

PLK4 MODULATORS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application Number 63/546,320, filed October 30, 2023, which is incorporated by reference herein in its entirety.

BACKGROUND

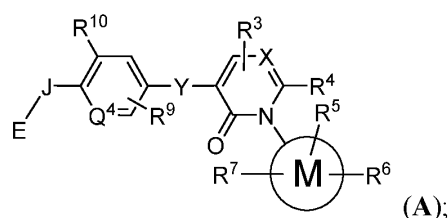
[0002] Polo-like kinases (PLKs) are a family of Ser/Thr kinases involved in multiple functions of cell division. There are five family members of PLKs, of which PLK4 has been identified as a critical component in regulating centriole duplication. Deregulation of PLK4 causes centrosome number abnormalities, mitotic defects, chromosomal instability, and tumorigenesis. Over expression of PLK4 has also been reported in many human cancers. See e.g., Zhang et al., *Front Oncol.* 2021; 11: 587554 and Zhao et al., *Journal of Cancer Research and Clinical Oncology* (2019) 145:2413–2422. Although small molecules targeting PLK4 have been shown to provide significant anticancer response, the medical field currently lacks sufficient PLK4 therapeutics needed to combat the ever growing battle with cancer.

INCORPORATION BY REFERENCE

[0003] Each patent, publication, and non-patent literature cited in the application is hereby incorporated by reference in its entirety as if each was incorporated by reference individually.

SUMMARY

[0004] Provided herein are compounds having the Formula A.



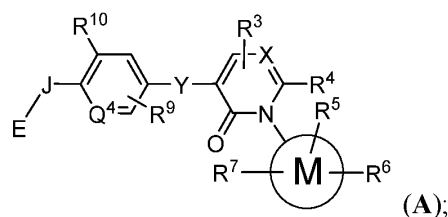
and pharmaceutically acceptable salts thereof, wherein E, J, Y, X, R⁴, R⁵, R⁶, R⁷, R⁹, R¹⁰, and Q⁴ are as defined herein. In one aspect, the compounds of Formula A modulate PLK4 (e.g., PLK4 inhibitors) and are useful in treating conditions responsive to the inhibition of PLK4 (e.g., cancer).

[0005] Pharmaceutical compositions comprising the compounds and pharmaceutically acceptable salts of the described compounds of Formula A, as well as methods for their preparation are also included.

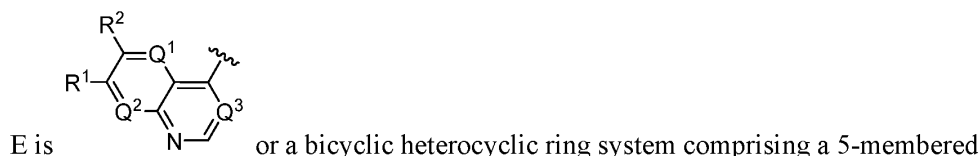
DETAILED DESCRIPTION

1. General Description of Compounds

[0006] In a first embodiment, provided is a compound having the Formula A:



or a pharmaceutically acceptable salt thereof, wherein



or a bicyclic heterocyclic ring system comprising a 5-membered ring ortho-fused to a 6-membered ring, wherein the bicyclic heterocyclic ring system is optionally substituted by 1 to 3 groups independently selected from halo, oxo, and (C₁-C₄)alkyl;

R¹ and R² are each independently -OR^a or -NR^bR^c; or R¹ and R², together with the carbon atoms to which R¹ and R² are bound, form a 5- to 7-membered heterocyclyl;

R^a is selected from (C₁-C₄)alkyl, 4- to 6-membered heterocyclyl, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), and -(C₁-C₄)alkyl[4- to 6-membered heterocyclyl], wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups independently selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C₁-C₄)alkyl, or R^b and R^c taken together with the nitrogen atom to which R^b and R^c are attached form a 4- to 6-membered heterocyclyl;

R³ is hydrogen or (C₁-C₄)alkoxy;

R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups independently selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, cyano, and -NH(C₁-C₄)alkyl;

Ring M is a 6-membered aryl or 6-membered heteroaryl;

R⁵ and R⁷ are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, hydroxy, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R⁶ is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy;

R⁸ and R⁹ are each independently hydrogen or halo;

J is O, NR¹¹, S, or CH₂;

R¹⁰ is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, or deuterated(C₁-C₄)alkyl, and R¹¹ is hydrogen; or R¹⁰ and R¹¹, together with the atoms to which R¹⁰ and R¹¹ are bound, form a 5-membered heterocyclyl;

each of Q¹ and Q² is independently CH or N;

Q³ is CR⁸ or N;

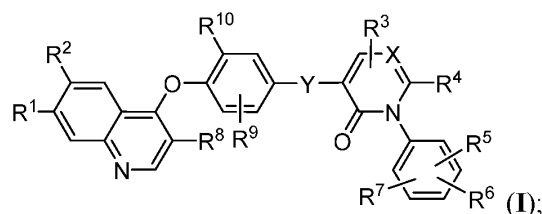
Q⁴ is N, CH, or a carbon atom attached to R⁹;

X is N, CH, or a carbon atom attached to R³; and

Y is -NHC(O)- or -C(O)NH-;

provided that: (i) if R⁴ is CH₃, then: (a) R⁵ is not hydrogen or (b) Q³ is CR⁸ wherein R⁸ is halo; and (ii) if Q¹ is N, Q² is CH, Q³ is CR⁸, and R⁴ is CH₃ or CH₂OH, then R⁸ is halo.

