



(51) International Patent Classification:

A61K 31/517 (2006.01)

(21) International Application Number:

PCT/US2024/038448

(22) International Filing Date:

18 July 2024 (18.07.2024)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/514,214 18 July 2023 (18.07.2023) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: METHOD OF ENHANCED ABSORPTION OF QUINOXALINE TYPE III RECEPTOR TYROSINE KINASE INHIBITORS

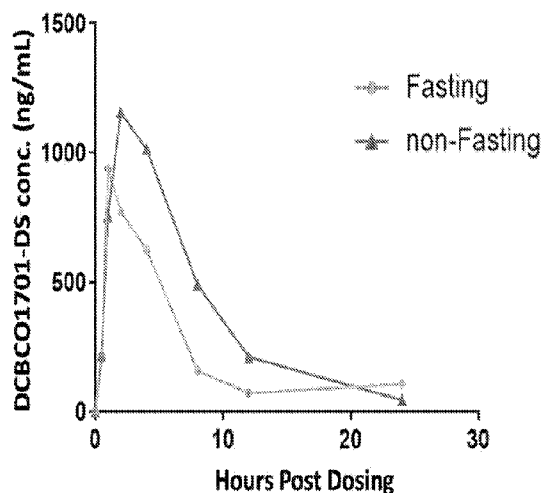
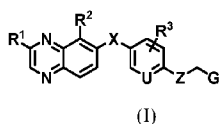


FIG. 2

(57) Abstract: A method of improving pharmacokinetics of a compound of formula (I) is provided, including administering a medicament including the compound of formula (I) to a subject in need thereof in a non-fasting state, wherein the compound of formula (I) has a structure of: Formula (I) or a stereoisomer, tautomer, prodrug, or pharmaceutically acceptable salt thereof. The compound of formula (I) can be used in the treatments of diseases or conditions mediated by CSF-1R, PDGFR, FLT3 or c-KIT kinases. Such diseases or conditions may include cancers, autoimmune diseases, and bone resorptive diseases.

METHOD OF ENHANCED ABSORPTION OF QUINOXALINE TYPE III RECEPTOR TYROSINE KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present disclosure claims priority to U.S. Provisional Application Serial No. 63/514,214 filed on July 18, 2023, the entirety of which is hereby incorporated by reference herein for all purposes.

FIELD OF INVENTION

[0002] The present invention relates to a method to deliver quinoxaline compounds which can function as type III receptor tyrosine kinase inhibitors into animals and/or human.

BACKGROUND OF INVENTION

[0003] Receptor tyrosine kinases (RTKs) are a sub-family of protein kinases Type III RTKs, including Colony-stimulating factor-1 receptor (CSF-1R), Platelet-derived growth factor receptor α (PDGFR α), PDGFR β , Fms-like tyrosine kinase 3 (FLT3) and c-KIT, are implicated in various proliferative, inflammatory, and autoimmune diseases. Small molecule inhibitors of type III RTKs provide a rational approach to treatments of these diseases.

[0004] CSF-1R, also known as macrophage colony-stimulating factor receptor (M-CSFR), is a receptor for the macrophage colony stimulating factor (M-CSF or CSF-1). Binding of M-CSF to its receptor activates signal transduction pathways, including PI3K/Akt and MAPK pathways, resulting in proliferation, survival, motility, and differentiation of cells of the monocyte/macrophage lineage, include the microglia. Elevated expression or activation of CSF-1R and/or its ligand have been found in a variety of cancers and elevated levels of M-CSF is associated with poor prognosis in certain cancers. M-CSF is one of several cytokines

implicated in the recruitment of tumor-associated macrophages (TAMs) that contribute to tumor angiogenesis and tumor progression to metastasis. Activation of CSF-1R also leads to proliferation and differentiation of osteoclast precursors, thereby mediating the process of bone resorption. Inhibition of CSF-1R therefore provides treatments of cancers, especially cancer invasion, angiogenesis, metastasis, immunotolerance, and bone metastases. Because of its role in osteoclast biology, CSF-1R is also an important therapeutic target for osteoporosis, inflammatory arthritis, and other inflammatory bone erosion.

[0005] Receptor tyrosine kinase of the Platelet growth factor receptor (PDGFR) kinases are implicated in various proliferative disorders, such as gliomas, sarcomas, chronic myelomonocytic leukemia (CML), and gastrointestinal, making them potential targets for anti-tumor therapy.

[0006] FLT3 plays an important role in the proliferation and differentiation of hematopoietic stem cells. More than a dozen FLT3 inhibitors are being developed, some of which have shown promising clinical effects against acute myeloid leukemia (AML). FLT3 receptor is also expressed in dendritic cell progenitors and inhibition of FLT3 down-regulates dendritic cell (DC)-mediated inflammatory and autoimmune responses.

[0007] c-KIT (or stem cell growth factor receptor (SCFR)) is another member of the PDGFR family, and c-KIT mutations are associated with gastrointestinal stromal tumors (GIST), mast cell/myeloid leukemia, seminomas/dysgerminomas, and melanomas. Gleevec[®] gained FDA-approval for c-KIT-mediated GIST in 2002.

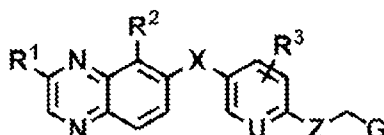
[0008] Although various tyrosine kinase inhibitors are shown to be useful therapeutics, there is still a need for type III kinase inhibitors.

SUMMARY OF INVENTION

[0009] The present invention relates to methods of delivery of quinoxaline compounds as activity inhibitors of kinases, such as CSF-1R, PDGFR, FLT-3 and/or c-KIT, into animals

and/or human for treating diseases mediated by such kinases, such as cancers, autoimmune diseases, bone resorptive diseases, and neurodegenerative diseases.

[0010] The present invention provides a method of improving pharmacokinetics of a compound of formula (I), including administering a medicament including the compound of formula (I), or a stereoisomer, tautomer, prodrug or pharmaceutically acceptable salt thereof to a subject in need thereof in a non-fasting state,



Formula (I)

wherein X, U, Z, G, R¹, R² and R³ are as defined herein.

[0011] Preferably, the compound of formula (I) is administered orally.

[0012] Preferably, the improving pharmacokinetics includes increasing the maximum plasma concentration (C_{max}) and/or bioavailability (AUC).

[0013] Preferably, the medicament further includes a carrier, diluent or excipient.

[0014] Preferably, the excipient includes a surfactant, a binder, a disintegrant and/or a lubricant.

[0015] Efficient delivery of drug compounds into the animal and/or the human body is critical to the therapeutic applications of the compounds. The better the delivery, the more therapeutic effects are expected from the drug compounds in the therapeutic treatments for the targeted diseases.

[0016] Embodiments of the invention are based on unexpected findings that delivery of said quinoxaline compounds that have low solubility in water but have high solubility in acidic buffers can be delivered more efficiently into biological bodies after/with food ingestion.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** illustrates pH changes in stomach before/after a meal in the prior art.

[0018] **FIG. 2** illustrates DCBCO1701-DS concentrations time course in blood samples of study 2 in accordance with an embodiment of the present invention.

[0019] **FIGs. 3A and 3B** illustrate pharmacokinetics of EI-1071 tablet in Beagle dogs about $C_{\max}$ and AUC, respectively, in accordance with an embodiment of the present invention.

DETAILED DESCRIPTION

[0020] While enumerated embodiments will be described, it will be understood that they are not intended to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

[0021] Definitions

[0022] For convenience, certain terms employed in the context of the present disclosure are collected here. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of the ordinary skill in the art to which this invention belongs.

[0023] The term “non-fasting” or “postprandial” as used herein means that the animals, such as dogs, receive a nutritionally balanced daily ration during the pre-test period and the whole test period.

[0024] The term “AUC” means “Area Under the Curve” and is used in its normal meaning, *i.e.* as the area under the plasma concentration-time curve from 0 to 24 hours, where the dosage form has been administered orally to animals, such as rats and dogs (beagle), under fasting or non-fasting conditions in the embodiments. The AUC has units of concentration times time. Once the experimental concentration-time points have been determined, the AUC may conveniently be calculated, *e.g.*, by a computer program or by the trapezoidal method.

[0025] As used herein, improved pharmacokinetics refers to improved $C_{\max}$ (the maximum plasma level), $T_{\max}$ (time to maximum plasma level), AUC or plasma half-life of the drug, or improved level of the drug in blood, liver or another tissue. Non-limiting examples of drugs whose pharmacokinetics can be improved by the compound of formula (I). In general, the amount of the compound of formula (I) in the tablet is sufficient to boost the *in vivo* pharmacokinetics of the co-formulated drug(s).

[0026] The term “alkyl” refers to a straight or branched monovalent saturated hydrocarbon containing, unless otherwise stated, 1-20 carbon atoms. The numerical ranges in this description are intended to include any number(s) in the defined range, as if the individual numbers have been separately disclosed. For example, an alkyl group of 1-20 carbons would include C_1 , C_2 , ... C_{20} , as well as C_1 - C_{20} , C_1 - C_{15} , C_1 - C_{10} , C_1 - C_6 , C_1 - C_4 , etc. Examples of alkyl include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *t*-butyl.

[0027] The term “alkenyl” refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (*e.g.*, C_2 - C_{10}) and one or more double bonds. Examples of alkenyl include ethenyl, propenyl, allyl, and 1,4-butadienyl.

[0028] The term “alkynyl” refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (*e.g.*, C_2 - C_{10}) and one or more triple bonds. Examples of alkynyl include ethynyl, 1-propynyl, 1- and 2-butynyl, and 1-methyl-2-butynyl.

[0029] The term “alkoxy” refers to an -O-alkyl radical, wherein the alkyl portion is as defined above. Examples of alkoxy include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy, *i*-butoxy, *s*-butoxy, and *t*-butoxy.

[0030] The term “acyloxy” refers to an -O-C(O)-R radical in which R can be H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl as defined herein.

[0031] The term “amino” refers to NH_2 . The term “alkylamino” refers to an $-\text{N}(\text{R})$ -alkyl radical, in which “alkyl” is as defined above and R can be H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl.

[0032] The term “cycloalkyl” refers to a monovalent saturated hydrocarbon ring system having 3 to 30 carbon atoms (*e.g.*, $\text{C}_3\text{-C}_6$ or $\text{C}_3\text{-C}_{12}$). Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and adamantanyl.

[0033] The term “cycloalkenyl” refers to a monovalent non-aromatic hydrocarbon ring system having 3 to 30 carbons (*e.g.*, $\text{C}_3\text{-C}_6$ or $\text{C}_3\text{-C}_{12}$) and one or more double bonds. Examples include cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[0034] The term “heterocycloalkyl” refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heterocycloalkyl groups include piperazinyl, pyrrolidinyl, piperidinyl, dioxanyl, morpholinyl, and tetrahydrofuranyl.

[0035] The term “heterocycloalkenyl” refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se) and one or more double bonds.

[0036] The term “aryl” refers to a monovalent 6-carbon monocyclic, 10-carbon bicyclic, or 14-carbon tricyclic aromatic ring system. Examples of aryl groups include phenyl, naphthyl, and anthracenyl.

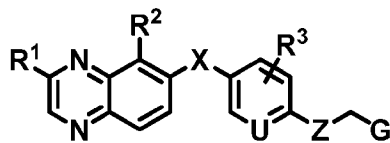
[0037] The term “aryloxy” refers to an $-\text{O}$ -aryl, wherein “aryl” is as defined above. The term “arylamino” refers to an $-\text{N}(\text{R})$ -aryl, wherein “aryl” is as defined above and R can be H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl. The term “heteroaryl” refers to a monovalent aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heteroaryl groups include pyridyl, furyl, imidazolyl, benzimidazolyl, pyrimidinyl, thienyl, quinolinyl, indolyl, thiazolyl, pyrrolyl,

isoquinolinyl, purinyl, oxazolyl, pyrazolyl, and carbazolyl. In all these terms, “aryl” portion is as defined above.

[0038] The above-described alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, amino, alkylamino, arylamino, alkoxy, aryloxy, aryl, and heteroaryl may be substituted or unsubstituted moieties. Possible substituents on amino, alkylamino, arylamino, alkoxy, aryloxy, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, and heteroaryl include C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₂₀ cycloalkyl, C₃-C₂₀ cycloalkenyl, C₁-C₂₀ heterocycloalkyl, C₁-C₂₀ heterocycloalkenyl, C₁-C₁₀ alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C₁-C₁₀ alkylamino, arylamino, hydroxy, halo, oxo (O=), thioxo (S=), thio, C₁-C₁₀ alkylthio, arylthio, C₁-C₁₀ alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, mercapto, amido, thioureido, thiocyanato, sulfonamido, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carbamido, carbamyl (-C(O)NH₂), carboxyl (-COOH), and carboxylic ester. Possible substituents on alkyl, alkenyl, or alkynyl include all of the above-recited substituents except C₁-C₁₀ alkyl. Cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl can also be fused with each other.

[0039] Embodiments of the invention relate to a method of improving pharmacokinetics of a compound of formula (I), comprising administering a medicament comprising the compound of formula (I) to a subject in need thereof in a non-fasting state,

wherein the compound of formula (I) has a structure of:



Formula (I)

or a stereoisomer, tautomer, prodrug, or pharmaceutically acceptable salt thereof,

wherein:

X is selected from the group consisting of CR⁴R⁵, NR⁶, O and S;

Z is selected from the group consisting of $\text{-NR}^7\text{-}$ and -O- ;

U is N or CR^8 ;

G is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycle, alkene and alkyne;

R^1 is selected from the group consisting of hydrogen, deuterium, halogen, amino, hydroxyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{C}_3\text{-C}_6$ cycloalkyl, $\text{C}_5\text{-C}_6$ cycloalkenyl, $\text{C}_1\text{-C}_6$ alkylamino, $\text{C}_1\text{-C}_6$ dialkylamino, $\text{C}_3\text{-C}_6$ cycloalkylamino, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_3\text{-C}_6$ cycloalkoxy, aryl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkylamino, dialkylamino, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylamino, cycloalkoxy, heterocyclyl, aryl and heteroaryl are optionally substituted with halogen, amino, hydroxyl, cyano, nitro, acyl, acyloxy, $\text{C}_1\text{-C}_4$ alkyl, hydroxyl $\text{C}_1\text{-C}_4$ alkyl, alkoxy $\text{C}_1\text{-C}_4$ alkyl, acyloxy $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $\text{C}_1\text{-C}_4$ dialkylamino, $\text{C}_3\text{-C}_6$ cycloalkyl, a 3-to-6 membered heterocyclyl, aryl, and a 5-to-6 membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, $\text{C}_1\text{-C}_6$ alkylamino, $\text{C}_1\text{-C}_6$ dialkylamino, $\text{C}_1\text{-C}_6$ alkoxy, carboxylic acid, $\text{C}_1\text{-C}_6$ alkyl carbonyl, $\text{C}_2\text{-C}_6$ alkenyl carbonyl, $\text{C}_1\text{-C}_6$ alkoxy carbonyl, amino carbonyl, $\text{C}_1\text{-C}_6$ alkylamino carbonyl and $\text{C}_1\text{-C}_6$ dialkylamino carbonyl;

R^3 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, $\text{C}_1\text{-C}_6$ alkylamino and $\text{C}_1\text{-C}_6$ dialkylamino;

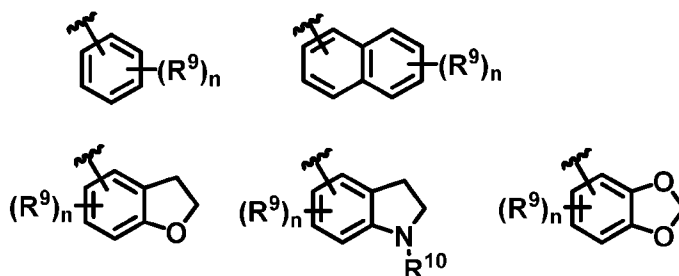
R^4 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_1\text{-C}_6$ alkoxy and aryl;

R^5 is selected from the group consisting of hydrogen, deuterium, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ haloalkyl;

R^6 is selected from the group consisting of hydrogen, $\text{C}_1\text{-C}_6$ alkyl and $\text{C}_1\text{-C}_6$ haloalkyl;

R^7 is selected from the group consisting of hydrogen, C₁-C₆ alkyl and C₁-C₆ haloalkyl; and
 R^8 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, C₁-C₆alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylamino and C₁-C₆ dialkylamino.

