH.

In addition, mutant forms of, for example FGFR or VEGFR2, can be identified by direct sequencing of, for example, tumour biopsies using PCR and methods to sequence PCR products directly as hereinbefore described. The skilled artisan will recognize that all  
25 such well-known techniques for detection of the over expression, activation or mutations of the aforementioned proteins could be applicable in the present case.

In screening by RT-PCR, the level of mRNA in the tumour is assessed by creating a cDNA copy of the mRNA followed by amplification of the cDNA by PCR. Methods of  
30 PCR amplification, the selection of primers, and conditions for amplification, are known to a person skilled in the art. Nucleic acid manipulations and PCR are carried out by standard methods, as described for example in Ausubel, F.M. *et al.*, eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc., or Innis, M.A. *et al.*, eds. (1990) PCR Protocols: a guide to methods and applications, Academic Press, San  
35 Diego. Reactions and manipulations involving nucleic acid techniques are also described in Sambrook *et al.*, (2001), 3<sup>rd</sup> Ed, Molecular Cloning: A Laboratory Manual,

Cold Spring Harbor Laboratory Press. Alternatively a commercially available kit for RT-PCR (for example Roche Molecular Biochemicals) may be used, or methodology as set forth in United States patents 4,666,828; 4,683,202; 4,801,531; 5,192,659, 5,272,057, 5,882,864, and 6,218,529 and incorporated herein by reference. An example of an in-situ hybridisation technique for assessing mRNA expression would be fluorescence in-situ hybridisation (FISH) (see Angerer (1987) Meth. Enzymol., **152**: 649).

Generally, in situ hybridization comprises the following major steps: (1) fixation of tissue to be analyzed; (2) prehybridization treatment of the sample to increase accessibility of target nucleic acid, and to reduce nonspecific binding; (3) hybridization of the mixture of nucleic acids to the nucleic acid in the biological structure or tissue; (4) post-hybridization washes to remove nucleic acid fragments not bound in the hybridization, and (5) detection of the hybridized nucleic acid fragments. The probes used in such applications are typically labelled, for example, with radioisotopes or fluorescent reporters. Preferred probes are sufficiently long, for example, from about 50, 100, or 200 nucleotides to about 1000 or more nucleotides, to enable specific hybridization with the target nucleic acid(s) under stringent conditions. Standard methods for carrying out FISH are described in Ausubel, F.M. *et al.*, eds. (2004) Current Protocols in Molecular Biology, John Wiley & Sons Inc and Fluorescence In Situ Hybridization: Technical Overview by John M. S. Bartlett in Molecular Diagnosis of Cancer, Methods and Protocols, 2nd ed.; ISBN: 1-59259-760-2; March 2004, pps. 077-088; Series: Methods in Molecular Medicine.

Methods for gene expression profiling are described by (DePrimo *et al.* (2003), *BMC Cancer*, **3**:3). Briefly, the protocol is as follows: double-stranded cDNA is synthesized from total RNA Using a (dT)24 oligomer for priming first-strand cDNA synthesis, followed by second strand cDNA synthesis with random hexamer primers. The double-stranded cDNA is used as a template for *in vitro* transcription of cRNA using biotinylated ribonucleotides. cRNA is chemically fragmented according to protocols described by Affymetrix (Santa Clara, CA, USA), and then hybridized overnight on Human Genome Arrays.

Alternatively, the protein products expressed from the mRNAs may be assayed by immunohistochemistry of tumour samples, solid phase immunoassay with microtitre plates, Western blotting, 2-dimensional SDS-polyacrylamide gel electrophoresis, ELISA, flow cytometry and other methods known in the art for detection of specific proteins.

Detection methods would include the use of site specific antibodies. The skilled person will recognize that all such well-known techniques for detection of upregulation of FGFR, and/or VEGFR, or detection of FGFR, and/or VEGFR variants or mutants could be applicable in the present case.

5

Abnormal levels of proteins such as FGFR or VEGFR can be measured using standard enzyme assays, for example, those assays described herein. Activation or overexpression could also be detected in a tissue sample, for example, a tumour tissue. By measuring the tyrosine kinase activity with an assay such as that from Chemicon International. The tyrosine kinase of interest would be immunoprecipitated from the sample lysate and its activity measured.

10

Alternative methods for the measurement of the over expression or activation of FGFR or VEGFR including the isoforms thereof, include the measurement of microvessel density. This can for example be measured using methods described by Orre and Rogers (Int J Cancer (1999), **84(2)** 101-8). Assay methods also include the use of markers, for example, in the case of VEGFR these include CD31, CD34 and CD105.

15

Therefore all of these techniques could also be used to identify tumours particularly suitable for treatment with the compounds of the invention.

20

The compounds of the invention are particular useful in treatment of a patient having a mutated FGFR. The G697C mutation in FGFR3 is observed in 62% of oral squamous cell carcinomas and causes constitutive activation of the kinase activity. Activating mutations of FGFR3 have also been identified in bladder carcinoma cases. These mutations were of 6 kinds with varying degrees of prevalence: R248C, S249C, G372C, S373C, Y375C, K652Q. In addition, a Gly388Arg polymorphism in FGFR4 has been found to be associated with increased incidence and aggressiveness of prostate, colon, lung, liver (HCC) and breast cancer.

25

30

Therefore in a further aspect the invention includes use of a compound according to the invention for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against FGFR.

35

Particular mutations a patient is screened for include G697C, R248C, S249C, G372C, S373C, Y375C, K652Q mutations in FGFR3 and Gly388Arg polymorphism in FGFR4.

5 In another aspect the invention includes a compound of the invention for use in the prophylaxis or treatment of cancer in a patient selected from a sub-population possessing a variant of the FGFR gene (for example G697C mutation in FGFR3 and Gly388Arg polymorphism in FGFR4).

10 MRI determination of vessel normalization (e.g. using MRI gradient echo, spin echo, and contrast enhancement to measure blood volume, relative vessel size, and vascular permeability) in combination with circulating biomarkers (circulating progenitor cells (CPCs), CECs, SDF1, and FGF2) may also be used to identify VEGFR2-resistant tumours for treatment with a compound of the invention.

### 15 **Pharmaceutical Compositions and Combinations**

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

20 In one embodiment the pharmaceutical composition (e.g. formulation) comprises at least one active compound of the invention together with one or more pharmaceutically acceptable carriers, adjuvants, excipients, diluents, fillers, buffers, stabilisers, preservatives, lubricants, or other materials well known to those skilled in the art and optionally other therapeutic or prophylactic agents.

25 To prepare the pharmaceutical compositions of this invention, an effective amount of a compound of the present invention, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. The pharmaceutical compositions can be in any form suitable for oral, parenteral, topical, 30 intranasal, ophthalmic, otic, rectal, intra-vaginal, or transdermal administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, 35 alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants,

binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

Because of their ease in administration, tablets and capsules represent the most

- 5 advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution.
- 10 Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect
- 15 to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.
- 20 Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,
- 25 injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.

- 30 Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable
- 35 solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The compound of the invention is administered in an amount sufficient to exert its anti-tumour activity.

5 Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that a therapeutically effective amount would be from 0.005 mg/kg to 100 mg/kg body weight, and in particular from 0.005 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as single, two, three, four or more sub-doses at appropriate intervals throughout  
10 the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.5 to 500 mg, in particular 1 mg to 500 mg, more in particular 10 mg to 500 mg of active ingredient per unit dosage form.

Depending on the mode of administration, the pharmaceutical composition will  
15 preferably comprise from 0.05 to 99 % by weight, more preferably from 0.1 to 70 % by weight, even more preferably from 0.1 to 50 % by weight of the compound of the present invention, and, from 1 to 99.95 % by weight, more preferably from 30 to 99.9 % by weight, even more preferably from 50 to 99.9 % by weight of a pharmaceutically acceptable carrier, all percentages being based on the total weight of the composition.

20 As another aspect of the present invention, a combination of a compound of the present invention with another anticancer agent is envisaged, especially for use as a medicine, more specifically for use in the treatment of cancer or related diseases.

25 For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents or adjuvants in cancer therapy. Examples of anti-cancer agents or adjuvants (supporting agents in the therapy) include but are not limited to:

- 30 - platinum coordination compounds for example cisplatin optionally combined with amifostine, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel, paclitaxel protein bound particles (Abraxane<sup>TM</sup>) or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example  
35 irinotecan, SN-38, topotecan, topotecan hcl;



- topoisomerase II inhibitors such as anti-tumour epipodophyllotoxins or podophyllotoxin derivatives for example etoposide, etoposide phosphate or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- 5 - anti-tumour nucleoside derivatives for example 5-fluorouracil, leucovorin, gemcitabine, gemcitabine hcl, capecitabine, cladribine, fludarabine, nelarabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine, thiotepa, mephalan (melphalan), lomustine, altretamine, busulfan, dacarbazine, estramustine, ifosfamide
- 10 optionally in combination with mesna, pipobroman, procarbazine, streptozocin, telozolomide, uracil;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin optionally in combination with dexrazoxane, doxil, idarubicin, mitoxantrone, epirubicin, epirubicin hcl, valrubicin;
- 15 - molecules that target the IGF-1 receptor for example picropodophilin;
- tetracarcin derivatives for example tetrocarcin A;
- glucocorticoiden for example prednisone;
- antibodies for example trastuzumab (HER2 antibody), rituximab (CD20 antibody), gemtuzumab, gemtuzumab ozogamicin, cetuximab, pertuzumab,
- 20 bevacizumab, alemtuzumab, eculizumab, ibritumomab tiuxetan, nofetumomab, panitumumab, tositumomab, CNTO 328;
- estrogen receptor antagonists or selective estrogen receptor modulators or inhibitors of estrogen synthesis for example tamoxifen, fulvestrant, toremifene, droloxifene, faslodex, raloxifene or letrozole;
- 25 - aromatase inhibitors such as exemestane, anastrozole, letrozole, testolactone and vorozole;
- differentiating agents such as retinoids, vitamin D or retinoic acid and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine or decitabine;
- 30 - antifolates for example premetrexed disodium;
- antibiotics for example antinomycin D, bleomycin, mitomycin C, dactinomycin, carminomycin, daunomycin, levamisole, plicamycin, mithramycin;
- antimetabolites for example clofarabine, aminopterin, cytosine arabinoside or methotrexate, azacitidine, cytarabine, floxuridine, pentostatin, thioguanine;
- 35 - apoptosis inducing agents and antiangiogenic agents such as Bcl-2 inhibitors for example YC 137, BH 312, ABT 737, gossypol, HA 14-1, TW 37 or decanoic acid;

- tubuline-binding agents for example combrestatin, colchicines or nocodazole;
- kinase inhibitors (e.g. EGFR (epithelial growth factor receptor) inhibitors, MTKI (multi target kinase inhibitors), mTOR inhibitors) for example flavoperidol, imatinib mesylate, erlotinib, gefitinib, dasatinib, lapatinib, lapatinib ditosylate,
- 5       soranib, sunitinib, sunitinib maleate, temsirolimus;
- farnesyltransferase inhibitors for example tipifarnib;
- histone deacetylase (HDAC) inhibitors for example sodium butyrate, suberoylanilide hydroxamide acid (SAHA), depsipeptide (FR 901228), NVP-LAQ824, R306465, JNJ-26481585, trichostatin A, vorinostat;
- 10       - Inhibitors of the ubiquitin-proteasome pathway for example PS-341, MLN .41 or bortezomib;
- Yondelis;
- Telomerase inhibitors for example telomestatin;
- Matrix metalloproteinase inhibitors for example batimastat, marimastat, prinostat
- 15       or metastat.
- Recombinant interleukins for example aldesleukin, denileukin diftitox, interferon alfa 2a, interferon alfa 2b, peginterferon alfa 2b
- MAPK inhibitors
- Retinoids for example alitretinoin, bexarotene, tretinoin
- 20       - Arsenic trioxide
- Asparaginase
- Steroids for example dromostanolone propionate, megestrol acetate, nandrolone (decanoate, phenpropionate), dexamethasone
- Gonadotropin releasing hormone agonists or antagonists for example abarelix,
- 25       goserelin acetate, histrelin acetate, leuprolide acetate
- Thalidomide, lenalidomide
- Mercaptopurine, mitotane, pamidronate, pegademase, pegaspargase, rasburicase
- BH3 mimetics for example ABT-737
- 30       - MEK inhibitors for example PD98059, AZD6244, CI-1040
- colony-stimulating factor analogs for example filgrastim, pegfilgrastim, sargramostim; erythropoietin or analogues thereof (e.g. darbepoetin alfa); interleukin 11; oprelvekin; zoledronate, zoledronic acid; fentanyl; bisphosphonate; palifermin.
- 35       - a steroidal cytochrome P450 17 $\alpha$ -hydroxylase-17,20-lyase inhibitor (CYP17), e.g. abiraterone, abiraterone acetate.

The compounds of the present invention also have therapeutic applications in sensitising tumour cells for radiotherapy and chemotherapy.

- 5 Hence the compounds of the present invention can be used as "radiosensitizer" and/or "chemosensitizer" or can be given in combination with another "radiosensitizer" and/or "chemosensitizer".

10 The term "radiosensitizer", as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of the cells to ionizing radiation and/or to promote the treatment of diseases which are treatable with ionizing radiation.

15 The term "chemosensitizer", as used herein, is defined as a molecule, preferably a low molecular weight molecule, administered to animals in therapeutically effective amounts to increase the sensitivity of cells to chemotherapy and/or promote the treatment of diseases which are treatable with chemotherapeutics.

20 Several mechanisms for the mode of action of radiosensitizers have been suggested in the literature including: hypoxic cell radiosensitizers ( e.g., 2- nitroimidazole compounds, and benzotriazine dioxide compounds) mimicking oxygen or alternatively behave like bio-reductive agents under hypoxia; non-hypoxic cell radiosensitizers (e.g., halogenated pyrimidines) can be analogues of DNA bases and preferentially incorporate into the DNA of cancer cells and thereby promote the radiation-induced breaking of DNA  
25 molecules and/or prevent the normal DNA repair mechanisms; and various other potential mechanisms of action have been hypothesized for radiosensitizers in the treatment of disease.

Many cancer treatment protocols currently employ radiosensitizers in conjunction with radiation of x-rays. Examples of x-ray activated radiosensitizers include, but are not  
30 limited to, the following: metronidazole, misonidazole, desmethylmisonidazole, pimonidazole, etanidazole, nimorazole, mitomycin C, RSU 1069, SR 4233, EO9, RB 6145, nicotinamide, 5-bromodeoxyuridine (BUdR), 5- iododeoxyuridine (IUdR), bromodeoxycytidine, fluorodeoxyuridine (FudR), hydroxyurea, cisplatin, and therapeutically effective analogs and derivatives of the same.

35 Photodynamic therapy (PDT) of cancers employs visible light as the radiation activator of the sensitizing agent. Examples of photodynamic radiosensitizers include the

following, but are not limited to: hematoporphyrin derivatives, Photofrin, benzoporphyrin derivatives, tin etioporphyrin, pheoborbide-a, bacteriochlorophyll-a, naphthalocyanines, phthalocyanines, zinc phthalocyanine, and therapeutically effective analogs and derivatives of the same.

- 5 Radiosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of radiosensitizers to the target cells; compounds which control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour with or without additional radiation; or  
10 other therapeutically effective compounds for treating cancer or other diseases.

- Chemosensitizers may be administered in conjunction with a therapeutically effective amount of one or more other compounds, including but not limited to: compounds which promote the incorporation of chemosensitizers to the target cells; compounds which  
15 control the flow of therapeutics, nutrients, and/or oxygen to the target cells; chemotherapeutic agents which act on the tumour or other therapeutically effective compounds for treating cancer or other disease. Calcium antagonists, for example verapamil, are found useful in combination with antineoplastic agents to establish chemosensitivity in tumor cells resistant to accepted chemotherapeutic agents and to  
20 potentiate the efficacy of such compounds in drug-sensitive malignancies.

- In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the one or more other medicinal agent and the compound according to the present invention may be formulated into various pharmaceutical forms  
25 for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing all components.

- The present invention therefore also relates to a pharmaceutical composition comprising  
30 the one or more other medicinal agent and the compound according to the present invention together with a pharmaceutical carrier.

- The present invention further relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of  
35 tumour cells.

The present invention further relates to a product containing as first active ingredient a compound according to the invention and as further active ingredient one or more anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

5

The one or more other medicinal agents and the compound according to the present invention may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two or more compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and compound of the present invention being administered, their route of administration, the particular tumour being treated and the particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

10

15

The weight ratio of the compound according to the present invention and the one or more other anticancer agent(s) when given as a combination may be determined by the person skilled in the art. Said ratio and the exact dosage and frequency of administration depends on the particular compound according to the invention and the other anticancer agent(s) used, the particular condition being treated, the severity of the condition being treated, the age, weight, gender, diet, time of administration and general physical condition of the particular patient, the mode of administration as well as other medication the individual may be taking, as is well known to those skilled in the art.

20

25

Furthermore, it is evident that the effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. A particular weight ratio for the present compound of formula (I) and another anticancer agent may range from 1/10 to 10/1, more in particular from 1/5 to 5/1, even more in particular from 1/3 to 3/1.

30

The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 50 to 400  $\text{mg}/\text{m}^2$ , particularly for cisplatin in a dosage of about 75  $\text{mg}/\text{m}^2$  and for carboplatin in about 300 $\text{mg}/\text{m}^2$  per course of treatment.

35

The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 75 to 250  $\text{mg}/\text{m}^2$ , particularly for paclitaxel in a dosage of about 175 to 250  $\text{mg}/\text{m}^2$  and for docetaxel in about 75 to 150  $\text{mg}/\text{m}^2$  per course of treatment.

The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 1 to 300  $\text{mg}/\text{m}^2$ , particularly for irinotecan in a dosage of about 100 to 350  $\text{mg}/\text{m}^2$  and for topotecan in about 1 to 2  $\text{mg}/\text{m}^2$  per course of treatment.

The anti-tumour podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 50 to 250  $\text{mg}/\text{m}^2$ , particularly for etoposide in a dosage of about 35 to 100  $\text{mg}/\text{m}^2$  and for teniposide in about 50 to 250  $\text{mg}/\text{m}^2$  per course of treatment.

The anti-tumour vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, particularly for vinblastine in a dosage of about 3 to 12  $\text{mg}/\text{m}^2$ , for vincristine in a dosage of about 1 to 2  $\text{mg}/\text{m}^2$ , and for vinorelbine in dosage of about 10 to 30  $\text{mg}/\text{m}^2$  per course of treatment.

The anti-tumour nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 700 to 1500  $\text{mg}/\text{m}^2$ , particularly for 5-FU in a dosage of 200 to 500  $\text{mg}/\text{m}^2$ , for gemcitabine in a dosage of about 800 to 1200  $\text{mg}/\text{m}^2$  and for capecitabine in about 1000 to 2500  $\text{mg}/\text{m}^2$  per course of treatment.

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 120 to 200  $\text{mg}/\text{m}^2$ , particularly for cyclophosphamide in a dosage of about 100 to 500  $\text{mg}/\text{m}^2$ , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200  $\text{mg}/\text{m}^2$ , and for lomustine in a dosage of about 100 to 150  $\text{mg}/\text{m}^2$  per course of treatment.

The anti-tumour anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter ( $\text{mg}/\text{m}^2$ ) of body surface area, for example 15 to

60 mg/m<sup>2</sup>, particularly for doxorubicin in a dosage of about 40 to 75 mg/m<sup>2</sup>, for daunorubicin in a dosage of about 25 to 45 mg/m<sup>2</sup>, and for idarubicin in a dosage of about 10 to 15 mg/m<sup>2</sup> per course of treatment.

- 5 The antiestrogen agent is advantageously administered in a dosage of about 1 to 100 mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of  
10 about 60 mg once a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100 mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60 mg once a day. Exemestane is advantageously  
15 administered orally in a dosage of about 25 mg once a day.

- Antibodies are advantageously administered in a dosage of about 1 to 5 mg per square meter (mg/m<sup>2</sup>) of body surface area, or as known in the art, if different. Trastuzumab is advantageously administered in a dosage of 1 to 5 mg per square meter (mg/m<sup>2</sup>) of  
20 body surface area, particularly 2 to 4 mg/m<sup>2</sup> per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

- The compounds of formula (I), the pharmaceutically acceptable addition salts, in  
25 particular pharmaceutically acceptable acid addition salts, and stereoisomeric forms thereof can have valuable diagnostic properties in that they can be used for detecting or identifying the formation of a complex between a labelled compound and other molecules, peptides, proteins, enzymes or receptors.

- 30 The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances, etc. Examples of the radioisotopes include <sup>125</sup>I, <sup>131</sup>I, <sup>3</sup>H and <sup>14</sup>C. Enzymes are usually made detectable by conjugation of an appropriate substrate which, in turn catalyses a detectable reaction. Examples thereof include, for example, beta-galactosidase, beta-glucosidase, alkaline phosphatase, peroxidase and malate dehydrogenase, preferably  
35

horseradish peroxidase. The luminous substances include, for example, luminol, luminol derivatives, luciferin, aequorin and luciferase.

Biological samples can be defined as body tissue or body fluids. Examples of body fluids are cerebrospinal fluid, blood, plasma, serum, urine, sputum, saliva and the like.

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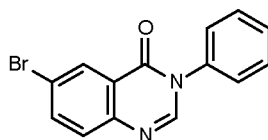
### General Synthetic Routes

The following examples illustrate the present invention but are examples only and are not intended to limit the scope of the claims in any way.

- 10 The values of salt stoichiometry or acid content in the compounds as provided herein, are those obtained experimentally and may vary dependent on the analytical method used (NMR for compounds 61', 62' and 73'). In case no salt form is indicated, the compound was obtained as a free base.
- 15 Hereinafter, the term 'DCM' means dichloromethane, 'Me' means methyl, 'Et' means ethyl, 'MeOH' means methanol, 'DMF' means dimethylformamide, 'Et<sub>2</sub>O' means diethyl ether, 'EtOAc' means ethyl acetate, Brettphos palladacycle : (CAS : 1148148-01-9) means Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2'-4'-6'-tri-*i*-propyl-1,1'-biphenyl][2-(2-aminoethyl)phenyl]palladium(II), 'PdCl<sub>2</sub>dppf' (CAS : 72287-26-4) means
- 20 1,1'-bis (diphenylphosphino) ferrocene dichloropalladium (II), 'THF' means tetrahydrofuran, 'ACN' means acetonitrile, 'SFC' means supercritical fluid chromatography, 'MgSO<sub>4</sub>' means magnesium sulfate, 'q.s.' means quantum sufficit, 'MP' means melting point, 'iPrNH<sub>2</sub>' means isopropylamine, 'DSC' means differential scanning calorimetry, 'DIPE' means diisopropylether, 'TBAF' means tetrabutylammonium fluoride,
- 25 'rt' means room temperature, 'Pd<sub>2</sub>dba<sub>3</sub>' means tris(dibenzylideneacetone)dipalladium(0), 'BINAP' means [1,1'-binaphthalene]-2,2'-diylbis[diphenylphosphine].

### A. Preparation of the intermediate compounds

#### Example A1:



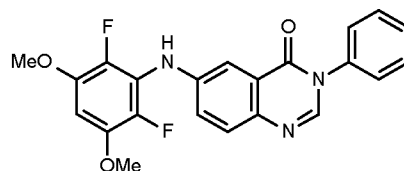
- 30 Preparation of intermediate 1:

2-Amino-5-bromobenzoic acid (50 g; 231.4 mmol) was dissolved in toluene (500 mL). Triethyl orthoformate was added (58 mL; 347.2 mmol) followed by acetic acid (1.3 mL; 23.1 mmol). The mixture was heated at 110 °C for 2.5 hours. The reaction was cooled



to room temperature and aniline (21 mL; 231.4 mmol) was added. The mixture was heated at 110 °C for another 20 hours. The resulting mixture was cooled at room temperature and filtered. The filtrate was crystallized from petroleum ether. The precipitate was filtered and recrystallized from a mixture of DCM and petroleum ether to afford 15.6 g (22 %) of intermediate 1.

MP = 178°C

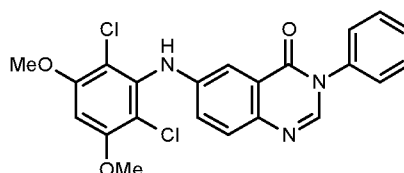


Preparation of intermediate 2:

A mixture of intermediate 1 (1.4 g; 4.6 mmol), 2,6-difluoro-3,5-dimethoxyaniline (1.3 g; 6.9 mmol), Brettphos palladacycle (0.18 g; 0.23 mmol) and cesium carbonate (4.5 g; 13.75 mmol) in toluene (60 mL) was heated at 100 °C for 5 hours. The mixture was cooled, poured onto cooled water and DCM was added. The solution was filtered through a pad of Celite® and the filtrate was extracted with DCM. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness.

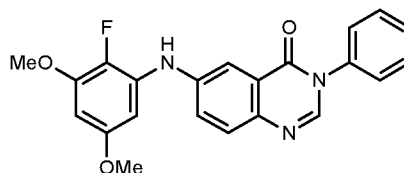
The residue (2.4 g) was purified by chromatography over silica gel (irregular SiOH 50g; mobile phase: 99% DCM, 1% MeOH). The fractions containing the product were collected and evaporated to dryness yielding 2.1g of an intermediate compound which was crystallized from a mixture of MeOH and Et<sub>2</sub>O to afford 704 mg (38 %) of intermediate 2.

