

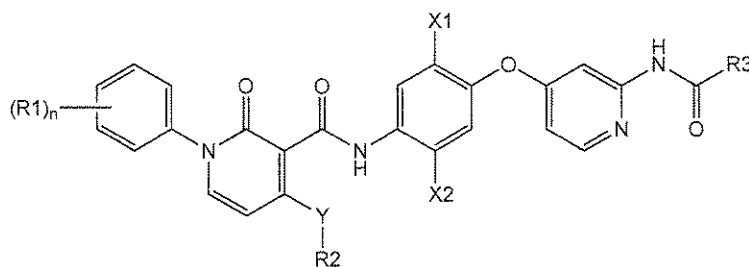
distinguish them from the essential target of interest referred to as the 'on target' of the inhibitor. A small molecule which inhibits multiple protein family members, while being potent against the target of interest, can be limited in its utility as a human therapeutic due to unintended side effects and toxicities introduced due to the consequences of inhibition of these 'off targets.'

[0008] Protein kinases constitute an important therapeutic protein family. There are approximately 518 human protein kinases. While inhibition of a desired kinase 'on target' is desirable for a human therapeutic, it is also desirable in many cases to provide a selective kinase inhibitor which does not substantially inhibit other kinase 'off targets' from within this protein family. Monoclonal antibodies are one approach to providing specific inhibitors to a specific kinase without inhibiting 'off targets.' Achieving this level of selectivity with small molecule inhibitors, however, is not as easily achievable nor as straightforward. Accordingly, there is a need for kinase inhibitors that are selective for a particular protein kinase.

Summary of the Invention

[0009] It has been unexpectedly found that compounds described herein exhibit potent and selective inhibition of c-MET kinase relative to other kinases. As such, compounds described herein find utility in the treatment of mammalian cancers and especially human cancers including, but not limited to, solid tumors, gastric cancers, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, non small cell lung cancer, breast cancers, kidney cancers, cervical carcinomas, metastasis of primary tumor sites, colonic cancers, myeloproliferative diseases, ciliopathies including polycystic kidney disease, diseases wherein the etiology or progression is dependent on c-MET kinase activity, or on the activity of oncogenic forms, aberrant fusion protein forms, and mutant forms of c-MET kinase.

[0009a] In a first aspect of the present disclosure, there is provided a compound of Formula I,



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof, wherein:

X1 is halogen;

X2 is halogen;

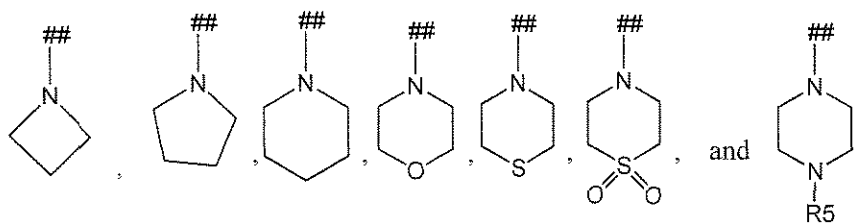
Y is O, -NH;

each R1 is individually and independently halogen, H, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, branched C3-C6 alkoxy, or cyano;

each R2 is individually and independently C1-C6 alkyl, deuterioC1-C6alkyl wherein the alkyl moiety can be partially or fully deuterated, C3-C8 branched alkyl, deuterioC3-C8 branched alkyl wherein the alkyl moiety can be partially or fully deuterated, C3-C8 cycloalkyl, C1-C6 alkoxy C1-C6 alkyl, branched C3-C6 alkoxy C1-C6 alkyl or (R7)R6N-C1-C6-alkyl;

R3 is C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, -NR6(R7), -R4, wherein each alkyl, branched or cycloalkyl may be optionally substituted with cyano, C1-C6alkoxy, or hydroxy;

each R4 is independently and individually selected from the group consisting of



and wherein the symbol (##) is the point of attachment of the R4 moiety;

