

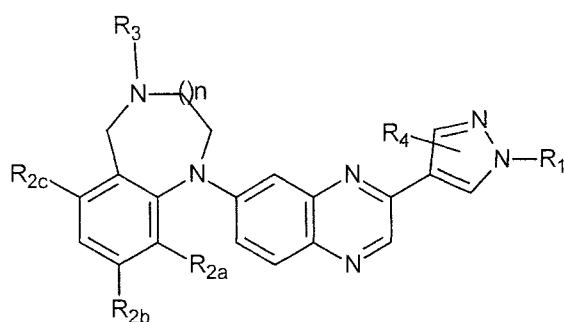
QUINOXALINE DERIVATIVES USEFUL AS FGFR KINASE MODULATORS

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 OF THE INVENTION

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



(I)

including any tautomeric or stereochemically isomeric form thereof, wherein n represents an integer equal to 1 or 2;

R₁ represents hydrogen, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyl substituted with -C(=O)NHCH₃, or C₁₋₆alkyl substituted with -S(=O)₂- C₁₋₄alkyl;

R_{2a} represents hydrogen, fluoro or chloro;

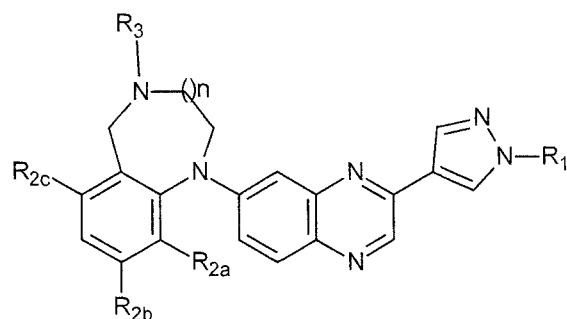
R_{2b} or R_{2c} each independently represent methoxy or hydroxyl;

R₃ represent hydrogen, C₁₋₆alkyl, C₃₋₆cycloalkyl, or C₁₋₂alkyl substituted with C₃₋₆cycloalkyl;

R₄ represents hydrogen, methyl or ethyl;

~~the a~~pharmaceutically acceptable salts thereof or the a solvates thereof.

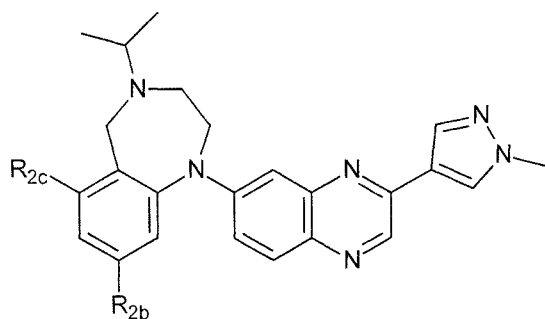
In one embodiment there is provided compounds of formula (Ia):



(Ia)

including any tautomeric or stereochemically isomeric form thereof, wherein

n represents an integer equal to 1 or 2;

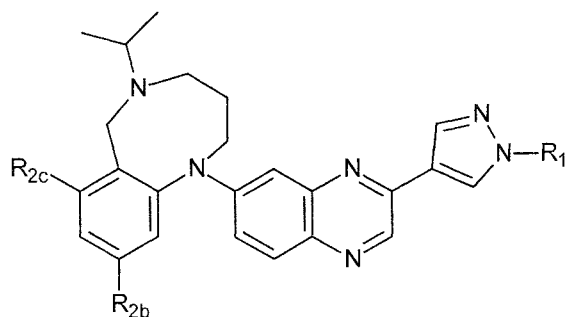


(Id)

including any tautomeric or stereochemically isomeric form thereof, wherein R_{2b} or R_{2c} each independently represent methoxy or hydroxyl; the pharmaceutically acceptable salts thereof or the solvates thereof.