[0007] In a second embodiment, provided is a compound having the Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R¹ and R² are each independently -OR^a or -NR^bR^c;

R^a is selected from (C₁-C₄)alkyl, 4- to 6-membered heterocyclyl, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), and -(C₁-C₄)alkyl[4- to 6-membered heterocyclyl], wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C₁-C₄)alkyl, or R^b and R^c taken together with the nitrogen atom to which they are attached form a 4- to 6-membered heterocyclyl;

R³ is hydrogen or (C₁-C₄)alkoxy;

R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to

3 groups selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, cyano, and NH(C₁-C₄)alkyl;

R⁵ and R⁷ are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R⁶ is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, deuterated (C₁-C₄)alkoxy;

R⁸ and R⁹ are each independently hydrogen or fluoro;

R¹⁰ is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, or deuterated(C₁-C₄)alkyl;

X is CH or N; and

Y is -NHC(O)- or -C(O)NH-; provided that if R⁴ is CH₃, then R⁵ is not hydrogen.

2. Definitions

[0008] When used in connection to describe a chemical group that may have multiple points of attachment, a hyphen (-) designates the point of attachment of that group to the variable to which it is defined. For example, -NH(C₁-C₄)alkyl means that the point of attachment for this group occurs on the nitrogen atom. In another example, the oxygen atom of the (C₁-C₄)alkoxy is the point of attachment in "-(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl]." In another example, the -(C₁-C₄)alkyl is the point of attachment in "-(C₁-C₄)alkyl(C₃-C₆)cycloalkyl."

[0009] The terms "halo" and "halogen" refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

[0010] The term "alkyl" when used alone or as part of a larger moiety, such as "haloalkyl", and the like, means saturated straight-chain or branched monovalent hydrocarbon radical.

Unless otherwise specified, an alkyl group typically has 1-4 carbon atoms, *i.e.*, (C₁-C₄)alkyl. The term "deuterated alkyl" refers to an alkyl group in which one or more hydrogen atoms have been replaced with deuterium.

[0011] "Acyl" means an alkyl, alkenyl, or alkynyl attached through a carbonyl group. For example, "(C₂-C₄)acyl" includes, for example, acetyl, propionyl, and butanoyl.

[0012] "Alkoxy" means an alkyl radical attached through an oxygen linking atom, represented by -O-alkyl. For example, "(C₁-C₄)alkoxy" includes methoxy, ethoxy, propoxy, and butoxy. The term "deuterated alkoxy" refers to an alkoxy group in which one or more hydrogen atoms have been replaced with deuterium.

[0013] The term "haloalkyl" includes mono, poly, and perhaloalkyl groups where the halogens are independently selected from fluorine, chlorine, bromine, and iodine (e.g., -CF₃, -CHF₂, etc.

[0014] "Haloalkoxy" is a haloalkyl group which is attached to another moiety via an oxygen atom such as, e.g., but are not limited to -OCHF₂ or -OCF₃.

[0015] The term “4- to 6-membered heterocyclyl” means a 4- to 6-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. The term “5- to 7-membered heterocyclyl” means a 5- to 7-membered saturated or partially unsaturated heterocyclic ring containing 1 to 4 heteroatoms independently selected from N, O, and S. A heterocyclyl ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. Examples of monocyclic saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, oxazolidinyl, piperazinyl, dioxanyl, oxetanyl, dioxolanyl, morpholinyl, dihydrofuranyl, dihydropyranyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, and tetrahydropyrimidinyl. Optional substituents on a heterocyclyl group may be present on any substitutable position and, include, *e.g.*, the position at which the heterocyclyl is attached.

[0016] The term “(C₃-C₆)cycloalkyl” means a hydrocarbon ring system that is completely saturated and contains from three to six carbon atoms. (C₃-C₆)cycloalkyl groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. It will be understood that when specified, optional substituents on a (C₃-C₆)cycloalkyl (*e.g.*, in the case of an optionally substituted (C₃-C₆)cycloalkyl) may be present on any substitutable position and, include, *e.g.*, the position at which the (C₃-C₆)cycloalkyl group is attached.

[0017] In some aspects, the described compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center.

“Enantiomer” means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that contain two or more asymmetrically substituted carbon atoms.

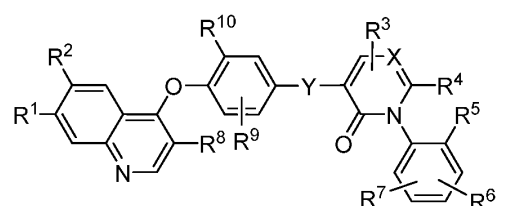
[0018] “Racemate” or “racemic mixture” means a mixture of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity, *i.e.*, they do not rotate the plane of polarized light.

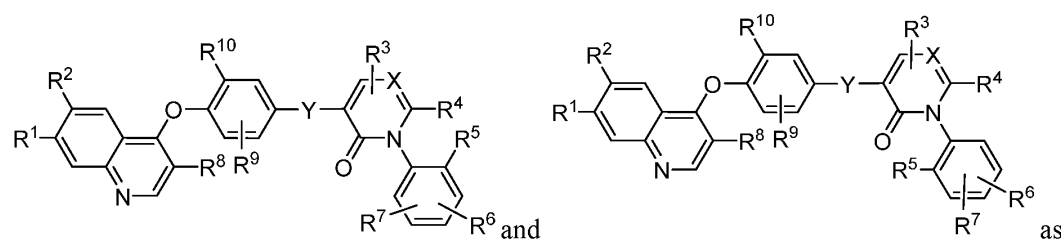
[0019] If the stereochemistry of a described compound is named or depicted by structure, in compositions comprising a population of molecules with a structure according to the described compound (*e.g.*, pharmaceutical compositions), the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 97%, 98%, 99%, or 99.9% by weight pure relative to all of the other stereoisomers in the population of molecules, unless specified otherwise. Percent by weight pure relative to all of the other stereoisomers is the ratio of the weight of one stereoisomer over the weight of the other stereoisomers.