MP = 156°C (DSC)



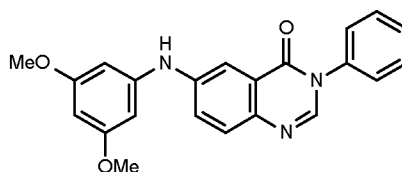
Preparation of intermediate 5:

Intermediate 5 was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2,6-dichloro-3,5-dimethoxyaniline as starting material (yield : 59 %).



Preparation of intermediate 7:

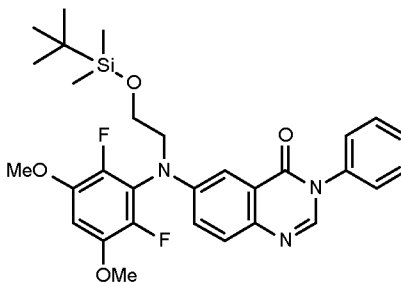
Intermediate **7** was prepared according to an analogous procedure as described for the synthesis of intermediate **2**, using 2-fluoro-3,5-dimethoxyaniline as starting material (yield : 52 %).



5 Preparation of intermediate **9**:

Intermediate **9** was prepared according to an analogous procedure as described for the synthesis of intermediate **2**, using 3,5-dimethoxyaniline as starting material (yield : 45 %).

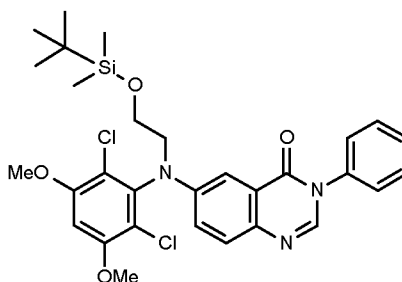
**Example A2:**



10 Preparation of intermediate **3**:

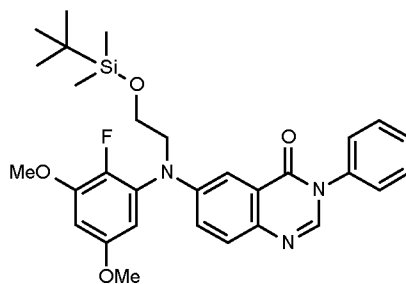
Under N<sub>2</sub> at 10 °C, sodium hydride (60 % in mineral oil) (0.4 g; 9 mmol) was added to a solution of intermediate **2** (1.24 g; 3 mmol) in DMF (12 mL). The solution was stirred at 10 °C for 30 minutes. Subsequently, a solution of (2-bromoethoxy)-tert-butyl dimethylsilane (1.4 mL; 6.7 mmol) in DMF (3 mL) was added dropwise. The solution was allowed to slowly rise to room temperature for 5 hours. The solution was poured onto cooled water and the product was extracted with EtOAc. The organic layer was washed with water, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness to give 2 g of intermediate **3** which was used as such in the next reaction step without any further treatment.

20



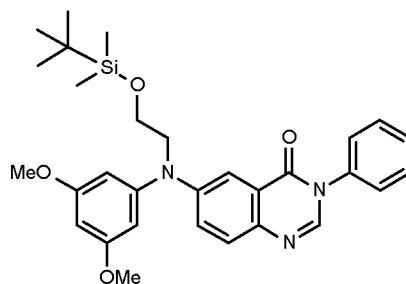
Preparation of intermediate **6**:

Intermediate **6** was prepared according to an analogous procedure as described for the synthesis of intermediate **3**, using intermediate **5** as starting material.



Preparation of intermediate **8**:

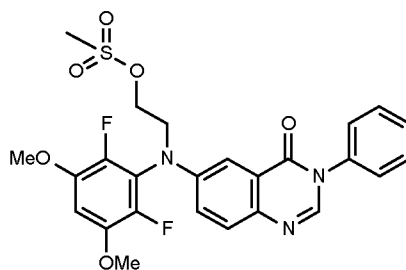
- 5 Intermediate **8** was prepared according to an analogous procedure as described for the synthesis of intermediate **3**, using intermediate **7** as starting material.



Preparation of intermediate **10**:

- 10 Intermediate **10** was prepared according to an analogous procedure as described for the synthesis of intermediate **3**, using intermediate **9** as starting material.

### Example A3:

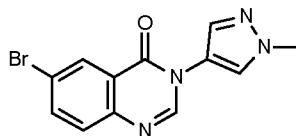


Preparation of intermediate **4** :

- 15 Methanesulfonyl chloride (0.3 mL; 3.75 mmol) was added drop wise to a solution of compound **1** (0.43 g; 0.94 mmol) and triethylamine (0.65 mL; 4.7 mmol) in DCM (20 mL) at 5 °C under N<sub>2</sub> flow. The reaction mixture was stirred at 5 °C for 2 hours, then poured onto ice water and DCM (q.s.) was added. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated to dryness at room temperature to give

0.5 g of intermediate **4** which was directly used as such in the next reaction step without any further treatment.

**Example A4:**



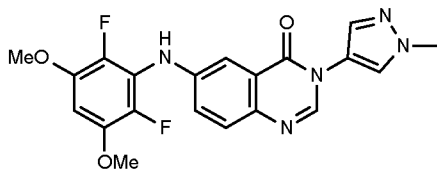
5 Preparation of intermediate **11**:

2-Amino-5-bromobenzoic acid (33.4 g; 154.4 mmol) was dissolved in toluene (2 L). Triethyl orthoformate was added (34 g; 231.7 mmol) followed by acetic acid (2 mL).

The mixture was heated at 110 °C for 2.5 hours. The reaction was cooled to room temperature and 4-amino-1-methylpyrazole (15 g; 154.4 mmol) was added. The

10 mixture was heated at 110 °C for another 20 hours. The resulting mixture was cooled to room temperature and filtered. The filtrate was crystallized from a mixture of toluene and petroleum ether. The precipitate was filtered and purified by chromatography over silica gel (irregular SiOH; mobile phase: DCM/MeOH 80/1). The fractions containing the product were collected and evaporated to dryness yielding 11 g (23 %) of

15 intermediate **11**.



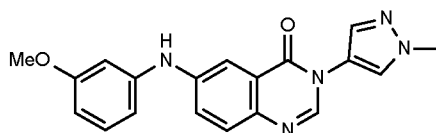
Preparation of intermediate **22**:

A mixture of intermediate **11** (1.4g; 4.6 mmol), 2,6-difluoro-3,5-dimethoxyaniline (1.4 g; 7.3 mmol), Brettphos palladacycle (0.18 g; 0.23 mmol) and cesium carbonate (4.5 g; 14 mmol) in toluene (60 mL) was heated at 100 °C overnight. The mixture was cooled, poured onto cooled water and EtOAc was added. The solution was filtered through a pad of Celite® (diatomaceous earth) and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness.

20 The residue (2.6 g) was purified by chromatography over silica gel (irregular SiOH, 300 g; mobile phase: 60% heptane, 5% MeOH, 35% EtOAc). The fractions containing the product were collected and evaporated to dryness yielding 1.1 g of an intermediate which was crystallized from Et<sub>2</sub>O yielding 1.06 g (56 %) of intermediate **22**.

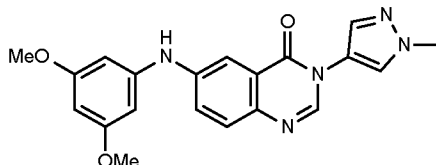
MP = 214°C (DSC)

127



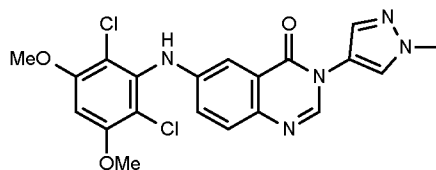
Preparation of intermediate **12**:

Intermediate **12** was prepared according to an analogous procedure as described for the synthesis of intermediate **22**, using *m*-anisidine as starting material (yield : 13 %).



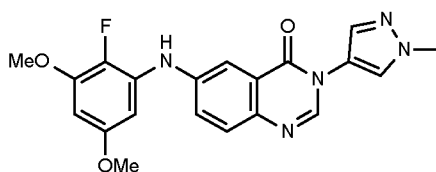
5 Preparation of intermediate **13**:

Intermediate **13** was prepared according to an analogous procedure as described for the synthesis of intermediate **22**, using 3,5-dimethoxyaniline as starting material (yield : 50 %).



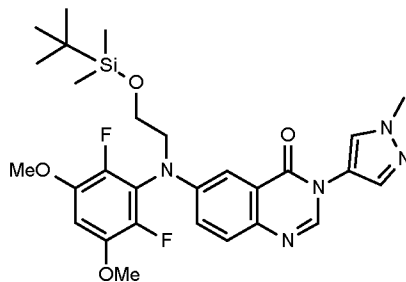
10 Preparation of intermediate **16**:

Intermediate **16** was prepared according to an analogous procedure as described for the synthesis of intermediate **22**, using 2,6-dichloro-3,5-dimethoxyaniline as starting material (yield : 45 %).

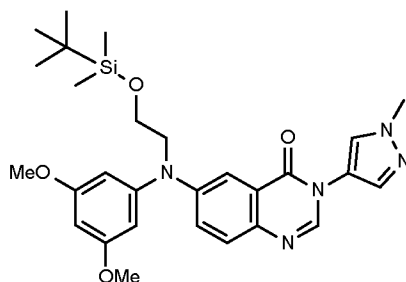


15 Preparation of intermediate **19**:

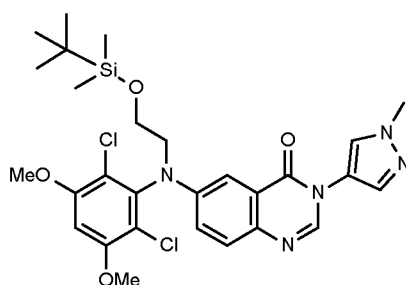
Intermediate **19** was prepared according to an analogous procedure as described for the synthesis of intermediate **22**, using 2-fluoro-3,5-dimethoxyaniline as starting material (yield : 7 %).

**Example A5:****Preparation of intermediate 23:**

Under N<sub>2</sub> at 10 °C, sodium hydride (60 % in mineral oil) (0.26 g; 6.4 mmol) was added to  
5 a solution of intermediate **22** (0.88g; 2mmol) in DMF (12 mL). The solution was stirred at  
10 °C for 30 minutes. Then, a solution of (2-bromoethoxy)-*tert*-butyldimethylsilane  
(1 mL; 4.7 mmol) in DMF (3mL) was added drop wise. The solution was allowed to  
slowly rise to room temperature for 5 hours. The solution was poured onto cooled water  
and the product was extracted with EtOAc. The organic layer was washed with water,  
10 dried over MgSO<sub>4</sub>, filtered and evaporated to dryness given 1.65 g of intermediate **23**  
which was directly used as such in the next reaction step without any further treatment.

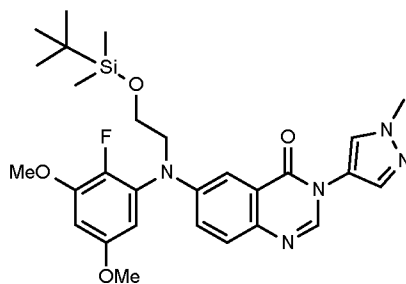
**Preparation of intermediate 14:**

Intermediate **14** was prepared according to an analogous procedure as described for the  
15 synthesis of intermediate 23, using intermediate 13 as starting material.

**Preparation of intermediate 17:**

Intermediate **17** was prepared according to an analogous procedure as described for the  
synthesis of intermediate 23, using intermediate 16 as starting material.

129

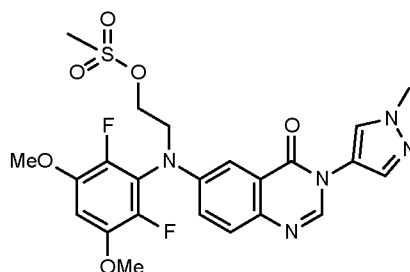


Preparation of intermediate **20**:

Intermediate **20** was prepared according to an analogous procedure as described for the synthesis of intermediate **23**, using intermediate **19** as starting material.

5

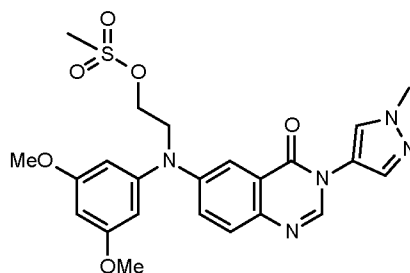
#### Example A6:



Preparation of intermediate **24** :

Methanesulfonyl chloride (0.5 mL; 6.4 mmol) was added drop wise to a solution of compound **18** (0.74 g; 1.6 mmol) and triethylamine (1.1 mL; 8 mmol) in DCM (10 mL) at 5 °C under N<sub>2</sub> flow. The reaction mixture was stirred at 5°C for 2 hours. The reaction mixture was poured onto iced water and DCM was added. The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the solvent was evaporated to dryness at room temperature to give 0.8 g of intermediate **24** which was directly used as such in the next step without any further treatment.

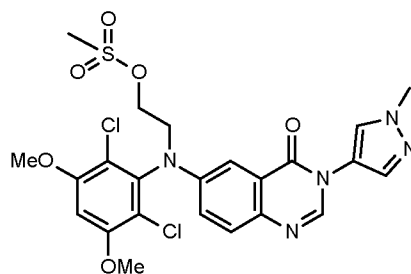
15



Preparation of intermediate **15** :

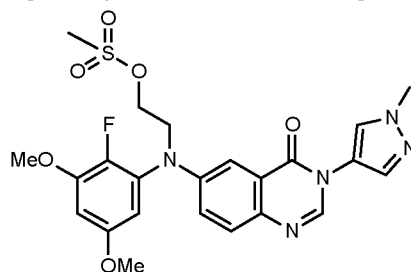
Intermediate **15** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **8** as starting material.

130



Preparation of intermediate **18**:

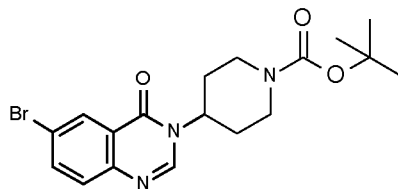
Intermediate **18** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **10** as starting material.



Preparation of intermediate **21**:

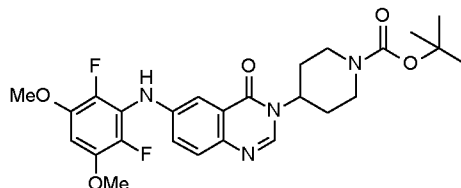
- 5 Intermediate **21** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **16** as starting material.

#### Example A7:



Preparation of intermediate **25**:

- 10 Intermediate **25** was prepared according to an analogous procedure as described for the synthesis of intermediate **1**, using 4-aminopiperidine-1-carboxylate as starting material (yield : 98 %).



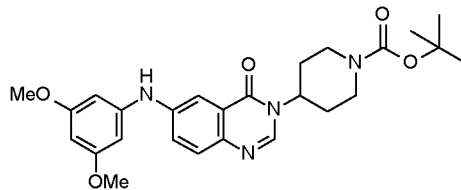
Preparation of intermediate **26**:

- 15 Pd<sub>2</sub>dba<sub>3</sub> (224mg; 0.245 mmol) and BINAP (305 mg; 0.49 mmol) was added to a solution of intermediate **25** (2g; 4.9 mmol), 2,6-difluoro-3,5-dimethoxyaniline (1.39g; 7.35 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (4.79g; 14.69 mmol) in dioxane (60 mL). The reaction mixture was heated overnight at 80°C. Then, it was poured onto cooled water and the aqueous layer was extracted with DCM. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent



was evaporated. The resulting residue was crystallized from DIPE to afford 1.90g of intermediate 26 (75%).

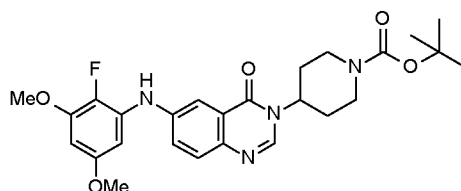
MP = 260°C (Kofler)



Preparation of intermediate 27:

- 5 Intermediate 27 was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 3,5-dimethoxyaniline and intermediate 25 as starting materials (yield : 84 %).

MP = 241°C (Kofler)

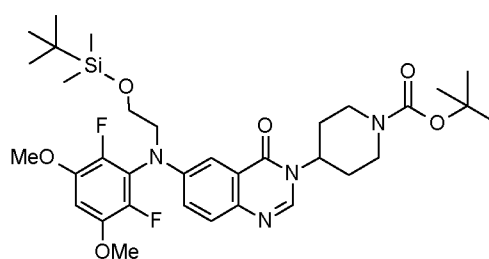


Preparation of intermediate 28:

- 10 Intermediate 28 was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2-fluoro-3,5-dimethoxyaniline and intermediate 25 as starting materials (yield : 70 %).

MP = 263°C (Kofler)

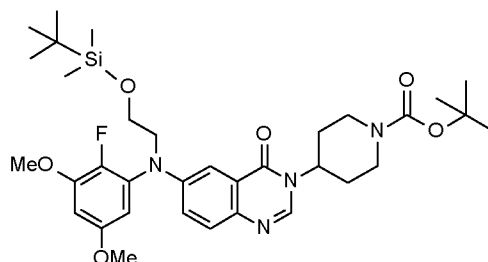
15 **Example A8:**



Preparation of intermediate 29:

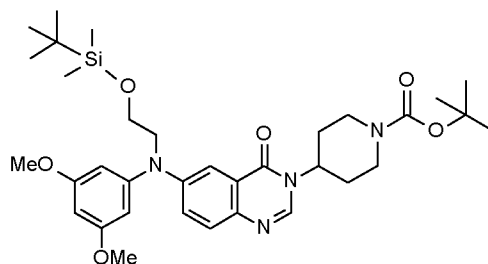
- 20 Under N<sub>2</sub> at -10 °C, sodium hydride (60 % in mineral oil) (116 mg; 2.904 mmol) was added to a solution of intermediate 26 (500 mg; 0.968 mmol) in DMF (15 mL). The reaction mixture was stirred at -10°C for 30 minutes. Then, (2-bromoethoxy)-*tert*-butyldimethylsilane (0.455 mL; 2.13 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature over 2 hours. The solution was poured onto ice/water and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue was purified by

chromatography over silica gel (irregular SiOH, 30g; mobile phase: gradient from 0% MeOH, 100% DCM to 2% MeOH, 98% DCM). The fractions containing the product were collected and evaporated to dryness yielding 436 mg (67 %) of intermediate **29**.



5 Preparation of intermediate **30**:

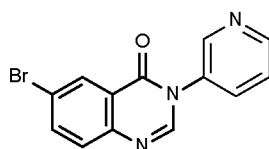
Intermediate **30** was prepared according to an analogous procedure as described for the synthesis of intermediate **29**, using intermediate **28** as starting material (yield : 77 %).



Preparation of intermediate **48**:

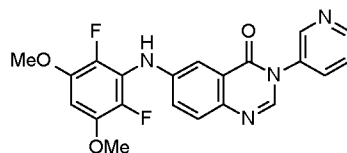
- 10 Intermediate **48** was prepared according to an analogous procedure as described for the synthesis of intermediate **29**, using intermediate **27** as starting material (yield : 64%).

**Example A9:**



Preparation of intermediate **31**:

- 15 Intermediate **31** was prepared according to an analogous procedure as described for the synthesis of intermediate **1**, using 3-aminopyridine as starting material (yield : 24%).

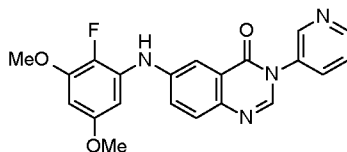


Preparation of intermediate **32**:

Intermediate **32** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2,6-difluoro-3,5-dimethoxyaniline and intermediate 31 as starting materials (yield : 51 %).

MP = 165°C (Kofler)

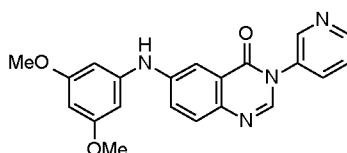
5



Preparation of intermediate **33**:

Intermediate **33** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2-difluoro-3,5-dimethoxyaniline and intermediate 31 as starting materials (yield : 23 %).

10 MP = 162°C (Kofler)



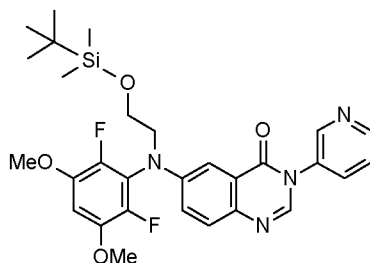
Preparation of intermediate **34**:

Intermediate **34** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 3,5-dimethoxyaniline and intermediate 31 as starting materials (yield : 80 %).

15

MP = 176°C (Kofler)

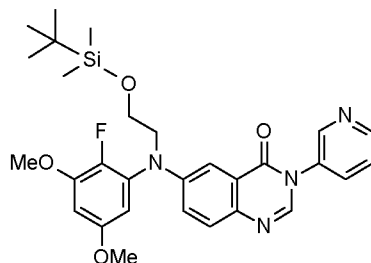
#### Example A10:



20 Preparation of intermediate **35**:

Intermediate **35** was prepared according to an analogous procedure as described for the synthesis of intermediate 23, using intermediate 32 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

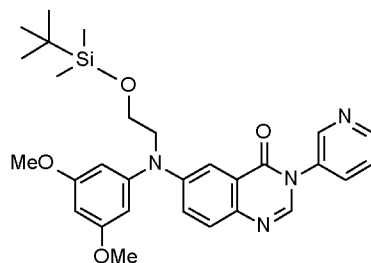
134



Preparation of intermediate **36**:

Intermediate **36** was prepared according to an analogous procedure as described for the synthesis of intermediate **23**, using intermediate **33** as starting material. This compound was directly used as such in the next reaction step without any further treatment.

5

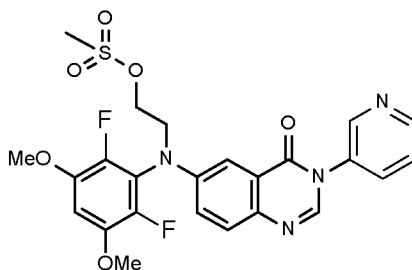


Preparation of intermediate **37**:

Intermediate **37** was prepared according to an analogous procedure as described for the synthesis of intermediate **23**, using intermediate **34** as starting material (yield : 61%).

10

#### Example A11:

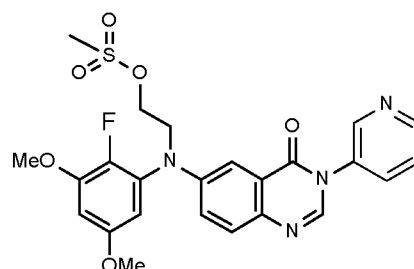


Preparation of intermediate **38** :

Intermediate **38** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **29** as starting material. This compound was directly used as such in the next reaction step without any further treatment.

15

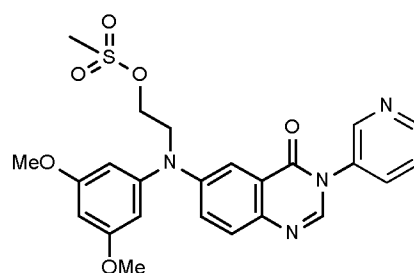
135



Preparation of intermediate **39** :

Intermediate **39** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 30 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

5

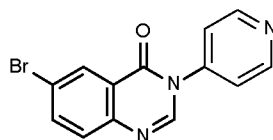


Preparation of intermediate **40** :

Intermediate **40** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 31 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

10

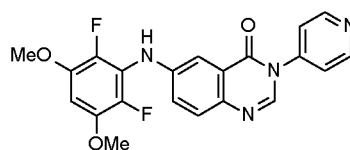
### Example A12:



Preparation of intermediate **41**:

Intermediate **41** was prepared according to an analogous procedure as described for the synthesis of intermediate 1, using 4-aminopyridine as starting material (yield : 29%).

15

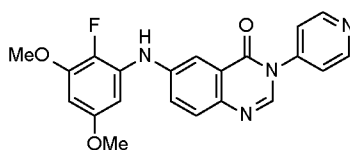


Preparation of intermediate **42**:

Intermediate **42** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2,6-difluoro-3,5-dimethoxyaniline and intermediate 41 as starting materials (yield : 19%).

100 mg of intermediate 42 were purified by achiral SFC (Stationary phase: 2 ethylpyridine 6 $\mu$ m 150x21.2mm), Mobile phase: 80% CO<sub>2</sub>, 20% MeOH(0.3% iPrNH<sub>2</sub>) to afford 84 mg of intermediate 42 (MP = 248°C (Kofler)).

5

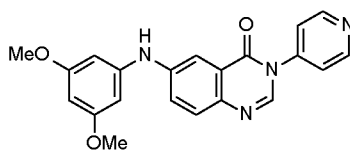


Preparation of intermediate **43**:

Intermediate **43** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 2-difluoro-3,5-dimethoxyaniline and intermediate 41 as starting materials (yield : 55 %).

10

150 mg of intermediate 43 was recrystallised from MeOH and DIPE yielding 107 mg of intermediate 43 (MP = 215°C (Kofler)).



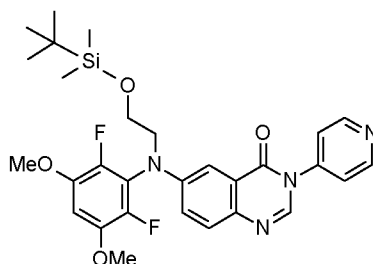
15 Preparation of intermediate **44**:

Intermediate **44** was prepared according to an analogous procedure as described for the synthesis of intermediate 2, using 3,5-dimethoxyaniline and intermediate 41 as starting materials (yield : 23%).