[0040] In some embodiments, G in a compound of Formula 1 may be selected from:



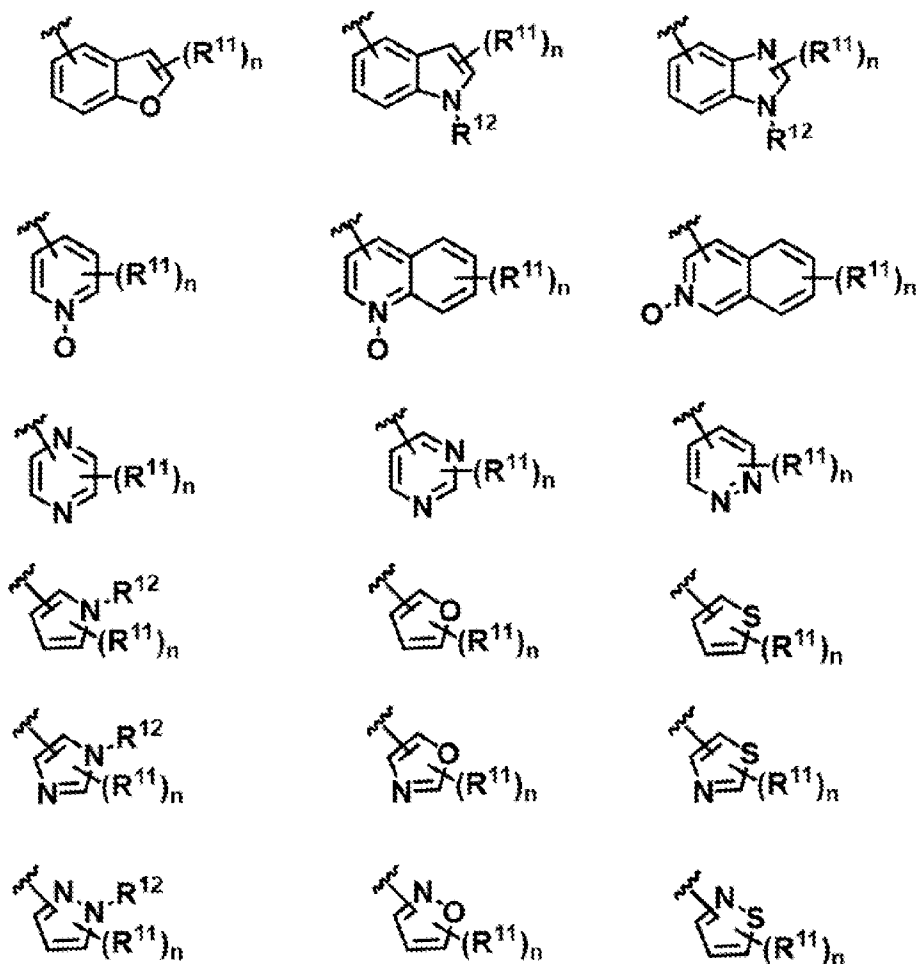
wherein

R^9 is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, C₁-C₆ alkoxy, C₁-C₆ alkoxy C₁-C₆ alkyl, C₁-C₆ dialkylamino, C₁-C₆ alkoxy, carboxylic acid, carbonyl C₁-C₆ alkoxy, carbonyl C₁-C₆ alkylamino, and carbonyl C₁-C₆ dialkylamino;

R^{10} is selected from the group consisting of hydrogen, C₁-C₆ alkyl and C₁-C₆ haloalkyl;
 and

each n is individually and independently 0, 1, 2, or 3.

[0041] In some embodiments, G in a compound of Formula 1 may be selected from:

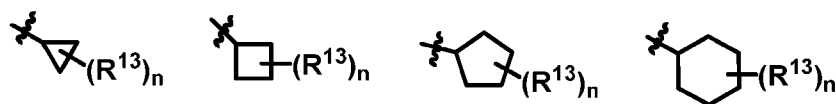


wherein

R^{11} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_6 alkyl, carboxylic acid, carbonyl C_1 - C_6 alkoxy, carbonyl C_1 - C_6 alkylamino and carbonyl C_1 - C_6 dialkylamino;

R^{12} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and each n is individually and independently 0, 1, 2, or 3.

[0042] In some embodiments, G in a compound of Formula 1 may be selected from:



wherein

R^{13} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl; and

each n is individually and independently 0, 1, 2, or 3.

[0043] In some embodiments, G in a compound of Formula 1 may be selected from:



wherein

R^{14} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl;

Q is selected from NR^{15} , O , and S , wherein R^{15} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and

each n is individually and independently 0, 1, 2, or 3.

[0044] In some embodiments, G in a compound of Formula 1 may be selected from:

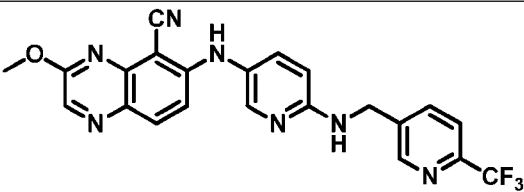
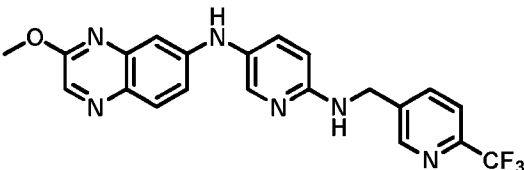
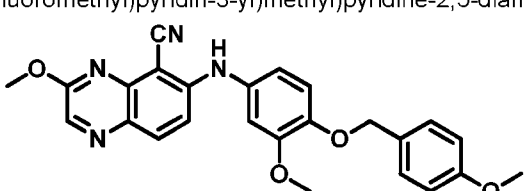
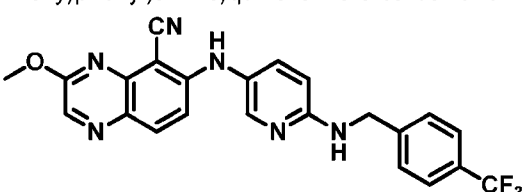
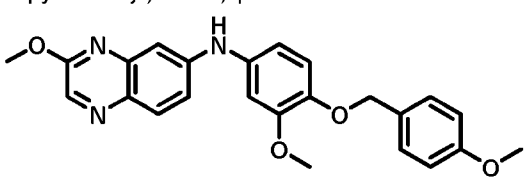


wherein R^{16} is selected from the group consisting of hydrogen, deuterium, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, 3-to-6 membered heterocyclyl, 5-to-6 membered heteroaryl, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl..

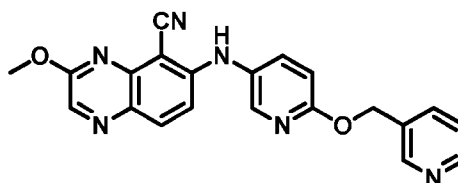
[0045] One skilled in the art would appreciate that in the above formula (I), all possible combinations or permutations of different substituents are within the scope of the invention.

Exemplary quinoxaline compounds of the present invention are listed in **Table 1**.

[0046] **Table 1.** Quinoxaline compounds

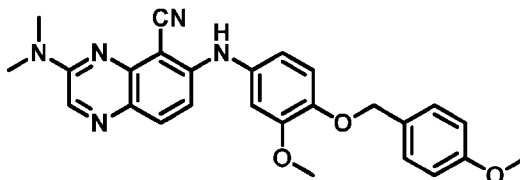
Compound No.	Structure
1	 3-methoxy-6-((6-(((6-(trifluoromethyl)pyridin-3-yl)methyl)amino)pyridin-3-yl)amino)quinoxaline-5-carbonitrile
2	 <i>N</i>⁵-(3-methoxyquinoxalin-6-yl)-<i>N</i>²-((6-(trifluoromethyl)pyridin-3-yl)methyl)pyridine-2,5-diamine
3	 3-methoxy-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile
4	 3-methoxy-6-((6-((4-(trifluoromethyl)benzyl)amino)pyridin-3-yl)amino)quinoxaline-5-carbonitrile
5	 3-methoxy-<i>N</i>-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)quinoxalin-6-amine

6



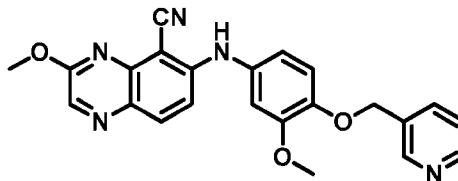
3-methoxy-6-((6-(pyridin-3-ylmethoxy) pyridin-3-yl)amino)quinoxaline-5-carbonitrile

7



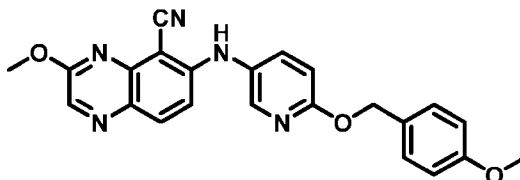
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8



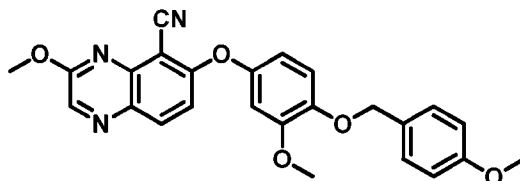
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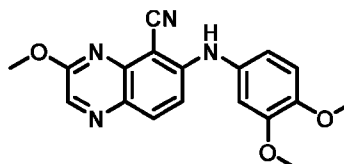
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10



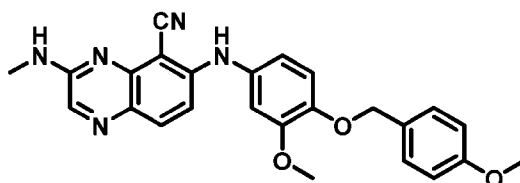
3-methoxy-6-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)quinoxaline-5-carbonitrile

11



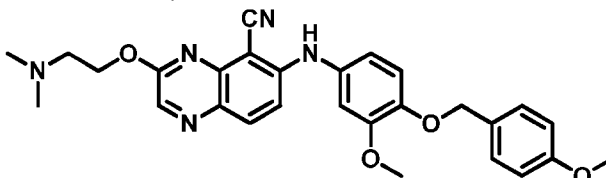
6-((3,4-dimethoxyphenyl)amino)-3-methoxyquinoxaline-5-carbonitrile

12



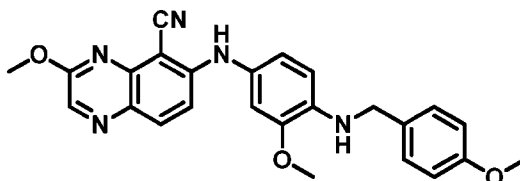
6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-
3-(methylamino)quinoxaline-5-carbonitrile

13



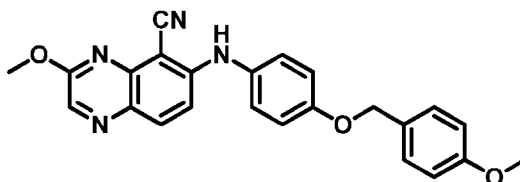
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methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

14



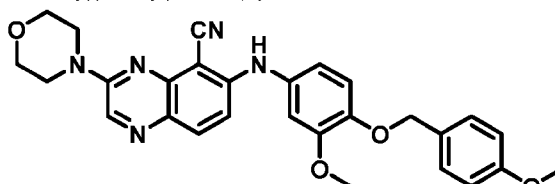
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amino)phenyl)amino)quinoxaline-5-carbonitrile

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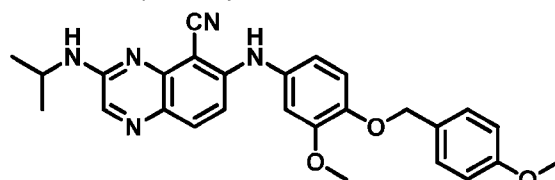
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oxy)phenyl)amino)quinoxaline-5-carbonitrile

16



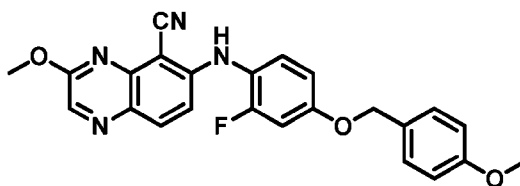
6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-
3-morpholinoquinoxaline-5-carbonitrile

17

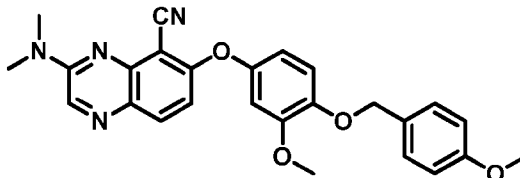


3-(isopropylamino)-6-((3-methoxy-4-((4-methoxybenzyl)
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18

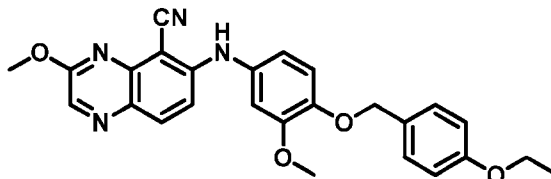
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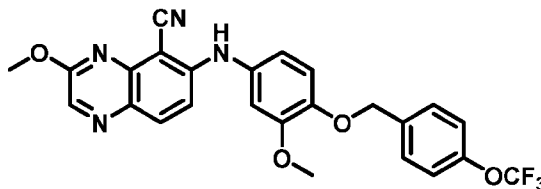


3-(dimethylamino)-6-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)quinoxaline-5-carbonitrile

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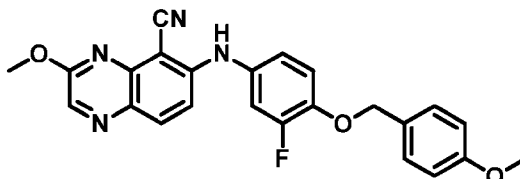
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21

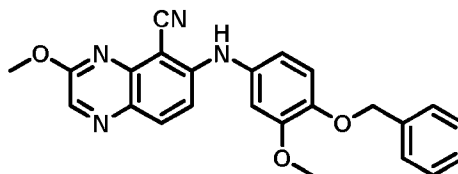


3-methoxy-6-((3-methoxy-4-((4-(trifluoromethoxy)benzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

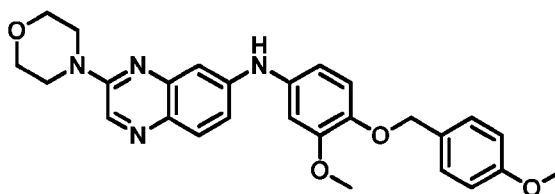
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6-((3-fluoro-4-((4-methoxybenzyl)oxy)phenyl)amino)-
3-methoxyquinoxaline-5-carbonitrile

23

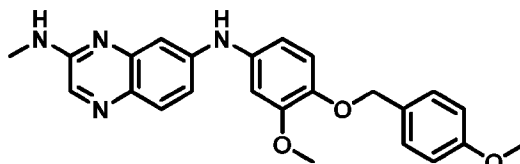
6-((4-(benzyloxy)-3-methoxyphenyl)amino)-
3-methoxyquinoxaline-5-carbonitrile

24



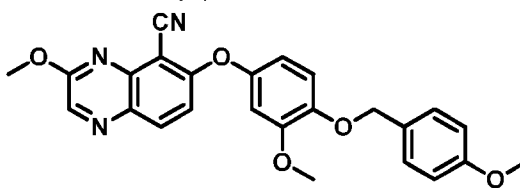
N-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)-3-morpholinoquinoxalin-6-amine

