

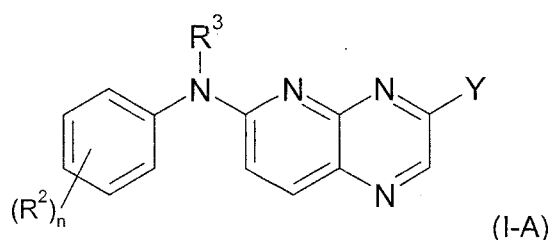
ANTICANCER PYRIDOPYRAZINES VIA THE INHIBITION OF FGFR KINASES

5 FIELD OF THE INVENTION

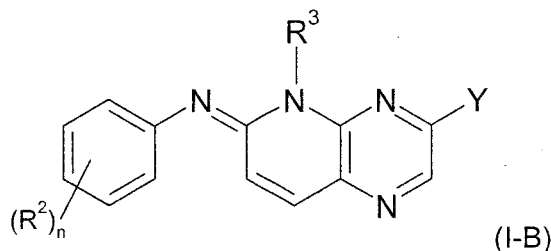
The invention relates to new pyridopyrazine derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

10 SUMMARY

The present According to a first aspect of the disclosure there is provided provides for compounds of formula (I):



or



including any tautomeric or stereochemically isomeric form thereof, wherein

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:

selected from halogen, C₁₋₄alkyl, C₁₋₄alkyloxy, cyano or amino; a 5- or 6-membered aromatic monocyclic heterocycle containing at least one heteroatom selected from N, O or S, said heterocycle being optionally substituted with 1, 2, 3 or 4 substituents each independently selected from halogen, C₁₋₄alkyl, C₁₋₄alkyloxy, cyano or amino; wherein said C₁₋₆ alkyl and C₃₋₈ cycloalkyl, may be optionally substituted by one or more R²⁰ groups

R²⁰ and R²¹ independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ alkanol -(CH₂)_n-O-C₁₋₆alkyl, or when attached to a nitrogen atom R²⁰ and R²¹ can be taken together to form with the nitrogen atom to which they are attached a monocyclic saturated 4, 5 or 6-membered ring which optionally contains a further heteroatom selected from O, S or N;

R²² and R²³ independently represent hydrogen, C₁₋₆ alkyl, or hydroxyC₁₋₆alkyl;

m independently represents an integer equal to 0, 1 or 2;

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

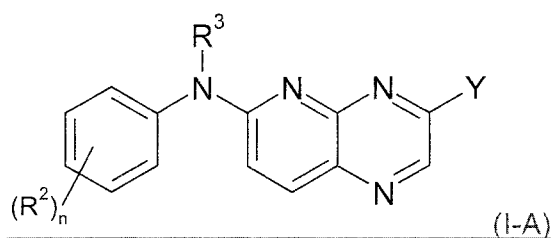
s independently represents an integer equal to 0, 1, 2, 3 or 4;

r independently represent an integer equal to 1, 2, 3, or 4;

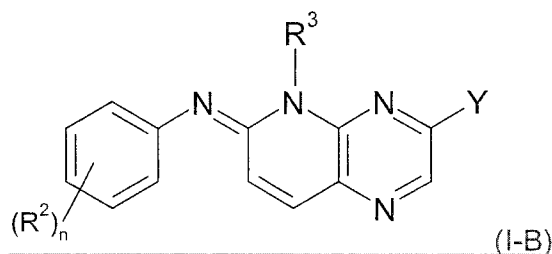
r1 independently represent an integer equal to 2, 3 or 4;

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

According to a first aspect of the disclosure there is provided a compound of formula (I-A) or (I-B):

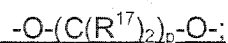
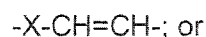
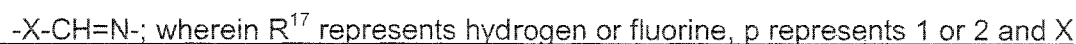


or



including any tautomeric or stereochemically isomeric form thereof, wherein

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:



represents O or S;

Y represents $-CR^{18}=N-OR^{19}$ or $-E-D$;

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;

E represents a bond;