MP = 216°C (Kofler)

20

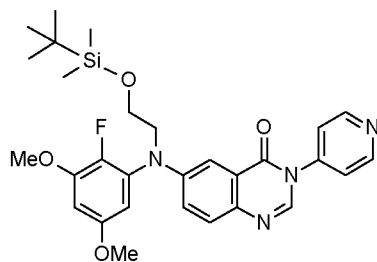
**Example A13:**



Preparation of intermediate **45**:

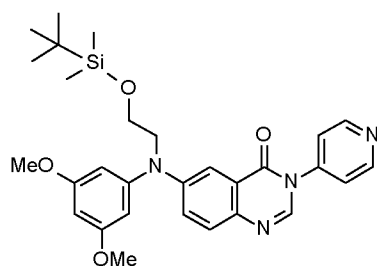
Intermediate **45** was prepared according to an analogous procedure as described for the synthesis of intermediate 23, using intermediate 42 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

25



Preparation of intermediate **46**:

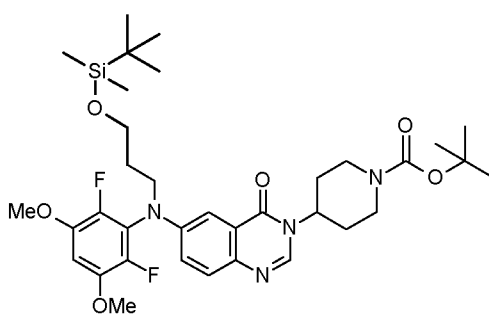
Intermediate **46** was prepared according to an analogous procedure as described for the synthesis of intermediate 23, using intermediate 43 as starting material. This compound  
 5 was directly used as such in the next reaction step without any further treatment.



Preparation of intermediate **47**:

Intermediate **47** was prepared according to an analogous procedure as described for the synthesis of intermediate 23, using intermediate 44 as starting material. This compound  
 10 was directly used as such in the next reaction step without any further treatment.

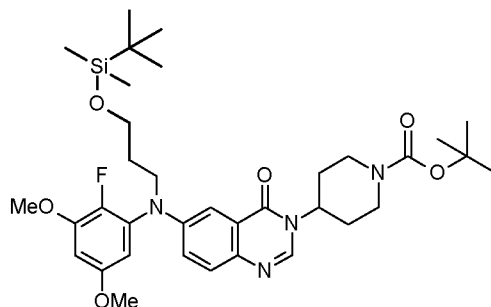
#### Example A14:



Preparation of intermediate **49**:

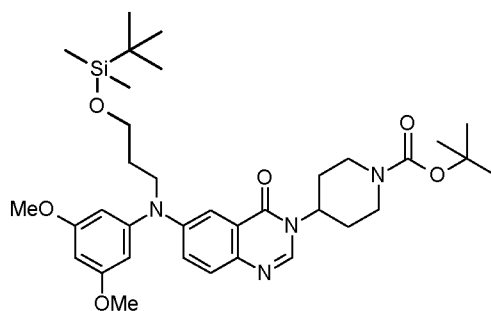
15 Sodium hydride (60 % in mineral oil) (116 mg; 2.904 mmol) was added at -10°C to a solution of intermediate **26** (500 mg; 0.968 mmol) in DMF (15 mL). The reaction mixture was stirred at -10°C for 30 minutes. Then, (3-bromopropoxy)-*tert*-butyldimethylsilane (0.48 mL; 2.13 mmol) was added dropwise. The reaction mixture was allowed to warm to 5°C over 2 hours. The solution was poured onto ice/water and the product was  
 20 extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>,

filtered and evaporated to dryness. The residue was crystallized from Et<sub>2</sub>O and the precipitate was filtered and dried yielding 347 mg of intermediate **49** (52 %).



Preparation of intermediate **50**:

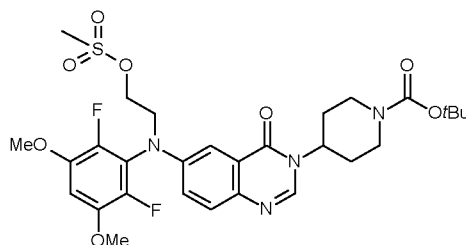
- 5 Intermediate **50** was prepared according to an analogous procedure as described for the synthesis of intermediate **49**, using intermediate **28** as starting material. (yield : 73 %)



Preparation of intermediate **51**:

- 10 Intermediate **51** was prepared according to an analogous procedure as described for the synthesis of intermediate **49**, using intermediate **27** as starting material. (yield : 88 %)

#### Example A15:

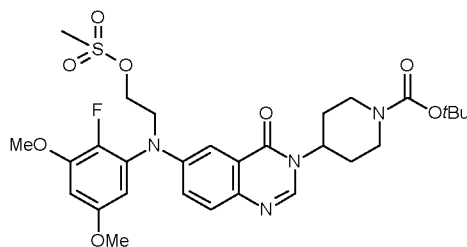


Preparation of intermediate **52** :

- 15 Intermediate **52** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **25** as starting material. This compound was directly used as such in the next reaction step without any further treatment.



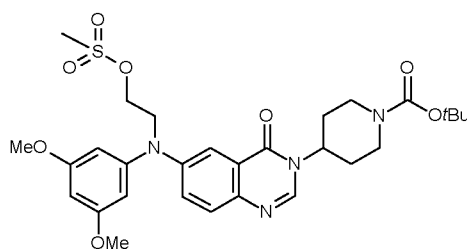
139



Preparation of intermediate **53** :

Intermediate **53** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 26 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

5

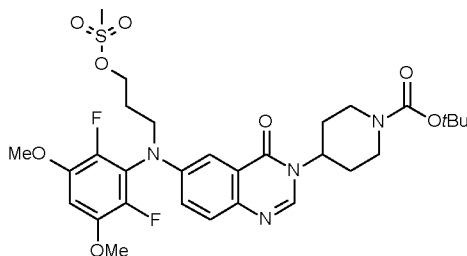


Preparation of intermediate **54** :

Intermediate **54** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 56 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

10

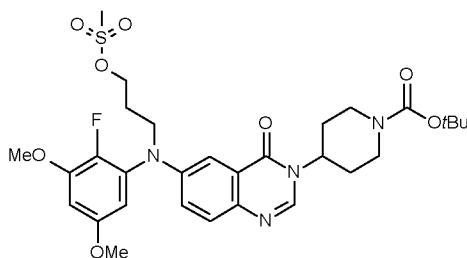
#### Example A16:



Preparation of intermediate **55** :

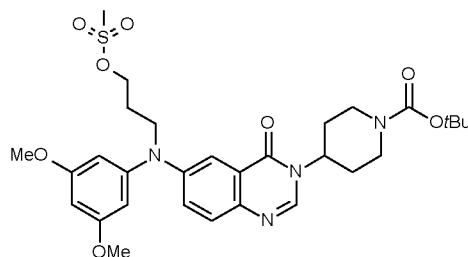
Intermediate **55** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 50 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

15



Preparation of intermediate **56** :

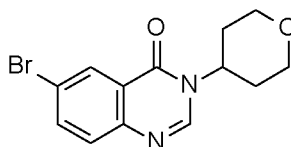
Intermediate **56** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **51** as starting material. This compound was directly used as such in the next reaction step without any further treatment.



5 Preparation of intermediate **57** :

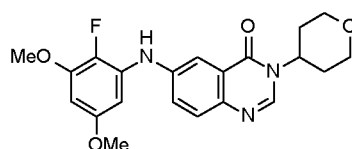
Intermediate **57** was prepared according to an analogous procedure as described for the synthesis of intermediate **24**, using compound **52** as starting material. This compound was directly used as such in the next reaction step without any further treatment.

10 **Example A17:**



Preparation of intermediate **58**:

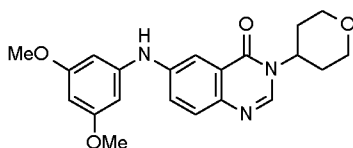
2-Amino-5-bromobenzoic acid (30 g; 138.9 mmol), triethyl orthoformate (30.9 g; 208.3 mmol) and acetic acid (0.9 mL) were dissolved in toluene (1.5 L). The mixture was heated at 110 °C for 2.5 hours. Then, tetrahydro-2H-pyran-4-amine (14.05 g; 138.9 mmol) was added and the reaction mixture was refluxed for 3 days. The resulting mixture was cooled at room temperature and filtered. The filtrate was concentrated and crystallized from a mixture of DCM and petroleum ether to afford 26.9 g (62 %) of intermediate **58**.



Preparation of intermediate **59**:

$\text{Pd}_2\text{dba}_3$  (296 mg; 0.32 mmol) and BINAP (403 mg; 0.65 mmol) were added to a solution of 2-fluoro-3,5-dimethoxyaniline (1.66 g; 9.70 mmol), intermediate **58** (2 g; 6.47 mmol) and  $\text{Cs}_2\text{CO}_3$  (6.32 g; 19.41 mmol) in 1,4-dioxane (80 mL). The mixture was heated at 80°C overnight. The solution was poured onto cooled water, the product was extracted with DCM. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and

evaporated to dryness. The residue was crystallized from DIPE. The precipitate was filtered to afford an intermediate residue (2.02g containing 81% of intermediate 59 based on LC/MS). 150 mg of this residue were purified by flash chromatography over silica gel (15-40µm, 4g, DCM/MeOH: 98/2). The fractions containing the product were collected and evaporated to dryness to give 62 mg of intermediate **59**.  
MP = 240°C (Kofler).

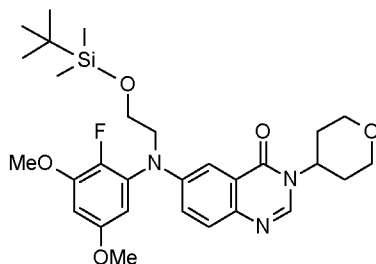


### Preparation of intermediate 60:

Intermediate **60** was prepared according to an analogous procedure as described for the synthesis of intermediate **2**, using 3,5-dimethoxyaniline and intermediate **58** as starting materials (yield : 85%).

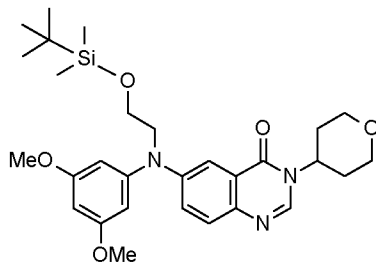
MP = 205°C (Kofler)

**Example A18:**



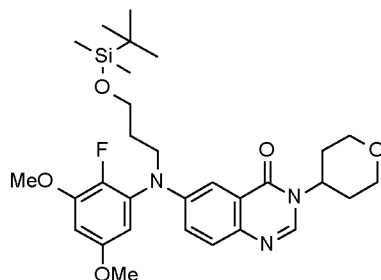
### Preparation of intermediate 61:

Intermediate **61** was prepared according to an analogous procedure as described for the synthesis of intermediate **29**, using intermediate **59** as starting material (yield : 31%).

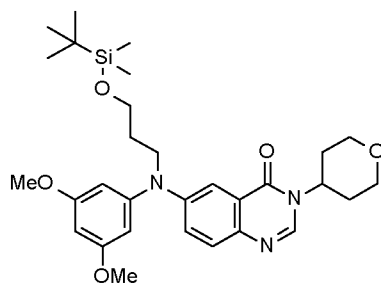


### Preparation of intermediate 62:

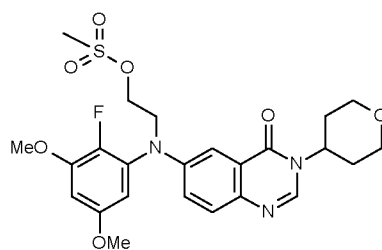
Intermediate **62** was prepared according to an analogous procedure as described for the synthesis of intermediate 29, using intermediate 60 as starting material (yield : 59%).

**Example A19:****Preparation of intermediate 63:**

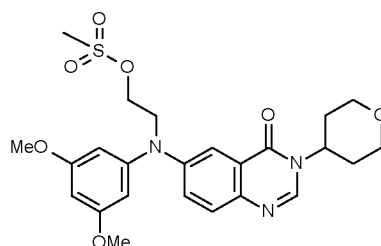
Under N<sub>2</sub> at 10°C, sodium hydride (60 % in mineral oil) (60 mg; 1.50 mmol) was added to a solution of intermediate 59 (200 mg; 0.50 mmol) in DMF (12 mL). The solution was stirred at 10°C for 30 minutes. Then a solution of (3-bromopropoxy)-*tert*-butyldimethylsilane (0.26 mL; 1.10 mmol) in DMF (3 mL) was added dropwise. The solution was stirred at 10°C for 5 hours. The solution was poured onto cooled water and the product was extracted with EtOAc. The organic layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (367 mg) was purified by flash chromatography over silica gel (15-40μm, 12g, DCM/MeOH: 99/1). The fractions containing the product were collected and evaporated to dryness to give 71 mg (26%) of intermediate 63.

**Preparation of intermediate 64:**

Intermediate 64 was prepared according to an analogous procedure as described for the synthesis of intermediate 49, using intermediate 60 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

**Example A20:****Preparation of intermediate 65 :**

Intermediate **65** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 63 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

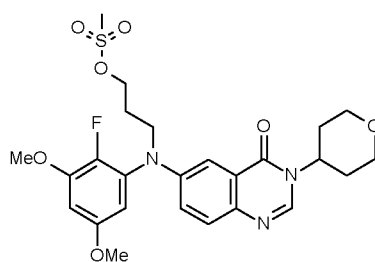


5 Preparation of intermediate **66** :

Intermediate **66** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 64 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

10

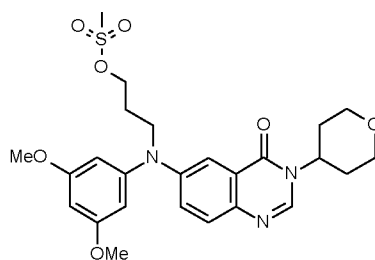
**Example A21:**



Preparation of intermediate **67** :

Intermediate **67** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 65 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

15



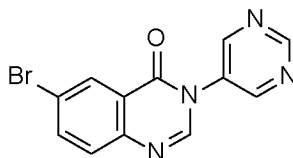
Preparation of intermediate **68** :

Intermediate **68** was prepared according to an analogous procedure as described for the synthesis of intermediate 24, using compound 66 as starting material. This compound was directly used as such in the next reaction step without any further treatment.

20

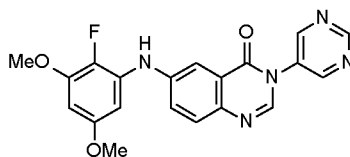
**Example A22:**

144



#### Preparation of intermediate 69:

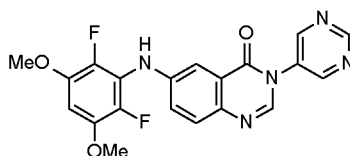
2-Amino-5-bromobenzoic acid (19.8 g; 91.6 mmol) was dissolved in xylene (870 mL). Triethyl orthoformate was added (20.4 g; 137.5 mmol) and the mixture was heated at 110 °C for 2.5 hours. The reaction was cooled to room temperature and 5-amino-  
 5 pyrimidine (9.51 g; 100 mmol) was added. The mixture was refluxed for another 48 hours. The resulting mixture was cooled at room temperature and evaporated until dryness. The residue was crystallized from a mixture of methanol and 2-isopropoxypropane and the precipitate was filtered. The residue was purified by chromatography over silica gel (mobile phase: gradient from DCM/MeOH 100/1 to 50%  
 10 DCM/ 50% MeOH). The fractions containing the product were collected and evaporated to dryness to give 6.1 g (22 %) of intermediate 69.



#### Preparation of intermediate 70:

Intermediate 70 was prepared according to an analogous procedure as described for the  
 15 synthesis of intermediate 2, using 2-fluoro-3,5-dimethoxyaniline and intermediate 69 as starting materials .

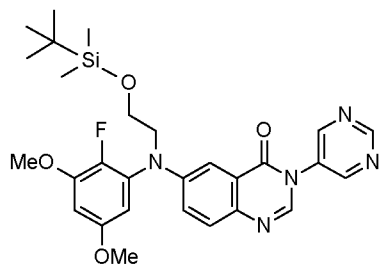
100 mg of crude intermediate 70 were purified by flash chromatography over silica gel (15-40µm, 4g, DCM/MeOH: 98/2). The fractions containing the product were collected and evaporated to dryness to give 35 mg of intermediate 70 (MP = 225°C (Kofler))  
 20



#### Preparation of intermediate 72:

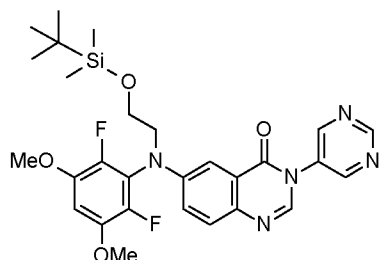
Intermediate 72 was prepared according to an analogous procedure as described for the  
 25 synthesis of intermediate 2, using 2,6-difluoro-3,5-dimethoxyaniline and intermediate 69 as starting materials (yield : 72 %).

MP = 187°C (Kofler)

**Example A23:**

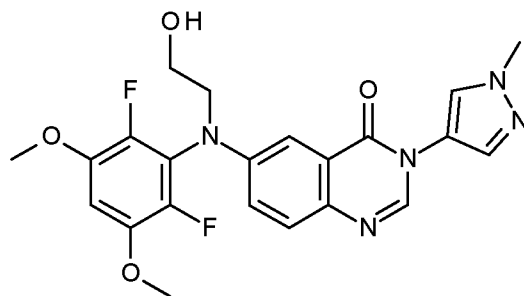
Preparation of intermediate **71**:

- 5 Intermediate **71** was prepared according to an analogous procedure as described for the synthesis of intermediate 29, using intermediate 70 as starting material (yield : 35 %).



Preparation of intermediate **73**:

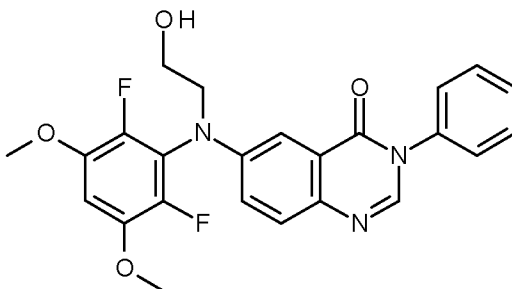
- 10 Intermediate **73** was prepared according to an analogous procedure as described for the synthesis of intermediate 29, using intermediate 72 as starting material (yield: 31 %).

**B. Preparation of the final compounds****Example B1:**

Preparation of compound **18**:

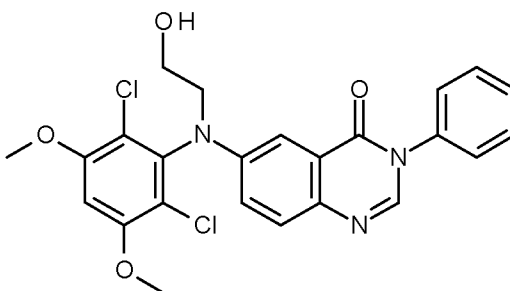
- 15 At 10°C, tetrabutylammonium fluoride (13 mL; 43 mmol) was added to a solution of intermediate **23** (1.65 g; 3 mmol) in THF (50 mL) and the mixture was stirred at room temperature for 8 hours. The solution was poured onto cooled water and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (1.3 g) was purified by chromatography over silica gel (Irregular SiOH, 15-40 µm, 300 g, Mobile phase: 97% DCM, 3% MeOH, 0.1% NH<sub>4</sub>OH). The fractions containing the product were collected and evaporated to dryness.
- 20

The residue (0.43 g) was crystallized from a mixture of MeOH and Et<sub>2</sub>O. The precipitate was filtered off and dried yielding 0.394 g (30 %) of compound **18** (MP: 165 °C (DSC)).



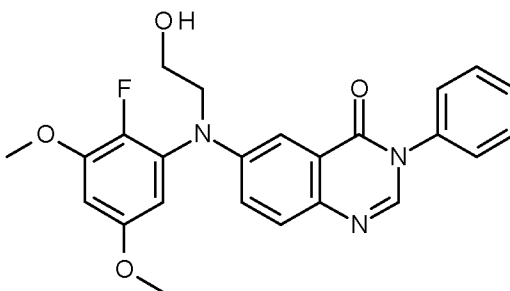
Preparation of compound **1** :

- 5 Compound **1** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **3** as starting material (yield: 34 %; MP: 169 °C (DSC)).



Preparation of compound **5**:

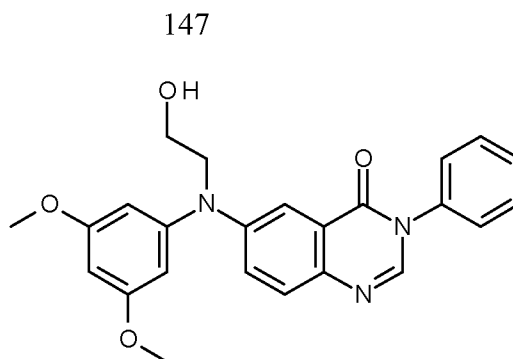
- 10 Compound **5** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **6** as starting material (yield: 43 %; MP: 251 °C (DSC)).



Preparation of compound **6**:

- 15 Compound **6** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **8** as starting material (yield: 36 %; MP: 183 °C (DSC)).

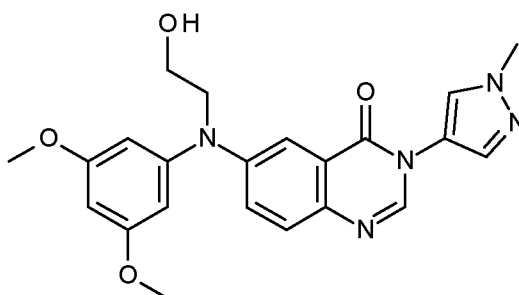




Preparation of compound **7**:

Compound **7** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **10** as starting material (yield: 20 %; MP: 171 °C (DSC)).

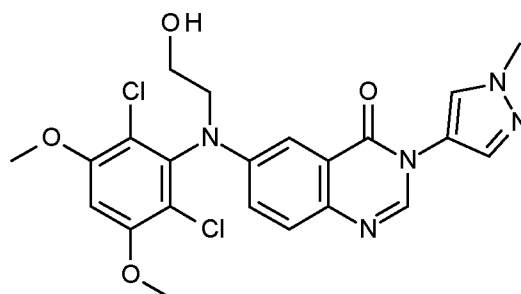
5



Preparation of compound **8**:

Compound **8** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **14** as starting material (yield: 29 %; MP: 185 °C (DSC)).

10

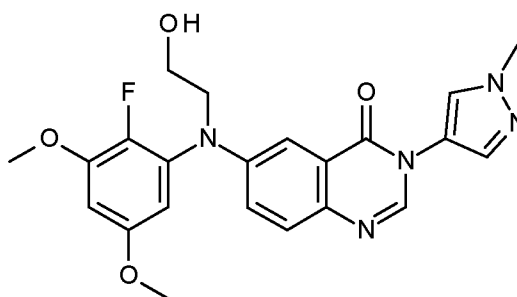


Preparation of compound **10**:

Compound **10** was prepared according to an analogous procedure as described for the synthesis of compound **18**, using intermediate **17** as starting material (yield: 55 %; MP: 223 °C (DSC)).

15

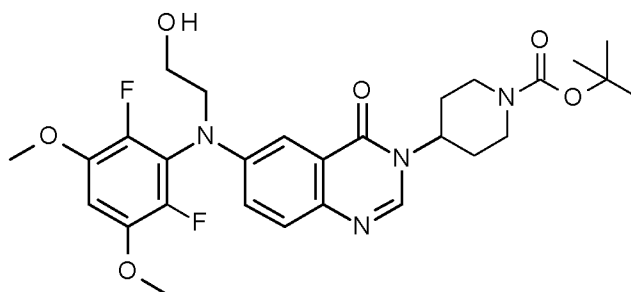
148



Preparation of compound **16**:

Compound 16 was prepared according to an analogous procedure as described for the synthesis of compound 18, using intermediate 20 as starting material (yield: 43 %; MP: 164 °C (DSC)).

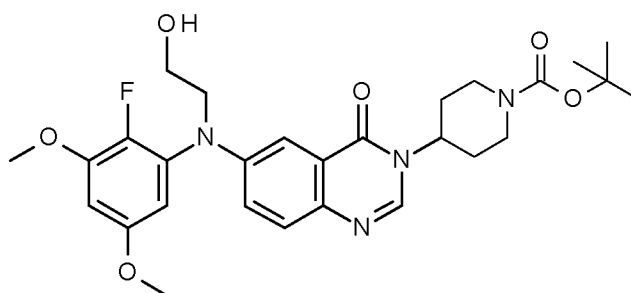
5



Preparation of compound **25**:

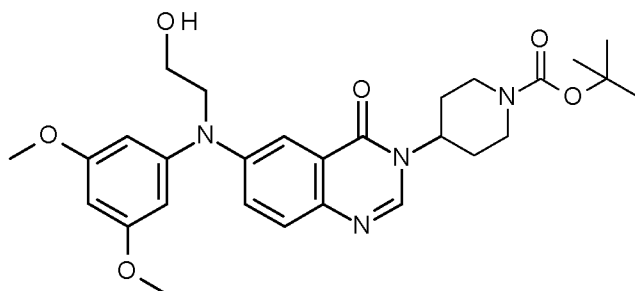
A solution of tetrabutylammonium fluoride 1M in THF (0.536 mL; 0.536 mmol) was added at 5°C to a solution of intermediate **29** (181 mg; 0.268 mmol) in THF and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with DCM and a 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> was added. The organic layer was filtered through Chromabond® and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 10g; mobile phase: gradient from 0.2% NH<sub>4</sub>OH, 2% MeOH, 98% DCM to 0.4% NH<sub>4</sub>OH, 4% MeOH, 96% DCM). The fractions containing the product were collected and evaporated to dryness yielding 148 mg (98%) of compound **25**.