R5 is C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, or C1-C6 alkoxyC1-C6 alkyl;

each R6 and R7 is individually and independently H, C1-C6 alkyl, or branched C3-C8 alkyl;

each cycloalkyl and R4 is independently and optionally substituted with -(R8)_p;

each R8 is individually and independently C1-C6 alkyl, branched C3-C8 alkyl, halogen, -(CH₂)_m-CN, -(CH₂)_m-OR6, -(CH₂)_m-NR6(R7), -(CH₂)_m-SO₂-C1-C6-alkyl, -(CH₂)_m-C(O)NR6(R7), -(CH₂)_m-C(O)-C4-C6-heterocyclyl, or -(CH₂)_m-C4-C6-heterocyclyl, wherein each alkyl or alkylene is optionally substituted with one or two C1-C6 alkyl;

each m is individually and independently 0, 1, 2, or 3;

n is 0, 1, 2, or 3;

p is 0, 1, 2, 3, or 4.

[0009b] In a second aspect of the present disclosure, there is provided a compound selected from the group consisting of N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-pivalamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-(ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-4-(methylamino)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-(ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-4-isopropoxy-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-4-isopropoxy-2-oxo-1,2-dihydropyridine-3-carboxamide, 1-(4-(2,5-difluoro-4-(1-(4-fluorophenyl)-4-(methylamino)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-2-yl)-3-methylurea, N-(4-((2-acetamidopyridin-4-yl)oxy)-5-chloro-2-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(5-chloro-2-fluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(5-chloro-4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-(3,3-dimethylurcido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, and N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-(ethoxy-d5)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009c] In a third aspect of the present disclosure, there is provided a compound N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009d] In a fourth aspect of the present disclosure, there is provided a compound N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009e] In a fifth aspect of the present disclosure, there is provided a compound N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009f] In a sixth aspect of the present disclosure, there is provided a compound N-(4-((2-(3,3-dimethylureido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009g] In a seventh aspect of the present disclosure, there is provided a compound N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.

[0009h] In an eighth aspect of the present disclosure, there is provided a use of a disclosed compound for the manufacture of a medicament for treating mammalian disease wherein the disease etiology or progression is at least partially mediated by a kinase activity, wherein the kinase is a wildtype form, a mutant oncogenic form, an aberrant fusion protein form or a polymorph, wherein the medicament is to be administered to a mammal in need thereof.

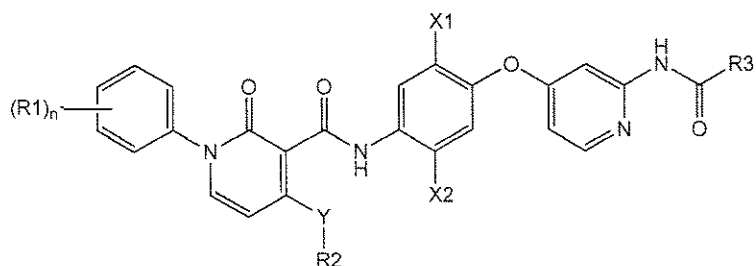
[0009i] In a ninth aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a disclosed compound and a pharmaceutically acceptable carrier.

[0009j] In a tenth aspect of the present disclosure, there is provided a use of a disclosed compound for the manufacture of a medicament for treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, or diseases characterized

by angiogenesis, such as solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, leukemias, papillary thyroid carcinoma, non-small cell lung cancer, mesothelioma, hypereosinophilic syndrome, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including retinopathies, diabetic retinopathy, age-related macular degeneration, or hypereosinophilic syndrome, wherein the medicament is to be administered to a patient in need thereof.

[0009k] In an eleventh aspect of the present disclosure, there is provided a use of a disclosed compound for the manufacture of a medicament for treating ciliopathies or polycystic kidney disease, wherein the medicament is to be administered to a patient in need thereof.