25



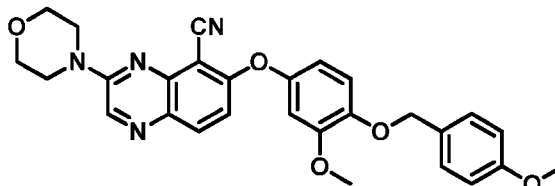
*N*⁷-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)-*N*²-methylquinoxaline-2,7-diamine

26



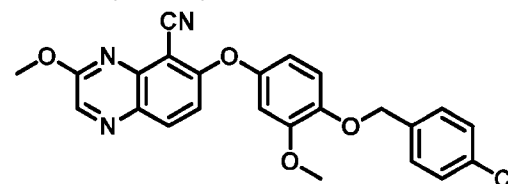
3-methoxy-6-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)quinoxaline-5-carbonitrile

27



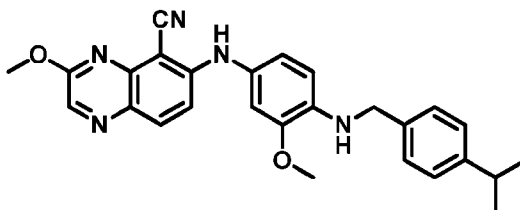
6-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)-3-morpholinoquinoxaline-5-carbonitrile

28



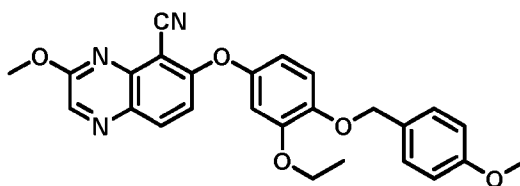
6-(4-((4-chlorobenzyl)oxy)-3-methoxyphenoxy)-3-methoxyquinoxaline-5-carbonitrile

29



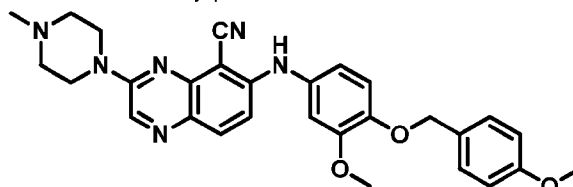
6-((4-((4-isopropylbenzyl)amino)-3-methoxyphenyl)amino)-3-methoxyquinoxaline-5-carbonitrile

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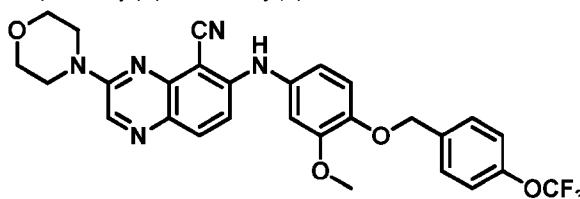
6-(3-ethoxy-4-((4-methoxybenzyl)oxy)phenoxy)-3-methoxyquinoxaline-5-carbonitrile

31



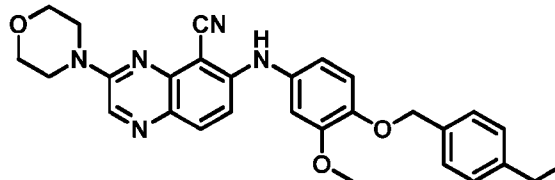
6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-(4-methylpiperazin-1-yl)quinoxaline-5-carbonitrile

32



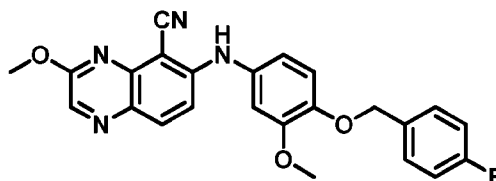
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33



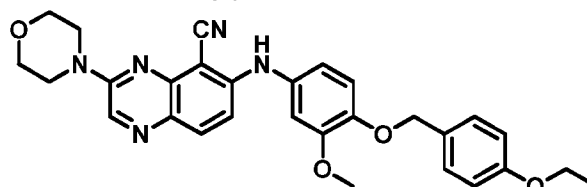
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34



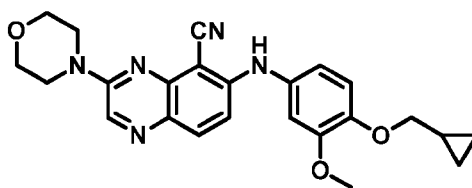
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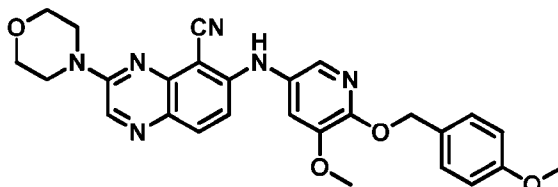
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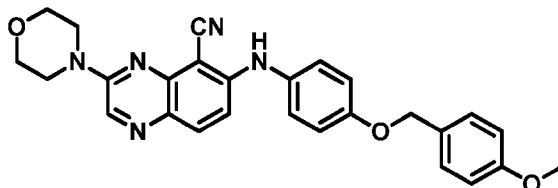
6-((4-(cyclopropylmethoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

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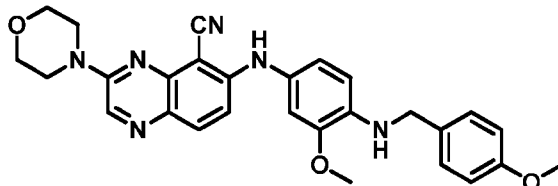
6-((5-methoxy-6-((4-methoxybenzyl)oxy)pyridin-3-yl)amino)-3-morpholinoquinoxaline-5-carbonitrile

38



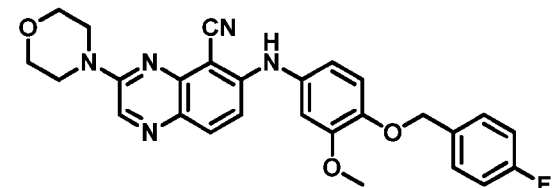
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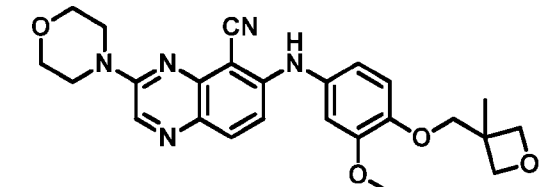
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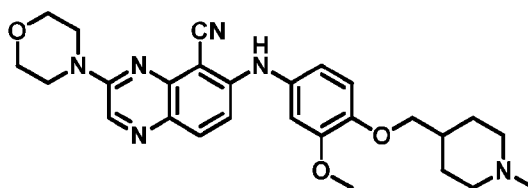
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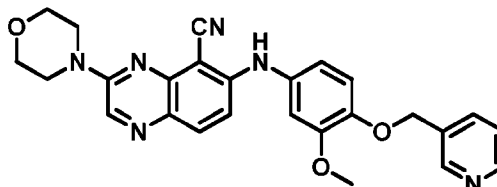
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42



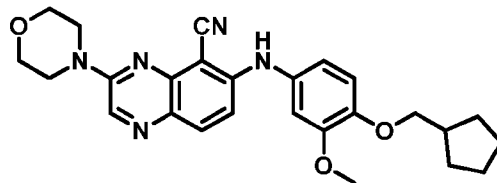
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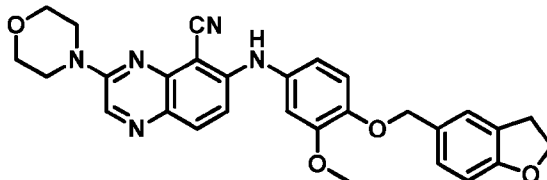
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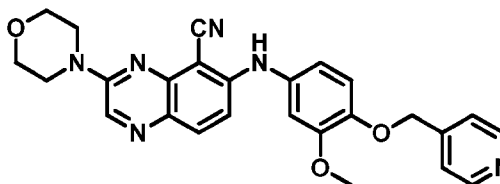
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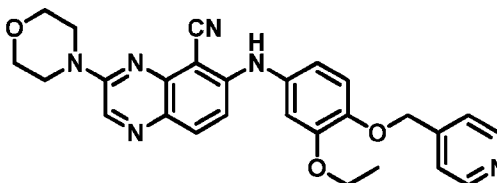
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46



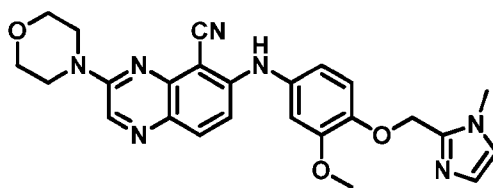
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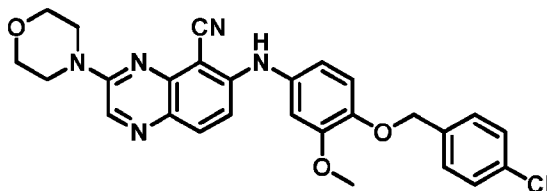
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48



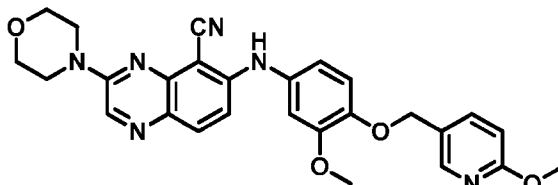
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49



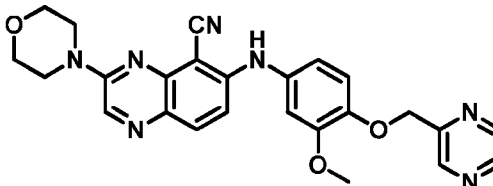
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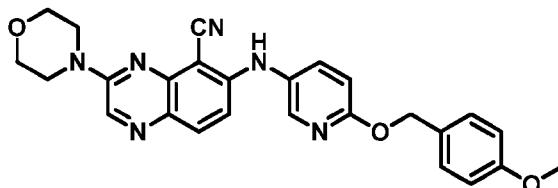
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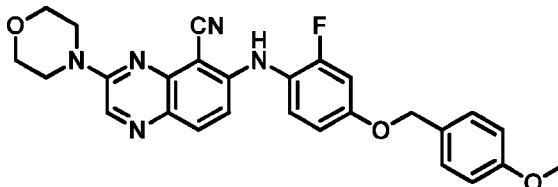
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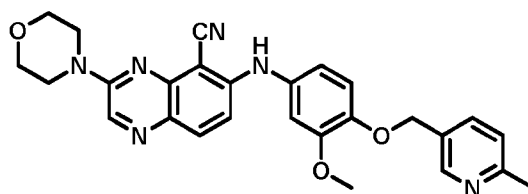
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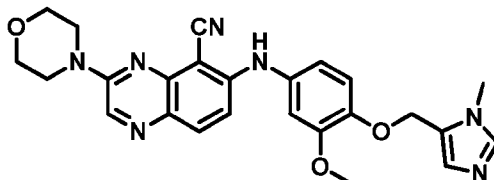
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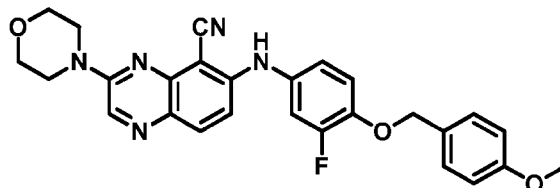
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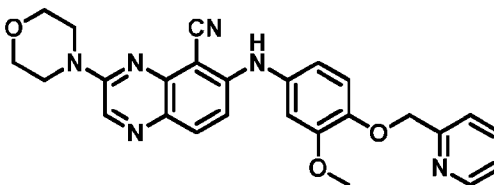
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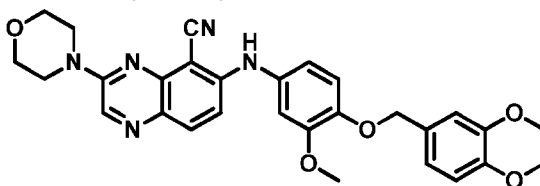
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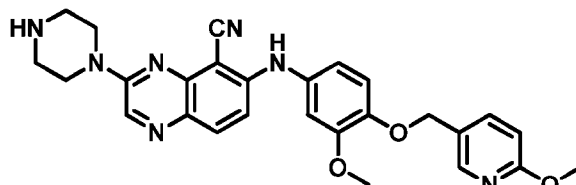
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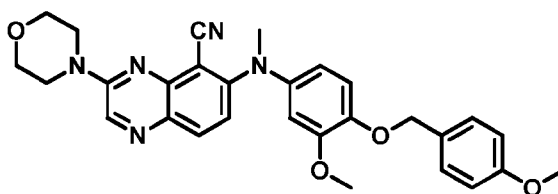
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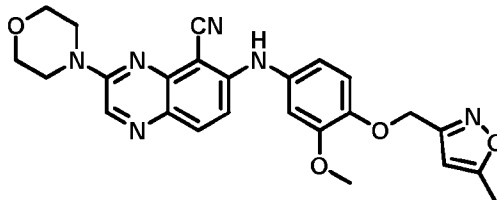
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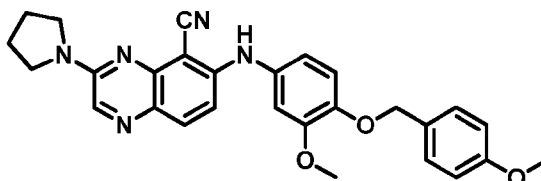
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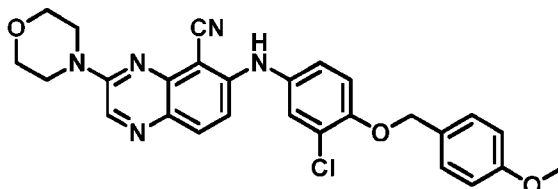
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62



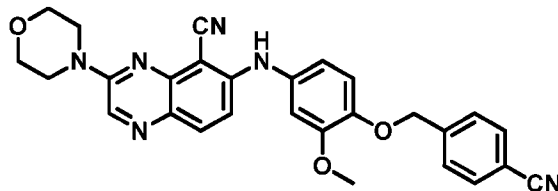
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63



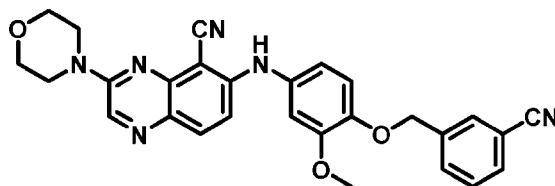
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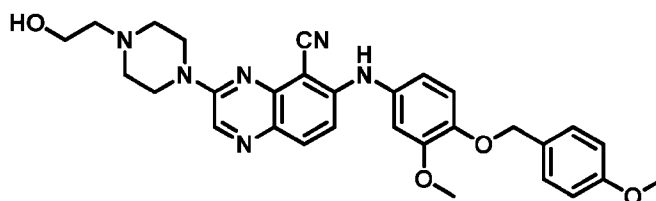
6-((4-((4-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

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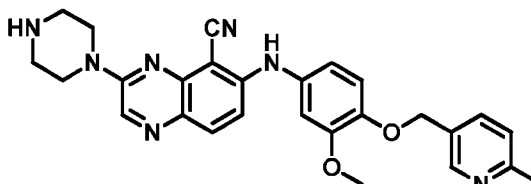
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66



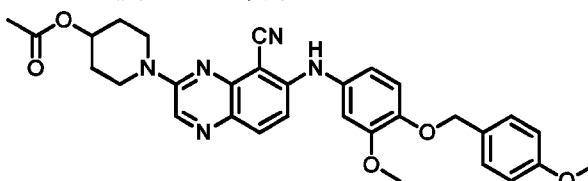
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67