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

- R^3 represents hydroxyl, C_{1-6} alkoxy, hydroxy C_{1-6} alkoxy, C_{1-6} alkoxy substituted with
- 5 $-\text{NR}^{10}\text{R}^{11}$, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halo C_{1-6} alkyl optionally substituted with $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, hydroxy C_{1-6} alkyl optionally substituted with $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ 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 $-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{C}(=\text{O})-\text{O}-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with C_{1-6} alkoxy C_{1-6} alkyl- $\text{O}-\text{C}(=\text{O})-$, C_{1-6} alkyl substituted with C_{1-6} alkoxy C_{1-6} alkyl- $\text{C}(=\text{O})-$, C_{1-6} alkyl substituted with $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, C_{1-6} alkoxy C_{1-6} alkyl
- 10 wherein each 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, 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 $-\text{O}-\text{C}(=\text{O})-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{C}(=\text{O})-\text{R}^9$, C_{1-6} alkyl substituted with hydroxyl and R^9 , C_{2-6} alkenyl
- 15 substituted with R^9 , C_{2-6} alkynyl substituted with R^9 , C_{1-6} alkyl substituted with $-\text{NR}^{10}\text{R}^{11}$, C_{2-6} alkenyl substituted with $-\text{NR}^{10}\text{R}^{11}$, C_{2-6} alkynyl substituted with $-\text{NR}^{10}\text{R}^{11}$, C_{1-6} alkyl substituted with hydroxyl and $-\text{NR}^{10}\text{R}^{11}$, C_{1-6} alkyl substituted with one or two halogens and $-\text{NR}^{10}\text{R}^{11}$, $-\text{C}_{1-6}$ alkyl- $\text{C}(\text{R}^{12})=\text{N}-\text{O}-\text{R}^{12}$, C_{1-6} alkyl substituted with $-\text{C}(=\text{O})-\text{NR}^{10}\text{R}^{11}$, C_{1-6} alkyl substituted with $-\text{O}-\text{C}(=\text{O})-\text{NR}^{10}\text{R}^{11}$, $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, $-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, C_{1-6} alkyl substituted with $-\text{NR}^{12}-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{NH}-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, C_{1-6} alkyl substituted with $-\text{NR}^{12}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, R^{13} , C_{1-6} alkyl substituted with $-\text{P}(=\text{O})(\text{OH})_2$ or C_{1-6} alkyl substituted with $-\text{P}(=\text{O})(\text{OC}_{1-6}\text{alkyl})_2$;
- 20
- 25

- R^4 and R^5 each independently represent hydrogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with $-\text{NR}^{14}\text{R}^{15}$, 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, $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, $-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, $-\text{C}(=\text{O})-\text{NR}^{14}\text{R}^{15}$, $-\text{C}(=\text{O})-\text{O}-\text{C}_{1-6}$ alkyl, $-\text{C}(=\text{O})-\text{R}^{13}$, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, C_{1-6} alkyl substituted with $-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, C_{1-6} alkyl substituted with $-\text{NH}-\text{S}(=\text{O})_2-\text{C}_{1-6}$ alkyl, C_{1-6} alkyl substituted with $-\text{NH}-\text{S}(=\text{O})_2$ -halo C_{1-6} alkyl, C_{1-6} alkyl substituted with $-\text{NH}-\text{S}(=\text{O})_2-\text{NR}^{14}\text{R}^{15}$, R^{13} or C_{1-6} alkyl substituted with R^{13} ;
- 30
- 35

- 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,

C₃₋₈cycloalkenyl, 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, C₁₋₆alkyl, cyanoC₁₋₆alkyl,

hydroxyl, carboxyl, hydroxyC₁₋₆alkyl, halogen, haloC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl, C₁₋₆alkoxy,

- 5 C₁₋₆alkoxyC₁₋₆alkyl, C₁₋₆alkyl-O-C(=O)-, -NR¹⁴R¹⁵, -C(=O)-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -C(=O)-NR¹⁴R¹⁵, -S(=O)₂-C₁₋₆alkyl, -S(=O)₂-haloC₁₋₆alkyl, -S(=O)₂-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -S(=O)₂-C₁₋₆alkyl, C₁₋₆alkyl substituted with -S(=O)₂-haloC₁₋₆alkyl, C₁₋₆alkyl substituted with -S(=O)₂-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -NH-S(=O)₂-C₁₋₆alkyl, C₁₋₆alkyl substituted with -NH-S(=O)₂-haloC₁₋₆alkyl or C₁₋₆alkyl
 10 substituted with -NH-S(=O)₂-NR¹⁴R¹⁵;

