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, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyhaloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl ~~wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups~~, hydroxyhaloC_{1-4}alkoxyC_{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:

-O-(C(R^{17})$_2$)$_p$-O-;

-X-CH=CH-; or

-X-CH=N-; wherein R^{17} represents hydrogen or fluorine, p represents 1 or 2 and X 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, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{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)$_2$-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 –NH-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^6, C_{1-6}alkyl substituted with R^6, –C(=O)-R^6, C_{1-6}alkyl substituted with –C(=O)-R^6, hydroxyC_{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^3 represents hydroxyl, C_{1-6}alkoxy, hydroxyC_{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~~, hydroxyC_{1-6}alkyl ~~optionally substituted with –O-C(=O)-C_{1-6}alkyl, hydroxyC_{2-6}alkenyl~~, hydroxyC_{2-6}alkynyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{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^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, C_{1-6}alkyl substituted with $-NR^{14}R^{15}$, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{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~~, $-S(=O)_2-C_{1-6}$alkyl, $-S(=O)_2$-haloC_{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 $-S(=O)_2$-haloC_{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-$S(=O)_2$-haloC_{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};

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, ~~cyanoC_{1-6}alkyl, hydroxyl, carboxyl, hydroxyC_{1-6}alkyl, halogen, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{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, $-S(=O)_2$-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 $-NH-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-NH-S(=O)_2$-haloC_{1-6}alkyl or C_{1-6}alkyl substituted with $-NH-S(=O)_2-NR^{14}R^{15}$~~;

R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^9 represents C_{3-8}cycloalkyl, C_{3-8}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_{3-8}cycloalkyl, C_{3-8}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_{1-4}alkyl, hydroxyl, carboxyl, hydroxyC_{1-4}alkyl, cyano, cyanoC_{1-4}alkyl, C_{1-4}alkyl-O-C(=O)-, C_{1-4}alkyl substituted with C_{1-4}alkyl-O-C(=O)-, C_{1-4}alkyl-C(=O)-, C_{1-4}alkoxyC_{1-4}alkyl ~~wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups~~, halogen, haloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkyl, $-NR^{14}R^{15}$, $-C(=O)-NR^{14}R^{15}$, C_{1-4}alkyl substituted with $-NR^{14}R^{15}$, C_{1-4}alkyl substituted with $-C(=O)-NR^{14}R^{15}$, C_{1-4}alkoxy, $-S(=O)_2-C_{1-4}$alkyl, $-S(=O)_2$-haloC_{1-4}alkyl, $-S(=O)_2-NR^{14}R^{15}$, C_{1-4}alkyl substituted with $-S(=O)_2-NR^{14}R^{15}$, C_{1-4}alkyl substituted with $-NH-S(=O)_2-C_{1-4}$alkyl, C_{1-4}alkyl substituted with $-NH-S(=O)_2$-haloC_{1-4}alkyl, C_{1-4}alkyl substituted with $-NH-S(=O)_2-NR^{14}R^{15}$, R^{13}, $-C(=O)-R^{13}$, C_{1-4}alkyl substituted with R^{13}, phenyl ~~optionally substituted with R^{16}~~, phenylC_{1-6}alkyl ~~wherein the phenyl is optionally substituted with 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 R^{16}~~;
or when two of the substituents of 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;

R^{10} and R^{11} each independently represent hydrogen, carboxyl, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with $-NR^{14}R^{15}$, C_{1-6}alkyl substituted with $-C(=O)-NR^{14}R^{15}$, haloC_{1-6}alkyl,

hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl ~~wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups~~, R^6, C_{1-6}alkyl substituted with R^6, -C(=O)-R^6, -C(=O)-C_{1-6}alkyl, –C(=O)-hydroxyC_{1-6}alkyl, -C(=O)-haloC_{1-6}alkyl,-C(=O)-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$Si(CH_3)_3$, –$S(=O)_2$-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 –NH-$S(=O)_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with –NH-$S(=O)_2$-haloC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, or C_{1-6}alkyl substituted with –NH-$S(=O)_2$-$NR^{14}R^{15}$;

R^{12} represents hydrogen or C_{1-4}alkyl ~~optionally substituted with C_{1-4}alkoxy~~;

R^{13} represents 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 C_{3-8}cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C_{1-6}alkyl, haloC_{1-6}alkyl, =O, cyano, -C(=O)-C_{1-6}alkyl, C_{1-6}alkoxy, or -$NR^{14}R^{15}$~~;

R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with ~~a substituent selected from~~ hydroxyl~~, C_{1-4}alkoxy, amino or mono-or di(C_{1-4}alkyl)amino~~;

R^{16} represents hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, -$NR^{14}R^{15}$ or –C(=O)$NR^{14}R^{15}$;