[0020] When a described compound is named or depicted by structure without indicating the stereochemistry, in compositions comprising a population of molecules with a structure according to the described compound (e.g., pharmaceutical compositions), it is to be understood that the composition encompasses compositions comprising one stereoisomer free of other stereoisomers, mixtures of stereoisomers, or mixtures of stereoisomers in which one or more stereoisomers is enriched relative to the other stereoisomer(s), unless specified otherwise.

[0021] In some embodiments, the compounds described herein exist as atropisomers. Atropisomers are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers. Unless indicated otherwise, when a described compound is named or depicted by structure without indicating that the structure is a single atropisomer, in compositions (e.g., pharmaceutical compositions) comprising a population of molecules with a structure according to the described compound, it is to be understood that the composition encompasses compositions comprising one atropisomer isomer free of other atropisomers, an equal mixture of atropisomers, or a mixtures of atropisomers in which one atropisomer is enriched relative to the other atropisomer.

[0022] For example, when R⁵ is not hydrogen and when R⁵ is ortho to the ring bearing R⁴ and R³

 , when used to describe the structure of a population of molecules in a composition, encompasses both atropisomers as a mixture i.e.,



well as each atropisomer in an enriched amount as described above.

[0023] As used herein, compositions comprising a “single atropisomer” means that the depicted or named compound is enriched in the composition with one atropisomer or another in an amount of e.g., at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, at least 97%, at least 98%, or at least 99% of a single atropisomer unless specified otherwise. In some embodiment, the compounds described herein are present and/or isolated as a pure single

atropisomer. A “pure single atropisomer” means that the compound is a single atrophic isomer with no other detectable amounts of other atropisomers.

[0024] In some embodiments, a compound (e.g., atropisomer) herein is characterized by specific optical rotation (otherwise referred to as “specific rotation”) as measured by a polarimeter. An compound that rotates the plane of polarization of plane polarized light in a clockwise direction corresponds with a positive specific optical rotation value, while an compound that rotates the plane of polarization of plane polarized light in a counterclockwise direction corresponds with a negative specific optical rotation value. Specific optical rotation is defined by $[\alpha]_{\lambda}^{\theta} = \alpha/\gamma l$, where α is the angle through which plane polarized light is rotated by a solution of mass concentration γ and path length l . θ is the Celsius temperature and λ the wavelength of the light at which the measurement is carried out.

[0025] In some embodiments, specific optical rotation of a compound herein is determined at the D line of sodium (589 nm) at 20 °C or 25 °C. In some embodiments, the specific optical rotation of a compound herein is determined using a solution of the compound. The solvent in the solution can be, for example, ethanol, methanol, DMSO, acetone, or water.

[0026] In some embodiments, a compound herein is characterized by its retention time (i.e. R_T) when subjected to liquid chromatography, such as, for example, high pressure liquid chromatography (HPLC) or supercritical fluid chromatography (SFC). For chiral compounds (e.g., an atropisomer herein), stereoisomers can be distinguished from one another by their retention times when subjected to liquid chromatography using a chiral stationary phase. For example, an atropisomer can be later-eluting or earlier-eluting relative to its enantiomer when subjected to chiral HPLC analysis.

[0027] The terms “subject” and “patient” may be used interchangeably, and means a mammal in need of treatment, e.g., companion animals (e.g., dogs, cats, and the like), farm animals (e.g., cows, pigs, horses, sheep, goats and the like) and laboratory animals (e.g., rats, mice, guinea pigs and the like). Typically, the subject is a human in need of treatment.

[0028] The term “inhibit,” “inhibition” or “inhibiting” includes a decrease in the baseline activity of a biological activity or process e.g., to inhibit the activity of PLK4.

[0029] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some aspects, treatment may be administered after one or more symptoms have developed, i.e., therapeutic treatment. In other aspects, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of exposure to a particular organism, or other susceptibility factors),

i.e., prophylactic treatment. Treatment may also be continued after symptoms have resolved, for example to delay their recurrence.

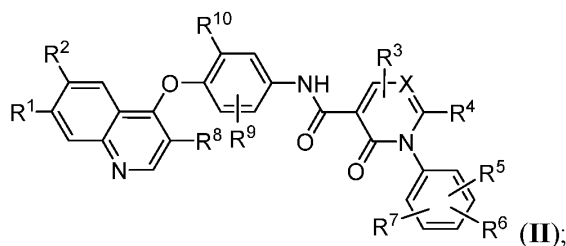
[0030] The term “pharmaceutically acceptable carrier” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions described herein include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0031] For use in medicines, the salts of the compounds described herein refer to non-toxic “pharmaceutically acceptable salts.” Pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable acid addition salts of the compounds described herein include e.g. salts of inorganic acids (such as hydrochloric acid, hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids). Compounds of the present teachings with acidic groups such as carboxylic acids can form pharmaceutically acceptable salts with pharmaceutically acceptable base(s). Suitable pharmaceutically acceptable basic salts include e.g., ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts). Compounds with a quaternary ammonium group also contain a counteranion such as chloride, bromide, iodide, acetate, perchlorate and the like. Other examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, benzoates and salts with amino acids such as glutamic acid.