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In one embodiment there is provided compounds of formula (Ie):

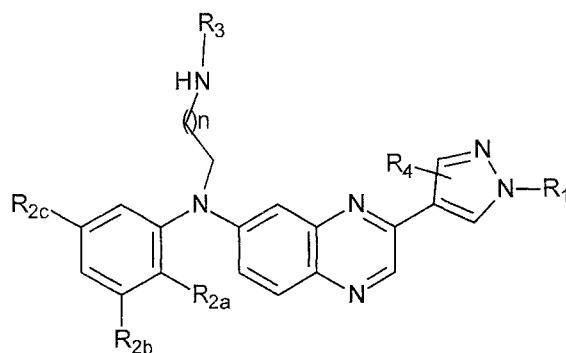


(Ie)

including any tautomeric or stereochemically isomeric form thereof, wherein R_1 represents hydrogen, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyl substituted with -
 10 $C(=O)NHCH_3$, or C_{1-6} alkyl substituted with $-S(=O)_2-C_{1-4}$ alkyl; R_{2b} or R_{2c} each independently represent methoxy or hydroxyl; the pharmaceutically acceptable salts thereof or the solvates thereof.

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In another aspect, there is provided a process for the preparation of a compound of formula (I) as defined herein, which process comprises:
reacting a compound of formula (II)



(II)

with formaldehyde in the presence of a suitable solvent, at a suitable temperature.

wherein R_1 , R_{2a} , R_{2b} , R_{2c} , R_3 , R_4 and n are as defined herein; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

In another aspect, there is provided a pharmaceutical composition comprising a compound as defined herein.

In another aspect, there is provided a compound as defined herein for use in therapy.

In another aspect, there is provided a compound as defined herein for use in the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.

In another aspect, there is provided a compound as defined herein for use in the prophylaxis or treatment of cancer.

In another aspect, there is provided a method of inhibiting a FGFR kinase, which method comprises contacting the kinase with a kinase-inhibiting compound as defined herein.

In another aspect, there is provided use of a compound 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.

In another aspect, there is provided use of a compound as defined herein for the manufacture of a medicament for the prophylaxis or treatment of cancer.

WO2006/092430, WO2008/003702, WO01/68047, WO2005/007099, WO2004/098494, WO2009/141386, WO2004/030635, WO2008/141065, WO2011/026579, WO2011/028947, WO2007/003419, WO00/42026, WO2012/154760, WO2011/047129, WO2003/076416, WO2002/096873, WO2000/055153, EP548934, US4166117, WO2011/135376, WO2012/073017, WO2013/061074, WO2013/061081, WO2013/061077, WO2013/061080, WO2013/179034, WO2013/179033, WO2014/174307 which each disclose a series of heterocyclyl derivatives.

DETAILED DESCRIPTION OF THE INVENTION

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

wherein R_1 , R_{2a} , R_{2b} , R_{2c} , R_3 , R_4 and n are as defined in claim 1; and optionally thereafter converting one compound of the formula (I) into another compound of the formula (I).

21. A pharmaceutical composition comprising a compound as defined in any one of claims 1 to 19.

22. A compound as defined in any one of claims 1 to 19 for use in therapy.

23. A compound as defined in any one of claims 1 to 19 for use in the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.

24. A compound as defined in any one of claims 1 to 19 for use in the prophylaxis or treatment of cancer.

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25. A compound for use in the treatment of cancer according to claim 24 wherein the cancer is bladder cancer, urothelial cancer, metastatic urothelial cancer, surgically unresectable urothelial cancer, breast cancer, glioblastoma, lung cancer, non small cell lung cancer, squamous cell lung cancer, adenocarcinoma of the lung, pulmonary adenocarcinoma, small cell lung cancer, ovarian cancer, endometrial cancer, cervical cancer, soft tissue sarcoma, head and neck squamous cell carcinoma, gastric cancer, oesophageal cancer, squamous cell carcinoma of the oesophagus, adenocarcinoma of the oesophagus, cholangiocarcinoma, hepatocellular carcinoma.

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26. A compound for use according to claim 25 wherein the cancer is urothelial cancer, metastatic urothelial cancer, or surgically unresectable urothelial cancer.

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27. A compound for use according to claim 25 wherein the cancer is bladder cancer.

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28. A compound for use according to claim 27 wherein the cancer is bladder cancer with a FGFR3 chromosomal translocation.