R⁷ and R⁸ each independently represent hydrogen, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, haloC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl or C₁₋₆alkoxyC₁₋₆alkyl;

- 15 R⁹ represents C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl containing at least one heteroatom selected from N, O or S, said C₃₋₈cycloalkyl, C₃₋₈cycloalkenyl, phenyl, naphthyl, or 3 to 12 membered monocyclic or bicyclic heterocyclyl each optionally and each independently being substituted with 1, 2, 3,
 20 4 or 5 substituents, each substituent independently being selected from =O, C₁₋₄alkyl, hydroxyl, carboxyl, hydroxyC₁₋₄alkyl, cyano, cyanoC₁₋₄alkyl, C₁₋₄alkyl-O-C(=O)-, C₁₋₄alkyl substituted with C₁₋₄alkyl-O-C(=O)-, C₁₋₄alkyl-C(=O)-, C₁₋₄alkoxyC₁₋₄alkyl wherein each C₁₋₄alkyl may optionally be substituted with one or two hydroxyl groups, halogen, haloC₁₋₄alkyl, hydroxyhaloC₁₋₄alkyl, -NR¹⁴R¹⁵, -C(=O)-NR¹⁴R¹⁵, C₁₋₄alkyl substituted with -NR¹⁴R¹⁵, C₁₋₄alkyl substituted with -C(=O)-NR¹⁴R¹⁵, C₁₋₄alkoxy, -S(=O)₂-C₁₋₄alkyl, -S(=O)₂-haloC₁₋₄alkyl, -S(=O)₂-NR¹⁴R¹⁵, C₁₋₄alkyl substituted with -S(=O)₂-NR¹⁴R¹⁵, C₁₋₄alkyl substituted with -NH-S(=O)₂-C₁₋₄alkyl, C₁₋₄alkyl substituted with -NH-S(=O)₂-haloC₁₋₄alkyl, C₁₋₄alkyl substituted with -NH-S(=O)₂-NR¹⁴R¹⁵, R¹³, -C(=O)-R¹³, C₁₋₄alkyl substituted with R¹³, phenyl optionally substituted with R¹⁶, phenylC₁₋₆alkyl wherein the phenyl is optionally substituted with R¹⁶, a 5
 25 or 6-membered aromatic monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S wherein said heterocyclyl is optionally substituted with R¹⁶;
 30 or when two of the substituents of R⁹ 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;

- 35 R¹⁰ and R¹¹ each independently represent hydrogen, carboxyl, C₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyl substituted with -NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -C(=O)-NR¹⁴R¹⁵, haloC₁₋₆alkyl,

hydroxyC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl, C₁₋₆alkoxy, C₁₋₆alkoxyC₁₋₆alkyl wherein each C₁₋₆alkyl may optionally be substituted with one or two hydroxyl groups, R⁶, C₁₋₆alkyl substituted with R⁶, -C(=O)-R⁶, -C(=O)-C₁₋₆alkyl, -C(=O)-hydroxyC₁₋₆alkyl, -C(=O)-haloC₁₋₆alkyl, -C(=O)-hydroxyhaloC₁₋₆alkyl, C₁₋₆alkyl substituted with -Si(CH₃)₃, -S(=O)₂-C₁₋₆alkyl, -S(=O)₂-haloC₁₋₆alkyl, -S(=O)₂-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -S(=O)₂-C₁₋₆alkyl, C₁₋₆alkyl substituted with -S(=O)₂-haloC₁₋₆alkyl, C₁₋₆alkyl substituted with -S(=O)₂-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with -NH-S(=O)₂-C₁₋₆alkyl, C₁₋₆alkyl substituted with -NH-S(=O)₂-haloC₁₋₆alkyl, C₁₋₆alkyl substituted with carboxyl, or C₁₋₆alkyl substituted with -NH-S(=O)₂-NR¹⁴R¹⁵;

10 R¹² represents hydrogen or C₁₋₄alkyl optionally substituted with C₁₋₄alkoxy;

R¹³ represents C₃₋₈cycloalkyl or a saturated 4 to 6-membered monocyclic heterocyclyl containing at least one heteroatom selected from N, O or S, wherein said C₃₋₈cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C₁₋₆alkyl, haloC₁₋₆alkyl, =O, cyano, -C(=O)-C₁₋₆alkyl, C₁₋₆alkoxy, or -NR¹⁴R¹⁵;