R^{18} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4}alkyl substituted with C_{3-8} cycloalkyl;

R^{19} represents hydrogen; C_{1-6} alkyl; C_{3-8} cycloalkyl; C_{1-6}alkyl substituted with -O-R^{20}; -$(CH_2)_r$-CN; -$(CH_2)_r$-$CONR^{20}R^{21}$; -$(CH_2)_{r1}$-$NR^{20}R^{21}$; -$(CH_2)_{r1}$-$NR^{20}COR^{21}$; -$(CH_2)_{r1}$-NR^{20}-$(CH_2)_s$-SO_2-R^{21}; -$(CH_2)_{r1}$-NH-SO_2-$NR^{20}R^{21}$; -$(CH_2)_{r1}$-$NR^{20}CO_2R^{21}$; -$(CH_2)_r$-$SO_2NR^{20}R^{21}$; ~~phenyl optionally substituted with 1, 2 , 3, 4 or 5 substituents each independently selected from halogen, C_{1-4}alkyl, C_{1-4}alkyloxy, 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, C_{1-4}alkyl, C_{1-4}alkyloxy, cyano or amino; wherein said C_{1-6} alkyl and C_{3-8} cycloalkyl, may be optionally substituted by one or more R^{20} groups~~

R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{1-6} alkanol $-(CH_2)_n-O-C_{1-6}$alkyl, or when attached to a nitrogen atom R^{20} and R^{21} 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~~;

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

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 or, a pharmaceutically acceptable salt thereof ~~or a solvate thereof~~.

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.

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.

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 cancer.

~~Preferred compounds of the present invention are compounds having an IC_{50} value of less than 1μM, more preferably less than 0.1 μM.~~

The ~~invention~~ disclosure 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~~example, there is provided a compound as defined herein for use in therapy, for use as a medicine. In a further ~~embodiment~~example, 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~~ disclosure may be useful in alleviating or reducing the incidence of cancer. Therefore, in a further example~~embodiment~~, there is provided a compound as defined herein for use in the prophylaxis or treatment, in particular the treatment, of cancer. In one example~~embodiment~~, the compound as defined herein is for use in the prophylaxis or treatment of FGFR-dependent cancer. In one example~~embodiment~~, the compound as defined herein is for use in the prophylaxis or treatment of cancer mediated by FGFR kinases.

Accordingly, the disclosure~~invention~~ provides *inter alia*:

- 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.
- 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 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.

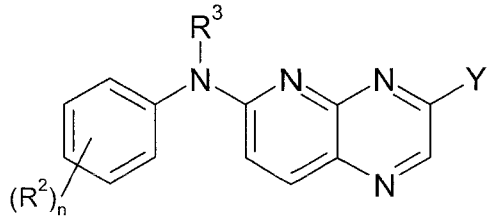
- A method of modulating a cellular process (for example cell division) by inhibiting the activity of a FGFR kinase using a compound of the formula (I) as defined herein.
- A compound of formula (I) as defined herein for use as a modulator of a cellular process (for example cell division) by inhibiting 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.
- ~~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 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 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.~~

In one ~~embodiment~~example, the disease mediated by FGFR kinases is a oncology related disease (e.g. cancer). In one example~~embodiment~~, the disease mediated by FGFR kinases is a non-oncology related disease (e.g. any disease disclosed herein excluding cancer). In

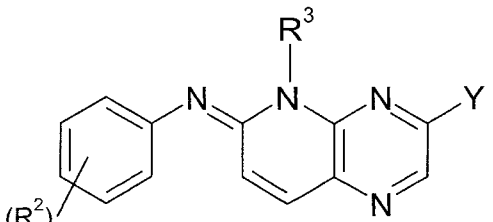
CLAIMS

1. A compound of formula (I-A) or (I-B):



(I-A)

or



(I-B)

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, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyhaloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, haloC_{1-4}alkoxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl ~~wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups~~, hydroxyhaloC_{1-4}alkoxyC_{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:

-O-(C(R^{17})$_2$)$_p$-O-;

-X-CH=CH-; or

-X-CH=N-; wherein R^{17} represents hydrogen or fluorine, p represents 1 or 2 and X 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, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{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, –$S(=O)_2$-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 –NH-$S(=O)_2$-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^6, C_{1-6}alkyl substituted with R^6, –C(=O)-R^6, C_{1-6}alkyl substituted with –C(=O)-R^6, hydroxyC_{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^3 represents hydroxyl, C_{1-6}alkoxy, hydroxyC_{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~~, hydroxyC_{1-6}alkyl ~~optionally substituted with –O-C(=O)-C_{1-6}alkyl~~, hydroxyC_{2-6}alkenyl, hydroxyC_{2-6}alkynyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{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^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, C_{1-6}alkyl substituted with -$NR^{14}R^{15}$, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{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~~, –$S(=O)_2$-C_{1-6}alkyl, –$S(=O)_2$-haloC_{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 -$S(=O)_2$-haloC_{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-$S(=O)_2$-haloC_{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};