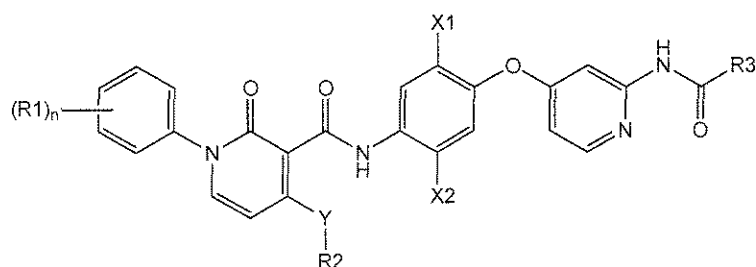
[0010] Specifically, pyridone amide compounds of **Formula I** are disclosed which find utility in the treatment of diseases as described above.



Formula I

wherein R1, R2, R3, m, X1, X2, and Y are as defined below for Formula I.

[0011] Accordingly, in one embodiment, the present ~~disclosure~~^{invention} comprises a compound of **Formula I**,



Formula I

or a pharmaceutically acceptable salt, hydrate, solvate, enantiomer, stereoisomer or tautomer thereof, wherein:

X1 is halogen;

X2 is halogen;

Y is O, -NH;

each R1 is individually and independently halogen, H, C1-C6 alkyl, C3-C8 branched alkyl, C3-C8 cycloalkyl, C1-C6 alkoxy, branched C3-C6 alkoxy, or cyano;

each R2 is individually and independently C1-C6 alkyl, deuterioC1-C6alkyl wherein the alkyl moiety can be partially or fully deuterated, C3-C8 branched alkyl, deuterioC3-C8 branched alkyl wherein the alkyl moiety can be partially or fully deuterated, C3-C8 cycloalkyl, C1-C6 alkoxy C1-C6 alkyl, branched C3-C6 alkoxy C1-C6 alkyl or (R7)R6N-C1-C6-alkyl;

[0050] In some embodiments, any one or more hydrogens of the alkyl substituents of R1, R2, R3, R5, R6, and R7 may be substituted with deuterium.

[0051] In some embodiments, the ~~invention~~present disclosure comprises a compound selected from the group consisting of N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-pivalamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-(ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-4-(methylamino)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-4-(ethylamino)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(4-((2-acetamidopyridin-4-yl)oxy)-2,5-difluorophenyl)-1-(4-fluorophenyl)-4-isopropoxy-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-1-(4-fluorophenyl)-4-isopropoxy-2-oxo-1,2-dihydropyridine-3-carboxamide, 1-(4-(2,5-difluoro-4-(1-(4-fluorophenyl)-4-(methylamino)-2-oxo-1,2-dihydropyridine-3-carboxamido)phenoxy)pyridin-2-yl)-3-methylurea, N-(4-((2-acetamidopyridin-4-yl)oxy)-5-chloro-2-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, N-(5-chloro-2-fluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,

N-(5-chloro-4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2-fluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
N-(4-((2-(3,3-dimethylureido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide,
or N-(2,5-difluoro-4-((2-propionamidopyridin-4-yl)oxy)phenyl)-4-(ethoxy-d5)-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, and pharmaceutically acceptable salts, solvates, hydrates and tautomers thereof.

[0052] In certain embodiments, the ~~invention~~present disclosure comprises a method of treating mammalian disease wherein the disease etiology or progression is at least partially mediated by a kinase activity, wherein the kinase is a wildtype form, a mutant oncogenic form, an aberrant fusion protein form or a polymorph, the method comprising administering to a mammal in need thereof an effective amount of a compound of formula I.

[0053] In certain embodiments, the disease etiology or progression is at least partially mediated by the kinase activity of c-MET, mutant oncogenic forms, aberrant fusion proteins, or polymorphs thereof.

[0054] In other embodiments, the ~~present invention~~disclosure comprises a pharmaceutical composition, comprising a compound of formula I and a pharmaceutically acceptable carrier.