R¹⁴ and R¹⁵ each independently represent hydrogen, or haloC₁₋₄alkyl, or C₁₋₄alkyl optionally substituted with a substituent selected from hydroxyl, C₁₋₄alkoxy, amino or mono-or di(C₁₋₄alkyl)amino;

R¹⁶ represents hydroxyl, halogen, cyano, C₁₋₄alkyl, C₁₋₄alkoxy, -NR¹⁴R¹⁵ or -C(=O)NR¹⁴R¹⁵;

R¹⁸ represents hydrogen, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₁₋₄alkyl substituted with C₃₋₈cycloalkyl;

R¹⁹ represents hydrogen; C₁₋₆alkyl; C₃₋₈cycloalkyl; C₁₋₆alkyl substituted with -O-R²⁰; -(CH₂)_r-CN; -(CH₂)_r-CONR²⁰R²¹; -(CH₂)_{r1}-NR²⁰R²¹; -(CH₂)_{r1}-NR²⁰COR²¹; -(CH₂)_{r1}-NR²⁰-(CH₂)₃-SO₂-R²¹; -(CH₂)_{r1}-NH-SO₂-NR²⁰R²¹; -(CH₂)_{r1}-NR²⁰CO₂R²¹; -(CH₂)_r-SO₂NR²⁰R²¹; phenyl optionally substituted with 1, 2, 3, 4 or 5 substituents each independently selected from halogen, C₁₋₄alkyl, C₁₋₄alkyloxy, cyano or amino; a 5- or 6-membered aromatic monocyclic heterocycle containing at least one heteroatom selected from N, O or S, said heterocycle being optionally substituted with 1, 2, 3 or 4 substituents each independently selected from halogen, C₁₋₄alkyl, C₁₋₄alkyloxy, cyano or amino; wherein said C₁₋₆alkyl and C₃₋₈cycloalkyl, may be optionally substituted by one or more R²⁰ groups

R²⁰ and R²¹ independently represent hydrogen, C₁₋₆ alkyl, C₁₋₆ alkanol -(CH₂)_n-O-C₁₋₆alkyl, or when attached to a nitrogen atom R²⁰ and R²¹ can be taken together to form with the nitrogen atom to which they are attached a monocyclic saturated 4, 5 or 6-membered ring which optionally contains a further heteroatom selected from O, S or N;

5

R²² and R²³ independently represent hydrogen, C₁₋₆ alkyl, or hydroxyC₁₋₆alkyl;

m independently represents an integer equal to 0, 1 or 2;

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

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

r independently represent an integer equal to 1, 2, 3, or 4;

r1 independently represent an integer equal to 2, 3 or 4;

a N-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

15 According to a second aspect of the disclosure there is provided a pharmaceutical composition comprising a compound of formula (I-A) or (I-B) as defined above.

According to a third aspect of the disclosure there is provided a compound as defined above for use in therapy.

20

According to a fourth aspect of the disclosure there is provided a compound as defined above for use in the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.

25 According to a fifth aspect of the disclosure there is provided a compound as defined above for use in the prophylaxis or treatment of cancer.

~~According to a sixth aspect of the disclosure there is provided use of a compound as defined above for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.~~

30

According to a ~~seventh~~ sixth aspect of the disclosure there is provided use of a compound as defined above for the manufacture of a medicament for the prophylaxis or treatment of cancer.

35

According to an ~~eight~~seventh aspect of the disclosure there is provided a compound as defined above for use in the treatment of cancer wherein said compound is used in combination with one or more anticancer agents.

- 5 According to an ~~ninth~~eighth aspect of the disclosure there is provided a compound as defined above for use in 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.
- 10 According to a ~~tenth~~ninth aspect of the disclosure there is provided a product containing as first active ingredient a compound as defined above 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.
- 15 WO1999/17759, WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO 2004/030635, WO 2008/141065, WO 2011/026579, WO 2011/028947, WO 00/42026, WO2008/138878, WO2004/104003, WO2004/104002, WO2007/079999, WO2007/054556, WO2010/084152, US2005/0272736, US2005/0272728, US2007/0123494, WO2011/135376 which each disclose a series of
- 20 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

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;