29. A compound for use according to claim 27 wherein the cancer is bladder cancer with a FGFR3 point mutation.

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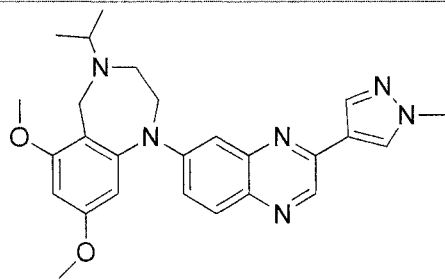
30. A compound for use in the treatment of cancer according to claim 24 wherein

(i) the cancer is a tumour with a mutant of FGFR1, FGFR2, FGFR3 or FGFR4; or(ii)
 the cancer is a tumour with a gain-of-function mutant of FGFR2 or FGFR3; or
 (iii) the cancer is a tumour with over-expression of FGFR1.

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31. A compound for use in the treatment of cancer according to claim 25 wherein the
 cancer is cholangiocarcinoma.

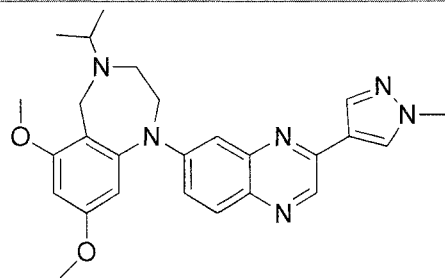
32. A compound for use in the treatment of cancer according to claim 24 wherein the



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compound is _____.

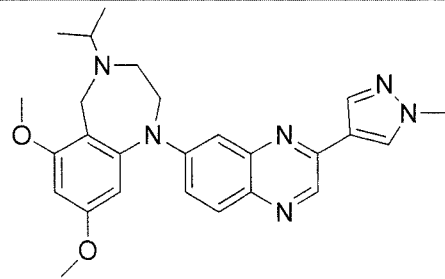
33. A compound for use in the treatment of cancer according to claim 26 wherein the



compound is _____.

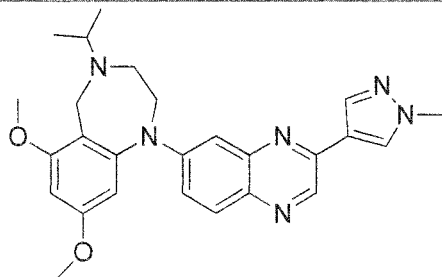
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34. A compound for use in the treatment of cancer according to claim 27 wherein the



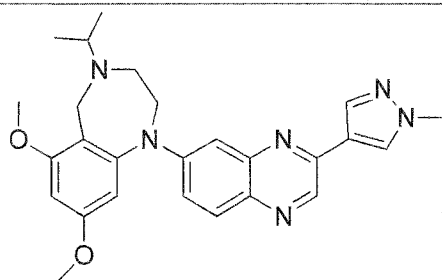
compound is _____.

35. A compound for use in the treatment of cancer according to claim 28 wherein the



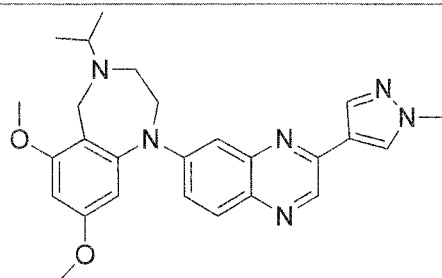
compound is

36. A compound for use in the treatment of cancer according to claim 29 wherein the



compound is

37. A compound for use in the treatment of cancer according to claim 31 wherein the



compound is

38. A method of inhibiting a FGFR kinase, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 19.

39. A method of inhibiting a FGFR kinase, which method comprises contacting the kinase with a kinase-inhibiting compound as defined in claim 18.

40. Use of a compound as defined in any one of claims 1 to 19 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a FGFR kinase.

41. Use of a compound as defined in any one of claims 1 to 19 for the manufacture of a medicament for the prophylaxis or treatment of cancer.

5 ~~27. Use of a compound as defined in any one of claims 1 to 19 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition as described herein.~~

10 ~~28. A method for the prophylaxis or treatment of a disease state or condition mediated by a EGFR kinase, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 19.~~

15 ~~29. A method for the prophylaxis or treatment of cancer, which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 19.~~