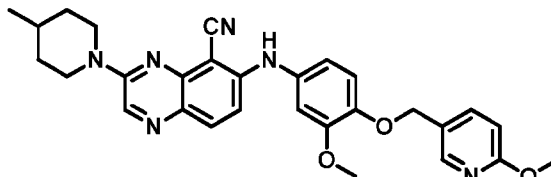
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68



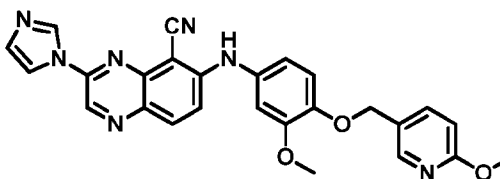
1-(8-cyano-7-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxalin-2-yl)piperidin-4-yl acetate

69



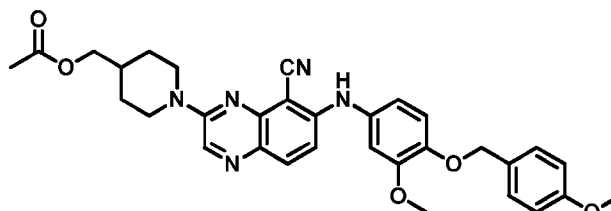
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70



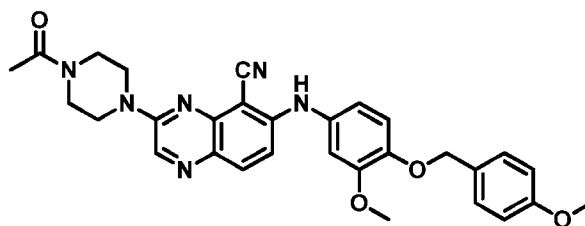
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71



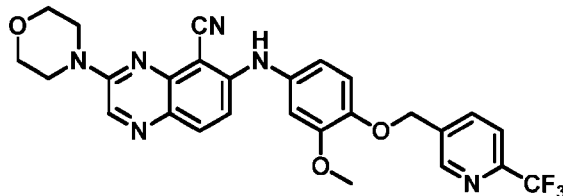
(1-(8-cyano-7-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxalin-2-yl)piperidin-4-yl)methyl acetate

72



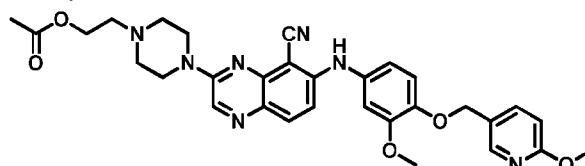
3-(4-acetylpiperazin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

73



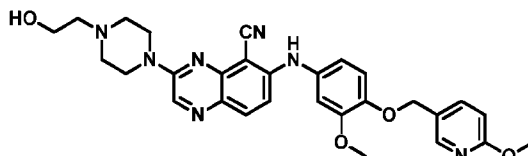
6-((3-methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

74



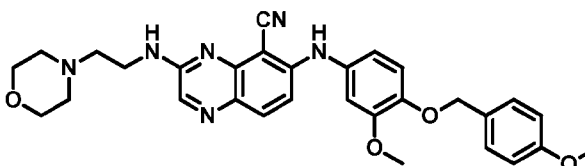
2-(4-(8-cyano-7-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxalin-2-yl)piperazin-1-yl)ethyl acetate

75



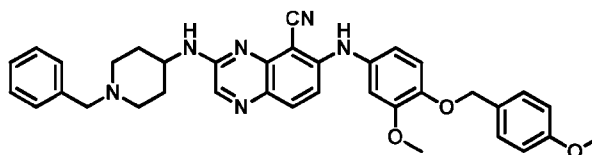
3-(4-(2-hydroxyethyl)piperazin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile

76



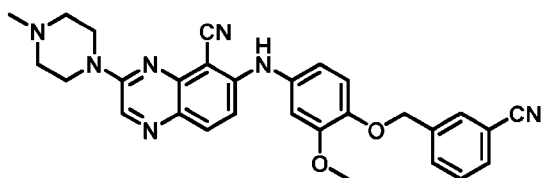
6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-((2-morpholinoethyl)amino)quinoxaline-5-carbonitrile

77



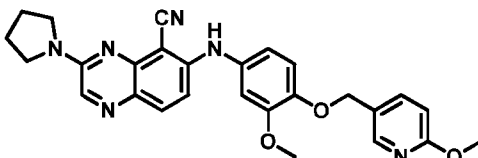
3-((1-benzylpiperidin-4-yl)amino)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

78



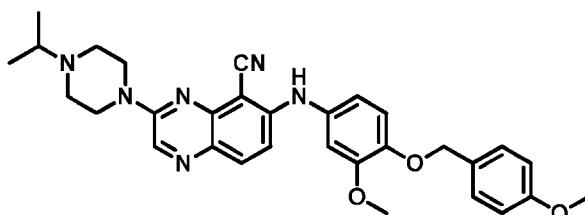
6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-
3-(4-methylpiperazin-1-yl)quinoxaline-5-carbonitrile

79



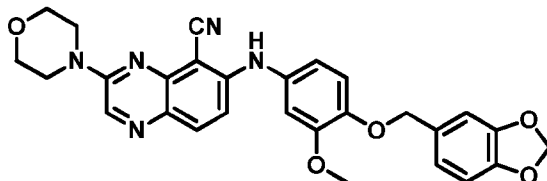
6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-
3-(pyrrolidin-1-yl)quinoxaline-5-carbonitrile

80



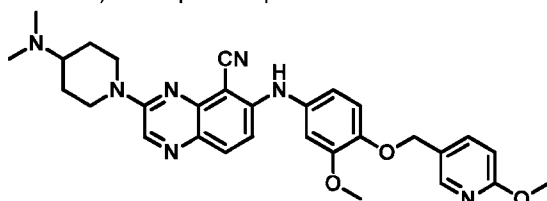
3-(4-isopropylpiperazin-1-yl)-6-((3-methoxy-4-((4-
methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

81



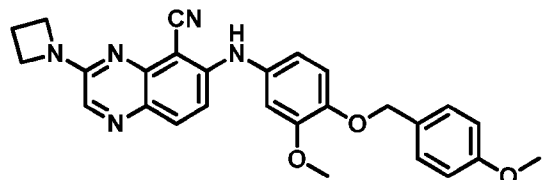
6-((4-(benzo[d][1,3]dioxol-5-yl)methoxy)-3-methoxyphenyl)
amino)-3-morpholinoquinoxaline-5-carbonitrile

82



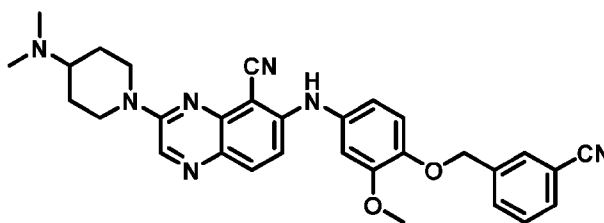
3-(4-(dimethylamino)piperidin-1-yl)-6-((3-methoxy-4-((6-methoxy
pyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile

83



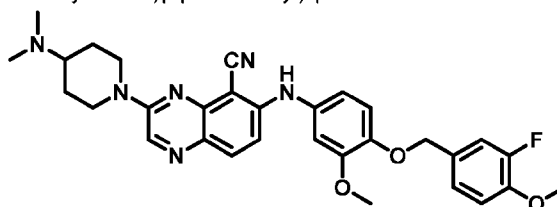
3-(azetidin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)
oxy)phenyl)amino)quinoxaline-5-carbonitrile

84



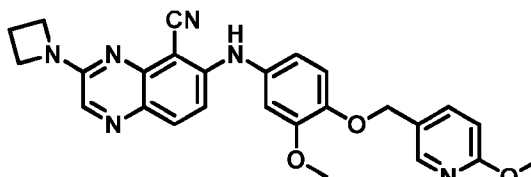
6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-(4-(dimethylamino)piperidin-1-yl)quinoxaline-5-carbonitrile

85



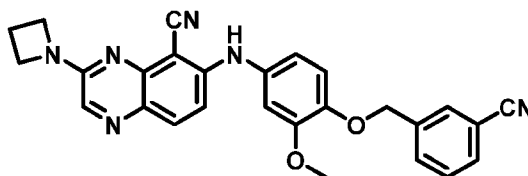
3-(4-(dimethylamino)piperidin-1-yl)-6-((4-((3-fluoro-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)quinoxaline-5-carbonitrile

86



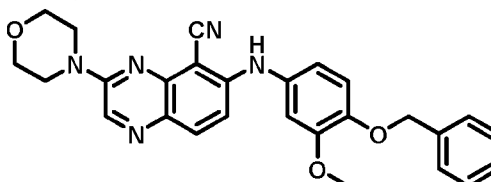
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87



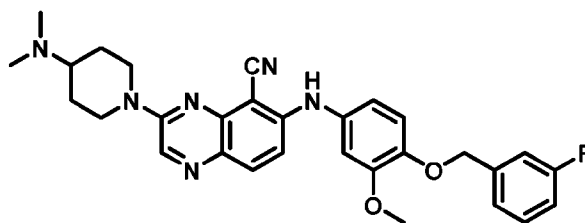
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88



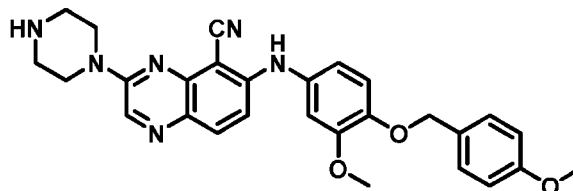
6-((4-(benzyloxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

89



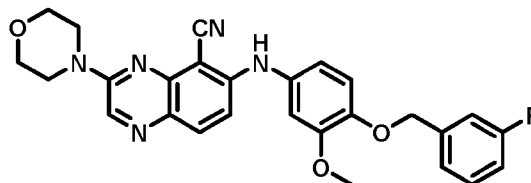
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90



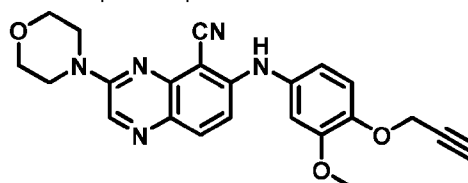
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91



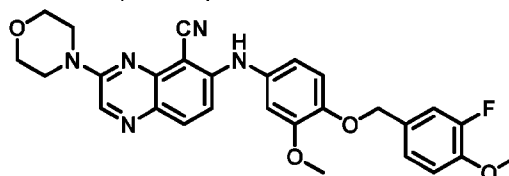
6-((4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

92



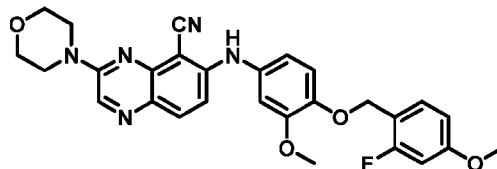
6-((3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

93



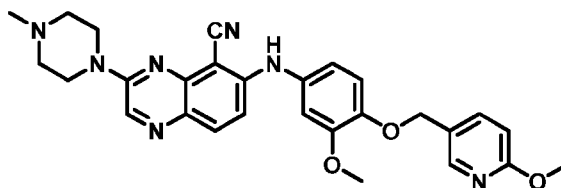
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94



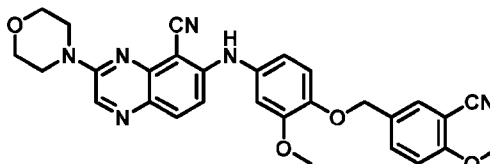
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95



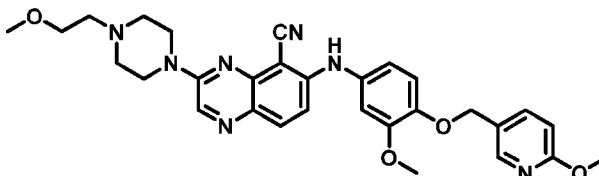
6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-methylpiperazin-1-yl)quinoxaline-5-carbonitrile

96



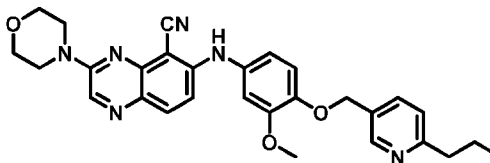
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97



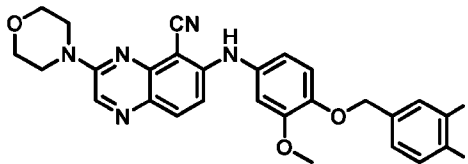
6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-(2-methoxyethyl)piperazin-1-yl)quinoxaline-5-carbonitrile

98



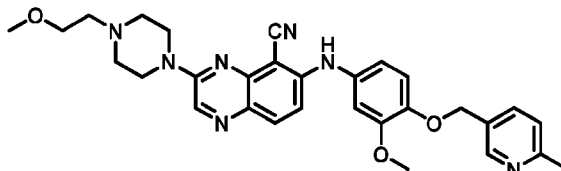
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99



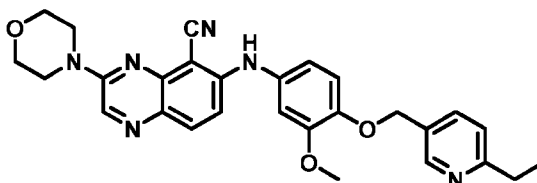
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100



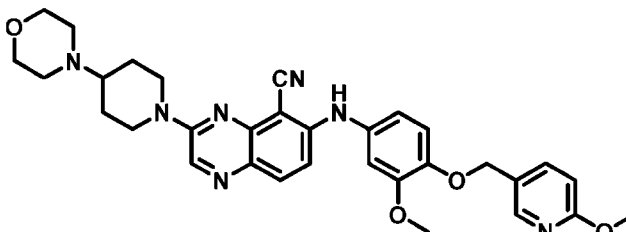
6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-(4-(2-methoxyethyl)piperazin-1-yl)quinoxaline-5-carbonitrile

101



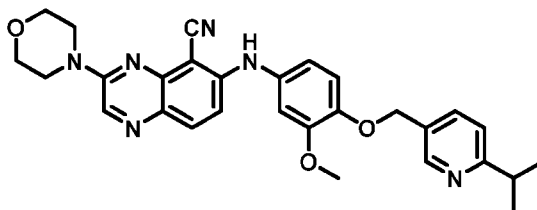
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102



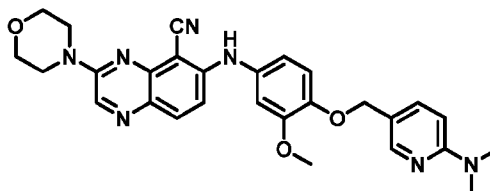
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103



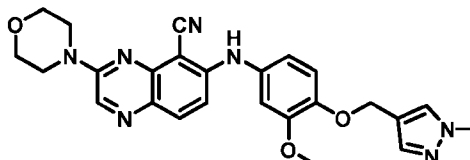
6-((4-((6-isopropylpyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

104



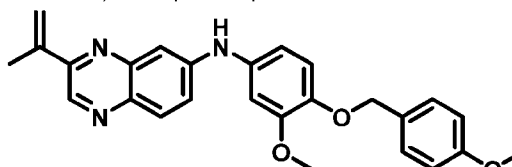
6-((4-((6-(dimethylamino)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

105



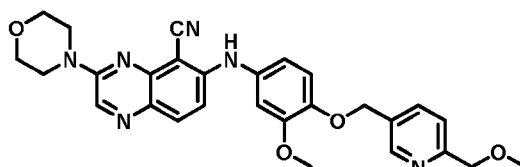
6-((3-methoxy-4-((1-methyl-1H-pyrazol-4-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

106



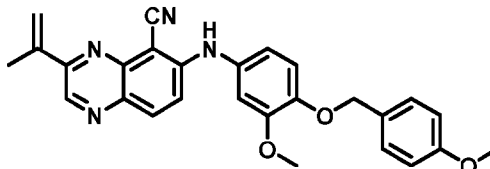
N-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)-3-(prop-1-en-2-yl)quinoxalin-6-amine