[0055] In certain embodiments, the composition comprises an additive selected from adjuvants, excipients, diluents, or stabilizers.

[0056] In some embodiments, the ~~invention~~present disclosure includes a method of treating cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, or diseases characterized by angiogenesis, such as solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases, chronic myelogenous leukemia, leukemias, papillary thyroid carcinoma, non-small cell lung cancer, mesothelioma, hypereosinophilic syndrome, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including retinopathies, diabetic retinopathy, age-related macular degeneration, hypereosinophilic

syndrome, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, mastocytosis, or mast cell leukemia, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0057] In some embodiments, the ~~invention~~present disclosure includes a method of treating ciliopathies or polycystic kidney disease, the method comprising administering to a patient in need thereof an effective amount of a compound of formula I.

[0058] In certain embodiments of the present methods, the compound is administered orally, parenterally, by inhalation, or subcutaneously.

[0059] The details of the ~~invention~~present disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present ~~invention~~disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the ~~invention~~present disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this ~~invention~~present disclosure belongs.

Detailed Description of the Invention

[0060] Throughout this disclosure, various patents, patent applications and publications are referenced. The disclosures of these patents, patent applications and publications in their entireties are incorporated into this disclosure by reference in order to more fully describe the state of the art as known to those skilled therein as of the date of this disclosure. This disclosure will govern in the instance that there is any inconsistency between the patents, patent applications and publications and this disclosure.

[0061] For convenience, certain terms employed in the specification, examples and claims are collected here. Unless defined otherwise, all technical and scientific terms used in this disclosure have the same meanings as commonly understood by one of ordinary skill in the art to

19. The compound N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.
20. The compound N-(4-((2-(3,3-dimethylureido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.
21. The compound N-(2,5-difluoro-4-((2-isobutyramidopyridin-4-yl)oxy)phenyl)-4-ethoxy-1-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3-carboxamide, or a pharmaceutically acceptable salt, solvate, hydrate or tautomer thereof.
22. Use of a compound of claim 1 for the manufacture of a medicament for~~A method of treating~~ mammalian disease wherein the disease etiology or progression is at least partially mediated by a kinase activity, wherein the kinase is a wildtype form, a mutant oncogenic form, an aberrant fusion protein form or a polymorph, wherein the medicament is to be administered~~method comprising administering to a mammal in need thereof an effective amount of a compound of claim 1.~~
23. ~~The method use~~ of claim 22, wherein the disease etiology or progression is at least partially mediated by the kinase activity of c-MET, mutant oncogenic forms, aberrant fusion proteins, or polymorphs thereof.
24. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.
25. The composition of claim 24, further comprising an additive selected from adjuvants, excipients, diluents, or stabilizers.
26. Use of a compound of claim 1 for the manufacture of a medicament for~~A method of treating~~ cancer, gastrointestinal stromal tumors, hyperproliferative diseases, metabolic diseases, neurodegenerative diseases, or diseases characterized by angiogenesis, such as solid tumors, melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, cervical carcinomas, metastasis of primary tumor sites, myeloproliferative diseases,

leukemias, papillary thyroid carcinoma, non-small cell lung cancer, mesothelioma, hypereosinophilic syndrome, colonic cancers, ocular diseases characterized by hyperproliferation leading to blindness including retinopathies, diabetic retinopathy, age-related macular degeneration, or hypereosinophilic syndrome, wherein the method medicament is to be administered comprising administering to a patient in need thereof an effective amount of a compound of claim 1.

27. Use of a compound of claim 1 for the manufacture of a medicament for~~A method of~~ treating ciliopathies or polycystic kidney disease, wherein the medicament is to be administered~~method comprising administering to a patient in need thereof an effective amount of a compound of claims 1.~~
28. ~~The method~~use of claims 22, 23, 26 or 27, wherein the ~~compound~~medicament is to be administered orally, parenterally, by inhalation, or subcutaneously.