

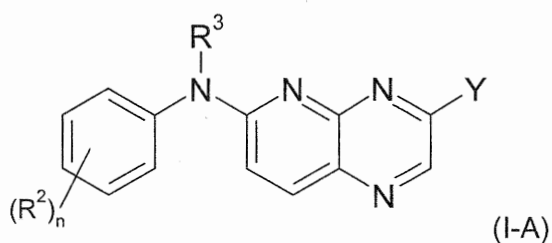
ANTICANCER PYRIDOPYRAZINES VIA THE INHIBITION OF FGFR KINASES

5 FIELD OF THE INVENTION

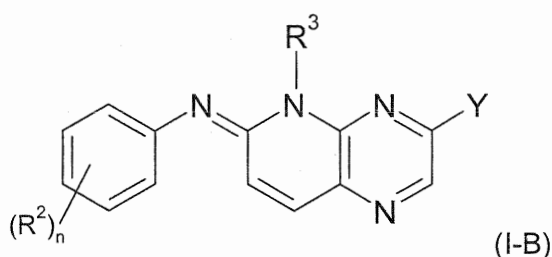
The invention relates to new pyridopyrazine derivative compounds, to pharmaceutical compositions comprising said compounds, to processes for the preparation of said compounds and to the use of said compounds in the treatment of diseases, e.g. cancer.

10 SUMMARY OF THE INVENTION

According to a first aspect of the ~~invention disclosure~~ there is provided 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
 5 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
 10 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;

~~the a~~ N-oxides thereof, the pharmaceutically acceptable salts thereof or the solvates 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 a disease state or condition mediated by a FGFR kinase.

According to a seventh 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.

According to an 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.

According to a ninth 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.

According to a tenth 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.

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 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

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 carbocycl, for example phenyl, or an optionally substituted 5 or 6 membered monocyclic heterocycl, for example an optionally substituted 5 or 6 membered saturated or aromatic heterocycl, 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.

14. A compound according to claim 13 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
 15 fluoro 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 $-NR^{10}R^{11}$, 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 carbocycl,
 20 for example phenyl, or an optionally substituted 5 or 6 membered monocyclic heterocycl, for example an optionally substituted 5 or 6 membered saturated or aromatic heterocycl, 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
 25 R^1 represents C_{1-6} alkyl, 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,
 30 an optionally substituted 5 membered 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
 35

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

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

25. A compound as claimed in claim 24 for use in the treatment of cancer wherein the cancer is selected from prostate cancer, bladder cancer, lung cancer such as NSCLC, breast cancer, gastric cancer, and liver cancer.

26. A compound as claimed in claim 24 for use in 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.

27. A compound as claimed in claim 24 for use in the treatment of cancer wherein the cancer is selected from lung cancer, in particular NSCLC, squamous cell carcinoma, liver cancer, kidney cancer, breast cancer, colon cancer, colorectal cancer, prostate cancer.

28. A compound as claimed in claim 24 for use in the treatment of cancer wherein the cancer is multiple myeloma.

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

30. A compound as claimed in claim 24 for use in the treatment of cancer wherein the cancer is bladder cancer.

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

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

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

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

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

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.

37. 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 cancer.

~~28. 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 as described herein.~~

~~29. 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 20.~~

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

39. A compound according to any one of claims 1 to 20 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.

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

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