107



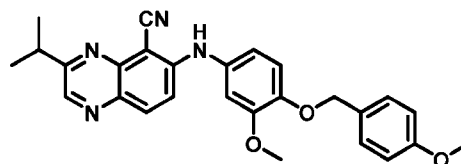
6-((3-methoxy-4-((6-(methoxymethyl)pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

108



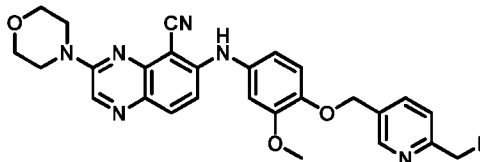
6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-(prop-1-en-2-yl)quinoxaline-5-carbonitrile

109



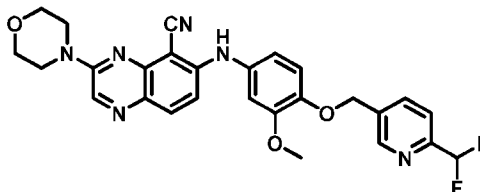
3-isopropyl-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile

110



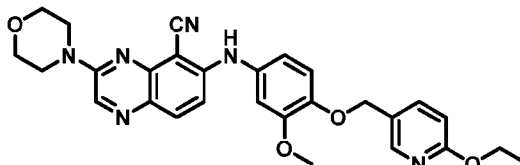
6-((4-((6-(fluoromethyl)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

111



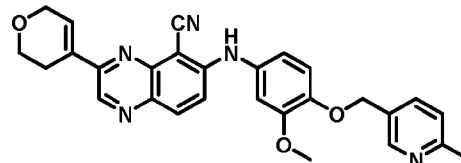
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112



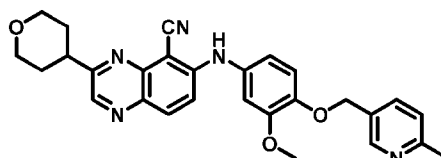
6-((4-((6-ethoxypyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

113



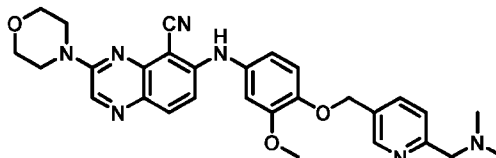
3-(3,6-dihydro-2H-pyran-4-yl)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile

114



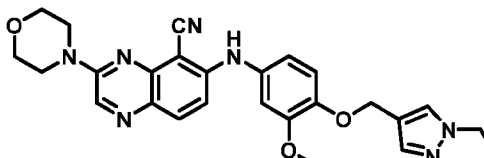
6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-(tetrahydro-2H-pyran-4-yl)quinoxaline-5-carbonitrile

115



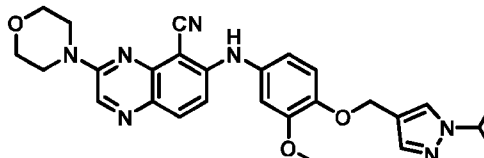
6-((4-((6-((dimethylamino)methyl)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

116



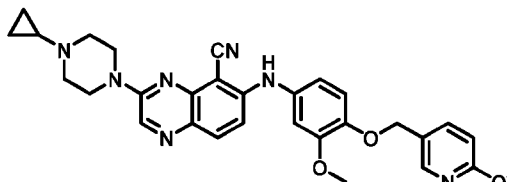
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117



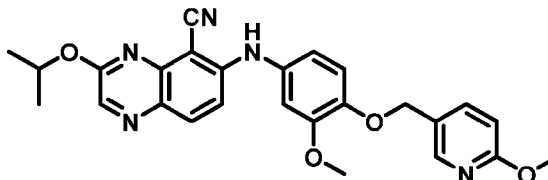
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118



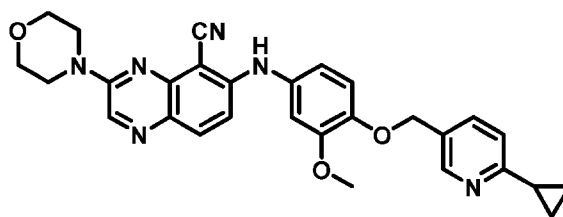
3-(4-cyclopropylpiperazin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile

119



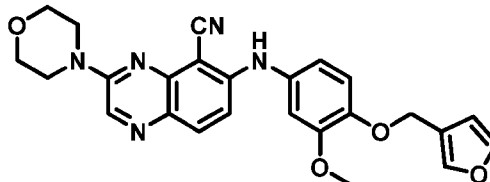
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120



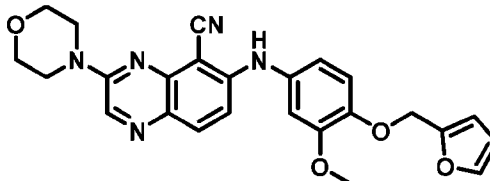
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121



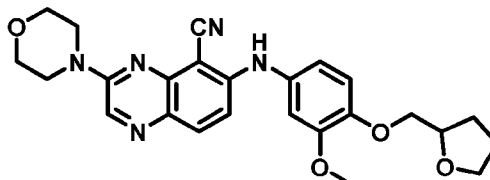
6-((4-(furan-3-ylmethoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

122



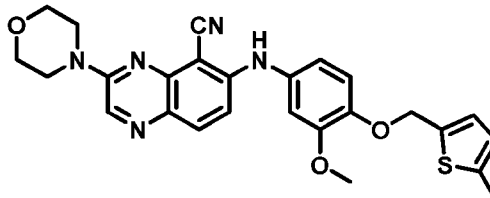
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123



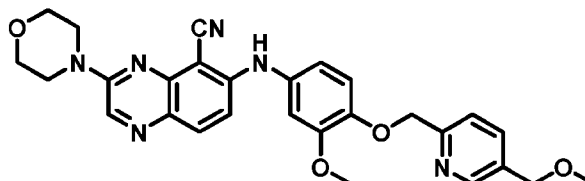
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124



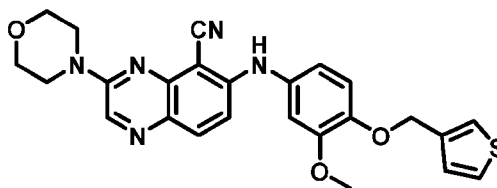
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125



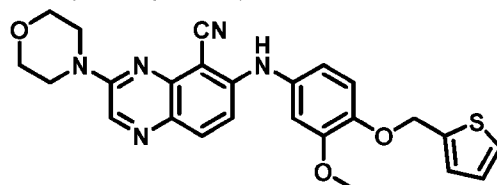
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126



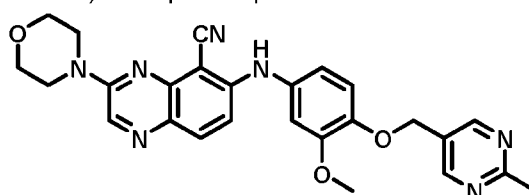
6-((3-methoxy-4-(thiophen-3-ylmethoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

127



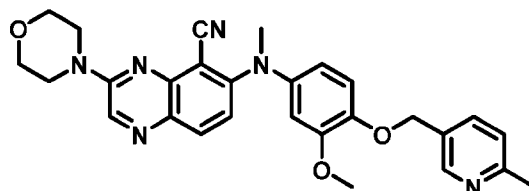
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128



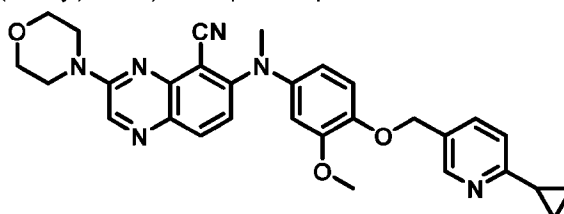
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129



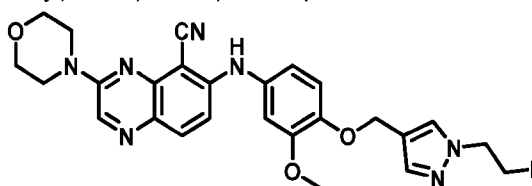
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130



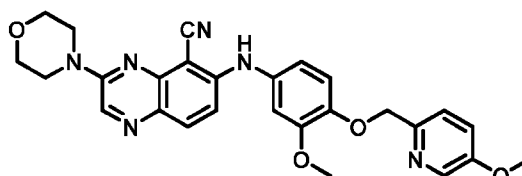
6-((4-((6-cyclopropylpyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

131



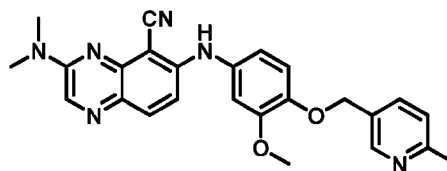
6-((4-((1-(2-fluoroethyl)-1H-pyrazol-4-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

132



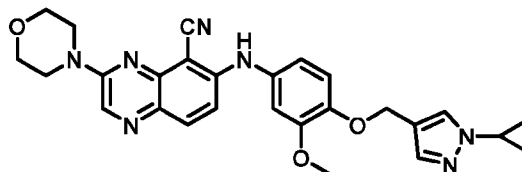
6-((3-methoxy-4-((5-methoxypyridin-2-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

133



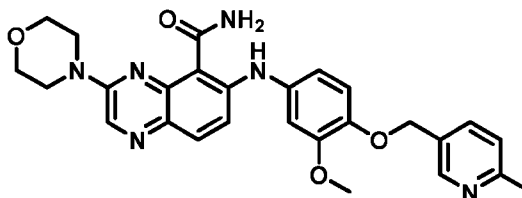
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134



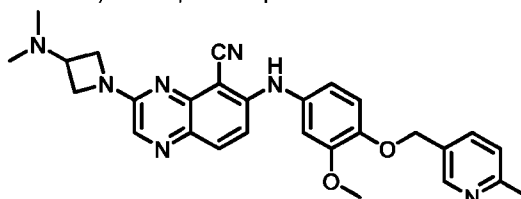
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135



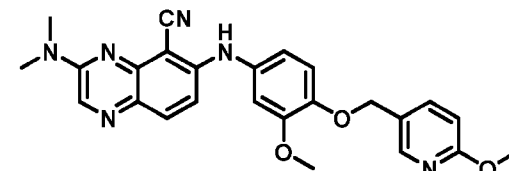
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136



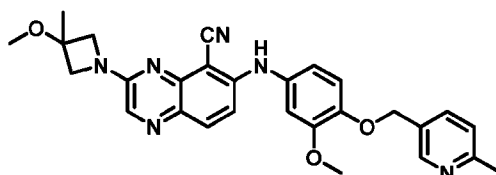
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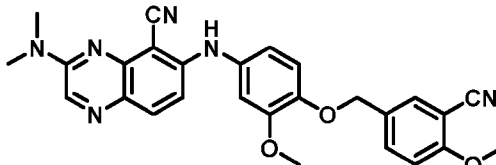
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138



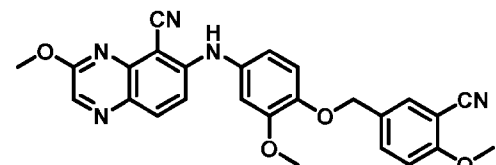
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139



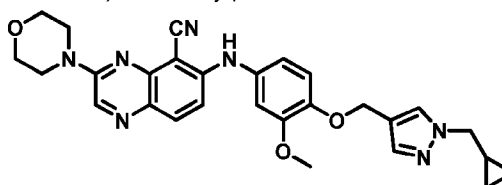
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140



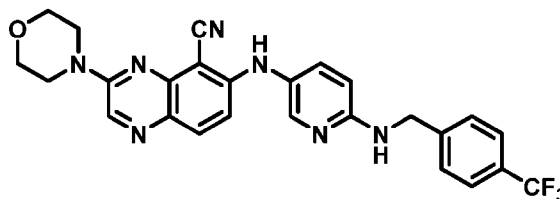
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141



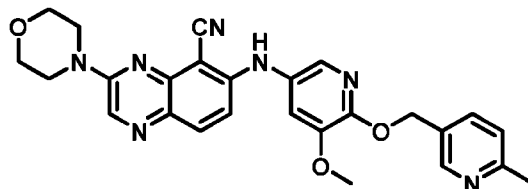
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142



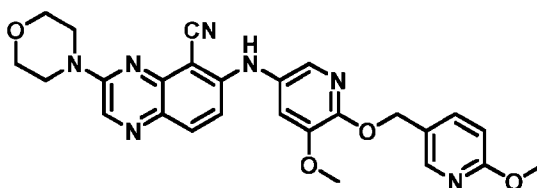
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143



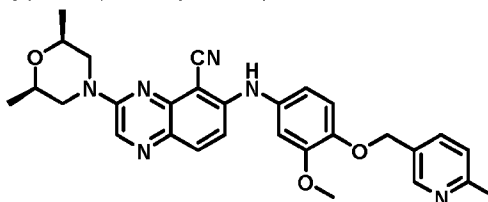
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144



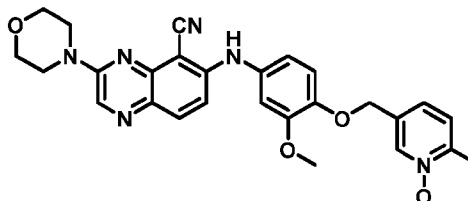
6-((5-methoxy-6-((6-methoxy-4-methylpyridin-3-yl)methoxy)pyridin-3-yl)amino)-3-morpholinoquinoxaline-5-carbonitrile

145



3-((2*S*,6*R*)-2,6-dimethylmorpholino)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile

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6-((3-methoxy-4-((6-methyl-1-(λ^1 -oxidaneyl)-1 λ^4 -pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile

[0047] Provided herein are compounds, and pharmaceutical compositions thereof, that are useful in the treatment or prevention of diseases, conditions and/or disorders modulated/mediated by (or associated with) a protein tyrosine kinase, such as CSF-1R, PDGFR, FLT-3 and/or c-KIT.

[0048] In an embodiment, the compound of formula (I) described above is administered orally. The medicament is in a form of tablet with 150 mg of the compound of formula (I). The compound of formula (I) shows a dose-adjusted AUC of the compound of formula (I) plasma concentration in dogs, under non-fasting conditions, of at least 170 kg*ng*hr/mL/mg. The compound of formula (I) shows a dose-adjusted C_{max} in dogs, under non-fasting conditions, of at least 20 kg*ng/mL/mg. The improving pharmacokinetics includes increasing the maximum plasma concentration (C_{max}) and/or bioavailability (AUC).

[0049] In an embodiment, the medicament further includes a carrier, diluent or excipient. The excipient may include a surfactant, a binder, a disintegrant and/or a lubricant.

[0050] The surfactant includes but are not limited to: betain, quaternary ammonium salts, polysorbates, sorbitan esters, a poloxamer and povidone[®] K-90. In one embodiment, the surfactant is povidone K-90.

[0051] The binder includes but are not limited to: starches, *e.g.*, potato, wheat or corn starch; microcrystalline cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hypromellose, and polyvinylpyrrolidone (*e.g.*, Povidone[®] K-90). In one embodiment, polyvinylpyrrolidone is used, preferably Povidone[®] K-90.

[0052] The disintegrant includes but are not limited to: maize starch, CMC-Ca, CMC-Na, microcrystalline cellulose, cross-linked polyvinylpyrrolidone (PVP), alginic acid, sodium alginate, and sodium starch glycolate (*e.g.*, sodium starch glycolate type A). In one embodiment, sodium starch glycolate, *e.g.*, sodium starch glycolate type A is used.

[0053] The lubricant includes but are not limited to: magnesium stearate, sodium stearyl fumarate, calcium stearate, zinc stearate, sodium stearate, stearic acid, aluminum stearate, leucine, behenate glyceryl esters, hydrogenated vegetable oils. In one embodiment, magnesium stearate is used.