[0032] The term “effective amount” or “therapeutically effective amount” refers to an amount of a compound described herein that will elicit a desired or beneficial biological or medical response of a subject e.g., a dosage of between 0.01 - 100 mg/kg body weight/day.

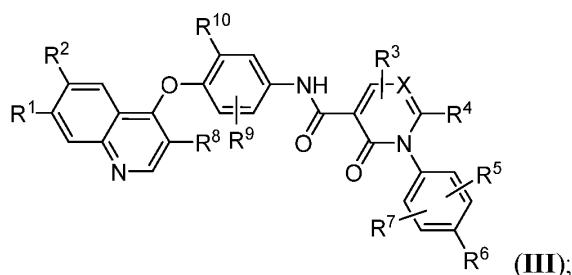
3. *Description of Exemplary Compounds:*

[0033] In a third embodiment, the compound of Formula **I** is of the Formula **II**:



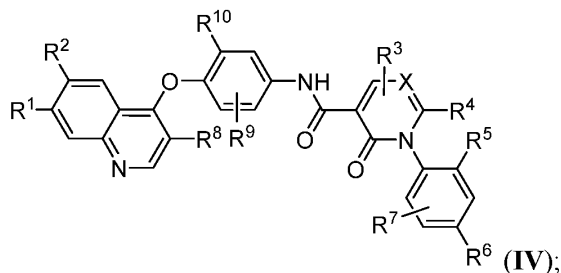
or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula I.

[0034] In a fourth embodiment, the compound of Formula I is of the Formula III:



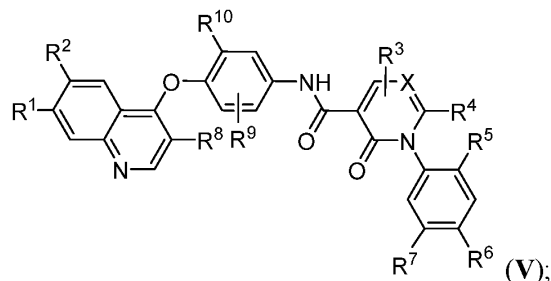
or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula I.

[0035] In a fifth embodiment, the compound of Formula I is of the Formula IV:



or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula I.

[0036] In a sixth embodiment, the compound of Formula I is of the Formula V:



or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula I.

[0037] In a seventh embodiment, R^{10} in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is halo, wherein the remaining variables are as described above for Formula **I**. Alternatively, as part of a seventh embodiment, R^{10} in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **I**.

[0038] In an eighth embodiment, R^5 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo, wherein the remaining variables are as described above for Formula **I** or the seventh embodiment. Alternatively, as part of a eighth embodiment, R^5 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo, wherein the remaining variables are as described above for Formula **I** or the seventh embodiment. In another alternative, as part of a eighth embodiment, R^5 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is CH₃, CF₃, or chloro, wherein the remaining variables are as described above for Formula **I** or the seventh embodiment.

[0039] In an ninth embodiment, X in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is CH, wherein the remaining variables are as described above for Formula **I** or the seventh or eighth embodiment.

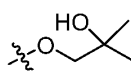
[0040] In a tenth embodiment, R^3 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is hydrogen, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to ninth embodiments.

[0041] In a eleventh embodiment, R^9 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is hydrogen, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to tenth embodiments.

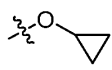
[0042] In an twelfth embodiment, R^8 in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to eleventh embodiments.

[0043] In a thirteenth embodiment, each R^a in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is independently selected from (C₁-C₄)alkyl, oxetanyl, cyclopropyl, cyclobutyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), -(C₁-C₄)alkyl[pyrrolidinyl], -(C₁-C₄)alkyl[piperizinyl], and -(C₁-C₄)alkyl[morpholinyl], wherein said cyclopropyl, cyclobutyl, piperazinyl, pyrrolidinyl, and oxetanyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to twelfth embodiments. Alternatively, as part of a

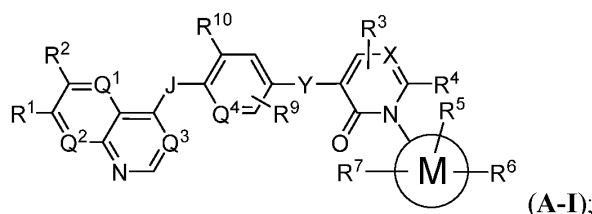
R⁷ in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof,

is hydrogen, fluoro, bromo, chloro, , or cyano.

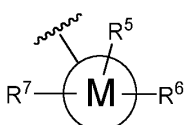
[0046] In a sixteenth embodiment, R⁶ in the compound of any one of Formulae **I** to **V**, or a

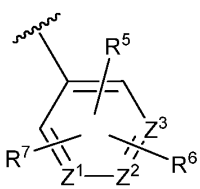
pharmaceutically acceptable salt thereof, is OCH₃, fluoro, OCHF₂, OCF₃, , OCD₃, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to fifteenth embodiments. Alternatively, as part of a sixteenth embodiment, R⁶ in the compound of any one of Formulae **I** to **V**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **I** or any one of the seventh to fifteenth embodiments.