5

E represents a bond, $(CR^{22}R^{23})_n$, C_{2-4} alkenediyl optionally substituted with R^{22} , C_{2-4} alkynediyl optionally substituted with R^{22} , $CO-(CR^{22}R^{23})_5$, $(CR^{22}R^{23})_5-CO$, $NR^{22}-(CR^{22}R^{23})_5$, $(CR^{22}R^{23})_5-NR^{22}$, $O-(CR^{22}R^{23})_5$, $(CR^{22}R^{23})_5-O$, $S(O)_m-(CR^{22}R^{23})_5$, $(CR^{22}R^{23})_5-S(O)_m$, $(CR^{22}R^{23})_5-CO-NR^{22}$, $(CR^{22}R^{23})_5$ or $(CR^{22}R^{23})_5-NR^{22}-CO$ $(CR^{22}R^{23})_5$;

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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 $-P(=O)(OC_{1-6}alkyl)_2$;

25

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, 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

35

with the nitrogen atom to which they are attached a monocyclic saturated 4, 5 or 6-membered ring which optionally contains a further heteroatom selected from O, S or N;

5 R^{22} and R^{23} independently represent hydrogen, C_{1-6} alkyl, or hydroxy C_{1-6} alkyl;

m independently represents an integer equal to 0, 1 or 2;

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

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

10 r independently represent an integer equal to 1, 2, 3, or 4;

r_1 independently represent an integer equal to 2, 3 or 4;

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

2. A compound according to claim 1 wherein the compound is a compound of formula
15 (I-A).

3. A compound according to claim 1 wherein the compound is a compound of formula (I-B).

20 4. A compound according to any one of the preceding claims wherein Y represents - $CR^{18}=N-OR^{19}$.

5. A compound according to any one of claims 1 to 3 wherein Y is -E-D.

25 ~~6. A compound according to claim 5 wherein E represents a bond, C_{2-4} alkenediyl, $CO-(CR^{22}R^{23})_s$, $(CR^{22}R^{23})_s-CO$, $NR^{22}-(CR^{22}R^{23})_s$, $(CR^{22}R^{23})_s-NR^{22}$, $(CR^{22}R^{23})_s-CO-NR^{22}-(CR^{22}R^{23})_s$ or $(CR^{22}R^{23})_s-NR^{22}-CO-(CR^{22}R^{23})_s$.~~

30 ~~7. A compound according to claim 6 wherein E represents a bond.~~

~~8. A compound according to any one of claims 5 to 7~~ claim 5 wherein D is optionally substituted pyrazolyl.

~~9. A compound according to any one of the preceding claims wherein R^2 is~~
35 independently selected from hydroxyl, halogen, cyano, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} alkoxy, hydroxy C_{1-4} alkyl, hydroxy C_{1-4} alkoxy, halo C_{1-4} alkoxy, C_{1-4} alkoxy C_{1-4} alkyl, R^{13} ,

C₁₋₄alkoxy substituted with R¹³, -C(=O)-R¹³, C₁₋₄alkyl substituted with NR⁷R⁸, C₁₋₄alkoxy substituted with NR⁷R⁸, -NR⁷R⁸ or -C(=O)-NR⁷R⁸.

408. A compound according to claim 9-7 wherein R² represents C₁₋₄alkoxy or halogen.

5

419. A compound according to any one of the preceding claims wherein R³ represents C₁₋₆alkyl, hydroxyC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyl substituted with -C(=O)-C₁₋₆alkyl, C₁₋₆alkoxyC₁₋₆alkyl wherein each C₁₋₆alkyl may optionally be substituted with one or two hydroxyl groups, C₁₋₆alkyl substituted with R⁹, C₁₋₆alkyl substituted with

10

-NR¹⁰R¹¹, C₁₋₆alkyl substituted with hydroxyl and -NR¹⁰R¹¹, C₁₋₆alkyl substituted with one or two halogens and -NR¹⁰R¹¹, C₁₋₆alkyl substituted with -C(=O)-O-C₁₋₆alkyl, C₁₋₆alkyl substituted with -O-C(=O)-NR¹⁰R¹¹, C₁₋₆alkyl substituted with carboxyl, C₁₋₆alkyl substituted with -NR¹²-S(=O)₂-C₁₋₆alkyl, C₁₋₆alkyl substituted with -NR¹²-S(=O)₂-NR¹⁴R¹⁵, C₁₋₆alkyl substituted with hydroxyl and R⁹, -C₁₋₆alkyl-C(R¹²)=N-O-R¹², C₁₋₆alkyl substituted with -C(=O)-NR¹⁰R¹¹, C₁₋₆alkyl substituted with -C(=O)-R⁹, C₂₋₆alkynyl substituted with R⁹, hydroxyC₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl or R¹³.