[0054] In some embodiments, the compound of formula (I) is formed as amorphous solid dispersions (ASDs) with but are not limited to: povidone[®], polymethacrylate derivatives, hydroxypropyl methyl cellulose (HPMC) and hydroxypropyl methylcellulose acetate succinate derivatives. In one embodiment, the compound of formula (I) is formed as ASDs with hydroxypropyl methylcellulose acetate succinate (HPMCAS) (named as “DCBCO1701-SP01” hereinafter).

[0055] In one embodiment, the compound of formula (I) is used to manufacture a medicament tablet with HPMCAS, povidone K-90, sodium starch glycolate type A and/or magnesium stearate (named as “EI-1071 tablet” hereinafter).

[0056] **Enhancement of absorption of quinoxaline type III receptor tyrosine kinase inhibitors**

[0057] **Food effects on drug compounds delivery**

[0058] Certain drugs that exhibit higher solubility in low pH environments may experience reduced maximum concentration (C_{max}) and area under the curve (AUC) following a meal. This phenomenon occurs because, under fasted conditions, the stomach environment in healthy individuals typically is around pH 1. However, after food consumption, gastric pH transiently increases a higher pH ranging from pH 4.5 to pH 4.98, and remaining elevated for up to 4.5 hours. As illustrated in **FIG. 1**^[1], the pH changes in stomach before and after a meal is illustrated. At baseline, median gastric pH was about pH 1, increased to pH 4.5 or higher with ingestion of a meal, and then returned to approximately pH 1 about 3-4 hours after the start of the meal. Consequently, it is expected that solubility of drugs with higher solubility in acidic environment may decrease if they are administered post-food consumption, therefore leading to reduced absorption of the drugs. Furthermore, relative to the fasted state, concomitant oral drug administration after food ingestion can severely impact systemic bioavailability due to changes in gastrointestinal physiology, which affect the drug's transit time, luminal dissolution, and permeability.

[0059] **Known examples in prior arts**^[2]:

[0060] **Repaglinide**: it exhibits higher solubility under low pH conditions. When administered with food, the mean T_{max} remains unchanged, while the mean C_{max} and AUC decrease by 20% and 12.4%, respectively.^[3]

[0061] **Telmisartan**: it exhibits higher solubility under low pH conditions. When administered in a non-fasted state, both mean C_{max} and AUC decrease.^[4]

[0062] The compound of formula (I) is administered to the subject in need in the non-fasting state. Non-fasting state (or fed state) means in particular that the patient is not fasted. Particularly this means that active agents are administered together with or after food intake, *e.g.*, a meal, such as breakfast, lunch and/or dinner, more particularly together with or after breakfast and/or dinner. In particular, the compound of formula (I) (and optionally an orally

available) is administered within 5 hours, more particularly within 4 hours, even more particularly within 3 hours, yet even more particularly within 2.5 hours, yet even more particularly within 2 hours, yet even more particularly within 60 minutes, yet even more particularly within 30 minutes after food intake, particularly a meal, more particularly a light meal, in particular a light breakfast and/or dinner. A recommendation by the physician for a light meal could be a small to medium portion of 1 or 2 of the following: fruit, yogurt, cereal, toast, croissant, bread, cold meat, cheese, or salad, with coffee, tea, juice, or milk or similar amounts of food, which typically amounts to around 150-300 kcal, while however the numbers and amounts may vary to some extent in the actual treatment setting, taking into account that the patients are typically treated ambulatory and thus for the most part determine their diet themselves.

[0063] In the case of twice daily administration of the compound of formula (I), the first administration may be within the time frames in relation to a breakfast or light breakfast as detailed above and particularly within 30 minutes after said breakfast or light breakfast; and the second administration may be within the time frames in relation to a dinner or light dinner as detailed above and particularly within 30 minutes after said dinner or light dinner. For the sake of completeness, food intake, meal, etc. logically refer to food intake, meal, etc. of the patient receiving the administration of the aforementioned agents.

[0064] **Experimental materials and methods**

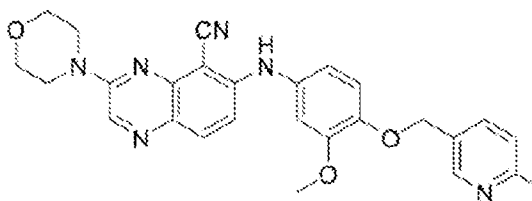
[0065] **The compound “DCBCO1701-DS:**

[0066] Chemical name: 6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

[0067] CAS Index name: 5-Quinoxalinecarbonitrile, 6-[[3-methoxy-4-[(6-methyl-3-pyridinyl)methoxy]phenyl]amino]-3-(4-morpholinyl)-;

[0068] CAS RN: 2222689-47-4; and

[0069] Structure:



[0070] **The ASDs “DCBCO1701-SP01”:**

[0071] A yellow powder contains DCBCO1701-DS, 20-40% w/w, and hydroxypropyl methylcellulose acetate succinate (HPMCAS), 60-80% w/w.

[0072] **The medicament “EI-1071 tablet”:**

[0073] Each EI-1071 tablet (750 mg/tablet) contains DCBCO1701-SP01 (60-70% w/w), povidone K-90 (4-8% w/w), sodium starch glycolate type A (25-30% w/w), and magnesium stearate (0.2-1% w/w).

[0074] **Chemical properties of the quinoxaline compound DCBCO1701-DS**

[0075] **Solubility of DCBCO1701-DS and DCBCO1701-SP01 in water and buffers of various pH**

[0076] As shown in **Table 2**, the solubility of DCBCO1701-DS was determined in pure water and buffers of various pH conditions: pH 1.2, pH 4.0, pH 6.8, and pH 7.4. DCBCO1701-DS is barely soluble in pure water and was determined as <1 µg/mL. However, the solubility thereof was measured 493.33 ± 125.70 µg /mL in pH 1.2 buffer and dropped significantly to become barely detectable 1.86 ± 0.11 µg/mL in pH 4.0 and < 1 µg/mL in pH 6.8 and pH 7.4. The solubility is significantly higher in an acidic buffer of pH 1.2.

[0077] **Table 2.** DCBCO1701-DS Solubility

DCBCO1701-DS Solubility	
Aqueous Solution	Solubility (µg/mL)
pH 1.2	493.33 ± 125.70
pH 4.0	1.86 ± 0.11
pH 6.8	< 1
pH 7.4	< 1

H ₂ O	< 1
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[0078] As shown in **Table 3**, the solubility of DCBCO1701-SP01 was determined in pure water and buffers of various pH conditions: pH 1.2, pH 4.0, and pH 6.8. Solubility of DCBCO1701-SP01 was barely soluble in pure water and was determined as 4.38 ± 0.05 $\mu\text{g/mL}$. The solubility of DCBCO1701-SP01 was measured 441.46 ± 76.06 $\mu\text{g/mL}$ in pH 1.2, which was similar to that of DCBCO1701-DS in pH 1.2. The solubility dropped significantly to barely detectable levels of 2.08 ± 0.70 $\mu\text{g/mL}$ in pH 4.5 and 7.52 ± 2.08 $\mu\text{g/mL}$ in pH 6.8, which was similar to that of pure water and was also similar to that of DCBCO1701-DS in similar pH conditions.

[0079] **Table 3.** DCBCO1701-SP01 Solubility

DCBCO1701-SP01 Solubility	
Aqueous Solution	Solubility ($\mu\text{g/mL}$)
pH 1.2	441.46 ± 76.06
pH 4.5	2.08 ± 0.70
pH 6.8	7.52 ± 2.08
H ₂ O	4.38 ± 0.05

[0080] HPMCAS-based ASDs have become well established in commercially available products and are widely utilized as a solubility enhancer to improve the solubility of poorly soluble drugs or as a precipitation inhibitor or stabilizer to achieve supersaturation and inhibit crystallization of drugs in the gastrointestinal tract. However, the results indicated that the solubility of DCBCO1701-DS in pure water and in various pH conditions is not significantly affected by other ingredients, HPMCAS, in DCBCO1701-SP01.

[0081] **Effects of food on absorption of DCBCO1701-DS compound in animals**

[0082] **Study 1**

[0083] Pharmacokinetics (PK) and bioavailability of DCBCO1701-DS in healthy Sprague Dawley male rats was studied in two formulations: DCBCO1701-DS and DCBCO1701-SP01,

of which each was suspended in 0.5% methylcellulose (0.5% MC) and was administered orally, also often mentioned as *per os* (PO), to rats which had been fasted for at least 10 hours, at a dose level, or at an equivalent dose level in case of DCBCO1701-SP01, of 10 mg/kg of DCBCO1701-DS once via jugular gavage. Blood samples were collected selected time points post dosing: pre-dose, 0.08, 0.25, 0.5, 1, 2, 4, 6, 8, 10, 24 hours. The concentration of DCBCO1701-DS in each blood sample was determined by liquid chromatography-tandem spectrometry (LC-MS/MS). Parameters of PK, including $C_{\max}$ and AUC were calculated as illustrated in **Table 4**.

[0084] **Table 4.** Pharmacokinetic study 1 in Sprague Dawley Rats (fasting)

Test Article	Administration (EQ DCBCO1701-DS ¹)	$C_{\max}$ ² (ng/mL)	$C_{\max}$ ² /Dose (kg*ng/mL/mg)	AUC _(0-∞) ³ (ng*hr/mL)	AUC/Dose (hr*kg*ng/mL/mg)
DCBCO1701-DS	Fasting PO ⁴ at 10 mg/kg	93.8	9.38	452	45.2
DCBCO1701-SP01	Fasting PO ⁴ at 10 mg/kg	364	36.4	1692	169.2

1. EQ DCBCO1701-DS: equivalent DCBCO1701-DS amount
2. $C_{\max}$: maximum observed concentration
3. AUC_(0-∞): area under the concentration-time curve from time 0 to the last measurable concentration
4. *Per os* (by mouth)

[0085] The results indicated that the absorption of the DCBCO1701-DS in rats was significantly higher in the form of DCBCO1701-SP01 than in the form of DCBCO1701-DS (*e.g.*, the AUC/Dose values SP01 vs DS = 169.2 vs 45.2).

[0086] Given that DCBCO1701 is highly soluble in low pH but barely soluble in other pH conditions, it may, like other drugs with similar physical properties, experience reduced $C_{\max}$ and AUC following a meal. To gain a comprehensive understanding the impacts of food on the PK profile of DBCCO1701-DS, two PK studies, study 2 and study 3, were conducted in Beagle dogs. The results are summarized in **Table 5** (study 2) and **Tables 6 and 7** (study 3) below.

[0087] All AUC data herein were dose adjusted to the 1 mg dose level. For the purposes herein, the AUC is determined within a dose range where the AUC increases proportionally with dose. Administration of 150 mg of the compound of formula (I), *e.g.*, EI-1071 tablet, to dogs is considered suitable for determining the AUC values as used herein. Protocol for the oral bioavailability studies in beagle dogs and the AUC calculations are described in U.S. Patent Application Publication No. 20050084529, the entire content of which is incorporated herein by reference.

[0088] **Study 2**

[0089] Dogs, fasted or non-fasting (postprandial), were administered EI-1071 tablets PO once at a dose level equivalent to 55 mg/kg of DCBCO1701-DS. Blood samples were collected at selected time points post dosing: pre-dose, 0.5, 1, 2, 4, 8, 12, 24 hours. Concentration of DCBCO1701-DS in each sample was determined by LC-MS/MS. The parameters of PK were calculated as shown in **Table 5** below:

[0090] **Table 5.** Pharmacokinetic study 2 in Beagle Dogs (fasting vs non-fasting)

Test Article	Administration (EQ DCBCO1701-DS ¹)	C _{max} ² (ng/mL)	C _{max} ² /Dose (kg*ng/mL/mg)	AUC ³ (ng*hr/mL)	AUC/Dose (hr*kg*ng/mL/mg)
EI-1071 Tablet	Fasting PO ⁴ at 55 mg/kg	963	17.9	6426	117.5
EI-1071 Tablet	Non-fasting PO ⁴ at 55 mg/kg	1230	22.2	9723	175.7

1. EQ DCBCO1701-DS: Equivalent DCBCO1701-DS amount
2. C_{max}: Maximum observed concentration
3. AUC: Area under the concentration-time curve
4. *Per os* (by mouth)

[0091] The results in **Table 5** indicated that the absorption of DCBCO1701-DS in animals was significantly higher if EI-1071 tablets were administered in non-fasting condition as shown by

the “AUC/Dose” values of non-fasting 175.7 vs fasting 117.5 and by the DCBCO1701-DS concentrations in blood samples time course in **FIG. 2**.

[0092] **Study 3**

[0093] A similar study as the study 2, but testing more dosing levels, was conducted in the study 3. The results were summarized in **Tables 6** and **7** and **FIGs. 3A and 3B** and indicated that the absorption of DCBCO1701-DS in animals was significantly higher if EI-1071 tablets were administered in non-fasting (or postprandial) condition in all three dosing amounts: 75 mg/10 kg, 150 mg/10 kg, 300 mg/10 kg, as shown by the “AUC/Dose” values of fasting vs postprandial conditions listed in **FIG. 3B**.

[0094] **Table 6**

Dose (EQ DCBCO1701-DS#) (mg/10 kg)	Fasting		Postprandial (after meal)	
	C _{max} Mean	N	C _{max} Mean	N
75	85.4 ± 31.1	4	261.5 ± 91.8	4
150	324.0 ± 135.7	4	608.8 ± 123.7	4
300	341.8 ± 165.5	4	814.3 ± 167.5	4

EQ DCBCO1701-DS: Equivalent DCBCO1701-DS amount

[0095] **Table 7**

Dose (EQ DCBCO1701-DS#) (mg/10 kg)	Fasting		Postprandial (after meal)	
	AUC Mean	N	AUC Mean	N
75	599.8 ± 145.5	4	1885.0 ± 351.4	4
150	2518.3 ± 1754.7	4	4395.0 ± 1480.6	4
300	2467.5 ± 1231.7	4	6772.5 ± 2511.3	4

EQ DCBCO1701-DS: Equivalent DCBCO1701-DS amount

[0096] Results from study 2 and study 3 concluded that, unlike those drugs Repaglinide, Nevirapine, and Telmisartan described earlier, food ingestion before dosing EI-1071 tablets significantly increased the absorption of DCBCO1701-DS in dogs.

[0097] **Conclusion**

[0098] The present invention provides unexpected findings that delivery of the quinoxaline compounds in the present invention that have low solubility in water but have high solubility

in acidic buffers can be delivered more efficiently into biological bodies after/with food ingestion to improve the treatment of diseases mediated by such kinases, such as cancers, autoimmune diseases, bone resorptive diseases, and neurodegenerative diseases.

[0099] Unless defined otherwise, all technical and scientific terms and any acronyms used herein have the same meanings as commonly understood by one of ordinary skill in the art in the field of this invention. Although any compositions, methods, kits, and means for communicating information similar or equivalent to those described herein can be used to practice this invention, the preferred compositions, methods, kits, and means for communicating information are described herein.

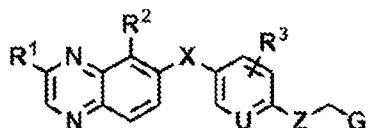
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1. Gardner, J. D., Ciociola, A. A. & Robinson, M. (2002). Measurement of meal-stimulated gastric acid secretion by *in vivo* gastric autotitration. *Journal of Applied Physiology*, 92(2), 427-434.92, 427-434 (2002).
2. Sieger, P., Cui, Y., & Scheuerer, S. (2017). pH-dependent solubility and permeability profiles: A useful tool for prediction of oral bioavailability. *European Journal of Pharmaceutical Sciences*, 105, 82-90.
3. US FDA drug label (Reference ID 4052550).
4. Burrell, L. M., & Johnston, C. I. (1997). Angiotensin II receptor antagonists. Potential in elderly patients with cardiovascular disease. *Drugs Aging*, 10(6), 421-434.