[0047] In a seventeenth embodiment, the compound of Formula **A** is of the Formula **A-I**:

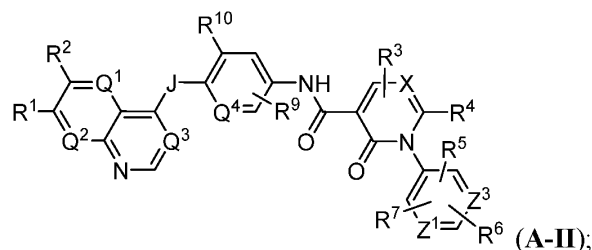


or a pharmaceutically acceptable salt thereof, wherein the variables are as described above for Formula **A**.

[0048] In an eighteenth embodiment,  in the compound of Formulae **A** or **A-**

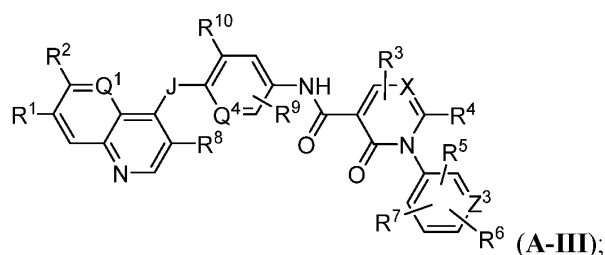
I, or a pharmaceutically acceptable salt thereof, is , wherein Z¹, Z², and Z³ are each independently N, CH, or a carbon atom bound to one of R⁵, R⁶, and R⁷, and the remaining variables are as described above for Formula **A**.

[0049] In a nineteenth embodiment, the compound of Formula **A** is of the Formula **A-II**:

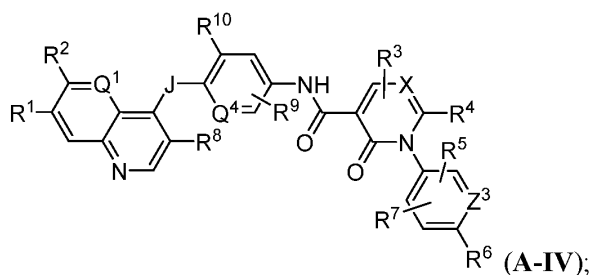


or a pharmaceutically acceptable salt thereof, wherein Z¹ and Z³ are as described in the eighteenth embodiment the remaining variables are as described above for Formula **A**.

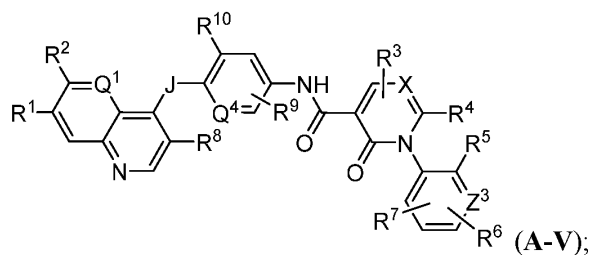
[0051] In a twenty-first embodiment, the compound of Formula **A** is of the Formula **A-III**:



[0052] In a twenty-second embodiment, the compound of Formula **A** is of the Formula **A-IV**:

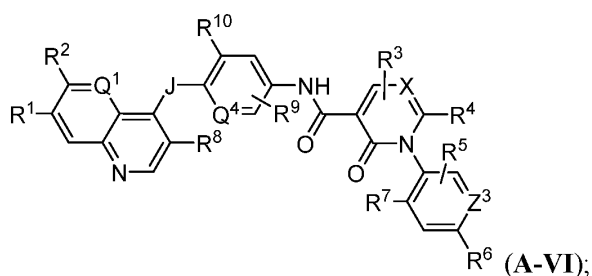


[0053] In a twenty-third embodiment, the compound of Formula **A** is of the Formula **A-V**:



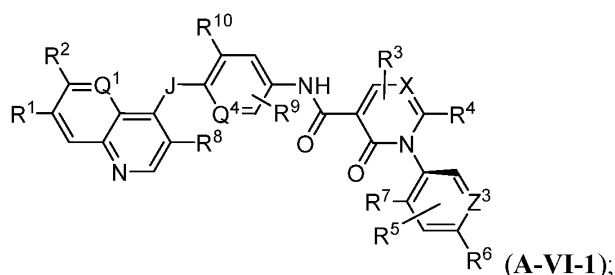
or a pharmaceutically acceptable salt thereof, wherein Z^3 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

[0054] In a twenty-fourth embodiment, the compound of Formula A is of the Formula A-VI:



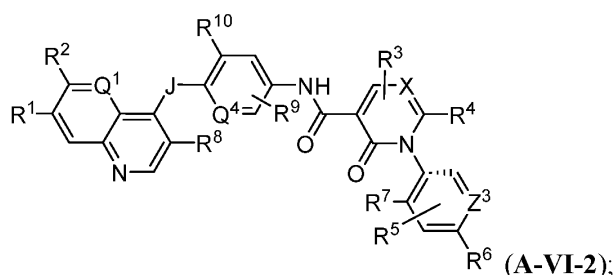
or a pharmaceutically acceptable salt thereof, wherein Z^3 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

[0055] In a twenty-fifth embodiment, the compound of Formula A is of the Formula A-VI-1:



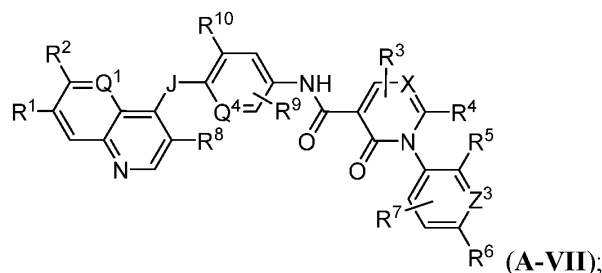
or a pharmaceutically acceptable salt thereof, wherein Z^3 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