15

4210. A compound according claim 1 wherein n represents an integer equal to 2, 3 or 4; and each R² represents C₁₋₄alkoxy, for example CH₃O-, or halogen, for example fluoro; R³ represents hydroxyC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl, C₁₋₆alkyl substituted with R⁹, C₁₋₆alkyl substituted with -NR¹⁰R¹¹, C₁₋₆alkoxyC₁₋₆alkyl wherein each C₁₋₆alkyl may optionally be substituted with one or two hydroxyl groups or with -O-C(=O)-C₁₋₆alkyl, C₂₋₆alkynyl substituted with R⁹, C₂₋₆alkynyl; Y represents -E-D wherein E represents a bond and D represents pyrazolyl substituted with C₁₋₆alkyl; R¹⁰ and R¹¹ represent hydrogen or C₁₋₆alkyl; R⁹ 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.

20

25

4311. A compound according to claim 1 wherein n represents an integer equal to 2, 3 or 4; and each R² represents C₁₋₄alkoxy, for example CH₃O-, halogen, for example fluoro or chloro, hydroxyl, C₁₋₄alkyl, for example methyl, or -C(=O)-NR⁷R⁸, for example -C(=O)-NH-CH₃; R³ represents C₁₋₆alkyl, for example methyl or ethyl, hydroxyC₁₋₆alkyl, hydroxyhaloC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyl substituted with carboxyl, C₁₋₆alkyl substituted with -C(=O)-O-C₁₋₆alkyl, C₁₋₆alkyl substituted with R⁹, C₁₋₆alkyl substituted

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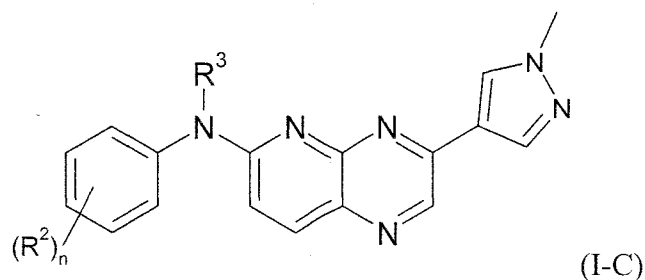
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with $-C(=O)-R^9$, C_{1-6} alkyl substituted with hydroxyl and R^9 , C_{1-6} alkyl substituted with $-NR^{10}R^{11}$, C_{1-6} alkyl substituted with $-C(=O)-NR^{10}R^{11}$, C_{1-6} alkyl substituted with $-S(=O)_2-$
 C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} 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} alkynyl substituted with R^9 ,
 5 C_{2-6} alkynyl; Y represents $-E-D$ wherein E represents a bond and D represents an
 optionally substituted monocyclic 6 membered carbocyclyl, for example phenyl, or an
 optionally substituted 5 or 6 membered monocyclic heterocyclyl, for example an
 optionally substituted 5 or 6 membered saturated or aromatic heterocyclyl, such as for
 example pyrazolyl, pyrrolyl, pyridinyl, morpholino, piperazinyl or piperdinyl, in
 10 particularly D represents pyrazolyl optionally substituted with C_{1-6} alkyl, more in
 particular D represents pyrazolyl substituted with C_{1-6} alkyl.