WHAT IS CLAIMED IS:

1. A method of improving pharmacokinetics of a compound of formula (I), comprising administering a medicament comprising the compound of formula (I) to a subject in need thereof in a non-fasting state,

wherein the compound of formula (I) has a structure of:



Formula (I)

or a stereoisomer, tautomer, prodrug, or pharmaceutically acceptable salt thereof,

wherein:

X is selected from the group consisting of CR^4R^5 , NR^6 , O and S;

Z is selected from the group consisting of $-\text{NR}^7-$ and $-\text{O}-$;

U is N or CR^8 ;

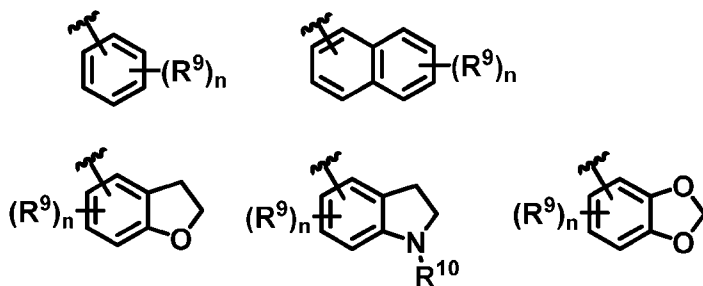
G is selected from the group consisting of aryl, heteroaryl, cycloalkyl, heterocycle and alkyne.

R^1 is selected from the group consisting of hydrogen, deuterium, halogen, amino, hydroxyl, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_5 - C_6 cycloalkenyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_3 - C_6 cycloalkylamino, C_1 - C_6 alkoxy, C_3 - C_6 cycloalkoxy, aryl, a 3-to-6 membered heterocyclyl, and a 5-to-6 membered heteroaryl, wherein the alkylamino, dialkylamino, alkoxy, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylamino, cycloalkoxy, heterocyclyl, aryl and heteroaryl are optionally substituted with halogen, amino, hydroxyl, cyano, nitro, acyl, acyloxy, C_1 - C_4 alkyl, hydroxyl C_1 - C_4 alkyl, alkoxy C_1 - C_4 alkyl, acyloxy C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 dialkylamino, C_3 - C_6 cycloalkyl, a 3-to-6 membered heterocyclyl, aryl, and a 5-to-6 membered heteroaryl;

R^2 is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, C_1 - C_6 alkyl carbonyl, C_2 - C_6 alkenyl carbonyl, C_1 - C_6 alkoxy carbonyl, amino carbonyl, C_1 - C_6 alkylamino carbonyl and C_1 - C_6 dialkylamino carbonyl;

R^3 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylamino and C_1 - C_6 dialkylamino;
 R^4 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy and aryl;
 R^5 is selected from the group consisting of hydrogen, deuterium, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl;
 R^6 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl;
 R^7 is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and
 R^8 is selected from the group consisting of hydrogen, deuterium, halogen, hydroxyl, amino, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 alkylamino and C_1 - C_6 dialkylamino.

2. The method of Claim 1, wherein G is selected from:

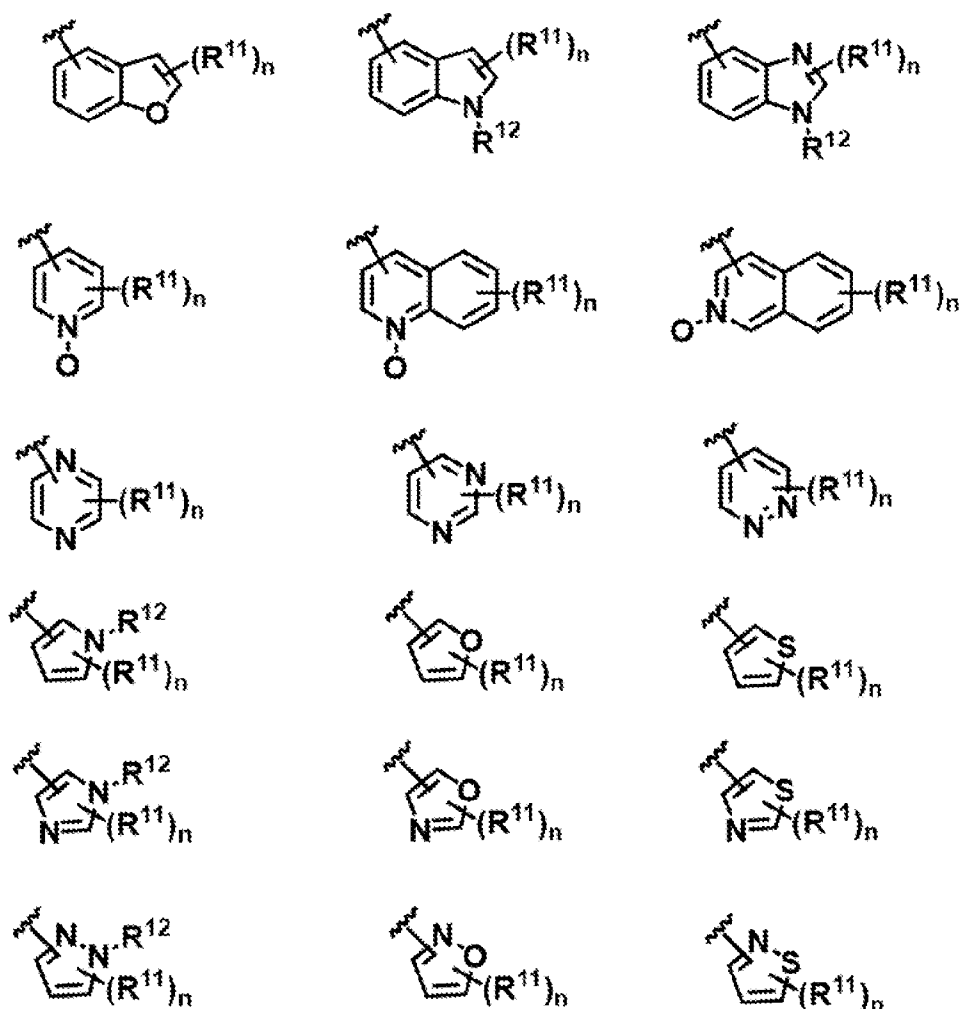


wherein

R^9 is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, C_1 - C_6 alkyl, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, carbonyl, C_1 - C_6 alkoxy, carbonyl, C_1 - C_6 alkylamino, and carbonyl C_1 - C_6 dialkylamino;

R^{10} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and
each n is individually and independently 0, 1, 2, or 3.

3. The method of Claim 1, wherein G is selected from:



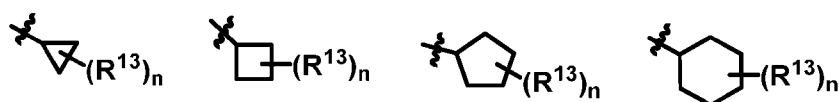
wherein

R^{11} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_3 - C_6 cycloalkyl, C_3 - C_6 cycloalkyl C_1 - C_6 alkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, C_1 - C_6 alkoxy C_1 - C_6 alkyl, carboxylic acid, carbonyl C_1 - C_6 alkoxy, carbonyl C_1 - C_6 alkylamino and carbonyl C_1 - C_6 dialkylamino;

R^{12} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and

each n is individually and independently 0, 1, 2, or 3.

4. The method of Claim 1, wherein G is selected from:



wherein

R^{13} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl; and

each n is individually and independently 0, 1, 2, or 3.

5. The method of Claim 1, wherein G is selected from:



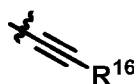
wherein

R^{14} is selected from the group consisting of hydrogen, deuterium, halogen, nitro, cyano, trifluoromethyl, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkylamino, C_1 - C_6 dialkylamino, C_1 - C_6 alkoxy, carboxylic acid, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl;

Q is selected from NR^{15} , O , and S , wherein R^{15} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl and C_1 - C_6 haloalkyl; and

each n is individually and independently 0, 1, 2, or 3.

6. The method of Claim 1, wherein G is:



wherein R^{16} is selected from the group consisting of hydrogen, deuterium, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, 3-to-6 membered heterocyclyl, 5-to-6 membered heteroaryl, C_1 - C_6 alkoxycarbonyl, C_1 - C_6 alkylaminocarbonyl and C_1 - C_6 dialkylaminocarbonyl.

7. The method of claim 1, wherein X is NH .

8. The method of claim 1, wherein Z is $-O-$.
9. The method of claim 1, where the compound of formula (I) is:
- 3-methoxy-6-(((6-((trifluoromethyl)pyridin-3-yl)methyl)amino)pyridin-3-yl)amino)quinoxaline-5-carbonitrile;
- N^5 -(3-methoxyquinoxalin-6-yl)- N^2 -((6-((trifluoromethyl)pyridin-3-yl)methyl)pyridine-2,5-diamine;
- 3-methoxy-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;
- 3-methoxy-6-((6-((4-((trifluoromethyl)benzyl)amino)pyridin-3-yl)amino)quinoxaline-5-carbonitrile;
- 3-methoxy-N-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)quinoxalin-6-amine;
- 3-methoxy-6-((6-(pyridin-3-ylmethoxy)pyridin-3-yl)amino)quinoxaline-5-carbonitrile;
- 3-(dimethylamino)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;
- 3-methoxy-6-((3-methoxy-4-(pyridin-3-ylmethoxy)phenyl)amino)quinoxaline-5-carbonitrile;
- 3-methoxy-6-((6-((4-methoxybenzyl)oxy)pyridin-3-yl)amino)quinoxaline-5-carbonitrile;
- 3-methoxy-6-(3-methoxy-4-((4-methoxybenzyl)oxy)phenoxy)quinoxaline-5-carbonitrile;
- 6-((3,4-dimethylphenyl)amino)-3-methoxyquinoxaline-5-carbonitrile;
- 6-((3-methoxy-4-(4-methoxybenzyloxy)phenyl)amino)-3-(methylamino)quinoxaline-5-carbonitrile;
- 3-(2-(dimethylamino)ethoxy)-6-(3-methoxy-4-(4-methoxybenzyloxy)phenylamino)-quinoxaline-5-carbonitrile;
- 3-methoxy-6-(3-methoxy-4-(4-methoxybenzylamino)phenylamino)quinoxaline-5-carbonitrile;
- 3-methoxy-6-(4-(4-methoxybenzyloxy)phenylamino)quinoxaline-5-carbonitrile;
- 6-(3-methoxy-4-(4-methoxybenzyloxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
- 3-(isopropylamino)-6-(3-methoxy-4-(4-methoxybenzyloxy)phenylamino)quinoxaline-5-carbonitrile;
- 6-(2-fluoro-4-(4-methoxybenzyloxy)phenylamino)-3-methoxyquinoxaline-5-carbonitrile;
- 3-(dimethylamino)-6-(3-methoxy-4-(4-methoxybenzyloxy)phenoxy)quinoxaline-5-carbonitrile;

6-(4-(4-ethoxybenzyloxy)-3-methoxyphenylamino)-3-methoxyquinoxaline-5-carbonitrile;
3-methoxy-6-(3-methoxy-4-(4-(trifluoromethoxy)benzyloxy)phenylamino)quinoxaline-5-carbonitrile;
6-(3-fluoro-4-(4-methoxybenzyloxy)phenylamino)-3-methoxyquinoxaline-5-carbonitrile;
6-(4-(benzyloxy)-3-methoxyphenylamino)-3-methoxyquinoxaline-5-carbonitrile;
N-(3-methoxy-4-(4-methoxybenzyloxy)phenyl)-3-morpholinoquinoxalin-6-amine;
N⁷-(3-methoxy-4-(4-methoxybenzyloxy)phenyl)-N²-methylquinoxaline-2,7-diamine;
3-methoxy-6-(3-methoxy-4-(4-methoxybenzyloxy)phenoxy)quinoxaline-5-carbonitrile;
6-(3-methoxy-4-(4-methoxybenzyloxy)phenoxy)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(4-chlorobenzyloxy)-3-methoxyphenoxy)-3-methoxyquinoxaline-5-carbonitrile;
6-(4-(4-isopropylbenzylamino)-3-methoxyphenylamino)-3-methoxyquinoxaline-5-carbonitrile;
6-(3-ethoxy-4-(4-methoxybenzyloxy)phenoxy)-3-methoxyquinoxaline-5-carbonitrile;
6-(3-methoxy-4-(4-methoxybenzyloxy)phenylamino)-3-(4-methylpiperazin-1-yl)quinoxaline-5-carbonitrile;
6-(3-methoxy-4-(4-(trifluoromethoxy)benzyloxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(4-ethylbenzyloxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(4-fluorobenzyloxy)-3-methoxyphenylamino)-3-methoxyquinoxaline-5-carbonitrile;
6-(4-(4-ethoxybenzyloxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(cyclopropylmethoxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(5-methoxy-6-(4-methoxybenzyloxy)pyridin-3-ylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(4-methoxybenzyloxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(3-methoxy-4-(4-methoxybenzylamino)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(4-(4-fluorobenzyloxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;
6-(3-methoxy-4-((3-methyloxetan-3-yl)methoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(3-methoxy-4-((1-methylpiperidin-4-yl)methoxy)phenylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-(3-methoxy-4-(pyridin-3-ylmethoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(4-(cyclopentylmethoxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(4-((2,3-dihydrobenzofuran-5-yl)methoxy)-3-methoxyphenylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-(3-methoxy-4-(pyridin-4-ylmethoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(3-ethoxy-4-(pyridin-4-ylmethoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((1-methyl-1H-imidazol-2-yl)methoxy)phenylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((4-(4-chlorobenzyloxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-(pyrazin-2-ylmethoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((6-(4-methoxybenzyloxy)pyridin-3-ylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((2-fluoro-4-(4-methoxybenzyloxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((1-methyl-1H-imidazol-5-yl)methoxy)phenylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-(3-fluoro-4-(4-methoxybenzyloxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(3-methoxy-4-(pyridin-2-ylmethoxy)phenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(4-(3,4-dimethoxybenzyloxy)-3-methoxyphenylamino)-3-morpholinoquinoxaline-5-carbonitrile;

6-(3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenylamino)-3-(piperazin-1-yl)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)(methylamino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((5-methylisoxazol-3-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-(pyrrolidin-1-yl)quinoxaline-5-carbonitrile;

6-((3-chloro-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((4-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-(4-(2-hydroxyethyl)piperazin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-(piperazin-1-yl)quinoxaline-5-carbonitrile;

1-(8-cyano-7-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxalin-2-yl)piperidin-4-yl acetate;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-methylpiperidin-1-yl)quinoxaline-5-carbonitrile;

3-(1H-imidazol-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

(1-(8-cyano-7-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxalin-2-yl)piperidin-4-yl)methyl acetate;

3-(4-acetylpiperazin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-(trifluoromethyl)pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

2-(4-(8-cyano-7-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxalin-2-yl)piperazin-1-yl)ethyl acetate;

3-(4-(2-hydroxyethyl)piperazin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-((2-morpholinoethyl)amino)quinoxaline-5-carbonitrile;

3-((1-benzylpiperidin-4-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-(4-methylpiperazin-1-yl)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(pyrrolidin-1-yl)quinoxaline-5-carbonitrile;

3-(4-isopropylpiperazin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-(benzo[d][1,3]dioxol-5-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-(4-(dimethylamino)piperidin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

3-(azetidin-1-yl)-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)-3-(4-(dimethylamino)piperidin-1-yl)quinoxaline-5-carbonitrile;

3-(4-(dimethylamino)piperidin-1-yl)-6-((4-((3-fluoro-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)quinoxaline-5-carbonitrile;

3-(azetidin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

3-(azetidin-1-yl)-6-((4-((3-cyanobenzyl)oxy)-3-methoxyphenyl)amino)quinoxaline-5-carbonitrile;