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~~, cyanoC_{1-6}alkyl, hydroxyl, carboxyl, hydroxyC_{1-6}alkyl, halogen, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{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, –$S(=O)_2$-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 –NH-S(=O)$_2$-C_{1-6}alkyl, C_{1-6}alkyl substituted with –NH-S(=O)$_2$-haloC_{1-6}alkyl or C_{1-6}alkyl substituted with –NH-S(=O)$_2$-$NR^{14}R^{15}$~~;

R^7 and R^8 each independently represent hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl or C_{1-6}alkoxyC_{1-6}alkyl;

R^9 represents C_{3-8}cycloalkyl, C_{3-8}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_{3-8}cycloalkyl, C_{3-8}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_{1-4}alkyl, hydroxyl, carboxyl, hydroxyC_{1-4}alkyl, cyano, cyanoC_{1-4}alkyl, C_{1-4}alkyl-O-C(=O)-, C_{1-4}alkyl substituted with C_{1-4}alkyl-O-C(=O)-, C_{1-4}alkyl-C(=O)-, C_{1-4}alkoxyC_{1-4}alkyl ~~wherein each C_{1-4}alkyl may optionally be substituted with one or two hydroxyl groups~~, halogen, haloC_{1-4}alkyl, hydroxyhaloC_{1-4}alkyl, -$NR^{14}R^{15}$, -C(=O)-$NR^{14}R^{15}$, C_{1-4}alkyl substituted with -$NR^{14}R^{15}$, C_{1-4}alkyl substituted with -C(=O)-$NR^{14}R^{15}$, C_{1-4}alkoxy, –S(=O)$_2$-C_{1-4}alkyl, –S(=O)$_2$-haloC_{1-4}alkyl, –S(=O)$_2$-$NR^{14}R^{15}$, C_{1-4}alkyl substituted with –S(=O)$_2$-$NR^{14}R^{15}$, C_{1-4}alkyl substituted with –NH-S(=O)$_2$-C_{1-4}alkyl, C_{1-4}alkyl substituted with –NH-S(=O)$_2$-haloC_{1-4}alkyl, C_{1-4}alkyl substituted with –NH-S(=O)$_2$-$NR^{14}R^{15}$, R^{13}, -C(=O)-R^{13}, C_{1-4}alkyl substituted with R^{13}, phenyl ~~optionally substituted with R^{16}~~, phenylC_{1-6}alkyl ~~wherein the phenyl is optionally substituted with 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 R^{16}~~;
or when two of the substituents of 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;

R^{10} and R^{11} each independently represent hydrogen, carboxyl, C_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkyl substituted with –$NR^{14}R^{15}$, C_{1-6}alkyl substituted with –C(=O)-$NR^{14}R^{15}$, haloC_{1-6}alkyl, hydroxyC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkyl ~~wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups~~, R^6, C_{1-6}alkyl substituted with R^6, -C(=O)-R^6, -C(=O)-C_{1-6}alkyl, –C(=O)-hydroxyC_{1-6}alkyl, -C(=O)-haloC_{1-6}alkyl,-C(=O)-hydroxyhaloC_{1-6}alkyl, C_{1-6}alkyl substituted with –$Si(CH_3)_3$, –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 $-NH-S(=O)_2-C_{1-6}$alkyl, C_{1-6}alkyl substituted with $-NH-S(=O)_2-$haloC_{1-6}alkyl, C_{1-6}alkyl substituted with carboxyl, or C_{1-6}alkyl substituted with $-NH-S(=O)_2-NR^{14}R^{15}$;

R^{12} represents hydrogen or C_{1-4}alkyl ~~optionally substituted with C_{1-4}alkoxy~~;

R^{13} represents 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 C_{3-8}cycloalkyl or monocyclic heterocyclyl is optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, hydroxyl, C_{1-6}alkyl, haloC_{1-6}alkyl, =O, cyano, $-C(=O)-C_{1-6}$alkyl, C_{1-6}alkoxy, or $-NR^{14}R^{15}$~~;

R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with ~~a substituent selected from~~ hydroxyl~~, C_{1-4}alkoxy, amino or mono-or di(C_{1-4}alkyl)amino~~;

R^{16} represents hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, $-NR^{14}R^{15}$ or $-C(=O)NR^{14}R^{15}$;

R^{18} represents hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{1-4}alkyl substituted with C_{3-8} cycloalkyl;