15



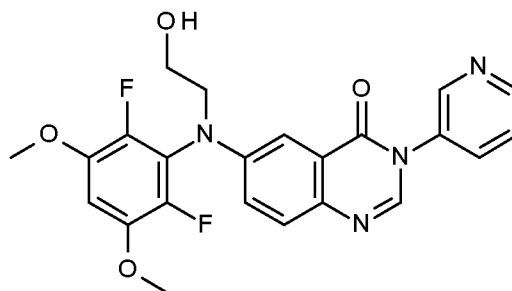
Preparation of compound **26**:

Compound 26 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 30 as starting material (yield : 100 %).



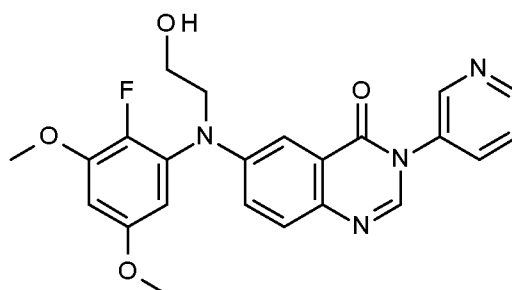
Preparation of compound **56**:

- 5 Compound 56 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 48 as starting material (yield : 89 %).



Preparation of compound **29** :

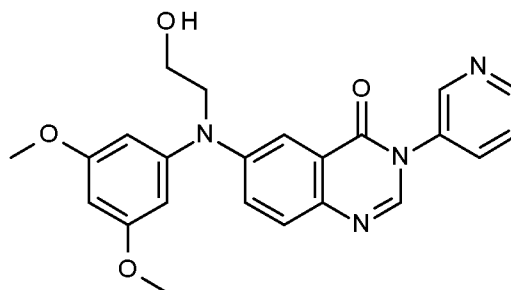
- 10 Compound 29 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 35 as starting material (yield : 28 %; MP: 112 °C (Kofler)).



Preparation of compound **30** :

- 15 Compound 30 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 36 as starting material (yield : 39 %; MP: 186 °C (Kofler)).

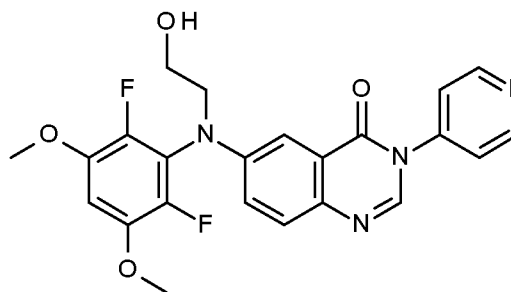
150



Preparation of compound **31** :

Compound 31 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 37 as starting material (yield : 54 %; MP: 168 °C (Kofler)).

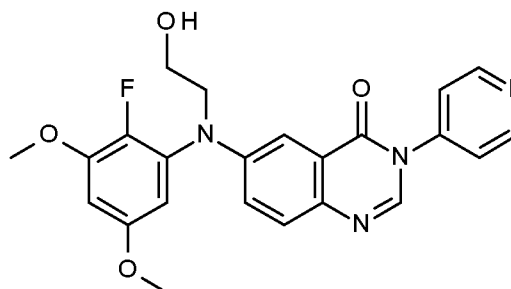
5



Preparation of compound **37** :

Compound 37 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 45 as starting material (yield : 37 %; MP: 198 °C (Kofler)).

10

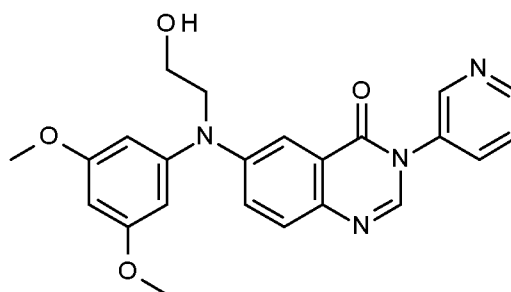


Preparation of compound **38** :

Compound 38 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 46 as starting material (yield : 17 %; MP: 209 °C (Kofler)).

15

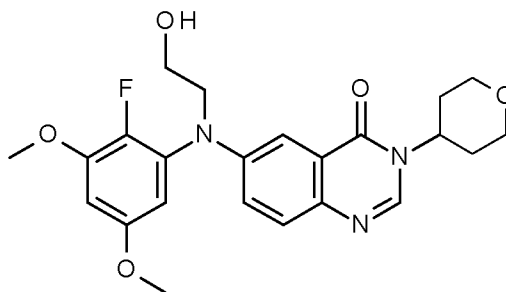
151



Preparation of compound **39** :

Compound 39 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 47 as starting material (yield : 18 %; MP: 177 °C (Kofler)).

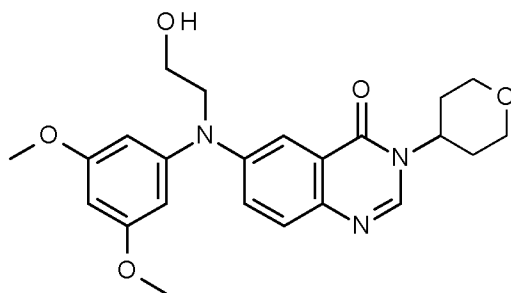
5



Preparation of compound **63**:

Compound 63 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 61 as starting material.

Purification by silica gel chromatography (Spherical bare silica 5 $\mu$ m 150x30.0mm, Mobile phase: Gradient from 0.2% NH<sub>4</sub>OH, 98% DCM, 2% MeOH to 0.8% NH<sub>4</sub>OH, 92% DCM, 8% MeOH). The pure fractions were collected and the solvent was evaporated yielding 171 mg of a fraction A. Fraction A was purified by achiral SFC (Stationary phase: CYANO 6 $\mu$ m 150x21.2mm, Mobile phase: 70% CO<sub>2</sub>, 30% MeOH (0.3% iPrNH<sub>2</sub>)). The fractions containing the product were collected and the solvent was evaporated to give 124 mg of a fraction B. 18 mg of this fraction B were washed with water. DCM was added and the mixture was filtered over a phase separator filter. The solvent was evaporated to give 8 mg of compound **63** (white; MP: 191°C (Kofler)).

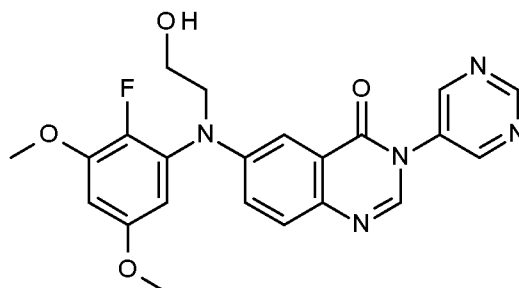


Preparation of compound **64** :

152

Compound 64 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 62 as starting material (yield : 88 %; MP: 204 °C (Kofler)).

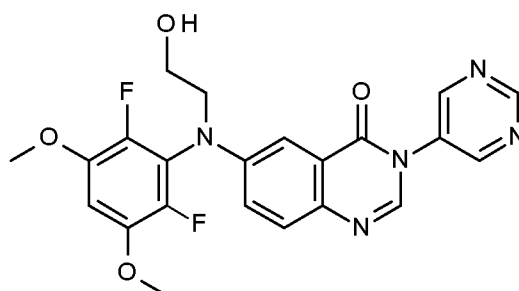
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Preparation of compound **74** :

Compound 74 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 71 as starting material (yield : 55 %; MP: 200 °C (Kofler)).

10

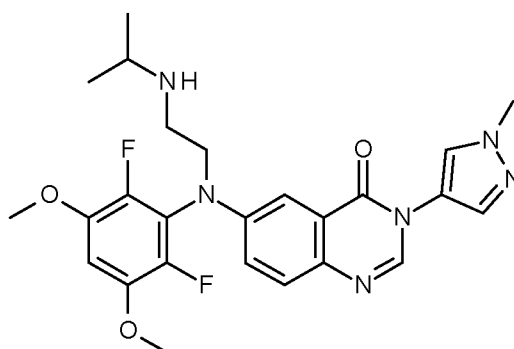


Preparation of compound **76** :

Compound 76 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 73 as starting material (yield : 86 %; MP: 178 °C (Kofler)).

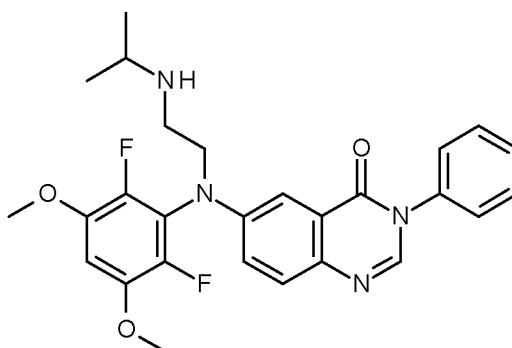
15

### Example B2:



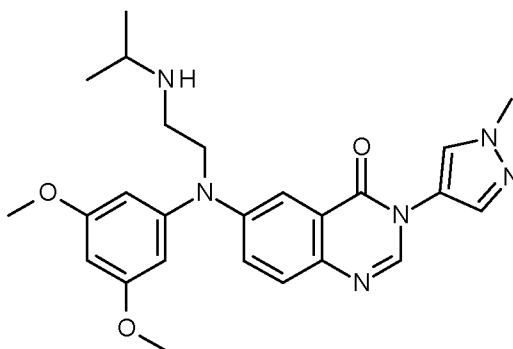
Preparation of compound **19**:

A mixture of intermediate **24** (0.37 g; 0.7 mmol) and isopropylamine (1.8 mL; 20.5 mmol) in acetonitrile (10 mL) was heated at 100 °C overnight in an autoclave. The solution was poured onto cooled water and the product was extracted with EtOAc. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to dryness. The residue (0.68 g) was purified by chromatography over silica gel (Spherical silica, 5 µm, 150\*30.0 mm, Mobile phase: Gradient from 0.2 % NH<sub>4</sub>OH, 98 % DCM, 2 % MeOH to 0.8 % NH<sub>4</sub>OH, 92 % DCM, 8 % MeOH). The fractions containing the product were collected and evaporated to dryness. The residue (0.26 g) was crystallized from a mixture of MeOH and Et<sub>2</sub>O. The precipitate was filtered off and dried yielding 0.190 g (56 %) of compound **19** (MP: 162 °C (DSC)).



Preparation of compound **2**:

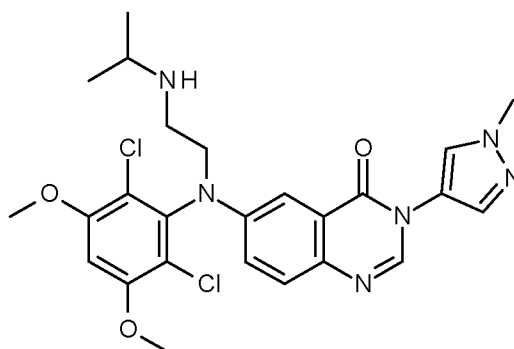
Compound **2** was prepared according to an analogous procedure as described for the synthesis of compound **19**, using intermediate **4** as starting material (yield: 33 %; MP: 124 °C (DSC)).



Preparation of compound **9**:

Compound **9** was prepared according to an analogous procedure as described for the synthesis of compound **19**, using intermediate **15** as starting material (yield: 28 %; MP: 142 °C (DSC)).

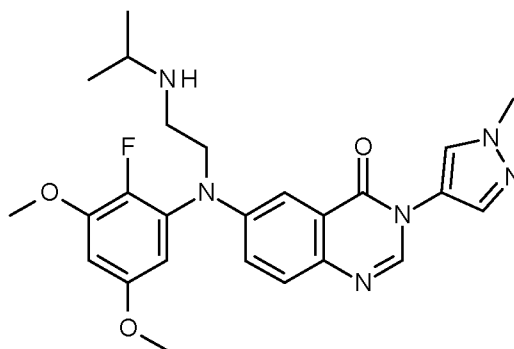
154



Preparation of compound **11**:

Compound 11 was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 18 as starting material (yield : 42 %; MP: 195 °C (DSC)).

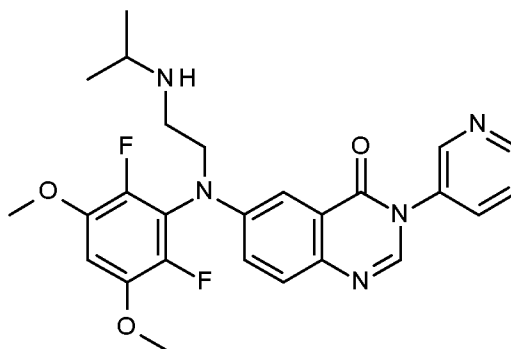
5



Preparation of compound **17**:

Compound 17 was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 21 as starting material (yield : 64 %; MP: 132 °C (DSC)).

10



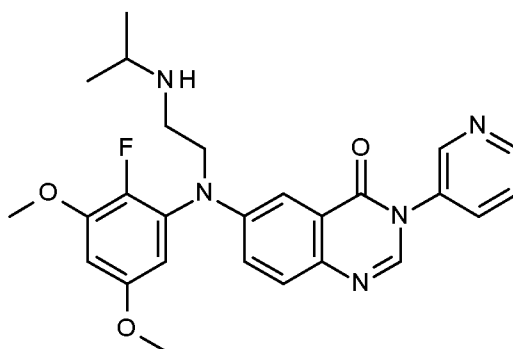
Preparation of compound **32**:

Compound 32 was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 38 as starting material (yield : 64 %; MP: 124 °C (Kofler)).

15



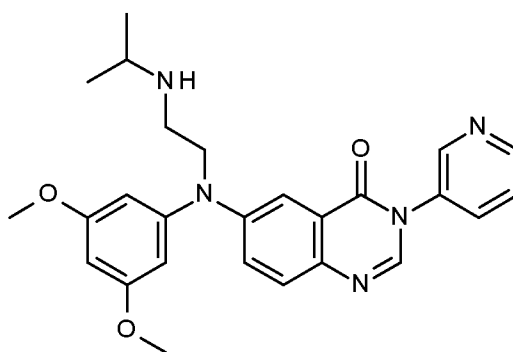
155



Preparation of compound **33**:

Compound 33 was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 39 as starting material (yield : 44 %; MP: 133 °C (Kofler)).

5

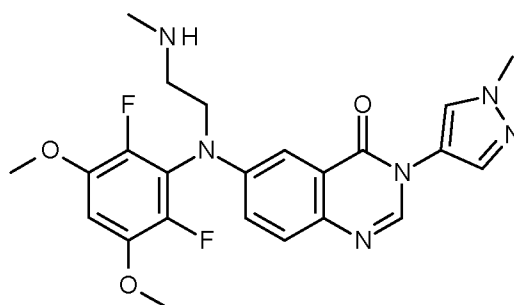


Preparation of compound **34**:

Compound 34 was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 40 as starting material (yield : 16 %; MP: 136 °C (Kofler)).

10

### Example B3:

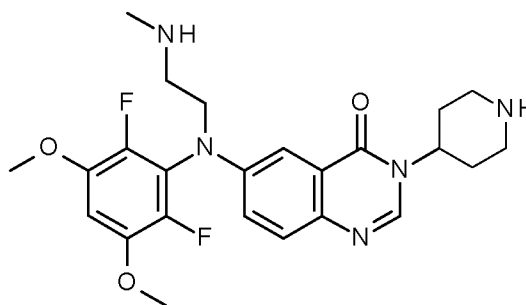


Preparation of compound **20**:

A mixture of intermediate **24** (0.79 g; 1.48 mmol) and methylamine (30 mL of a 2 M solution in THF; 59 mmol) was heated at 70°C overnight in an autoclave. The solution

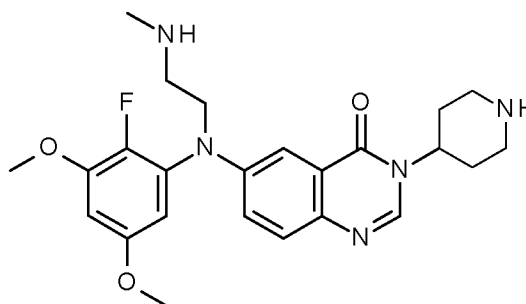
15

was poured onto cooled water and the product was extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness. The residue (0.54 g) was purified by chromatography over silica gel (Irregular  $\text{SiOH}$ , 15-40  $\mu\text{m}$  30 g, Mobile phase: 0.1 %  $\text{NH}_4\text{OH}$ , 95 % DCM, 5 % MeOH). The fractions containing the product were collected and evaporated to dryness. The residue (0.19 g) was crystallized from a mixture of ACN and  $\text{Et}_2\text{O}$ . The precipitate was filtered and dried yielding 0.094 g (14 %) of compound **20** (MP: 141 °C (DSC)).



Preparation of compound **57**:

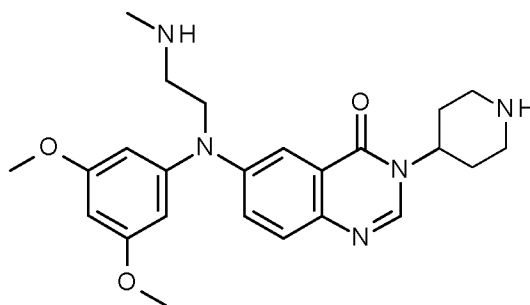
- 10 A mixture of intermediate **52** (194 mg; 0.304 mmol), methylamine (6 mL of a 2 M solution in THF; 12 mmol) was heated at 70°C for 18 hours in a sealed tube. The reaction mixture was evaporated to dryness. Trifluoroacetic acid (0.5 mL; 6.534 mmol) was added dropwise at 5°C to a solution of the residue in DCM (5 mL). The reaction mixture was allowed to warm slowly to room temperature and stirred for 18 hours.
- 15 The reaction mixture was diluted with DCM and a 10% aqueous solution of  $\text{K}_2\text{CO}_3$  was added. The organic layer was filtered through a phase separator filter and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular  $\text{SiOH}$ , 40g; mobile phase: 1%  $\text{NH}_4\text{OH}$ , 89% DCM, 10% MeOH). The fractions containing the product were collected and evaporated to dryness. The residue was crystallized from DIPE and the precipitate was filtered and dried yielding 48 mg (33 %) of compound **57** (MP: gum 90°C (Kofler))
- 20



Preparation of compound **58**:

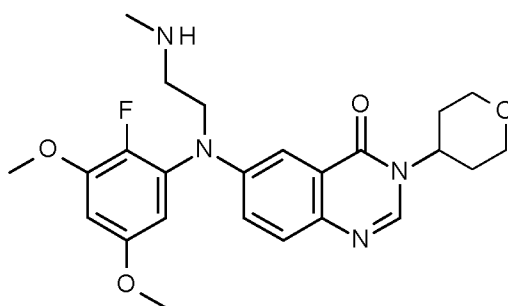
157

Compound 58 was prepared according to an analogous procedure as described for the synthesis of compound 57, using intermediate 53 as starting material (yield : 41 %; MP: 176°C (Kofler)).



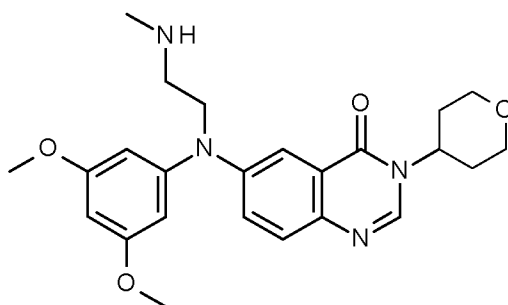
5 Preparation of compound **59**:

Compound 59 was prepared according to an analogous procedure as described for the synthesis of compound 57, using intermediate 54 as starting material (yield : 35 %; MP: 139°C (Kofler)).



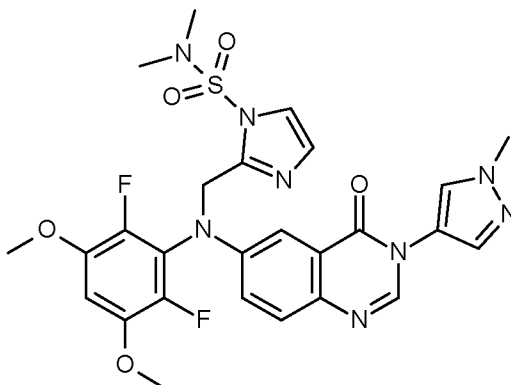
10 Preparation of compound **70**:

Compound 70 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 65 as starting material (yield : 18 %, MP = 178°C (kofler)).

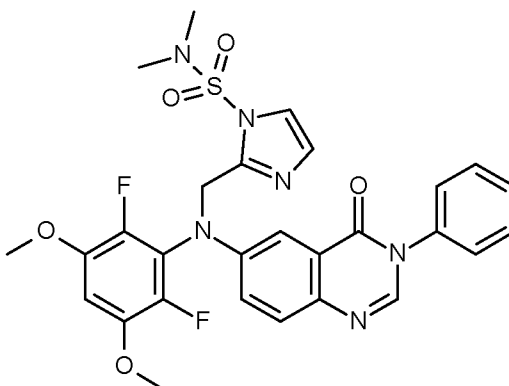


15 Preparation of compound **71**:

Compound 71 was prepared according to an analogous procedure as described for the synthesis of compound 20, using intermediate 66 as starting material (yield : 79 %, MP : 135°C (Kofler)).

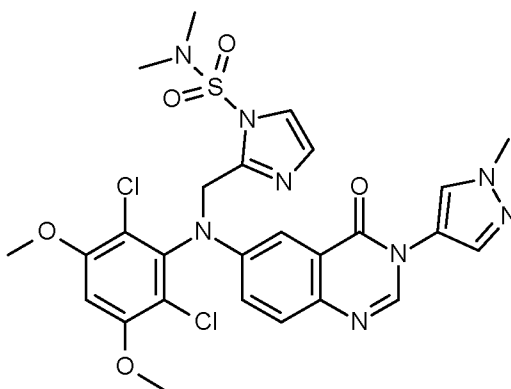
**Example B4:****Preparation of compound 21:**

Under N<sub>2</sub> at 10 °C, sodium hydride (60 % in mineral oil) (0.29 g; 7.3 mmol) was added to a solution of intermediate **22** (1 g; 2.4 mmol) in DMF (8 mL). The solution was stirred at 10 °C for 30 minutes. Then, a solution of 2-(chloromethyl)-*N,N*-dimethyl-1*H*-imidazole-sulfonamide (1 g; 4.9 mmol) in DMF (3 mL) was added drop wise and the reaction mixture was allowed to warm to room temperature for 5 hours. The solution was poured onto cooled water and the product was extracted with EtOAc. The organic layer was washed by water and dried over MgSO<sub>4</sub>, filtered and evaporated to dryness yielding 1.8 g (quantitative) of compound **21**.

**Preparation of compound 3:**

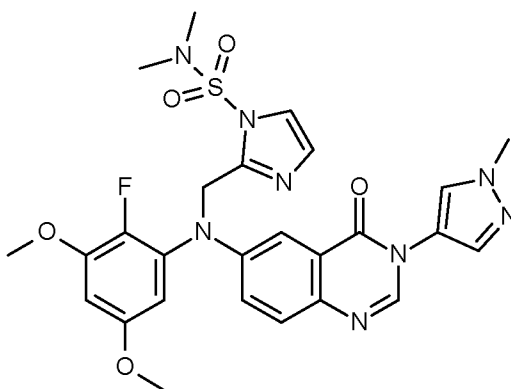
Compound 3 was prepared according to an analogous procedure as described for the synthesis of compound 21, using intermediate 2 as starting material (yield : 15 %).

159



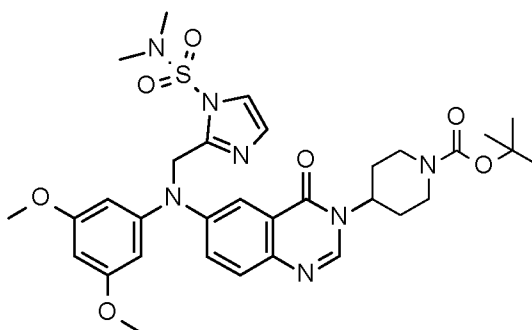
Preparation of compound **12**:

Compound **12** was prepared according to an analogous procedure as described for the synthesis of compound **21**, using intermediate **16** as starting material (quantitative yield).



5 Preparation of compound **14**:

Compound **14** was prepared according to an analogous procedure as described for the synthesis of compound **21**, using intermediate **19** as starting material (quantitative yield).

