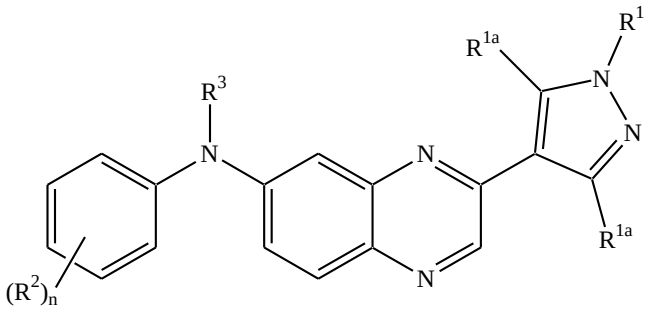
PYRAZOLYL QUINOXALINE KINASE INHIBITORS

FIELD OF THE INVENTION

The invention relates to new quinoxaline 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

According to the disclosure there is provided compounds of formula (I):



(I)

including any tautomeric or stereochemically isomeric form thereof, wherein

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

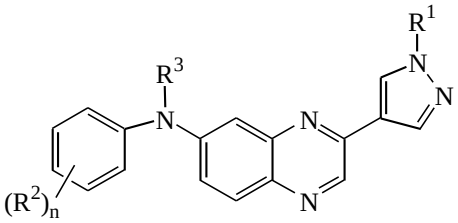
R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, hydroxyhaloC_{1-6}alkyl, cyanoC_{1-4}alkyl, C_{1-6}alkoxyC_{1-6}alkyl wherein each C_{1-6}alkyl may optionally be substituted with one or two hydroxyl groups, C_{1-6}alkyl substituted with **-**NR^4R^5, C_{1-6}alkyl 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_{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)$_2$;

each R^{1a} is independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl substituted with amino or mono- or di(C_{1-4}alkyl)amino or -NH(C_{3-8}cycloalkyl), cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro atoms;

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

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

In one example there is provided compounds of formula (I^0):



(I)

including any stereochemically isomeric form thereof, wherein

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

R^1 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, 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, C_{1-6}alkyl substituted with -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_{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)$(OC_{1-6}alkyl)_2$;

each R^2 is independently selected from 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 or -C(=O)-NR^7R^8;

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 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, -C(=O)-C_{1-6}alkyl, C_{1-6}alkoxy, or -$NR^{14}R^{15}$;

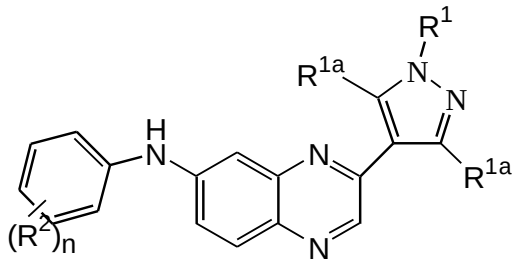
R^{14} and R^{15} each independently represent hydrogen, or haloC_{1-4}alkyl, or C_{1-4}alkyl optionally substituted with a substituent selected from hydroxyl, C_{1-4}alkoxy, amino or mono-or di(C_{1-4}alkyl)amino;

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

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

WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO 2004/030635, WO 2008/141065, WO 2011/026579, WO 2011/028947 and WO 00/42026 which each disclose a series of heterocyclyl derivatives.

According to one aspect of the disclosure, there is provided a compound of formula (VI):



(VI)

including any tautomeric or stereochemically isomeric form thereof, wherein

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

R^1 represents hydrogen, 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, C_{1-6}alkyl substituted with -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_{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 -$P(=O)(OC_{1-6}alkyl)_2$;

each R^{1a} is independently selected from hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkyl substituted with amino or mono- or di(C_{1-4}alkyl)amino or -NH(C_{3-8}cycloalkyl), cyanoC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, and C_{1-4}alkyl substituted with one or more fluoro atoms;

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;

R^4 and R^5 each independently represent hydrogen, C_{1-6}alkyl, 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$_{1-6}$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^{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, -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;

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

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. I', I'', I''', I^0, $I^{0'}$, $I^{0''}$, $I^{0'''}$), sub-groups, preferences, embodiments and examples as defined herein.

The prefix "C_{x-y}" (where x and y are integers) as used herein refers to the number of carbon atoms in a given group. Thus, a C_{1-6}alkyl group contains from 1 to 6 carbon