R^{19} represents hydrogen; C_{1-6} alkyl; C_{3-8} cycloalkyl; C_{1-6}alkyl substituted with $-O-R^{20}$; $-(CH_2)_r-CN$; $-(CH_2)_r-CONR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}COR^{21}$; $-(CH_2)_{r1}-NR^{20}-(CH_2)_s-SO_2-R^{21}$; $-(CH_2)_{r1}-NH-SO_2-NR^{20}R^{21}$; $-(CH_2)_{r1}-NR^{20}CO_2R^{21}$; $-(CH_2)_r-SO_2NR^{20}R^{21}$; phenyl ~~optionally substituted with 1, 2 , 3, 4 or 5 substituents each independently selected from halogen, C_{1-4}alkyl, C_{1-4}alkyloxy, 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, C_{1-4}alkyl, C_{1-4}alkyloxy, cyano or amino; wherein said C_{1-6} alkyl and C_{3-8} cycloalkyl, may be optionally substituted by one or more R^{20} groups~~

R^{20} and R^{21} independently represent hydrogen, C_{1-6} alkyl, C_{1-6} alkanol $-(CH_2)_n-O-C_{1-6}$alkyl, or when attached to a nitrogen atom R^{20} and R^{21} 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~~;

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

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, or a pharmaceutically acceptable salt thereof ~~or a solvate thereof~~.

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

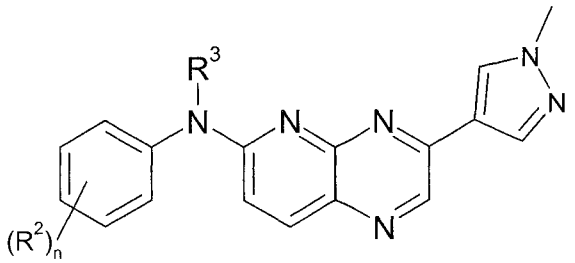
3. A compound according to claim 1 wherein the compound is a compound of formula (I-B).

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.

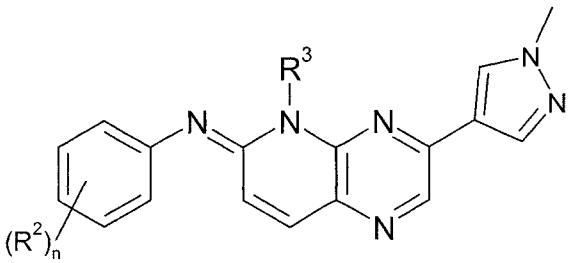
6. A compound according to claim 5 wherein D is optionally substituted pyrazolyl.

7. A compound according to any one of the preceding claims wherein R^2 is independently selected from hydroxyl, halogen, cyano, C_{1-4}alkyl, C_{2-4}alkenyl, C_{1-4}alkoxy, hydroxyC_{1-4}alkyl, hydroxyC_{1-4}alkoxy, haloC_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl, R^{13},



(I-C)

or

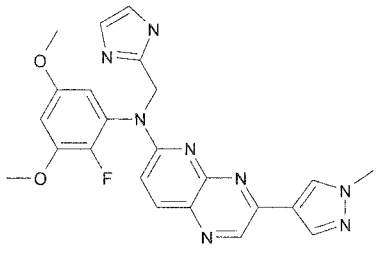


(I-D)

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 or a pharmaceutically acceptable salt thereof ~~or a solvate thereof~~.

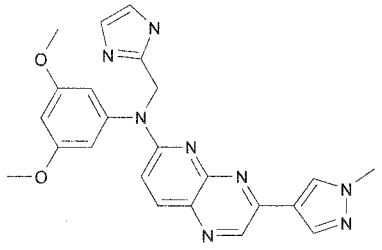
14. A compound according to claim 13, wherein R^2 represents C_{1-4}alkoxy (for example CH_3O-) or halogen (for example fluoro) or hydroxyl; R^3 represents C_{1-4}alkyl (e.g. $-CH_2-$ or $-CH_2-CH_2-CH_2-$) substituted with R^9 (e.g. wherein R^9 represents an optionally substituted aromatic 5 membered monocyclic heterocyclyl, for example unsubstituted imidazolyl (e.g. imidazol-2-yl), or unsubstituted triazolyl (e.g.triazol-3-yl) or 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 $-CH_2CH_2NHCH_3$ 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.

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



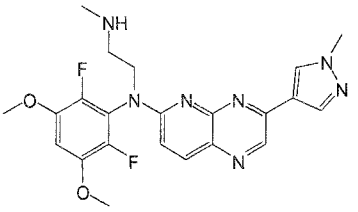
a *N*-oxide thereof or, a pharmaceutically acceptable salt thereof ~~or a solvate thereof~~.

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



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

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



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

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

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

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

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