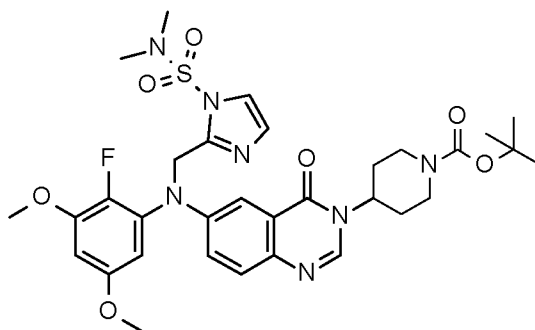


Preparation of compound **27**:

- 10 Under N<sub>2</sub> at -30 °C, sodium hydride (60 % in mineral oil) (125 mg; 3.121 mmol) was added to a solution of intermediate **27** (500 mg; 1.04 mmol) in DMF (15 mL). The reaction mixture was stirred at -10°C for 30 minutes. Then a solution of 2-(chloromethyl)-*N,N*-dimethyl-1*H*-imidazole-sulfonamide (512 mg; 2.289 mmol) in DMF (5 mL) was

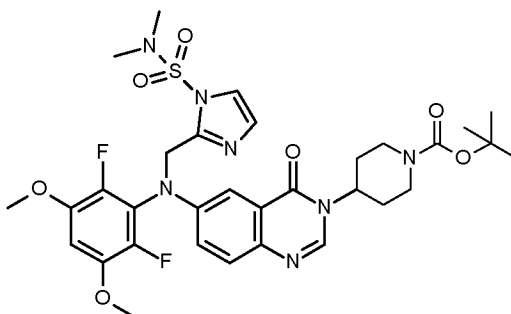
added dropwise. The reaction mixture was stirred below  $-10^{\circ}\text{C}$  for 1 hour, then 1 hour at  $0^{\circ}\text{C}$  and was allowed to warm up to room temperature (1 hour more). The solution was poured onto ice/water and the product was extracted with EtOAc. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular  $\text{SiOH}$ , 30g, 30 $\mu\text{m}$ ; mobile phase: gradient from 100% DCM to 0.2%  $\text{NH}_4\text{OH}$ , 2% MeOH, 98% DCM). The fractions containing the product were collected and evaporated to dryness yielding 325 mg (47%) of compound **27**.

MP: gum,  $100^{\circ}\text{C}$  (Kofler).



Preparation of compound **28**:

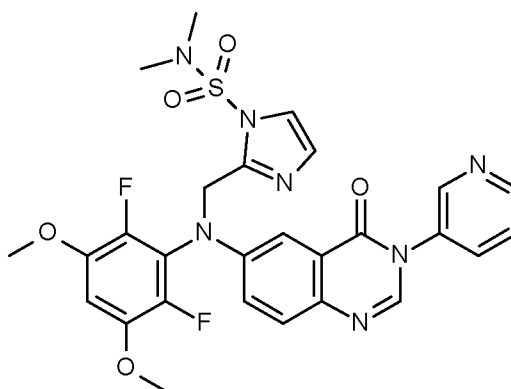
Compound 28 was prepared according to an analogous procedure as described for the synthesis of compound 27, using intermediate 28 as starting material (yield : 73%; MP: gum,  $90^{\circ}\text{C}$  (Kofler)).



Preparation of compound **42**:

Compound 42 was prepared according to an analogous procedure as described for the synthesis of compound 27, using intermediate 26 as starting material (yield : 52%; MP:  $168^{\circ}\text{C}$  (Kofler)).

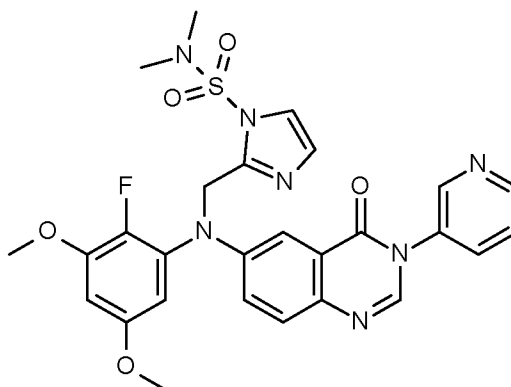
161



Preparation of compound **35**:

Compound 35 was prepared according to an analogous procedure as described for the synthesis of compound 21, using intermediate 32 as starting material (yield : 9 %; MP: 128°C (Kofler)).

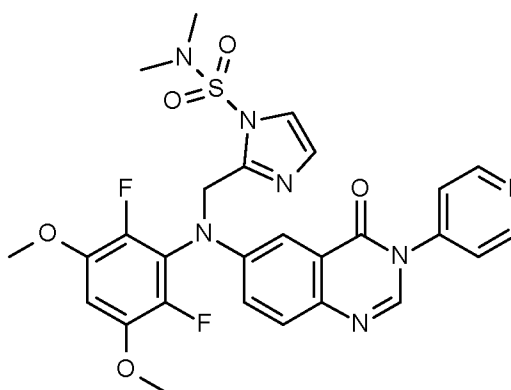
5



Preparation of compound **36**:

Compound 36 was prepared according to an analogous procedure as described for the synthesis of compound 21, using intermediate 33 as starting material (yield : 11 %; MP: 108°C (Kofler)).

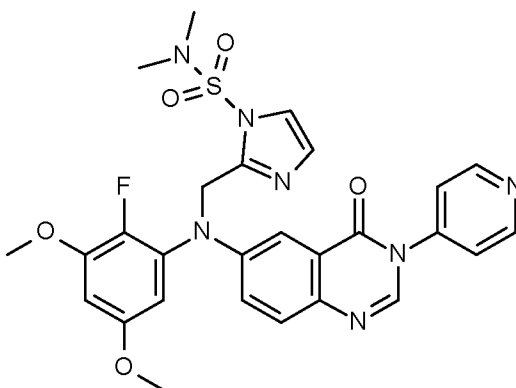
10



Preparation of compound **40**:

Compound 40 was prepared according to an analogous procedure as described for the synthesis of compound 21, using intermediate 42 as starting material (yield : 16 %; MP: 139°C (Kofler)).

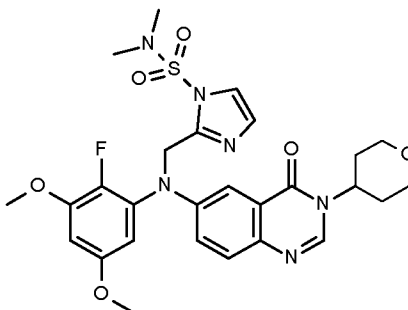
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Preparation of compound **41**:

Compound 41 was prepared according to an analogous procedure as described for the synthesis of compound 21, using intermediate 43 as starting material (yield : 13 %; MP: gum at 109°C (Kofler)).

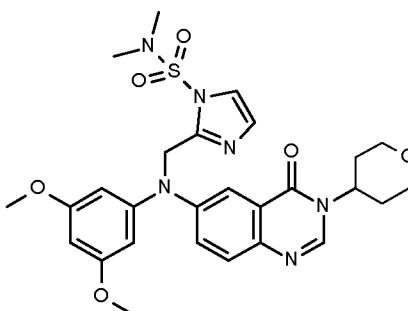
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Preparation of compound **67**:

Compound 67 was prepared according to an analogous procedure as described for the synthesis of compound 27, using intermediate 59 as starting material (yield : 11 %; MP: 189°C (kofler)).

15



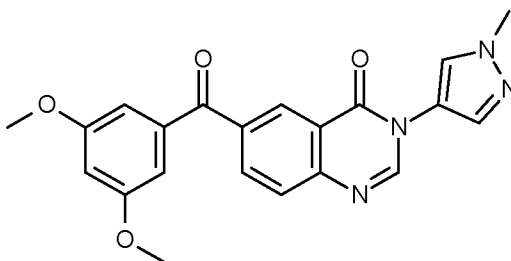
Preparation of compound **68**:



Compound 68 was prepared according to an analogous procedure as described for the synthesis of compound 27, using intermediate 60 as starting material.

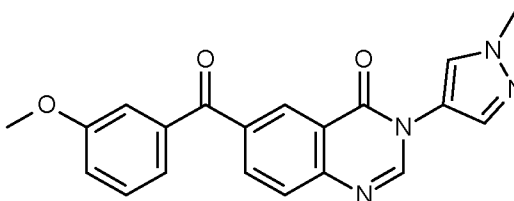
- 5 Purification by chromatography over silica gel (Irregular SiOH 20-45 $\mu$ m 450g, Mobile phase: 40% Heptane, 10% MeOH (+10% NH<sub>4</sub>OH), 50% EtOAc) gave 2 fractions of compound 68: 430 mg (26%, MP: 182°C (kofler)) and 910 mg (57 %).

#### Example B5:



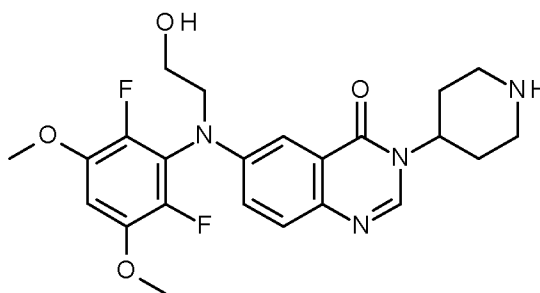
Preparation of compound **24**:

- 10 Intermediate **11** (0.2 g; 0.66 mmol), 3,5-dimethoxyphenyl boronic acid (0.18 g; 0.98 mmol), tricyclohexylphosphine (0.018 g; 0.065 mmol), palladium (II) acetate (47 % Pd) (0.015 g; 0.065 mmol), and triethylamine (0.183 mL; 1.31 mmol) in toluene (10 mL) were stirred under carbon monoxide (10 bar) at 100 °C for 18 hours in an autoclave. The solution was cooled, poured onto cooled water and EtOAc was added. The solution was
- 15 filtered through a pad of Celite®. The filtrate was extracted with EtOAc and the organic layer was washed with water, dried over MgSO<sub>4</sub> and evaporated to dryness. The residue (344 g) was purified by chromatography over silica gel (Spherical silica, 5  $\mu$ m, 150x30.0 mm, Mobile phase: Gradient from 71% Heptane, 1% MeOH (+10% NH<sub>4</sub>OH), 28% EtOAc to 0% heptane, 20% MeOH (+10% NH<sub>4</sub>OH), 80% EtOAc). The fractions
- 20 containing the product were collected and evaporated to dryness. The resulting residue (56 mg) was crystallized from Et<sub>2</sub>O. The precipitate was filtered and dried affording 43 mg (17 %) of compound **24** (MP: 194 °C (kofler)).

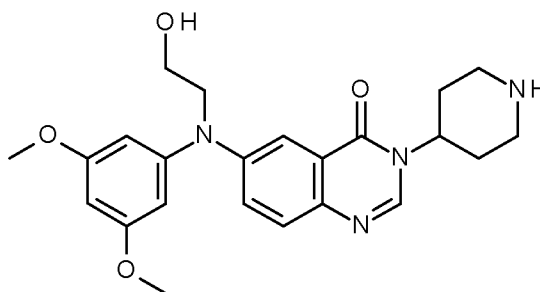


Preparation of compound **23**:

- 25 Compound 23 was prepared according to an analogous procedure as described for the synthesis of compound 24, using intermediate 11 and 3-methoxyphenyl boronic acid as starting materials (yield :11 %).

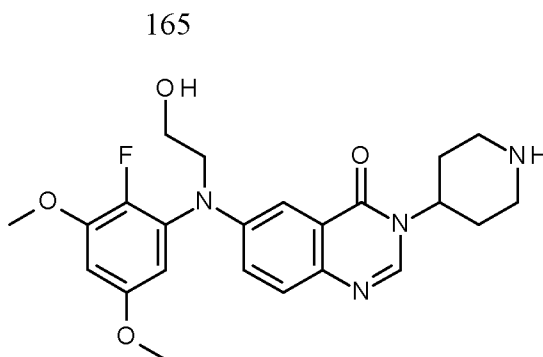
**Example B6:****Preparation of compound 46:**

Trifluoroacetic acid (34  $\mu$ L; 4.445 mmol) was added dropwise at 5°C to a solution of intermediate **29** (150 mg; 0.222 mmol) in DCM (5 mL). The reaction mixture was allowed to warm slowly to room temperature and stirred for 48 hours. The reaction mixture was diluted with DCM and a 10% aqueous solution of  $K_2CO_3$  was added. The organic layer was filtered through a phase separator filter and evaporated to dryness. The residue was purified by chromatography over silica gel (Spherical bare silica 5 $\mu$ m 150x30.0mm; mobile phase: gradient from 0.4%  $NH_4OH$ , 96% DCM, 4% MeOH to 1.7%  $NH_4OH$ , 83% DCM, 17% MeOH). The fractions containing the product were collected and evaporated to dryness yielding 40 mg of compound **46** (39%; MP: 186°C (Kofler)).

**Preparation of compound 47:**

Compound

**47** was prepared according to an analogous procedure as described for the synthesis of compound **46**, using intermediate **48** as starting material (yield : 14 %; MP: 165°C (Kofler)).



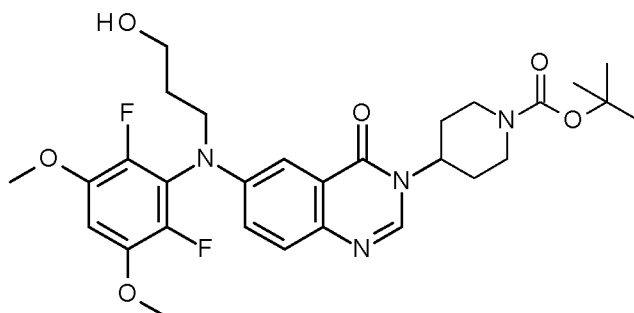
Preparation of compound **48**:

Compound

48 was prepared according to an analogous procedure as described for the synthesis of compound 46, using intermediate 30 as starting material (yield : 53 %; MP: 173°C (Kofler)).

5

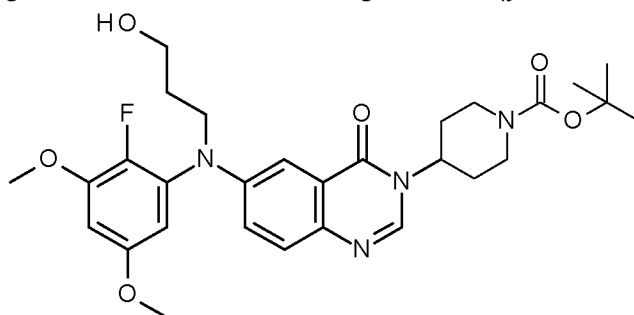
#### Example B7:



Preparation of compound **50**:

Compound 50 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 49 as starting material (yield : 81 %).

10

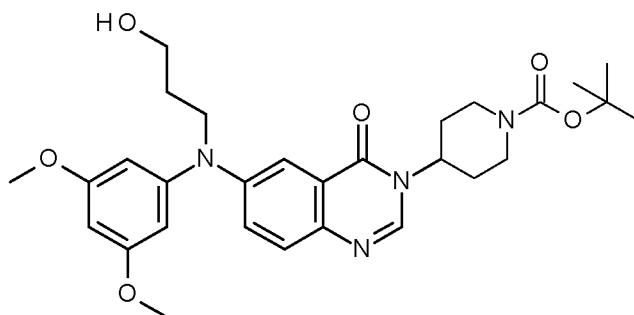


Preparation of compound **51**:

Compound 51 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 50 as starting material (yield : 100 %).

15

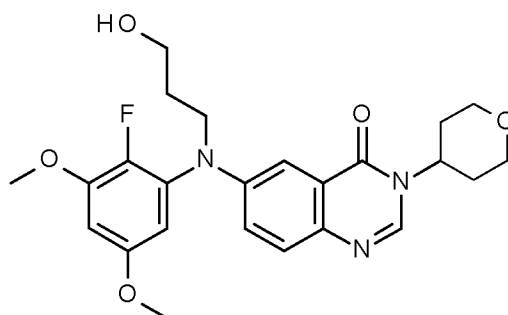
166



Preparation of compound **52**:

Compound 52 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 51 as starting material (yield : 100 %).

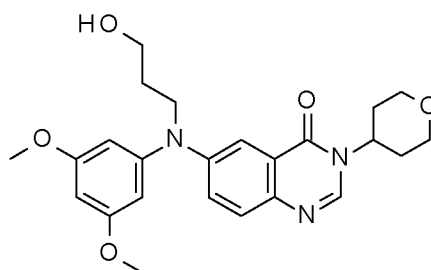
5



Preparation of compound **65**:

Compound 65 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 63 as starting material (yield : 47 %, MP : 164°C (Kofler)).

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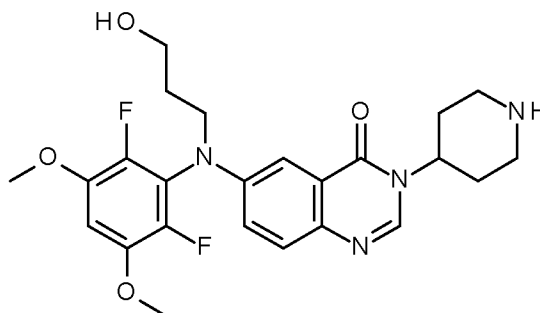


Preparation of compound **66**:

Compound 66 was prepared according to an analogous procedure as described for the synthesis of compound 25, using intermediate 64 as starting material (yield : 68%,).

15 Purification by chromatography over silica gel (irregular SiOH 15-40µm 300g MERCK, Mobile phase: 43% Heptane, 7% MeOH (+10% NH<sub>4</sub>OH), 50% EtOAc) gave 2 fractions of compound 66: 228 mg (39%; MP : 178°C (Kofler) and 162 mg (28%).

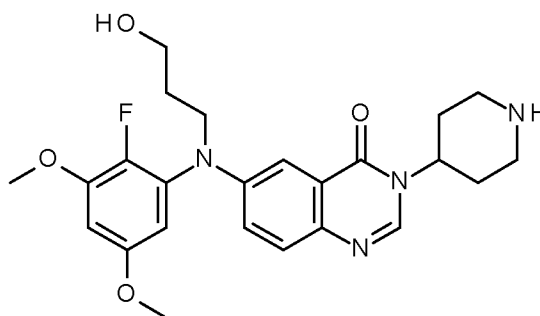
167

**Example B8:**

Preparation of compound **53**:

Compound 53 was prepared according to an analogous procedure as described for the synthesis of compound 46, using intermediate 49 as starting material (yield : 36 %, MP: 184°C (Kofler)).

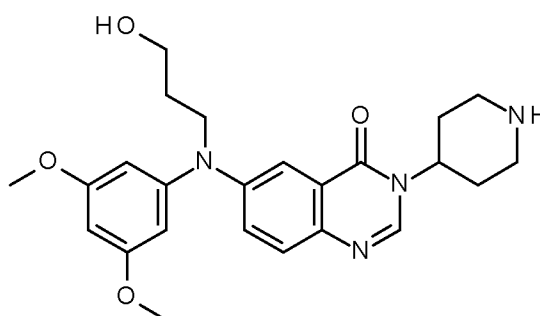
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Preparation of compound **54**:

Compound 54 was prepared according to an analogous procedure as described for the synthesis of compound 46, using intermediate 50 as starting material (yield : 53 %, MP: 167°C (Kofler)).

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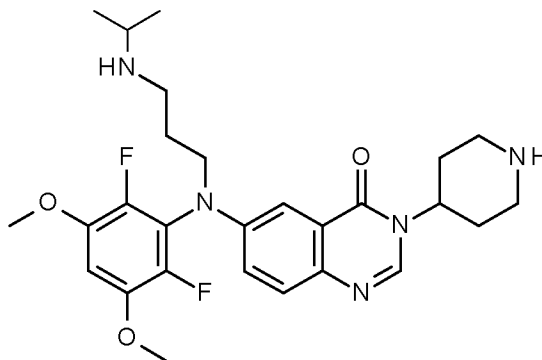


Preparation of compound **55**:

Compound 55 was prepared according to an analogous procedure as described for the synthesis of compound 46, using intermediate 51 as starting material (yield : 34 %, MP: 167°C (Kofler)).

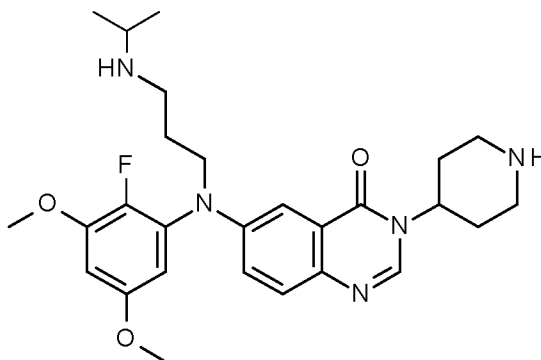
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168

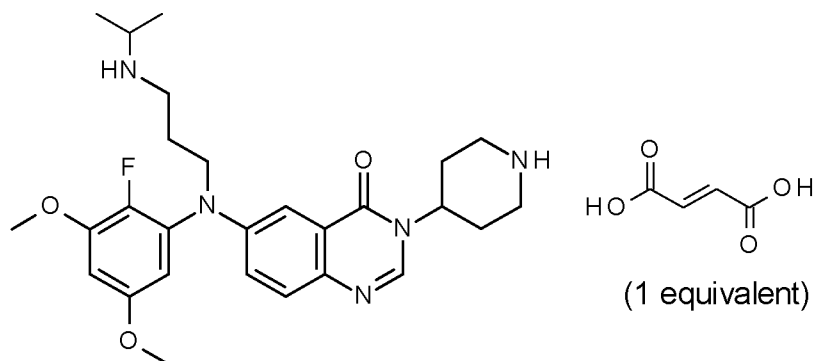
**Example B9:****Preparation of compound 60:**

A mixture of intermediate **55** (150 mg; 0.23 mmol) and isopropylamine (0.6 mL; 6.9 mmol) in acetonitrile (6 mL) was heated at 100°C for 2 hours in a sealed tube. The reaction mixture was evaporated to dryness. Trifluoroacetic acid (1 mL; 13.07 mmol) was added dropwise at 5°C to a solution of the previous residue (140 mg) in DCM (10 mL). The reaction mixture was allowed to warm slowly to room temperature and stirred for 18 hours. The reaction mixture was diluted with DCM and a 10% aqueous solution of K<sub>2</sub>CO<sub>3</sub> was added. The organic layer was filtered through a phase separator filter and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 40g; mobile phase: 1% NH<sub>4</sub>OH, 89% DCM, 10% MeOH). The fractions containing the product were collected and evaporated to dryness. The residue (87 mg; 73%) was crystallized from ACN and the precipitate was filtered and dried yielding 22 mg (18%) of compound **60** (MP: 126°C (Kofler)).

169

Preparation of compound **61**:

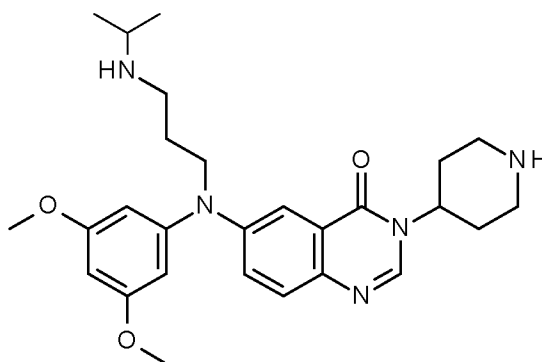
and

compound **61'**

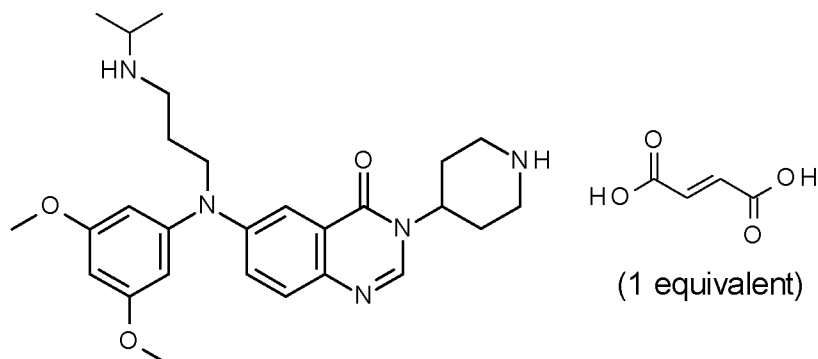
Compound **61** was prepared according to an analogous procedure as described for the synthesis of compound **60**, using intermediate **56** as starting material (yield : 41%).

- 5 Compound **61** (97 mg ; 0.19 mmol) was dissolved in ACN and fumaric acid (23 mg; 0.195 mmol) was added. The product was crystallized from ACN. The precipitate was filtered and dried yielding 104 mg (36 %) of compound **61'** (MP: 140°C (gum, Kofler)).

170

Preparation of compound **62**:

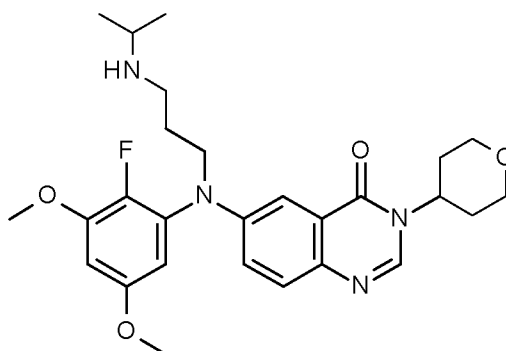
and

compound **62'**

Compound **62** was prepared according to an analogous procedure as described for the synthesis of compound **60**, using intermediate **57** as starting material (yield : 63%).

- 5 Compound **62** (170 mg; 0.35 mmol) was dissolved in ACN and fumaric acid (41 mg; 0.354 mmol) was added. The product was crystallized from ACN/EtOH. The precipitate was filtered and dried yielding 180 mg (54%) of compound **62'** (MP: 255°C (Kofler)).