6-((4-(benzyloxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-(4-(dimethylamino)piperidin-1-yl)-6-((4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)amino)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-(piperazin-1-yl)quinoxaline-5-carbonitrile;

6-((4-((3-fluorobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-(prop-2-yn-1-yloxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((3-fluoro-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((4-((2-fluoro-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-methyl-piperazin-1-yl)quinoxaline-5-carbonitrile;

6-((4-((3-cyano-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-(2-methoxyethyl)piperazin-1-yl)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-propylpyridin-3-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((4-((3,4-difluorobenzyl)oxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-(4-(2-methoxyethyl)piperazin-1-yl)quinoxaline-5-carbonitrile;

6-((4-((6-ethylpyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)-3-(4-morpholino-piperidin-1-yl)quinoxaline-5-carbonitrile;

6-((4-((6-isopropylpyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((4-((6-(dimethylamino)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((1-methyl-1H-pyrazol-4-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

N-(3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)-3-(prop-1-en-2-yl)quinoxalin-6-amine;

6-((3-methoxy-4-((6-(methoxymethyl)pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)-3-(prop-1-en-2-yl)quinoxaline-5-carbonitrile;

3-isopropyl-6-((3-methoxy-4-((4-methoxybenzyl)oxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((6-(fluoromethyl)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((6-(difluoromethyl)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((6-ethoxypyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-(3,6-dihydro-2H-pyran-4-yl)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-(tetrahydro-2H-pyran-4-yl)quinoxaline-5-carbonitrile;

6-((4-((6-((dimethylamino)methyl)pyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((1-ethyl-1H-pyrazol-4-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((1-propyl-1H-pyrazol-4-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-(4-cyclopropylpiperazin-1-yl)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

3-isopropoxy-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((6-cyclopropylpyridin-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-(furan-3-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-(furan-2-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((tetrahydrofuran-2-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((5-methylthiophen-2-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((5-(methoxymethyl)pyridin-2-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-(thiophen-3-ylmethoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-(thiophen-2-ylmethoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((2-methylpyrimidin-5-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)(methyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

6-((4-((6-cyclopropylpyridin-3-yl)methoxy)-3-methoxyphenyl)(methyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((4-((1-(2-fluoroethyl)-1H-pyrazol-4-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((5-methoxypyridin-2-yl)methoxy)phenyl)amino)-3-morpholino-quinoxaline-5-carbonitrile;

3-(dimethylamino)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((1-cyclopropyl-1H-pyrazol-4-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carboxamide;

3-(3-(dimethylamino)azetidin-1-yl)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

3-(dimethylamino)-6-((3-methoxy-4-((6-methoxypyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

3-(3-methoxy-3-methylazetidin-1-yl)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile;

6-((4-((3-cyano-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)-3-(dimethylamino)quinoxaline-5-carbonitrile;

6-((4-((3-cyano-4-methoxybenzyl)oxy)-3-methoxyphenyl)amino)-3-methoxyquinoxaline-5-carbonitrile;

6-((4-((1-(cyclopropylmethyl)-1H-pyrazol-4-yl)methoxy)-3-methoxyphenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-morpholino-6-((6-((4-(trifluoromethyl)benzyl)amino)pyridin-3-yl)amino)quinoxaline-5-carbonitrile;

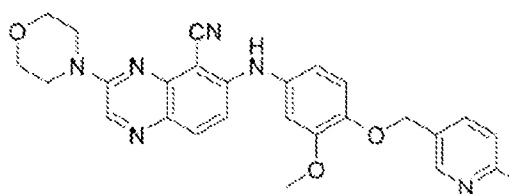
6-((5-methoxy-6-((6-methylpyridin-3-yl)methoxy)pyridin-3-yl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

6-((5-methoxy-6-((6-methoxypyridin-3-yl)methoxy)pyridin-3-yl)amino)-3-morpholinoquinoxaline-5-carbonitrile;

3-((2S,6R)-2,6-dimethylmorpholino)-6-((3-methoxy-4-((6-methylpyridin-3-yl)methoxy)phenyl)amino)quinoxaline-5-carbonitrile; or

6-((3-methoxy-4-((6-methyl-1-(λ^1 -oxidaneyl)-1 λ^4 -pyridin-3-yl)methoxy)phenyl)amino)-3-morpholinoquinoxaline-5-carbonitrile.

10. The method of claim 1, wherein the compound of formula (I) is



11. The method of claim 1, wherein the compound of formula (I) is administered orally.
12. The method of claim 1, wherein the improving pharmacokinetics comprising increasing the maximum plasma concentration (C_{max}) and/or bioavailability (AUC).
13. The method of claim 1, wherein the medicament further comprises a carrier, diluent or excipient.
14. The method of claim 13, wherein the excipient comprises a surfactant, a binder, a disintegrant and/or a lubricant.

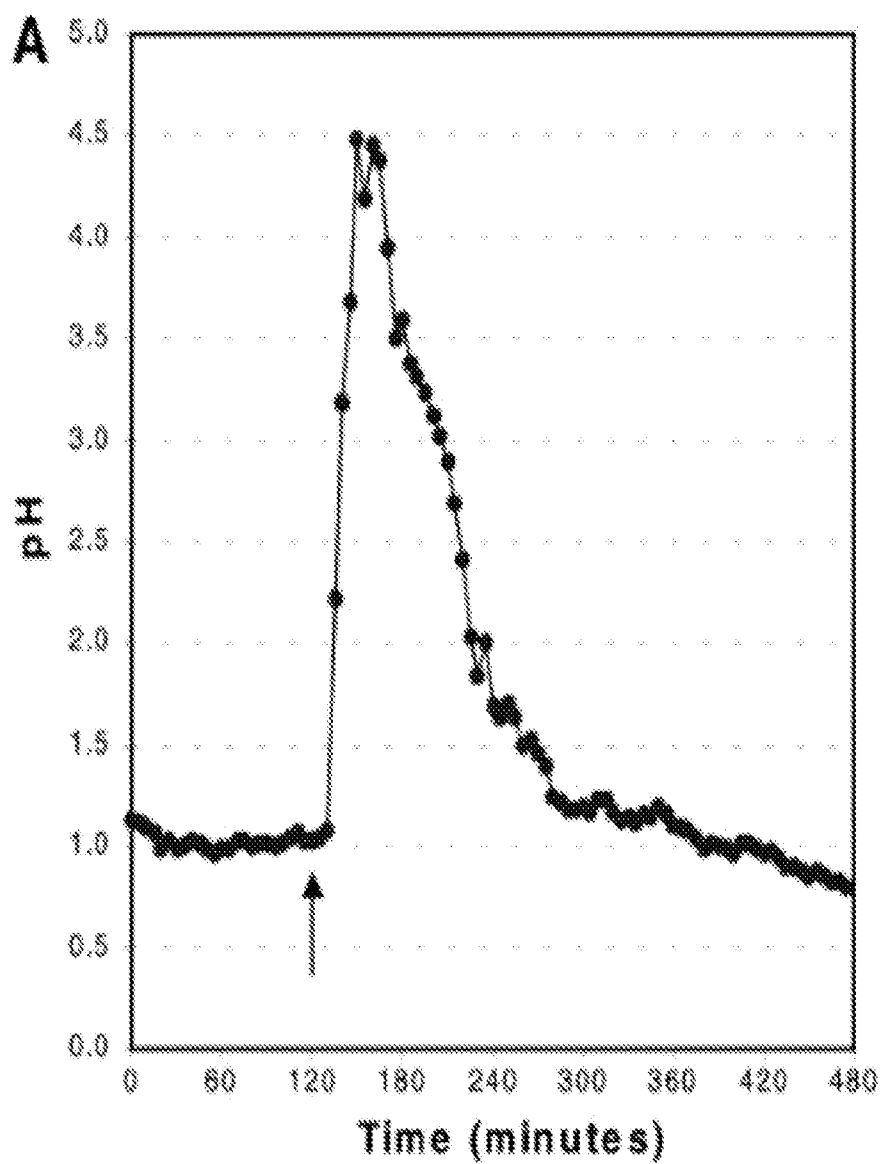


FIG. 1 (Prior Art)

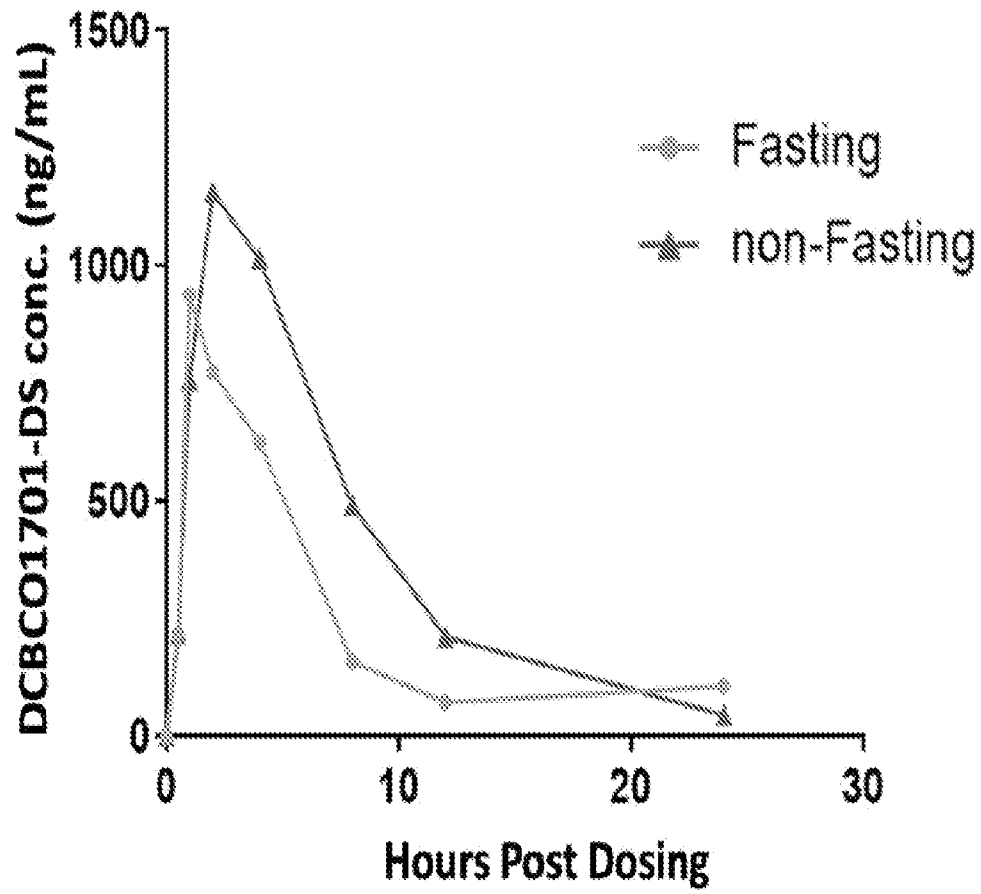


FIG. 2

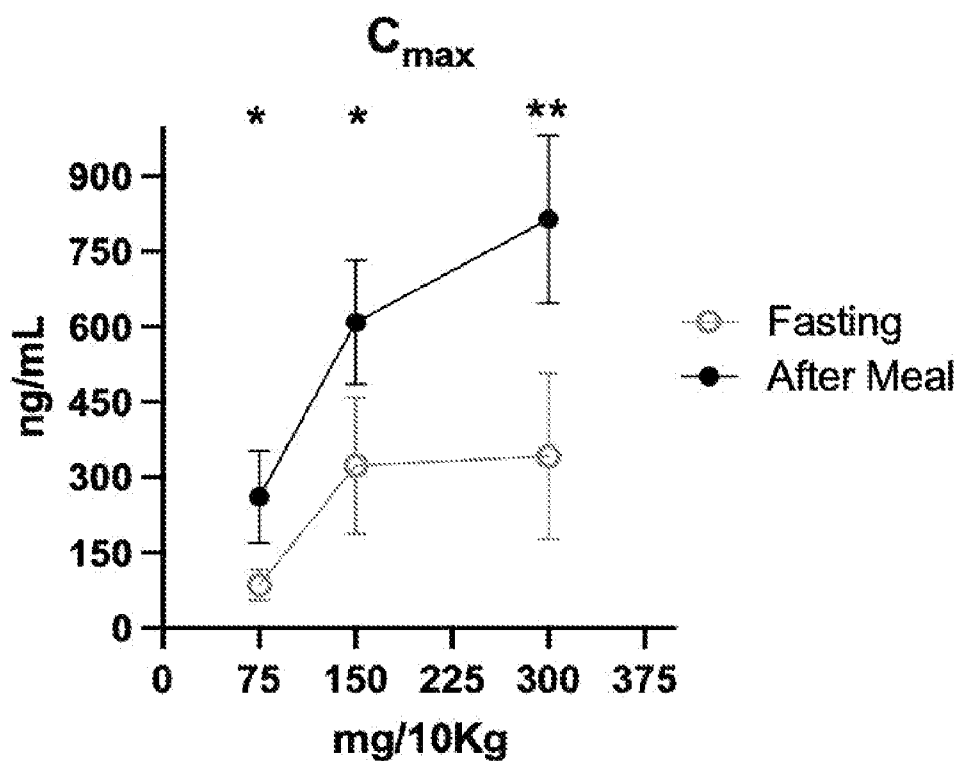


FIG. 3A

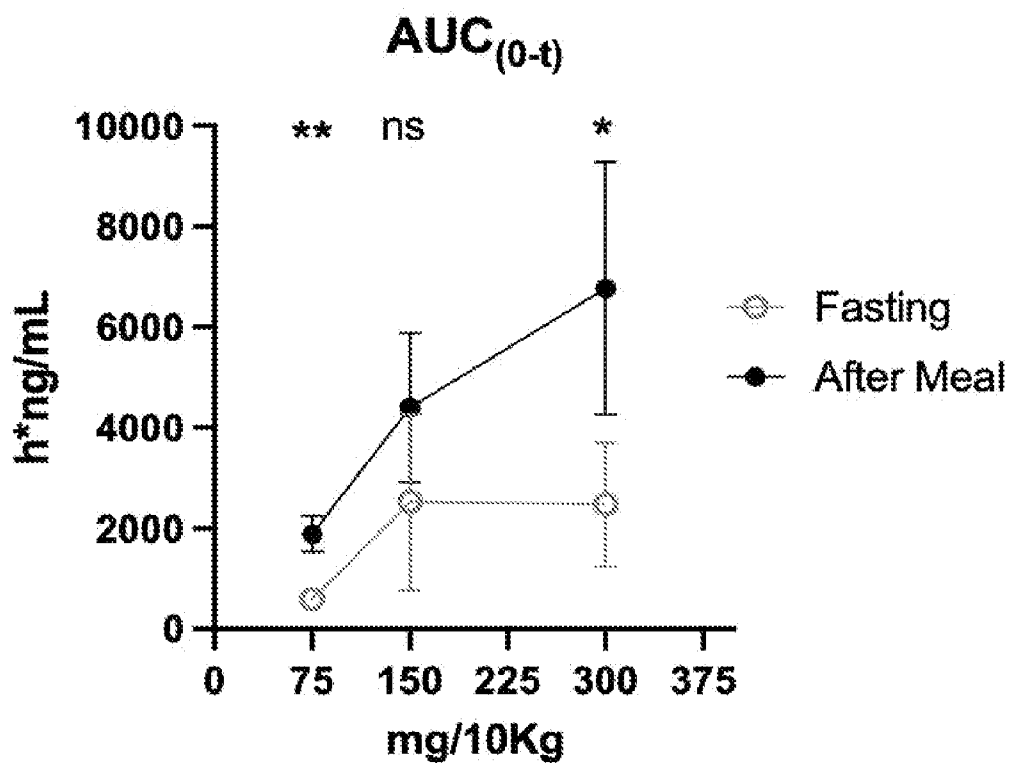


FIG. 3B