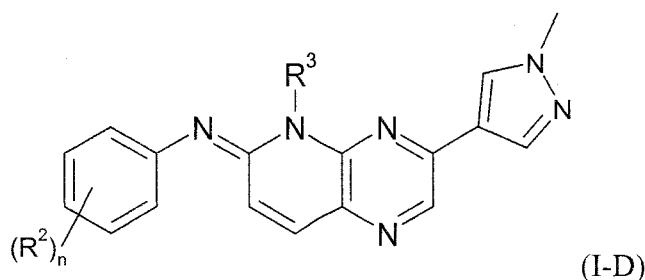
4412. A compound according to claim 1 wherein n represents an integer equal to 2, 3 or
 4; and each R^2 represents C_{1-4} alkoxy, for example CH_3O- , halogen, for example fluoro
 15 or chloro, hydroxyl, C_{1-4} alkyl, for example methyl, or $-C(=O)-NR^7R^8$, for example $-$
 $C(=O)-NH-CH_3$; R^3 represents C_{1-6} alkyl, for example methyl or ethyl, hydroxy C_{1-6} alkyl,
 hydroxyhalo C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyl substituted with carboxyl, C_{1-6} alkyl
 substituted with $-C(=O)-O-C_{1-6}$ alkyl, C_{1-6} alkyl substituted with R^9 , C_{1-6} alkyl substituted
 with $-C(=O)-R^9$, C_{1-6} alkyl substituted with hydroxyl and R^9 , C_{1-6} alkyl substituted with $-$
 20 $NR^{10}R^{11}$, C_{1-6} alkyl substituted with $-C(=O)-NR^{10}R^{11}$, C_{1-6} alkyl substituted with $-S(=O)_2-$
 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} alkynyl substituted with R^9 ,
 C_{2-6} alkynyl; Y represents $-E-D$ wherein E represents a bond and D represents an
 optionally substituted monocyclic 6 membered carbocyclyl, for example phenyl, or an
 25 optionally substituted 5 or 6 membered monocyclic heterocyclyl, for example an
 optionally substituted 5 or 6 membered saturated or aromatic heterocyclyl, such as for
 example pyrazolyl, pyrrolyl, pyridinyl, morpholino, piperazinyl or piperdinyl, in
 particularly D represents pyrazolyl optionally substituted with C_{1-6} alkyl, more in
 particular D represents pyrazolyl substituted with C_{1-6} alkyl, and R^1 represents C_{1-6} alkyl,
 30 hydroxy 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, C_{1-6} alkyl substituted with $-$
 NR^4R^5 , C_{1-6} alkyl substituted with $-S(=O)_2-C_{1-6}$ alkyl, R^6 , C_{1-6} alkyl substituted with R^6 ; R^9
 represents an optionally substituted 4 membered saturated heterocycle, an optionally
 substituted 5 membered saturated heterocycle, an optionally substituted 5 membered
 35 aromatic heterocycle, an optionally substituted 6 membered saturated heterocycle, an
 optionally substituted 6 membered aromatic heterocycle, an optionally substituted
 bicyclic heterocycle, or C_{3-6} cycloalkyl; R^{10} and

- R¹¹ represent hydrogen, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, -C(=O)-C₁₋₆alkyl, or R⁶; R⁶ represents a 4 membered monocyclic saturated heterocycle, or a 6-membered monocyclic saturated heterocyclyl, or a 5-membered monocyclic aromatic heterocycle;
- 5 R⁴ and R⁵ represent hydrogen; R⁷ and R⁸ each independently represent hydrogen or C₁₋₆alkyl, R¹⁴ and R¹⁵ each independently represent hydrogen or C₁₋₄alkyl optionally substituted with hydroxyl.

- 15 ~~15~~13. A compound according to claim 1 wherein the compound is a compound of formula (I-C) or (I-D)



or

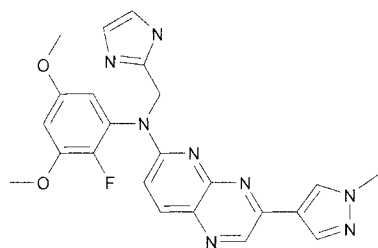


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including any tautomeric or stereochemically isomeric form thereof;
 wherein n , R^2 and R^3 are as defined in any of the preceding claims;
 a N -oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

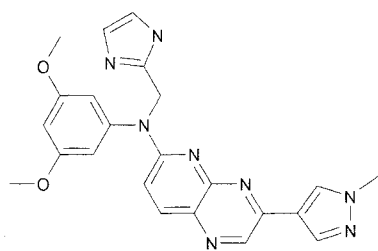
- 10 ~~46~~14. A compound according to claim ~~15~~13, wherein R^2 represents C_{1-4} alkoxy (for example CH_3O-) or halogen (for example fluoro) or hydroxyl; R^3 represents C_{1-4} alkyl (e.g. $-CH_2-$ or $-CH_2-CH_2-CH_2-$) substituted with R^9 (e.g. wherein R^9 represents an optionally substituted aromatic 5 membered monocyclic heterocyclyl, for example unsubstituted imidazolyl (e.g. imidazol-2-yl), or unsubstituted triazolyl (e.g. triazol-3-yl) or
- 15 R^9 represents an optionally substituted saturated 5 membered monocyclic heterocyclyl, for example 2-pyrrolidinonyl (e.g. 2-pyrrolidinon-5-yl or 2-pyrrolidinon-1-yl) or 2-oxazolidinonyl (e.g. 2-oxazolidinon-5-yl)) or R^3 represents C_{1-4} alkyl (e.g. $-CH_2CH_2-$) substituted with $-NR^{10}R^{11}$ wherein one of R^{10} and R^{11} represents hydrogen and the other represents C_{1-6} alkyl, for example $-CH_3$ or $-CH(CH_3)_2$ (e.g. R^3 represents $-$
- 20 $CH_2CH_2NHCH_3$ or $-CH_2CH_2NHCH(CH_3)_2$, or $-C(=O)-C_{1-6}$ alkyl, for example $-C(=O)-CH_3$ (e.g. R^3 represents $-CH_2CH_2NH-C(=O)-CH_3$), or R^6 (e.g. wherein R^6 represents an optionally substituted 4 membered saturated heterocycle (e.g. oxetanyl)); n is 2, 3, or 4.