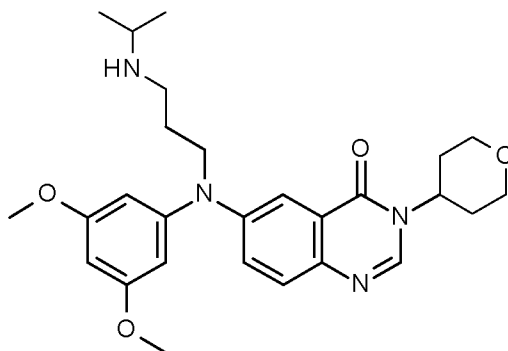
10

Preparation of compound **72**:

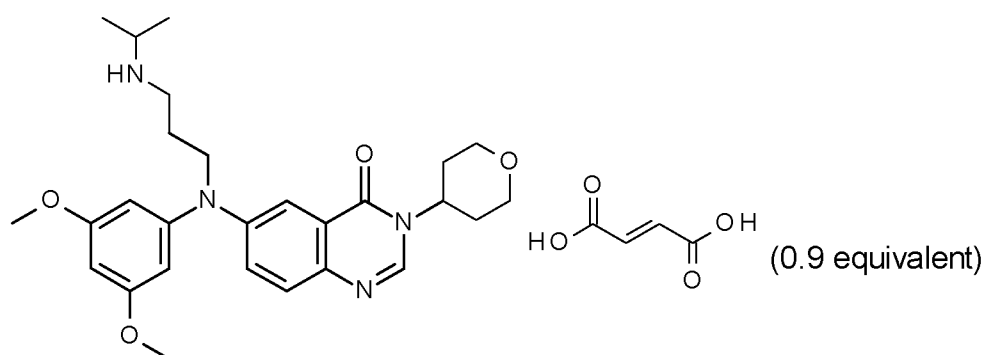
Compound **72** was prepared according to an analogous procedure as described for the synthesis of compound **19**, using intermediate **67** as starting material (yield : 40 %; MP: gum, 80 °C (Kofler)).



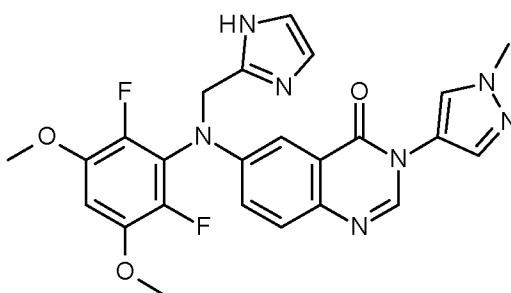
171

Preparation of compound **73**:

and compound

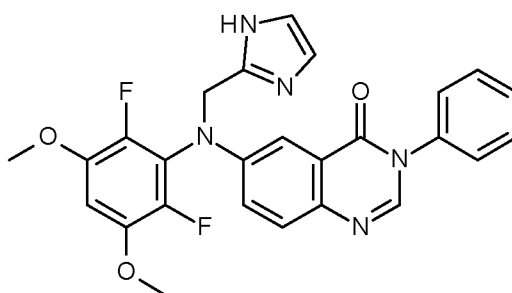
**73'**

- 5 Compound **73** was prepared according to an analogous procedure as described for the synthesis of compound 19, using intermediate 68 as starting material (yield :75 %). Fumaric acid (41 mg; 0.35 mmol) was added to a solution of compound 73 (171 mg; 0.35 mmol) in acetone (1 mL). The mixture was stirred at rt for 2 hours. The precipitate was filtered, washed with few acetone and dried to give 186 mg (48%) of compound **73'**
- 10 (MP: 240°C (Kofler)).

**Conversion C1:**Preparation of compound **22**:

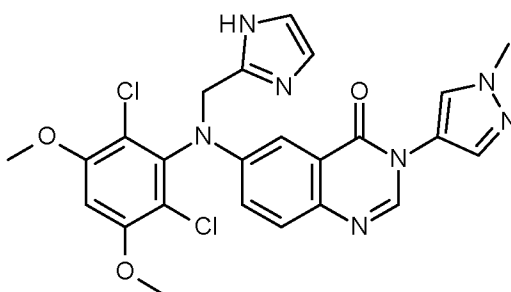
- A mixture of compound **21** (1.45 g; 2 mmol) in HCl 6 N (2.8 mL) and dioxane (10 mL)
- 15 was heated at 100 °C for 2 hours. The solution was cooled down to room temperature,

poured onto cooled water, basified with  $\text{NH}_4\text{OH}$  and the product was extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$ , filtered and evaporated to dryness. The residue (1.22 g) was purified by chromatography over silica gel (Irregular SiOH, 15-40  $\mu\text{m}$ , 40 g, Mobile phase: 96 % DCM, 4 % MeOH, 0.1 %  $\text{NH}_4\text{OH}$ ). The fractions containing the product were collected and evaporated to dryness. The residue (0.6 g) was purified again by chromatography (Irregular SiOH, 15-40  $\mu\text{m}$ , 40 g, Mobile phase: 95% DCM, 5% MeOH, 0.5%  $\text{NH}_4\text{OH}$ ). The fractions containing the product were collected and evaporated to dryness. The resulting residue (0.4 g) purified by achiral SFC (Stationary phase: 2-ethylpyridine, 6  $\mu\text{m}$  150x21.2mm), Mobile phase: 80 %  $\text{CO}_2$ , 20 % MeOH (0.3 %  $\text{iPrNH}_2$ ). The fractions containing the product were collected and evaporated to dryness. The residue (0.206 g) was crystallized from a mixture of ACN and  $\text{Et}_2\text{O}$ . the precipitate was filtered and dried yielding 0.17 g (17 %) of compound **22** (MP: 231 °C (DSC)).



Preparation of compound **4**:

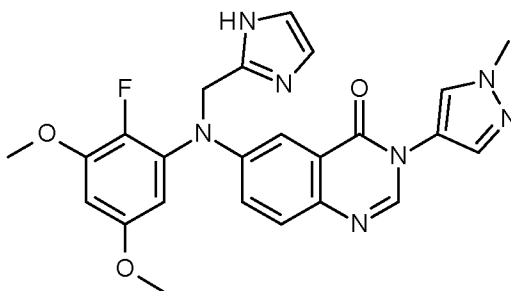
Compound **4** was prepared according to an analogous procedure as described for the synthesis of compound **22**, using compound **3** as starting material (yield : 46 %).



Preparation of compound **13**:

Compound **13** was prepared according to an analogous procedure as described for the synthesis of compound **22**, using compound **12** as starting material (yield : 20 %).

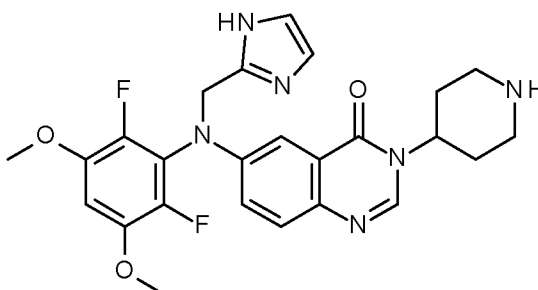
173



Preparation of compound **15**:

Compound 15 was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 14 as starting material (yield : 22 %) MP: 212 °C (DSC)).

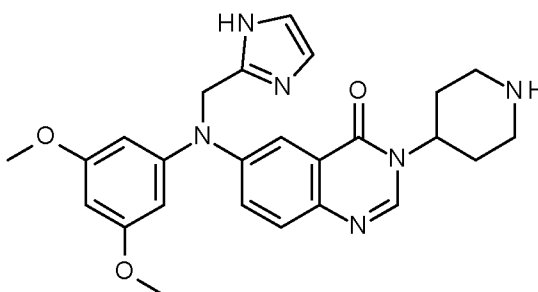
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Preparation of compound **43**:

Compound 43 was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 42 as starting material (yield : 38 %, MP: 223°C (Kofler)).

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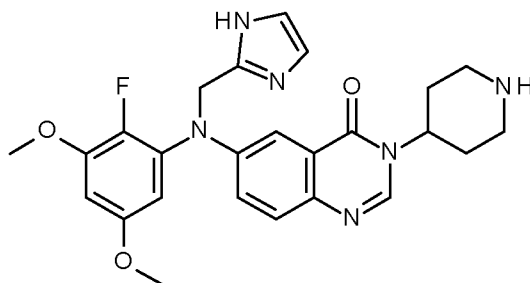
Preparation of compound **44**:

Compound 44 was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 27 as starting material (yield : 42 %, MP: 220°C (Kofler)).

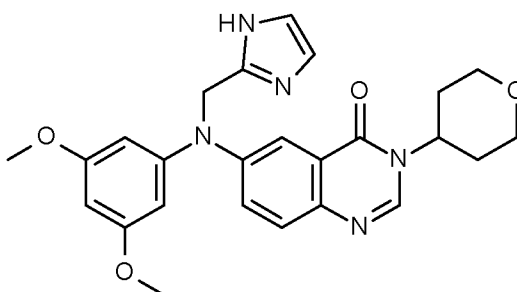
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Preparation of compound **45**:

174

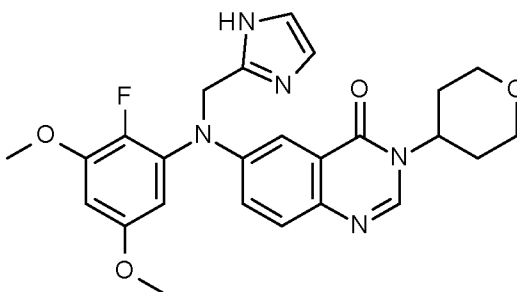


Compound 45 was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 28 as starting material (yield : 59 %, MP: 260°C (Kofler)).



5 Preparation of compound **69**:

Compound 69 was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 68 as starting material (yield : 82 %, MP: 260°C (Kofler)).



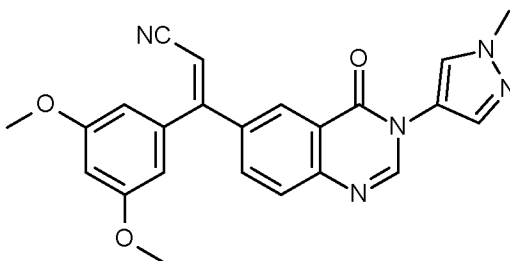
Preparation of compound **75**:

- 10 Compound **75** was prepared according to an analogous procedure as described for the synthesis of compound 22, using compound 67 as starting material (yield : 37 %, MP: >260°C (Kofler)).

Conversion C2:

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175



#### Preparation of compound **49**:

A mixture of compound **24** and (triphenylphosphoranylidene)acetonitrile in toluene was refluxed all over the week end. The reaction mixture was cooled to room temperature, poured onto a 10% aqueous solution of  $K_2CO_3$  and extracted with EtOAc/MeOH. The organic layer was decanted, dried over  $MgSO_4$ , filtered and evaporated to dryness. The residue was purified by chromatography over silica gel (irregular SiOH, 15-40 $\mu$ m, 40g; mobile phase: 42% Heptane, 8% MeOH (+10%  $NH_4OH$ ), 50% EtOAc). The fractions containing the product were collected and evaporated to dryness yielding an intermediate residue (22mg) which was taken up with  $Et_2O$ . The precipitate was filtered and dried yielding 16 mg of compound **49** (8%, MP: 217°C (Kofler)).

#### Analytical Part

##### LCMS (Liquid chromatography/Mass spectrometry)

The LC measurement was performed using a UPLC (Ultra Performance Liquid Chromatography) Acquity (Waters) system comprising a binary pump with degasser, an autosampler, a diode-array detector (DAD) and a column as specified in the respective methods below, the column is hold at a temperature of 40°C. Flow from the column was brought to a MS detector. The MS detector was configured with an electrospray ionization source. The capillary needle voltage was 3 kV and the source temperature was maintained at 130 °C on the Quattro (triple quadrupole mass spectrometer from Waters). Nitrogen was used as the nebulizer gas. Data acquisition was performed with a Waters-Micromass MassLynx-Openlynx data system.

Reversed phase UPLC was carried out on a Waters Acquity BEH (bridged ethylsiloxane/silica hybrid) C18 column (1.7  $\mu$ m, 2.1 x 100 mm) with a flow rate of 0.343 ml/min. Two mobile phases (mobile phase A: 95 % 7 mM ammonium acetate / 5 % acetonitrile; mobile phase B: 100 % acetonitrile) were employed to run a gradient condition from 84.2 % A and 15.8 % B (hold for 0.49 minutes) to 10.5 % A and 89.5 % B in 2.18 minutes, hold for 1.94 min and back to the initial conditions in 0.73 min, hold for 0.73 minutes. An injection volume of 2  $\mu$ l was used. Cone voltage was 20V for positive and negative ionization mode. Mass spectra were acquired by scanning from 100 to 1000 in 0.2 seconds using an interscan delay of 0.1 seconds.

### Melting points

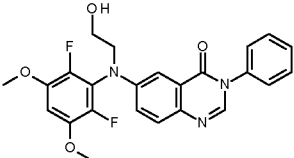
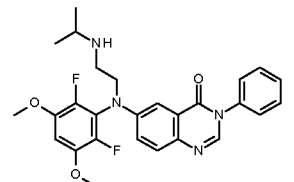
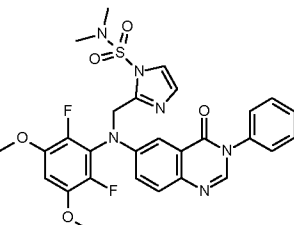
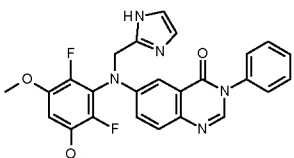
For a number of compounds, melting points (MP) were determined with a DSC1 (Mettler-Toledo). Melting points were measured with a temperature gradient of 10 °C/minute. Maximum temperature was 350 °C. Values are peak values.”

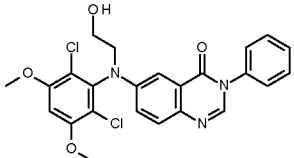
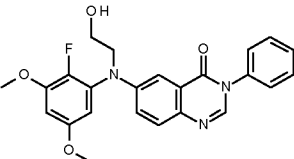
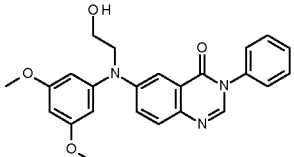
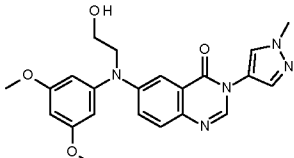
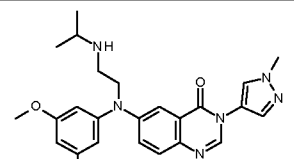
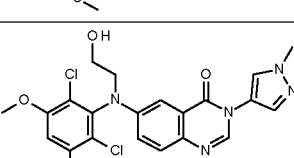
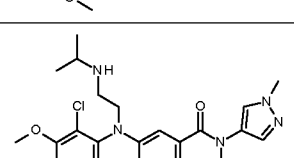
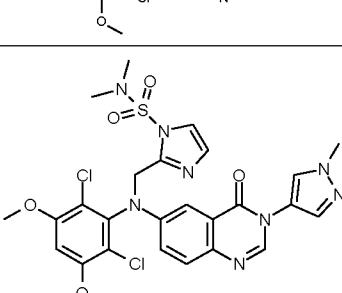
- 5 For a number of compounds, melting points were obtained with a Kofler hot bench, consisting of a heated plate with linear temperature gradient, a sliding pointer and a temperature scale in degrees Celsius.

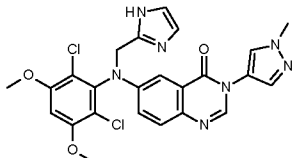
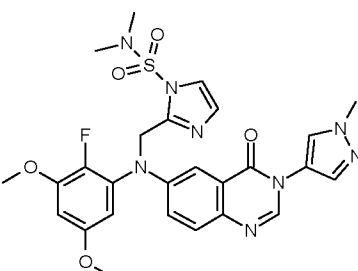
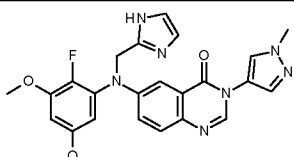
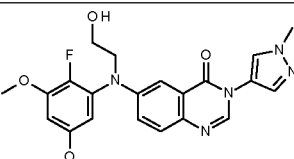
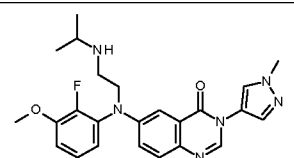
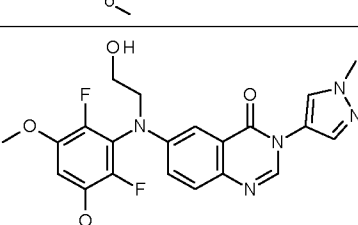
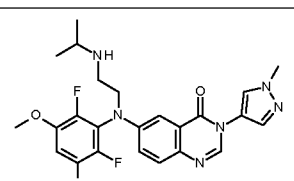
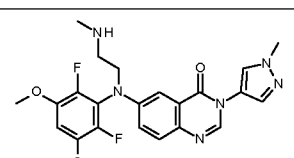
### NMR

- 10 The NMR experiments were carried out using a Bruker Avance 500 III using internal deuterium lock and equipped with reverse triple-resonance (<sup>1</sup>H, <sup>13</sup>C, <sup>15</sup>N TXI) probe head. Chemical shifts (δ) are reported in parts per million (ppm).

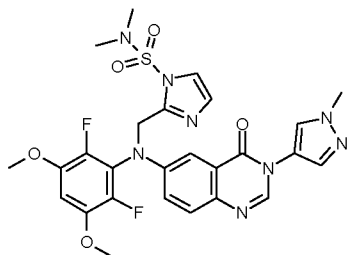
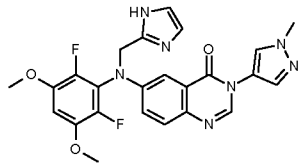
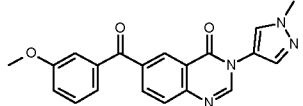
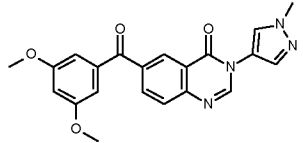
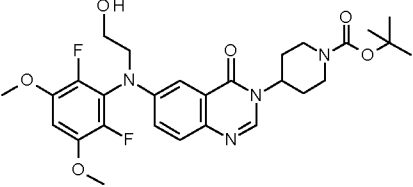
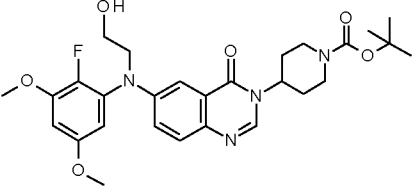
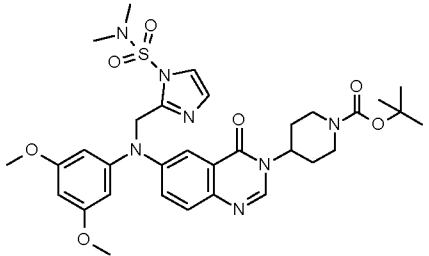
Table: Co. No. means compound number; Retention time (R<sub>t</sub>) in minutes; MP means melting point (°C); dec means decomposition; n.d. means not determined.

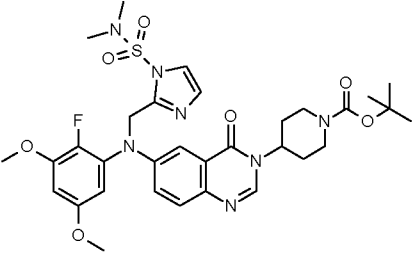
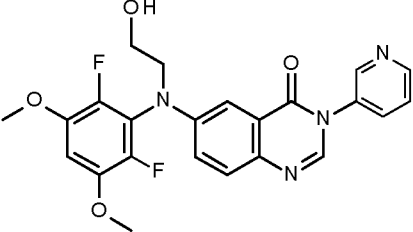
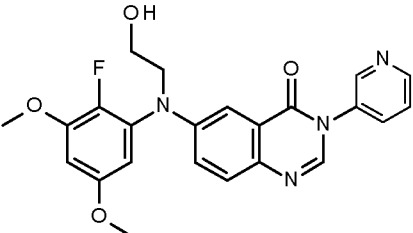
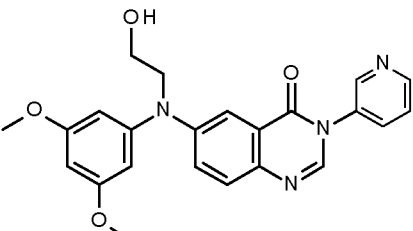
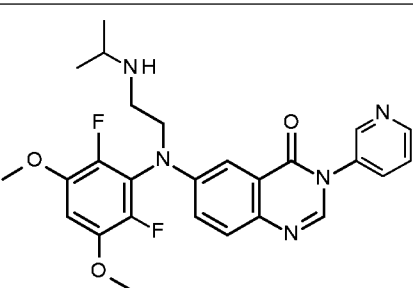
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
1		169	DSC	2.61	454
2		124	DSC	2.52	495
3		n.d.	-	n.d.	n.d.
4		n.d.	-	2.50	490

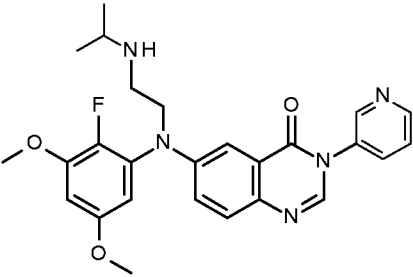
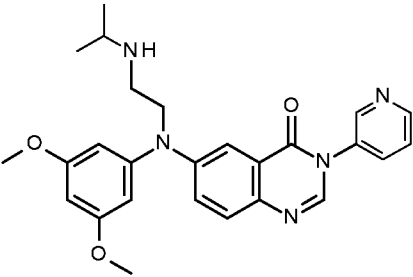
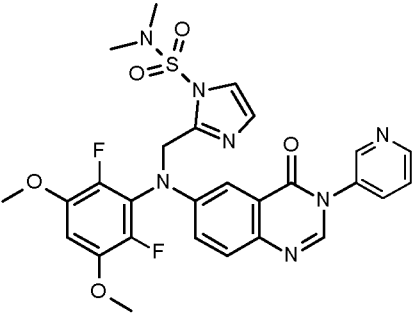
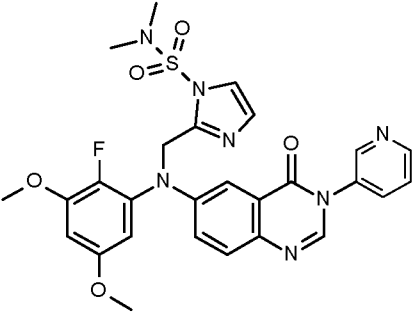
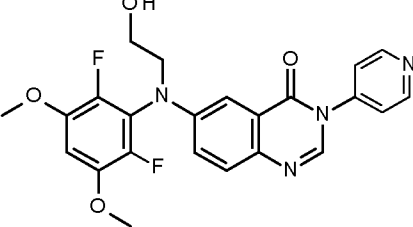
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
5		251	DSC	2.71	486
6		183	DSC	2.62	436
7		171	DSC	2.66	418
8		185	DSC	2.28	422
9		142	DSC	2.14	463
10		223	DSC	2.33	490
11		195	DSC	2.24	n.d.
12		n.d.	-	n.d.	n.d.