[0056] In a twenty-sixth embodiment, the compound of Formula A is of the Formula A-VI-2:



or a pharmaceutically acceptable salt thereof, wherein Z^3 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

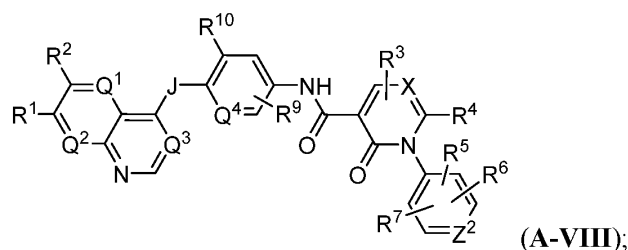
[0057] In a twenty-seventh embodiment, the compound of Formula A is of the Formula A-VII:



or a pharmaceutically acceptable salt thereof, wherein Z^3 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

[0058] In a twenty-eighth embodiment, Z^3 in a compound of any one of Formulae **A-II**, **A-III**, **A-IV**, **A-V**, **A-VI**, **A-VI-1**, **A-VI-2**, and **A-VII**, or a pharmaceutically acceptable salt thereof, is N, wherein the remaining variables are as described above for Formula A.

[0059] In a twenty-ninth embodiment, the compound of Formula A is of the Formula **A-VIII**:



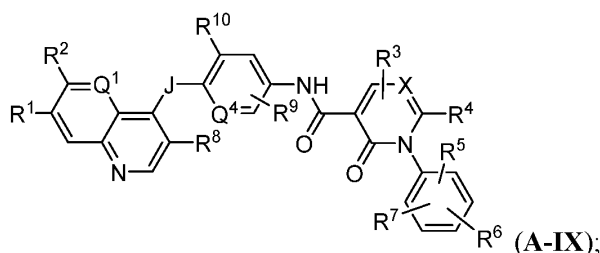
or a pharmaceutically acceptable salt thereof, wherein Z^2 is as described in the eighteenth embodiment and the remaining variables are as described above for Formula A.

[0060] In a thirtieth embodiment, Z^2 in a compound of Formula **A-VIII** or the eighteenth embodiment, or a pharmaceutically acceptable salt thereof is N, wherein the remaining variables are as described above for Formula A.

[0061] In a thirty-first embodiment, in a compound of any one of Formulae **A**, **A-II**, and **A-VIII** or the eighteenth embodiment, Q^1 and Q^2 each are CH, and Q^3 is CR^8 , wherein the remaining variables are as described above for Formula A or the eighteenth, twentieth, or twenty-eighth embodiments. Alternatively, as a part of a thirty-first embodiment, in a compound of any one of Formulae **A**, **A-II**, and **A-VIII** or the eighteenth embodiment, Q^1 and Q^2 each are CH, and Q^3 is N, wherein the remaining variables are as described above for Formula A or the eighteenth, twentieth, or twenty-eighth embodiments. In another alternative, as a part of a thirty-first embodiment, in a compound of any one of Formulae **A**, **A-II**, and **A-VIII** or the eighteenth embodiment, Q^1 is N, Q^2 is CH, and Q^3 is CR^8 , wherein the remaining variables are as described above for Formula A or the eighteenth, twentieth, or twenty-eighth embodiments. In yet another alternative, as a part of a thirty-first embodiment, in a compound of any one of Formulae **A**, **A-II**, and **A-VIII** or the eighteenth embodiment, Q^1 is CH, Q^2 is N, and Q^3 is CR^8 , wherein the

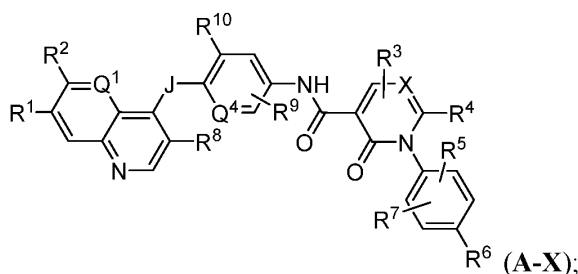
remaining variables are as described above for Formula A or the eighteenth, twentieth, or twenty-eighth embodiments.

[0062] In a thirty-second embodiment, the compound of Formula A is of the Formula A-IX:



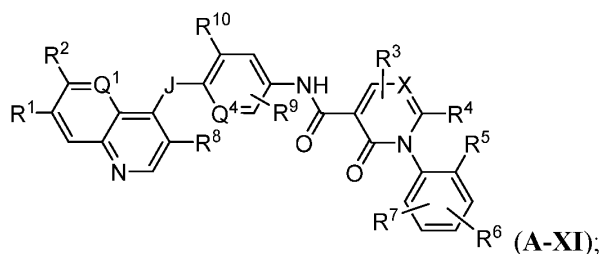
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0063] In a thirty-third embodiment, the compound of Formula A is of the Formula A-X:



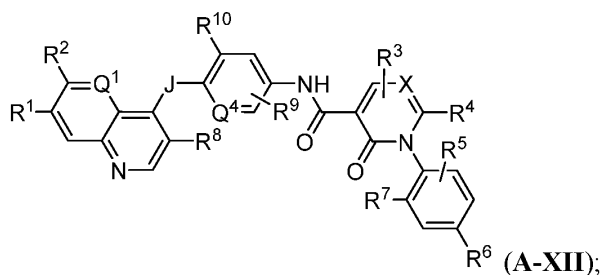
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0064] In a thirty-fourth embodiment, the compound of Formula A is of the Formula A-XI:



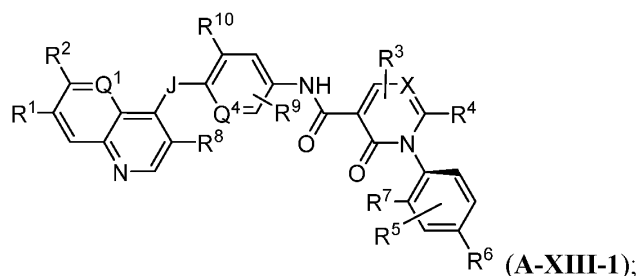
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0065] In a thirty-fifth embodiment, the compound of Formula A is of the Formula A-XII:



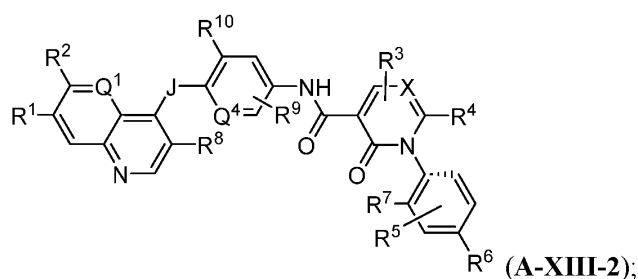
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0066] In a thirty-sixth embodiment, the compound of Formula A is of the Formula A-XIII-1:



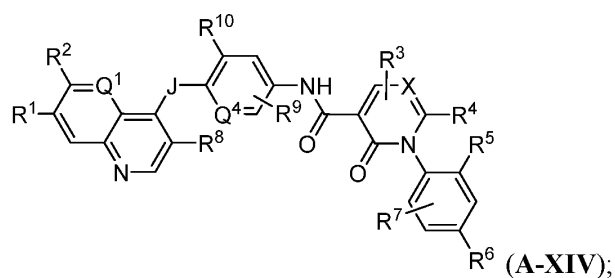
or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0067] In a thirty-seventh embodiment, the compound of Formula A is of the Formula A-XIII-2:



or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0068] In a thirty-eighth embodiment, the compound of Formula A is of the Formula A-XIV:

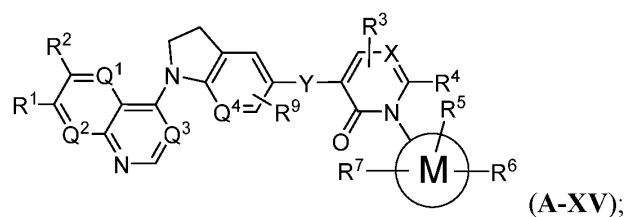


or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula A.

[0069] In a thirty-ninth embodiment, J in the compound of any one of Formulae A and A-I to A-XIV, or a pharmaceutically acceptable salt thereof, is O, wherein the remaining variables are as described above for Formula A or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, and thirty-first embodiments. Alternatively, as a part of a thirty-ninth embodiment, J in the compound of any one of Formulae A and A-I to A-XIV, or a pharmaceutically acceptable salt thereof, is S, wherein the remaining variables are as described above for Formula A or any

one of the eighteenth, twentieth, twenty-eighth, thirtieth, and thirty-first embodiments. In another alternative, as a part of a thirty-ninth embodiment, J in the compound of any one of Formulae **A** and **A-I** to **A-XIV**, or a pharmaceutically acceptable salt thereof, is CH₂, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, and thirty-first embodiments. In yet another alternative, as a part of a thirty-ninth embodiment, J in the compound of any one of Formulae **A** and **A-I** to **A-XIV**, or a pharmaceutically acceptable salt thereof, is NR¹¹, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, and thirty-first embodiments.

[0070] In a fortieth embodiment, the compound of Formula **A** is of the Formula **A-XV**:



or a pharmaceutically acceptable salt thereof, wherein the remaining variables are as described above for Formula **A** or the eighteenth embodiment.

[0071] In a forty-first embodiment, R¹⁰ in the compound of any one of Formulae **A** and **A-I** to **A-XIV**, or a pharmaceutically acceptable salt thereof, is halo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, and thirty-ninth embodiments. Alternatively, as a part of a forty-first embodiment, R¹⁰ in the compound of any one of Formulae **A** and **A-I** to **A-XIV**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, and thirty-ninth embodiments.

[0072] In a forty-second embodiment, Q¹ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is N, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-ninth, and forty-first embodiments. Alternatively, as a part of a forty-second embodiment, Q¹ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is CH, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-ninth, and forty-first embodiments.

[0073] In a forty-third embodiment, Q⁴ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is N, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth,

thirtieth, thirty-first, thirty-ninth, forty-first, and forty-second embodiments. Alternatively, as a part of a forty-third embodiment, Q^4 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is a carbon atom bound to R^9 , wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, and forty-second embodiments.

[0074] In a forty-fourth embodiment, R^9 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is hydrogen, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, and forty-third embodiments. Alternatively, as a part of a forty-fourth embodiment, R^9 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, and forty-third embodiments.