~~47~~15. A compound according to claim 1 wherein the compound is



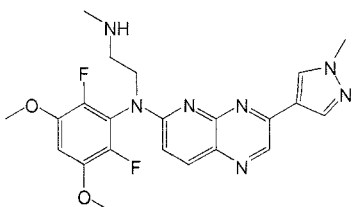
a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

~~48~~16. A compound according to claim 1 wherein the compound is



5 a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

~~49~~17. A compound according to claim 1 wherein the compound is



10 a *N*-oxide thereof, a pharmaceutically acceptable salt thereof or a solvate thereof.

~~20~~18. A compound according to any one of claims 1 to ~~49~~17 or a pharmaceutically acceptable salt or solvate thereof.

15 ~~24~~19. A pharmaceutical composition comprising a compound of formula (I-A) or (I-B) as claimed in any one of claims 1 to ~~20~~18.

~~22~~20. A compound as claimed in any one of claims 1 to ~~20~~18 for use in therapy.

20 ~~23~~21. A compound as claimed in any one of claims 1 to ~~20~~18 for use in the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.

2422. A compound as claimed in any one of claims 1 to 20-18 for use in the prophylaxis or treatment of cancer.

2523. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
5 the cancer is selected from prostate cancer, bladder cancer, lung cancer such as non-small cell lung cancer (NSCLC), breast cancer, gastric cancer, and liver cancer.

2624. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
10 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.

2725. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
15 the cancer is selected from lung cancer, in particular non-small cell lung cancer (NSCLC), squamous cell carcinoma, liver cancer, kidney cancer, breast cancer, colon cancer, colorectal cancer, prostate cancer.

2826. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
20 the cancer is multiple myeloma.

2927. A compound as claimed in claim 28-26 for use in the treatment of cancer wherein
the cancer is t(4;14) translocation positive multiple myeloma.

3028. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
25 the cancer is bladder cancer.

3129. A compound as claimed in claim 30-28 for use in the treatment of cancer wherein
the cancer is bladder cancer with a FGFR3 chromosomal translocation.

3230. A compound as claimed in claim 30-28 for use in the treatment of cancer wherein
30 the cancer is bladder cancer with a FGFR3 point mutation.

3331. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
35 the cancer is a tumour with a mutant of FGFR1, FGFR2, FGFR3 or FGFR4.

3432. A compound as claimed in claim 24-22 for use in the treatment of cancer wherein
the cancer is a tumour with a gain-of-function mutant of FGFR2 or FGFR3.

~~35~~33. A compound as claimed in claim ~~24~~22 for use in the treatment of cancer wherein the cancer is a tumour with over-expression of FGFR1.

5 ~~36. Use of a compound as claimed in any one of claims 1 to 20 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.~~

10 ~~37~~34. Use of a compound as claimed in any one of claims 1 to ~~20~~18 for the manufacture of a medicament for the prophylaxis or treatment of cancer.

~~38~~35. A compound according to any one of claims 1 to ~~20~~18 for use in the treatment of cancer wherein said compound is used in combination with one or more anticancer agents.

15 ~~39~~36. A compound according to any one of claims 1 to ~~20~~18 for use in 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.

20 ~~40~~37. A product containing as first active ingredient a compound according to any one of claims 1 to ~~20~~18 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.

25 ~~41~~38. A product of claim ~~40~~37 wherein the one or more anticancer agents comprises a kinase inhibitor.