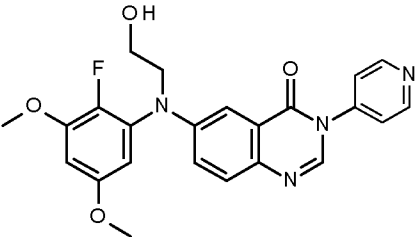
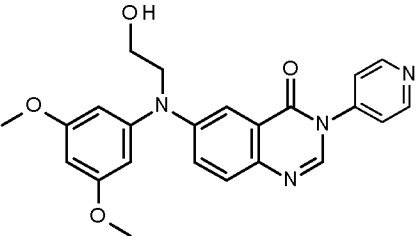
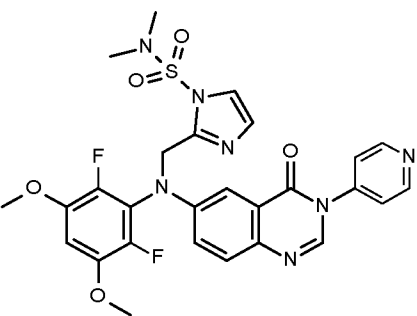
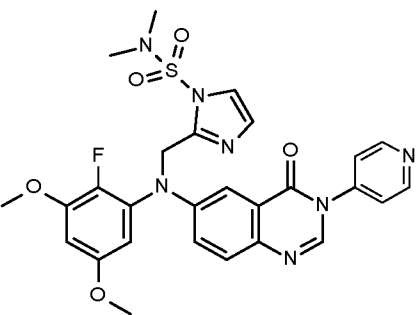
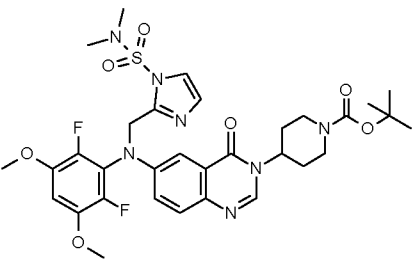
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
13		dec	K	2.24	526
14		n.d.	-	n.d.	n.d.
15		212	DSC	2.17	476
16		164	DSC	2.24	440
17		132	DSC	2.13	481
18		165	DSC	2.22	458
19		162	DSC	2.12	499
20		141	DSC	1.95	471

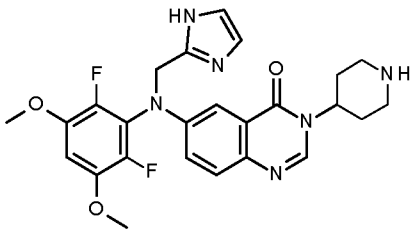
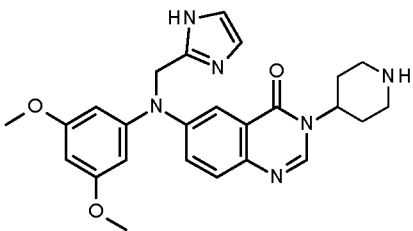
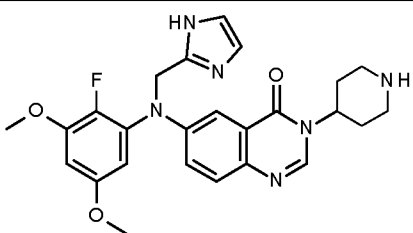
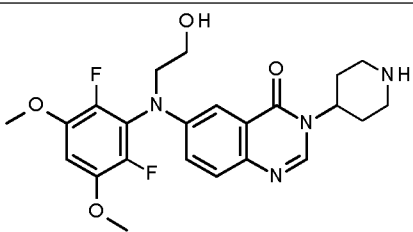
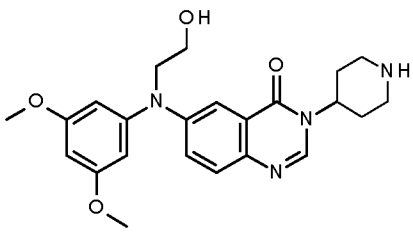
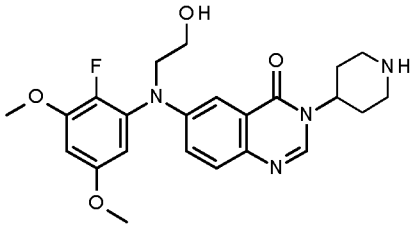


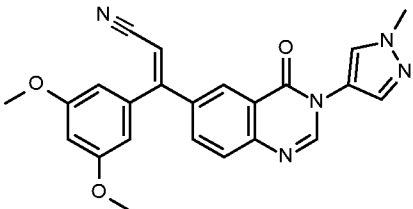
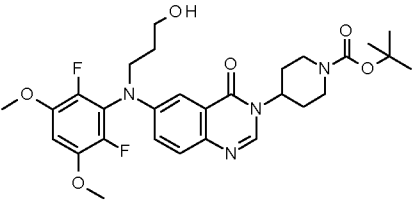
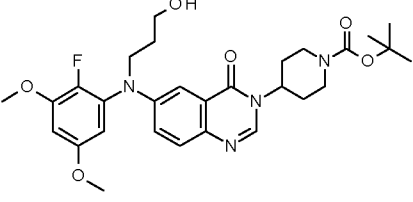
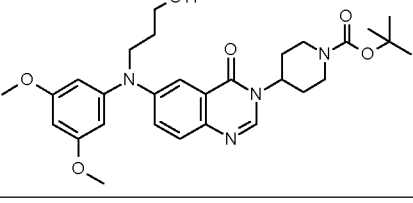
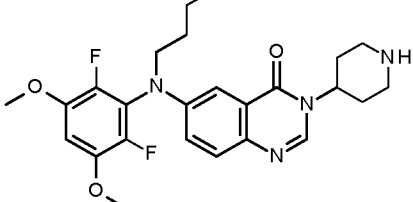
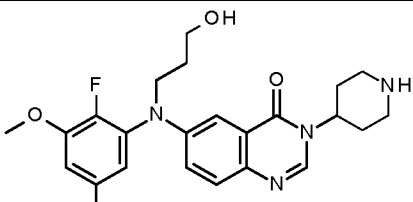
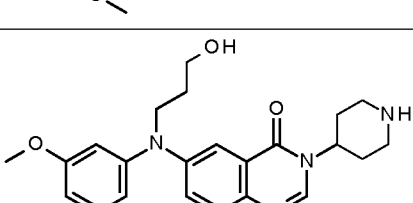
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
21		n.d.	-	n.d.	n.d.
22		231	DSC	2.14	494
23		n.d.	-	2.47	361
24		194	K	2.53	391
25		n.d.	-	n.d.	n.d.
26		n.d.	-	n.d.	n.d.
27		100 (gum)	K	3.14	668

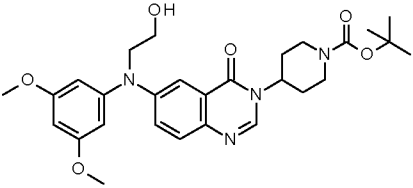
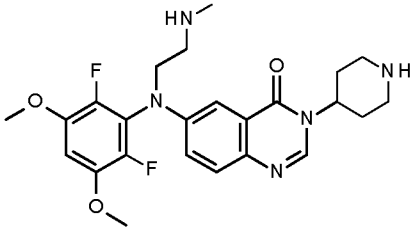
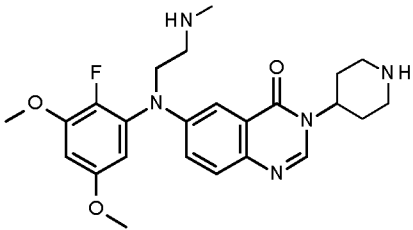
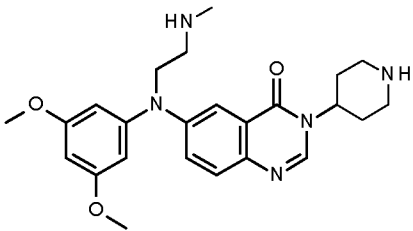
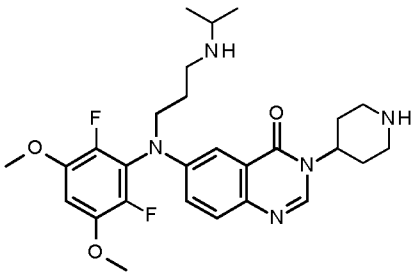
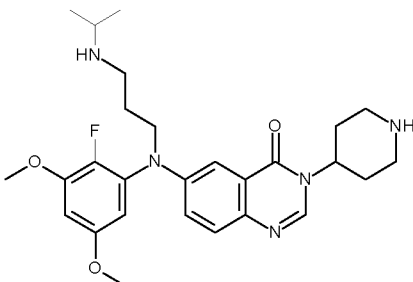
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
28		90 (gum)	K	3.09	686
29		112	K	2.24	455
30		186	K	2.26	437
31		168	K	2.32	419
32		124	K	2.14	493

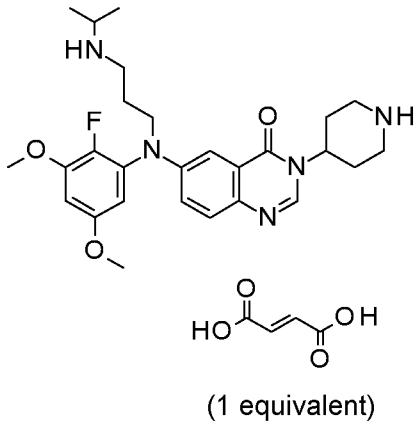
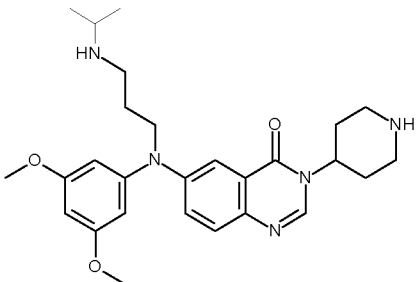
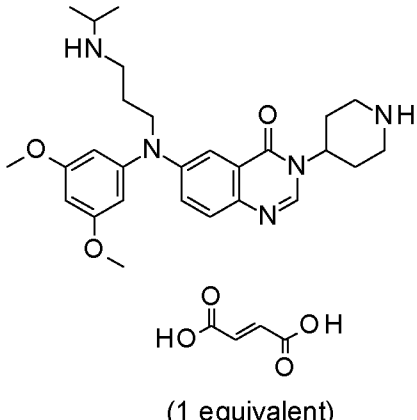
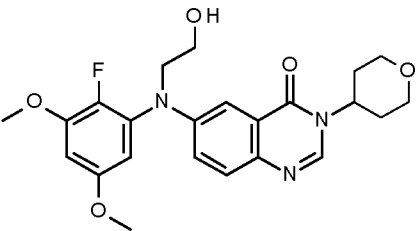
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
33		133	K	2.14	478
34		136	K	2.14	460
35		128	K	2.53	598
36		108	K	2.61	580
37		198	K	2.23	455

Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
38		209	K	2.26	437
39		177	K	2.29	419
40		139	K	2.53	598
41		109 (gum)	K	2.60	580
42		168	K	3.02	704

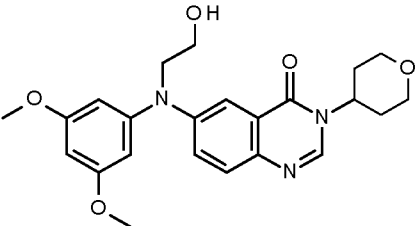
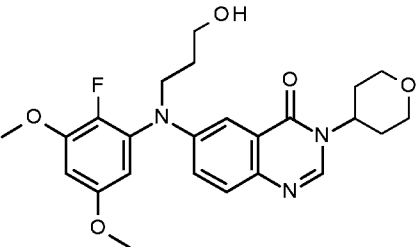
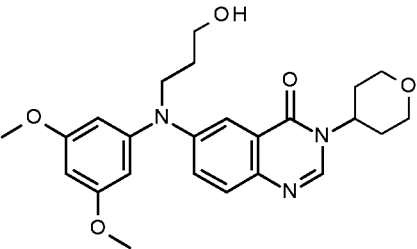
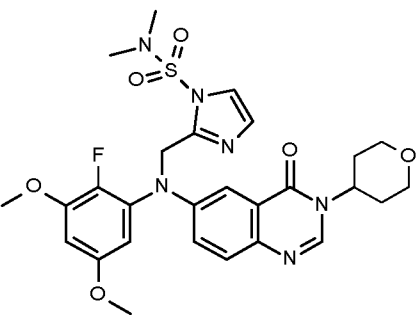
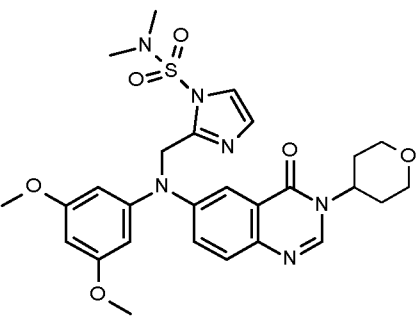
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
43		223	K	1.89	497
44		220	K	1.95	461
45		260	K	1.94	479
46		186	K	1.91	461
47		165	K	1.96	425
48		173	K	1.94	443

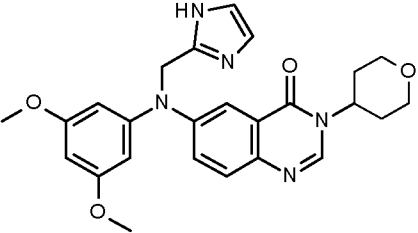
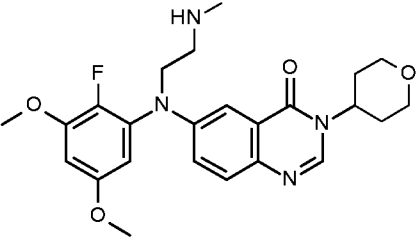
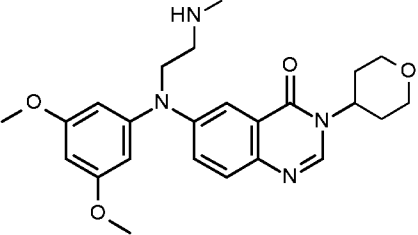
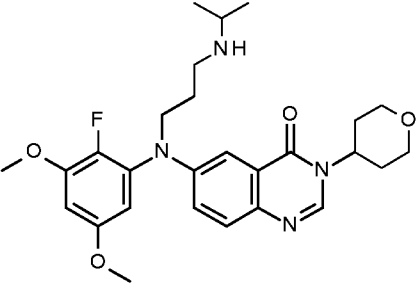
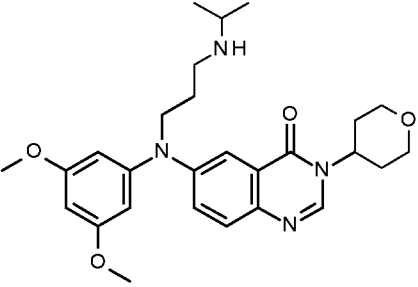
Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
49		217	K	2.59	414
50		n.d.	-	n.d.	n.d.
51		n.d.	-	n.d.	n.d.
52		n.d.	-	n.d.	n.d.
53		184	K	1.97	475
54		167	K	2.00	457
55		167	K	2.03	439

Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
56		n.d.	-	n.d.	n.d.
57		90 (gum)	K	1.93	474
58		176	K	2.19	456
59		139	K	2.13	438
60		126	K	2.14	516
61		n.d.	-	n.d.	n.d.

Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
61'	 (1 equivalent)	140 (gum)	K	2.16	498
62		n.d.	-	n.d.	n.d.
62'	 (1 equivalent)	255 (gum)	K	2.40	480
63		191	K	2.30	444



Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
64		204	K	2.34	426
65		164	K	2.36	458
66		178	K	2.4	440
67		189	K	2.67	587
68		182	K	2.7	569

Co. No.	Compound	MP	(Kofler(K) or DSC)	R <sub>t</sub>	[M+H] <sup>+</sup>
69		260	K	2.26	462
70		178	K	2.03	457
71		135	K	2.05	439
72		80 (gum)	K	2.18	499
73		n.d.	-	2.20	481



<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 8.24 (s, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.26 (d, *J* = 2.8 Hz, 1H), 7.21 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.08 (t, *J* = 8.2 Hz, 1H), 3.92 (s, 6H), 3.89 (s, 3H), 3.75 (t, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.34 - 2.21 (m, 4H)

5

**Compound 22**

<sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>) δ 11.87 (br. s., 1H), 8.25 (s, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.51 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.44 (d, *J* = 2.8 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 7.00 (s, 1H), 6.81 (s, 1H), 4.85 (s, 2H), 3.89 (s, 9H)

10

**Pharmacological part****Biological assays A****FGFR1 (enzymatic assay)**

In a final reaction volume of 30 μL, FGFR1 (h) (25 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6mM MnCl<sub>2</sub>, 1 mM DTT, 0,1 mM Na<sub>3</sub>VO<sub>4</sub>, 0,01% Triton-X-100, 500 nM Bln-Flt3 and 5 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC<sub>50</sub> (M) and pIC<sub>50</sub> (-logIC<sub>50</sub>) value.

**FGFR2 (enzymatic assay)**

In a final reaction volume of 30 μL, FGFR2 (h) (150 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6mM MnCl<sub>2</sub>, 1 mM DTT, 0,1 mM Na<sub>3</sub>VO<sub>4</sub>, 0,01% Triton-X-100, 500 nM Bln-Flt3 and 0.4 μM ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10 μM to 0.1 nM) was determined and used to calculate an IC<sub>50</sub> (M) and pIC<sub>50</sub> (-logIC<sub>50</sub>) value.

FGFR3 (enzymatic assay)

In a final reaction volume of 30  $\mu$ L, FGFR3 (h) (40 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6mM  $\text{MnCl}_2$ , 1 mM DTT, 0,1 mM  $\text{Na}_3\text{VO}_4$ , 0,01% Triton-X-100, 500 nM Bln-Flt3 and 25  $\mu$ M ATP in the presence of compound (1% DMSO final). After  
5 incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this  
10 assay, the inhibitory effect of different compound concentrations (range 10  $\mu$ M to 0.1 nM) was determined and used to calculate an  $\text{IC}_{50}$  (M) and  $\text{pIC}_{50}$  (-log $\text{IC}_{50}$ ) value.

FGFR4 (enzymatic assay)

In a final reaction volume of 30  $\mu$ L, FGFR4 (h) (60 ng/ml) was incubated with 50 mM  
15 HEPES pH 7.5, 6mM  $\text{MnCl}_2$ , 1 mM DTT, 0,1 mM  $\text{Na}_3\text{VO}_4$ , 0,01% Triton-X-100, 500 nM Bln-Flt3 and 5  $\mu$ M ATP in the presence of compound (1% DMSO final). After incubation for 60 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy  
20 Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10  $\mu$ M to 0.1 nM) was determined and used to calculate an  $\text{IC}_{50}$  (M) and  $\text{pIC}_{50}$  (-log $\text{IC}_{50}$ ) value.

KDR (VEGFR2) (enzymatic assay)

In a final reaction volume of 30  $\mu$ L, KDR (h) (150 ng/ml) was incubated with 50 mM HEPES pH 7.5, 6mM  $\text{MnCl}_2$ , 1 mM DTT, 0,1 mM  $\text{Na}_3\text{VO}_4$ , 0,01% Triton-X-100, 500 nM Bln-Flt3 and 3  $\mu$ M ATP in the presence of compound (1% DMSO final). After incubation for 120 minutes at room temperature the reaction was stopped with 2.27 nM EU-anti P-Tyr, 7 mM EDTA, 31.25 nM SA-XL-665 and 0.02% BSA which was present for 60 minutes at room temperature. Time-Resolved Fluorescence Resonance Energy  
30 Transfer (TR-FRET) signal (ex340 nm. Em 620 nm, em 655 nm) was measured afterwards and results are expressed in RFU (Relative Fluorescence Units). In this assay, the inhibitory effect of different compound concentrations (range 10  $\mu$ M to 0.1  
35 nM) was determined and used to calculate an  $\text{IC}_{50}$  (M) and  $\text{pIC}_{50}$  (-log $\text{IC}_{50}$ ) value.

Ba/F3-FGFR1 (minus IL3 or plus IL3) (cellular proliferation assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 µl cell culture medium (phenol red free RPMI-1640, 10 % FBS, 2 mM L-Glutamine and 50 µg/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR1-transfected cells. Cells were put in an incubator at 37°C and 5 % CO<sub>2</sub>. After 24 hours, 10 µl of Alamar Blue solution (0.5 mM K<sub>3</sub>Fe(CN)<sub>6</sub>, 0.5 mM K<sub>4</sub>Fe(CN)<sub>6</sub>, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37°C and 5% CO<sub>2</sub> before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluorescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 µM to 0.1 nM) was determined and used to calculate an IC<sub>50</sub> (M) and pIC<sub>50</sub> (-logIC<sub>50</sub>) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-FGFR3 (minus IL3 or plus IL3) (cellular proliferation assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 µl cell culture medium (phenol red free RPMI-1640, 10 % FBS, 2 mM L-Glutamine and 50 µg/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR3-transfected cells. Cells were put in an incubator at 37°C and 5 % CO<sub>2</sub>. After 24 hours, 10 µl of Alamar Blue solution (0.5 mM K<sub>3</sub>Fe(CN)<sub>6</sub>, 0.5 mM K<sub>4</sub>Fe(CN)<sub>6</sub>, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37°C and 5% CO<sub>2</sub> before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluorescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10 µM to 0.1 nM) was determined and used to calculate an IC<sub>50</sub> (M) and pIC<sub>50</sub> (-logIC<sub>50</sub>) value. As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-KDR (minus IL3 or plus IL3) (cellular proliferation assay)

In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50 µl cell culture medium (phenol red free RPMI-1640, 10 % FBS, 2 mM L-Glutamine and 50 µg/ml Gentamycin) containing 20000 cells per well of Ba/F3-KDR-transfected cells. Cells were put in an incubator at 37°C and 5 % CO<sub>2</sub>. After 24 hours, 10 µl of Alamar Blue solution (0.5 mM K<sub>3</sub>Fe(CN)<sub>6</sub>, 0.5 mM K<sub>4</sub>Fe(CN)<sub>6</sub>, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37°C and 5% CO<sub>2</sub>

before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluorescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10  $\mu$ M to 0.1 nM) was determined and used to calculate an  $IC_{50}$  (M) and  $pIC_{50}$  ( $-\log IC_{50}$ ) value.

- 5 As a counterscreen the same experiment was performed in the presence of 10 ng/ml murine IL3.

Ba/F3-FGFR4 (cellular proliferation assay)

- 10 In a 384 well plate, 100 nl of compound dilution in DMSO was sprayed before adding 50  $\mu$ l cell culture medium (phenol red free RPMI-1640, 10 % FBS, 2 mM L-Glutamine and 50  $\mu$ g/ml Gentamycin) containing 20000 cells per well of Ba/F3-FGFR4-transfected cells. Cells were put in an incubator at 37°C and 5 % CO<sub>2</sub>. After 24 hours, 10  $\mu$ l of Alamar Blue solution (0.5 mM K<sub>3</sub>Fe(CN)<sub>6</sub>, 0.5 mM K<sub>4</sub>Fe(CN)<sub>6</sub>, 0.15 mM Resazurin and 100 mM Phosphate Buffer) was added to the wells, incubated for 4 hours at 37°C and
- 15 5% CO<sub>2</sub> before RFU's (Relative Fluorescence Units) (ex. 540 nm., em. 590 nm.) were measured in a fluorescence plate reader.

In this assay, the inhibitory effect of different compound concentrations (range 10  $\mu$ M to 0.1 nM) was determined and used to calculate an  $IC_{50}$  (M) and  $pIC_{50}$  ( $-\log IC_{50}$ ) value.

- 20 Data for the compounds of the invention in the above assays are provided in Table A1 (n.d. means not determined)

Table A1:

Comp. No.	FGFR <sub>1</sub> pIC50	FGFR 2 pIC50	FGFR3 pIC50	FGFR 4 pIC50	VEGFR KDR pIC50	BAF3-FGFR1 (MIN IL3 pIC50)	BAF3-FGFR1 (PLUS IL3 pIC50)	BAF3-FGFR3 (MIN IL3 pIC50)	BAF3-FGFR3 (PLUS IL3 pIC50)	BAF3-KDR (MIN IL3 pIC50)	BAF3-KDR (PLUS IL3 pIC50)	BAF3-FGFR4 (pIC50)
4	7.8	7.9	8.1	7.6	<6	6.1	<5	6.2	<5	<5	<5	5.4
24	<6	6.1	6.1	<6	<6	<5	<5	<5	<5	<5	<5	<5
23	<6	<6	<6	<6	<6	<5	<5	<5	<5	<5	<5	<5
20	8.0	7.9	7.9	7.6	6.8	7.6	<5	7.6	<5	6.0	<5	6.7
17	8.1	8.0	7.8	7.5	6.9	7.6	<5	7.7	<5	5.5	<5	6.8
15	8.3	8.3	8.6	8.1	6.4	6.7	<5	~7.15	<5	<5	<5	5.8
13	7.8	7.8	7.9	6.9	6.6	5.5	<5	5.9	<5	5.1	<5	5.2
22	8.4	8.3	8.5	8.3	6.9	6.8	<5	7.4	<5	5.3	<5	6.7
2	8.2	7.6	7.6	7.4	6.6	7.7	<5	7.6	<5	5.7	<5	6.3
19	8.3	7.8	7.8	7.7	6.9	8.8	<5	8.6	<5	6.2	<5	8.2
6	7.1	7.3	7.4	6.5	<6	5.5	<5	5.5	<5	<5	<5	5.0
11	7.9	7.2	7.4	6.8	6.3	7.4	<5	7.3	<5	5.4	<5	6.3
7	6.2	6.4	6.5	5.4	<6	<5	<5	<5	<5	<5	<5	<5
9	8.3	8.2	8.0	7.3	6.3	7.2	<5	~7.09	<5	5.2	<5	6.2
5	7.2	7.4	7.6	6.3	~6	5.5	<5	5.3	<5	<5	<5	<5
16	7.9	8.3	8.6	7.6	6.7	6.3	<5	6.4	<5	5.2	<5	5.7
18	8.8	8.6	8.8	8.3	7.4	7.2	<5	~7.68	<5	5.6	<5	6.6
10	7.9	7.8	8.1	6.7	6.3	6.2	<5	6.3	<5	~5	<5	5.1



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Comp. No.	FGFR 1 pIC50	FGFR 2 pIC50	FGFR3 pIC50	FGFR 4 pIC50	VEGFR KDR pIC50	BAF3- FGFR1 (MIN IL3 pIC50)	BAF3- FGFR1 (PLUS IL3 pIC50)	BAF3- FGFR3 (MIN IL3 pIC50)	BAF3- FGFR3 (PLUS IL3 pIC50)	BAF3- KDR (MIN IL3 pIC50)	BAF3- KDR (PLUS IL3 pIC50)	BAF3- FGFR4 (pIC50)
1	8.0	8.2	8.2	7.4	6.6	6.0	<5	6.4	<5	~5	<5	5.6
8	7.3	7.6	7.7	6.8	6.1	5.4	<5	5.6	<5	<5	<5	5.2

Biological assays BEnzyme Binding Assays (KINOMEScan®)

Kinase enzyme binding affinities of compounds disclosed herein were determined using the KINOMEScan® technology performed by DiscoverRx Corporation, San Diego,

- 5 California, USA ([www.kinomescan.com](http://www.kinomescan.com)). Table B1 reports the obtained pKd values (-log Kd; Kd (M) is inhibitor binding constant):

Table B1

Compound	FGFR1_pKd	FGFR2_pKd	FGFR3_pKd	FGFR4_pKd	VEGFR2_pKd
76	7.2	7.8	7.5	6.7	<5.5
75	7.4	8.0	7.8	6.7	<5.5
67	6.5	6.6	6.1	<5.5	<5.5
70	7.5	7.4	7.1	7.0	<5.5
69	6.8	7.3	6.8	6.0	<5.5
43	7.8	8.1	7.7	7.3	<5.5
45	7.1	7.5	7.1	6.3	<5.5
44	6.4	6.8	6.4	<5.5	<5.5
60	8.2	8.3	7.9	7.4	6.0
61'	7.3	7.7	7.2	6.7	<5.5
63	6.4	7.2	6.9	5.8	<5.5
68	5.9	6.0	<5.5	<5.5	<5.5
71	6.2	6.4	5.9	<5.5	<5.5
59	6.0	<5.5	<5.5	<5.5	<5.5
58	6.5	6.4	6.2	5.7	<5.5
57	7.5	7.4	7.2	6.8	5.7
73'	6.9	7.2	6.7	5.9	5.5
73	7.2	7.3	6.8	5.9	<5.5
64	6.2	6.4	6.0	<5.5	<5.5
72	8.1	8.0	7.8	7.3	5.6
74	6.1	6.9	6.4	5.7	<5.5
66	5.9	6.3	5.9	<5.5	<5.5
53	7.3	7.5	7.2	6.7	<5.5
54	6.1	6.5	6.2	<5.5	<5.5
55	<5.5	5.6	5.6	<5.5	<5.5
47	<5.5	<5.5	<5.5	<5.5	<5.5
46	7.0	7.4	7.0	6.1	<5.5
48	5.9	6.2	6.1	<5.5	<5.5
65	6.7	7.3	7.1	6.0	<5.5
36	6.8	7.0	6.6	5.9	<5.5
32	8.7	7.9	8.2	8.1	6.6
40	7.4	7.5	7.2	6.6	5.8

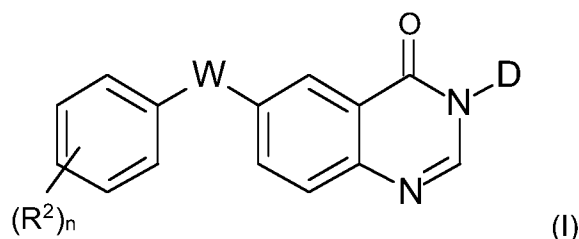
Compound	FGFR1_pKd	FGFR2_pKd	FGFR3_pKd	FGFR4_pKd	VEGFR2_pKd
35	7.3	7.8	7.4	6.9	5.9
29	7.8	8.5	8.2	7.3	6.2
39	6.1	6.7	6.6	5.5	<5.5
38	7.0	7.7	7.5	6.8	<5.5
37	7.8	8.6	8.3	7.3	6.0
41	7.0	7.5	6.9	6.1	<5.5
34	7.2	7.3	6.9	6.2	<5.5
33	8.3	7.8	8.1	7.6	5.8
30	6.6	7.4	7.2	6.3	<5.5
31	6.0	6.3	6.0	<5.5	<5.5
49	5.7	6.4	6.1	<5.5	<5.5
19	8.8	8.3	8.3	8.3	7.8
7	<6	>6	>6	<6	<6

The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

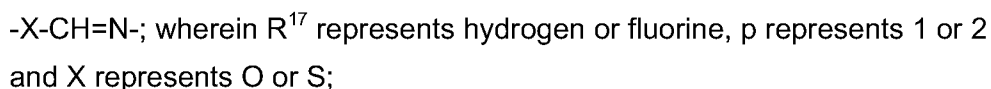
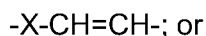
The claims defining the invention are as follows:

1. A compound of formula (I):



including any tautomeric or stereochemically isomeric form thereof, wherein W is  $-N(R^3)-$  or  $-C(R^{3a}R^{3b})-$ ;

each  $R^2$  is independently selected from hydroxyl, halogen, cyano,  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy, hydroxy $C_{1-4}$ alkyl, hydroxy $C_{1-4}$ alkoxy, halo $C_{1-4}$ alkyl, halo $C_{1-4}$ alkoxy, hydroxyhalo $C_{1-4}$ alkyl, hydroxyhalo $C_{1-4}$ alkoxy,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, halo $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl wherein each  $C_{1-4}$ alkyl may optionally be substituted with one or two hydroxyl groups, hydroxyhalo $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $R^{13}$ ,  $C_{1-4}$ alkyl substituted with  $R^{13}$ ,  $C_{1-4}$ alkyl substituted with  $-C(=O)-R^{13}$ ,  $C_{1-4}$ alkoxy substituted with  $R^{13}$ ,  $C_{1-4}$ alkoxy substituted with  $-C(=O)-R^{13}$ ,  $-C(=O)-R^{13}$ ,  $C_{1-4}$ alkyl substituted with  $-NR^7R^8$ ,  $C_{1-4}$ alkyl substituted with  $-C(=O)-NR^7R^8$ ,  $C_{1-4}$ alkoxy substituted with  $-NR^7R^8$ ,  $C_{1-4}$ alkoxy substituted with  $-C(=O)-NR^7R^8$ ,  $-NR^7R^8$  and  $-C(=O)-NR^7R^8$ ; or when two  $R^2$  groups are attached to adjacent carbon atoms they may be taken together to form a radical of formula:



D represents a 3 to 12 ring membered monocyclic or bicyclic carbocyclyl or a 3 to 12 ring membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or more (e.g. 1, 2 or 3)  $R^1$  groups;

$R^1$  represents hydrogen, halo, cyano,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy,  $-C(=O)-O-$   $C_{1-6}$ alkyl,  $C_{2-4}$ alkenyl, hydroxy $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl, hydroxyhalo $C_{1-6}$ alkyl, cyano $C_{1-4}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or two

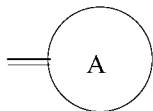
hydroxyl groups,  $-NR^4R^5$ ,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^4R^5$ ,  $-C(=O)-NR^4R^5$ ,  $-C(=O)-C_{1-6}$ alkyl- $-NR^4R^5$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-NR^4R^5$ ,  $-S(=O)_2-C_{1-6}$ alkyl,  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^6$ ,  $C_{1-6}$ alkyl substituted with  $R^6$ ,  $-C(=O)-R^6$ ,  $C_{1-6}$ alkyl substituted with  $-C(=O)-R^6$ , hydroxy $C_{1-6}$ alkyl substituted with  $R^6$ ,  $C_{1-6}$ alkyl substituted with  $-Si(CH_3)_3$ ,  $C_{1-6}$ alkyl substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}$ alkyl substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;

$R^{3a}$  represents  $-NR^{10}R^{11}$ , hydroxyl,  $C_{1-6}$ alkoxy, hydroxy $C_{1-6}$ alkoxy,  $C_{1-6}$ alkoxy substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, halo $C_{1-6}$ alkyl optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl, hydroxy $C_{1-6}$ alkyl optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl, hydroxy $C_{2-6}$ alkenyl, hydroxy $C_{2-6}$ alkynyl, hydroxyhalo $C_{1-6}$ alkyl, cyano $C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with carboxyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-O-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $O-C(=O)-$ ,  $C_{1-6}$ alkyl substituted with  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl- $C(=O)-$ ,  $C_{1-6}$ alkyl substituted with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy $C_{1-6}$ alkyl wherein each  $C_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl substituted with  $C_{1-6}$ alkoxy,  $C_{2-6}$ alkynyl substituted with  $C_{1-6}$ alkoxy,  $C_{1-6}$ alkyl substituted with  $R^9$  and optionally substituted with  $-O-C(=O)-C_{1-6}$ alkyl,  $C_{1-6}$ alkyl substituted with  $-C(=O)-R^9$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $R^9$ ,  $C_{2-6}$ alkenyl substituted with  $R^9$ ,  $C_{2-6}$ alkynyl substituted with  $R^9$ ,  $C_{1-6}$ alkyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkenyl substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}$ alkynyl substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}$ alkyl substituted with one or two halogens and  $-NR^{10}R^{11}$ ,

$-C_{1-6}alkyl-C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2$ -halo $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}alkyl$  substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}alkyl$  substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;

$R^{3b}$  represents hydrogen or hydroxyl; provided that if  $R^{3a}$  represents  $-NR^{10}R^{11}$ , then  $R^{3b}$  represents hydrogen; or

$R^{3a}$  and  $R^{3b}$  are taken together to form  $=O$ , to form  $=NR^{10}$ , to form cyclopropyl together with the carbon atom to which they are attached, to form  $=CH-C_{0-4}alkyl$  substituted with



$R^{3c}$ , or to form wherein ring A is a monocyclic 5 to 7 membered saturated heterocycle containing one heteroatom selected from N, O or S, said heteroatom not being positioned in alpha position of the double bond, wherein ring A is optionally being substituted with cyano,  $C_{1-4}alkyl$ , hydroxy $C_{1-4}alkyl$ ,  $H_2N-C_{1-4}alkyl$ ,  $(C_{1-4}alkyl)NH-C_{1-4}alkyl$ ,  $(C_{1-4}alkyl)_2N-C_{1-4}alkyl$ ,  $(haloC_{1-4}alkyl)NH-C_{1-4}alkyl$ ,  $C_{1-4}alkoxyC_{1-4}alkyl$ ,  $-C(=O)-NH_2$ ,  $-C(=O)-NH(C_{1-4}alkyl)$ ,  $-C(=O)-N(C_{1-4}alkyl)_2$ ;

- 10  $R^{3c}$  represents hydrogen, hydroxyl,  $C_{1-6}alkoxy$ ,  $R^9$ ,  $-NR^{10}R^{11}$ ,  $-C(=O)-NR^{14}R^{15}$ , cyano,  $-C(=O)-C_{1-6}alkyl$  or  $-CH(OH)-C_{1-6}alkyl$ ;

- $R^3$  represents hydroxyl,  $C_{1-6}alkoxy$ , hydroxy $C_{1-6}alkoxy$ ,  $C_{1-6}alkoxy$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$ ,  $C_{2-6}alkenyl$ ,  $C_{2-6}alkynyl$ ,  $haloC_{1-6}alkyl$  optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{1-6}alkyl$  optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ , hydroxy $C_{2-6}alkenyl$ , hydroxy $C_{2-6}alkynyl$ , hydroxy $haloC_{1-6}alkyl$ , cyano $C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with carboxyl,  $C_{1-6}alkyl$  substituted with  $-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-O-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-O-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  $C_{1-6}alkoxyC_{1-6}alkyl-C(=O)-$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkoxyC_{1-6}alkyl$  wherein each  $C_{1-6}alkyl$  may optionally be substituted with one or two hydroxyl groups or with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{2-6}alkenyl$  substituted with  $C_{1-6}alkoxy$ ,  $C_{2-6}alkynyl$  substituted with  $C_{1-6}alkoxy$ ,  $C_{1-6}alkyl$  substituted with  $R^9$  and optionally substituted with  $-O-C(=O)-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-R^9$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $R^9$ ,  $C_{2-6}alkenyl$  substituted with  $R^9$ ,  $C_{2-6}alkynyl$  substituted with  $R^9$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}alkenyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{2-6}alkynyl$  substituted with  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with hydroxyl and  $-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with one or two halogens and  $-NR^{10}R^{11}$ ,  $-C_{1-6}alkyl-C(R^{12})=N-O-R^{12}$ ,  $C_{1-6}alkyl$  substituted with  $-C(=O)-NR^{10}R^{11}$ ,  $C_{1-6}alkyl$  substituted with  $-O-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_2-C_{1-6}alkyl$ ,  $-S(=O)_2-haloC_{1-6}alkyl$ ,  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-S(=O)_2-NR^{14}R^{15}$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-C_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NH-S(=O)_2-haloC_{1-6}alkyl$ ,  $C_{1-6}alkyl$  substituted with  $-NR^{12}-S(=O)_2-NR^{14}R^{15}$ ,  $R^{13}$ ,  $C_{1-6}alkyl$  substituted with  $-P(=O)(OH)_2$  or  $C_{1-6}alkyl$  substituted with  $-P(=O)(OC_{1-6}alkyl)_2$ ;

R<sup>4</sup> and R<sup>5</sup> each independently represent hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>14</sup>R<sup>15</sup>, hydroxyC<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl wherein each C<sub>1-6</sub>alkyl may optionally be substituted with one or two hydroxyl groups,  
 5 -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, -C(=O)-NR<sup>14</sup>R<sup>15</sup>,  
 -C(=O)-O-C<sub>1-6</sub>alkyl, -C(=O)-R<sup>13</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>,  
 C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  
 -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, R<sup>13</sup> or  
 10 C<sub>1-6</sub>alkyl substituted with R<sup>13</sup>;

R<sup>6</sup> represents C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S; said  
 C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, 4 to 7-membered monocyclic heterocyclyl,  
 15 optionally and each independently being substituted by 1, 2, 3, 4 or 5 substituents,  
 each substituent independently being selected from cyano, C<sub>1-6</sub>alkyl, cyanoC<sub>1-6</sub>alkyl,  
 hydroxyl, carboxyl, hydroxyC<sub>1-6</sub>alkyl, halogen, haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy,  
 C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl-O-C(=O)-, -NR<sup>14</sup>R<sup>15</sup>, -C(=O)-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted  
 20 with -NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -C(=O)-NR<sup>14</sup>R<sup>15</sup>, -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl,  
 -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl,  
 C<sub>1-6</sub>alkyl substituted with -S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with  
 -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>, C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted  
 with -NH-S(=O)<sub>2</sub>-haloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkyl substituted with -NH-S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

25 R<sup>7</sup> and R<sup>8</sup> each independently represent hydrogen, C<sub>1-6</sub>alkyl, hydroxyC<sub>1-6</sub>alkyl,  
 haloC<sub>1-6</sub>alkyl, hydroxyhaloC<sub>1-6</sub>alkyl or C<sub>1-6</sub>alkoxyC<sub>1-6</sub>alkyl;

R<sup>9</sup> represents C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered  
 30 monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N,  
 O or S, said C<sub>3-8</sub>cycloalkyl, C<sub>3-8</sub>cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered  
 monocyclic or bicyclic heterocyclyl each optionally and each independently being  
 substituted with 1, 2, 3, 4 or 5 substituents, each substituent independently being  
 selected from =O, C<sub>1-4</sub>alkyl, hydroxyl, carboxyl, hydroxyC<sub>1-4</sub>alkyl, cyano, cyanoC<sub>1-4</sub>alkyl,  
 35 C<sub>1-4</sub>alkyl-O-C(=O)-, C<sub>1-4</sub>alkyl substituted with C<sub>1-4</sub>alkyl-O-C(=O)-, C<sub>1-4</sub>alkyl-C(=O)-,  
 C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl wherein each C<sub>1-4</sub>alkyl may optionally be substituted with one or  
 two hydroxyl groups, halogen, haloC<sub>1-4</sub>alkyl, hydroxyhaloC<sub>1-4</sub>alkyl, -NR<sup>14</sup>R<sup>15</sup>, -C(=O)-

$\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-4}$ alkoxy,  $-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl,  $-\text{S}(=\text{O})_2\text{-haloC}_{1-4}\text{alkyl}$ ,  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-4}$ alkyl substituted with  
 $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{C}_{1-4}$ alkyl,  $\text{C}_{1-4}$ alkyl substituted  
 5 with  $-\text{NH}-\text{S}(=\text{O})_2\text{-haloC}_{1-4}\text{alkyl}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{R}^{13}$ ,  
 $-\text{C}(=\text{O})-\text{R}^{13}$ ,  $\text{C}_{1-4}$ alkyl substituted with  $\text{R}^{13}$ , phenyl optionally substituted with  $\text{R}^{16}$ ,  
 phenyl $\text{C}_{1-6}$ alkyl wherein the phenyl is optionally substituted with  $\text{R}^{16}$ , a 5 or 6-  
 membered aromatic monocyclic heterocyclyl containing at least one heteroatom  
 selected from N, O or S wherein said heterocyclyl is optionally substituted with  $\text{R}^{16}$ ;  
 10 or when two of the substituents of  $\text{R}^9$  are attached to the same atom, they may be  
 taken together to form a 4 to 7-membered saturated monocyclic heterocyclyl containing  
 at least one heteroatom selected from N, O or S;

$\text{R}^{10}$  and  $\text{R}^{11}$  each independently represent hydrogen, carboxyl,  $\text{C}_{1-6}$ alkyl, cyano $\text{C}_{1-6}$ alkyl,  
 15  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{C}(=\text{O})-\text{NR}^{14}\text{R}^{15}$ ,  
 halo $\text{C}_{1-6}$ alkyl, hydroxy $\text{C}_{1-6}$ alkyl, hydroxyhalo $\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy,  $\text{C}_{1-6}$ alkoxy $\text{C}_{1-6}$ alkyl  
 wherein each  $\text{C}_{1-6}$ alkyl may optionally be substituted with one or two hydroxyl groups,  
 $\text{R}^6$ ,  $\text{C}_{1-6}$ alkyl substituted with  $\text{R}^6$ ,  $-\text{C}(=\text{O})-\text{R}^6$ ,  $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $-\text{C}(=\text{O})\text{-hydroxyC}_{1-6}\text{alkyl}$ ,  
 $-\text{C}(=\text{O})\text{-haloC}_{1-6}\text{alkyl}$ ,  $-\text{C}(=\text{O})\text{-hydroxyhaloC}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{Si}(\text{CH}_3)_3$ ,  
 20  $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $-\text{S}(=\text{O})_2\text{-haloC}_{1-6}\text{alkyl}$ ,  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  
 $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{S}(=\text{O})_2\text{-haloC}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}$ alkyl substituted  
 with  $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ,  $\text{C}_{1-6}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkyl  
 substituted with  $-\text{NH}-\text{S}(=\text{O})_2\text{-haloC}_{1-6}\text{alkyl}$ ,  $\text{C}_{1-6}$ alkyl substituted with carboxyl, or  $\text{C}_{1-}$   
 $\text{C}_{1-6}$ alkyl substituted with  $-\text{NH}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$ ;

25  $\text{R}^{12}$  represents hydrogen or  $\text{C}_{1-4}$ alkyl optionally substituted with  $\text{C}_{1-4}$ alkoxy;

$\text{R}^{13}$  represents  $\text{C}_{3-8}$ cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl  
 containing at least one heteroatom selected from N, O or S, wherein said  $\text{C}_{3-8}$ cycloalkyl  
 30 or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each  
 independently selected from halogen, hydroxyl,  $\text{C}_{1-6}$ alkyl, halo $\text{C}_{1-6}$ alkyl,  $=\text{O}$ , cyano,  
 $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl,  $\text{C}_{1-6}$ alkoxy, or  $-\text{NR}^{14}\text{R}^{15}$ ;

$\text{R}^{14}$  and  $\text{R}^{15}$  each independently represent hydrogen, or halo $\text{C}_{1-4}$ alkyl, or  $\text{C}_{1-4}$ alkyl  
 35 optionally substituted with a substituent selected from hydroxyl,  $\text{C}_{1-4}$ alkoxy, amino or  
 mono-or di( $\text{C}_{1-4}$ alkyl)amino;



R<sup>16</sup> represents hydroxyl, halogen, cyano, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, -NR<sup>14</sup>R<sup>15</sup> or -C(=O)NR<sup>14</sup>R<sup>15</sup>;

n independently represents an integer equal to 0, 1, 2, 3 or 4;

5 a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

2. A compound according to claim 1 wherein D is optionally substituted pyrazolyl.

3. A compound according to claim 1 or 2 wherein W is -N(R<sup>3</sup>)-.  
10

4. A compound according to claim 1 or 2 wherein W is -C(R<sup>3a</sup>R<sup>3b</sup>)-.

5. A compound according to any one of the preceding claims wherein R<sup>1</sup> represents C<sub>1-6</sub>alkyl.  
15

6. A compound according to any one of the preceding claims wherein R<sup>2</sup> represents C<sub>1-4</sub>alkoxy or halo.

7. A compound according to any one of claims 1 to 3, 5 or 6 wherein R<sup>3</sup> represents  
20 hydroxC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup> or C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>.

8. A compound according to claim 1 wherein  
D is pyrazolyl or phenyl, each optionally substituted with C<sub>1-4</sub>alkyl;  
W is -N(R<sup>3</sup>)- or -C(=O)-;  
25 R<sup>3</sup> is hydroxC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or  
C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> is imidazolyl optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl.  
30

9. A compound according to claim 1 wherein  
W is -N(R<sup>3</sup>)- or -C(=O)-; in particular W is -N(R<sup>3</sup>)-;  
each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;  
D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered  
35 monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S,  
wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or  
more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or  
C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one  
5 heteroatom selected from N, O or S, said 5 membered monocyclic heterocyclyl  
optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

10

10. A compound according to claim 1 wherein

W is -N(R<sup>3</sup>)- or -C(R<sup>3a</sup>R<sup>3b</sup>)-;

each R<sup>2</sup> is halogen or C<sub>1-4</sub>alkoxy;

D represents a 5 to 6 ring membered monocyclic carbocyclyl or a 5 to 6 ring membered  
15 monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S,  
wherein said carbocyclyl and heterocyclyl may each be optionally substituted by one or  
more (e.g. 1, 2 or 3) R<sup>1</sup> groups;

R<sup>1</sup> represents C<sub>1-6</sub>alkyl or -C(=O)-O-C<sub>1-6</sub>alkyl;

R<sup>3</sup> represents hydroxyC<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkyl substituted with R<sup>9</sup>, or  
20 C<sub>1-6</sub>alkyl substituted with -NR<sup>10</sup>R<sup>11</sup>;

R<sup>3a</sup> and R<sup>3b</sup> are taken together to form =O or =CH-C<sub>0-4</sub>alkyl substituted with R<sup>3c</sup>;  
R<sup>3c</sup> is cyano;

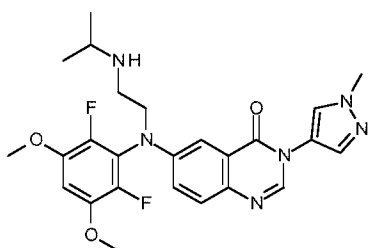
R<sup>9</sup> represents a 5 membered monocyclic heterocyclyl containing at least one  
heteroatom selected from N, O or S, said 5 membered monocyclic heterocyclyl  
25 optionally substituted with -S(=O)<sub>2</sub>-NR<sup>14</sup>R<sup>15</sup>;

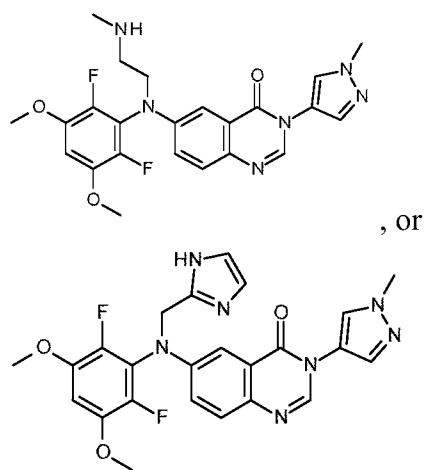
R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen or C<sub>1-6</sub>alkyl;

R<sup>14</sup> and R<sup>15</sup> represent C<sub>1-4</sub>alkyl;

n independently represents an integer equal to 1, 2, 3 or 4.

30 11. A compound according to claim 1 wherein the compound is





12. A compound according to any one of claims 1 to 11 or a pharmaceutically acceptable salt or solvate thereof.
- 5 13. A compound as claimed in any one of claims 1 to 12 for use in therapy.
14. A pharmaceutical composition comprising a compound of formula (I) as claimed in any one of claims 1 to 12.
- 10 15. A compound as claimed in any one of claims 1 to 12 for use in the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.
16. A compound as claimed in any one of claims 1 to 12 for use in the prophylaxis or treatment of cancer.
- 15 17. Use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.
- 20 18. Use of a compound as claimed in any one of claims 1 to 12 for the manufacture of a medicament for the prophylaxis or treatment of cancer mediated by a FGFR kinase.
19. A method for the prophylaxis or treatment of cancer mediated by a FGFR kinase which method comprises administering to a subject in need thereof a compound of the
- 25 formula (I) as claimed in any one of claims 1 to 12.
20. The method according to claim 19 for

- (i) the treatment of cancer wherein the cancer is selected from prostate cancer, bladder cancer, lung cancer, breast cancer, gastric cancer, and liver cancer; or
- 5 (ii) the treatment of cancer wherein the lung cancer is non-small cell lung cancer; or
- (iii) the treatment of cancer wherein the cancer is selected from multiple myeloma, myeloproliferative disorders, endometrial cancer, prostate cancer, bladder cancer, lung cancer, ovarian cancer, breast cancer, gastric cancer, colorectal cancer, and oral squamous cell carcinoma; or
- 10 (iv) the treatment of cancer wherein the cancer is selected from lung cancer, squamous cell carcinoma, liver cancer, kidney cancer, breast cancer, colon cancer, colorectal cancer, prostate cancer; or
- 15 (v) the treatment of cancer wherein the cancer is multiple myeloma; or
- (vi) the treatment of cancer wherein the cancer is t(4;14) translocation positive multiple myeloma.
- 20 21. The method according to claim 19 for
- (i) the treatment of cancer wherein the cancer is bladder cancer; or
- (ii) the treatment of cancer wherein the cancer is bladder cancer with a FGFR3 chromosomal translocation; or
- 25 (iii) the treatment of cancer wherein the cancer is bladder cancer with a FGFR3 point mutation.
22. The method according to claim 19 for
- 30 (i) the treatment of cancer wherein the cancer is a tumour with a mutant of FGFR1, FGFR2, FGFR3 or FGFR4; or
- (ii) the treatment of cancer wherein the cancer is a tumour with a gain-of-function mutant of FGFR2 or FGFR3; or
- 35

(iii) the treatment of cancer wherein the cancer is a tumour with over-expression of FGFR1.

5 23. The method according to claim 19 for the treatment of cancer wherein said compound is used in combination with one or more anticancer agents.

10 24. The method according to claim 19 for the treatment of cancer wherein said compound is used in combination with one or more anticancer agents and wherein the one or more anticancer agents comprises a kinase inhibitor.

25. A combination of a compound of formula (I) according to any one of claims 1 to 12 with one or more anticancer agents.

15 26. A product containing as first active ingredient a compound of formula (I) according to any one of claims 1 to 12 and as further active ingredient one or more anticancer agents, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

20 27. A method for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase, which method comprises administering to a subject in need thereof a compound of the formula (I) as claimed in any one of claims 1 to 12.