[0075] In a forty-fifth embodiment, R^5 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is hydrogen, cyano, hydroxy, (C_1-C_4) alkyl, halo (C_1-C_4) alkyl, or halo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, forty-third, and forty-fourth embodiments. Alternatively, as a part of a forty-fifth embodiment, R^5 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is (C_1-C_4) alkyl, halo (C_1-C_4) alkyl, cyano, hydroxy, or halo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, forty-third, and forty-fourth embodiments. In another alternative, as a part of a forty-fifth embodiment, R^5 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is CH_3 , CF_3 , cyano, hydroxy, fluoro, chloro, or bromo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, forty-third, and forty-fourth embodiments.

[0076] In a forty-sixth embodiment, X in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is CH , wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, forty-third, forty-fourth, and forty-fifth embodiments. Alternatively, as a part of a forty-sixth embodiment, X in the compound of any

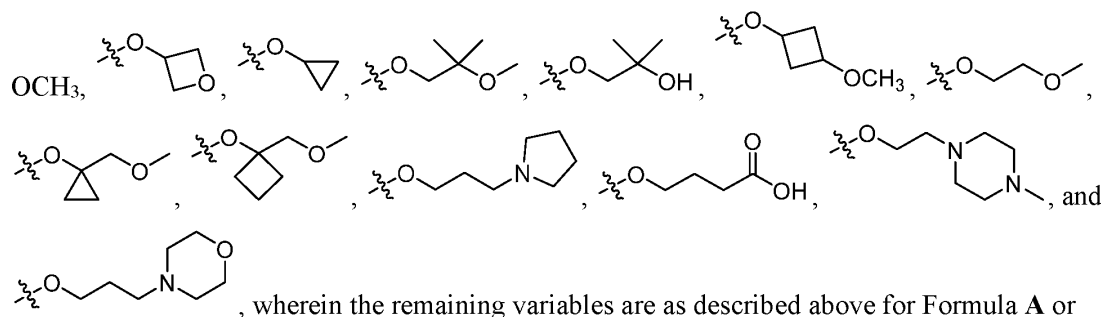
one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is N, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, forty-first, forty-second, forty-third, forty-fourth, and forty-fifth embodiments.

[0077] In a forty-seventh embodiment, R^3 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is hydrogen, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to forty-sixth embodiments.

[0078] In a forty-eighth embodiment, R^8 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-ninth, and forty-first to forty-seventh embodiments. Alternatively, as a part of a forty-eighth embodiment, R^8 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is hydrogen, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-ninth, and forty-first to forty-seventh embodiments.

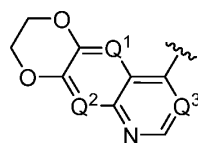
[0079] In a forty-ninth embodiment, R^a in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is independently selected from (C₁-C₄)alkyl, oxetanyl, cyclopropyl, cyclobutyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), -(C₁-C₄)alkyl[pyrrolidinyl], -(C₁-C₄)alkyl[piperizinyl], and -(C₁-C₄)alkyl[morpholinyl], wherein said cyclopropyl, cyclobutyl, piperazinyl, pyrrolidinyl, and oxetanyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to forty-eighth embodiments.

[0080] In a fiftieth embodiment, R^1 and R^2 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, are each independently selected from

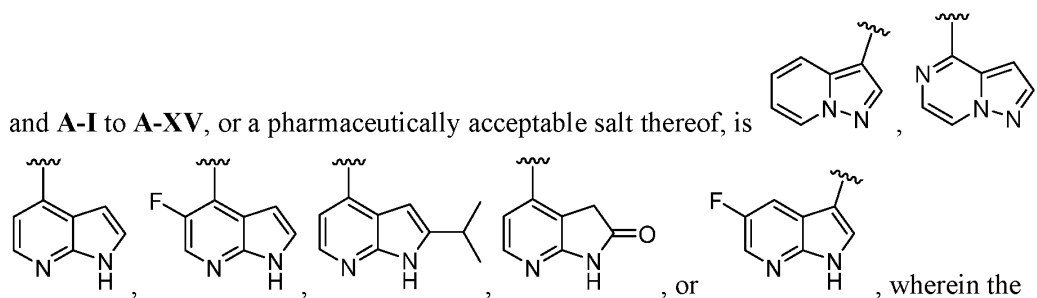


any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to forty-eighth embodiments.

[0081] In a fifty-first embodiment, E in the compound of any one of Formulae **A** and **A-I** to **A-**



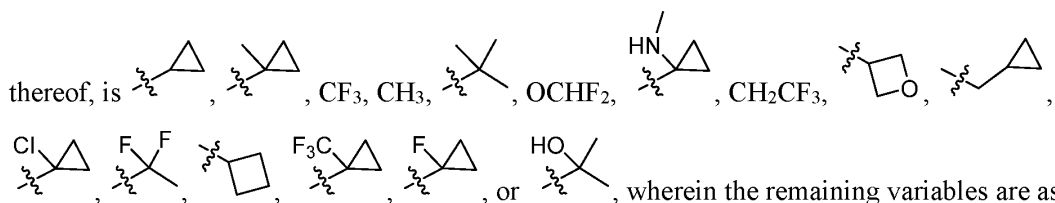
XV, or a pharmaceutically acceptable salt thereof, is , wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fiftieth embodiments. Alternatively, as a part of a fifty-first embodiment, E in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is pyrazolo[1,5-a]pyridyl, pyrazolo[1,5-a]pyrazolyl, 1H-pyrrolo[2,3-b]pyridyl, 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one, each of which is optionally substituted with 1 to 3 groups independently selected from halo and (C₁-C₄)alkyl, wherein the remaining variables are as described above for Formula **A**. In another alternative, as a part of a fifty-first embodiment, E in the compound of any one of Formulae **A**



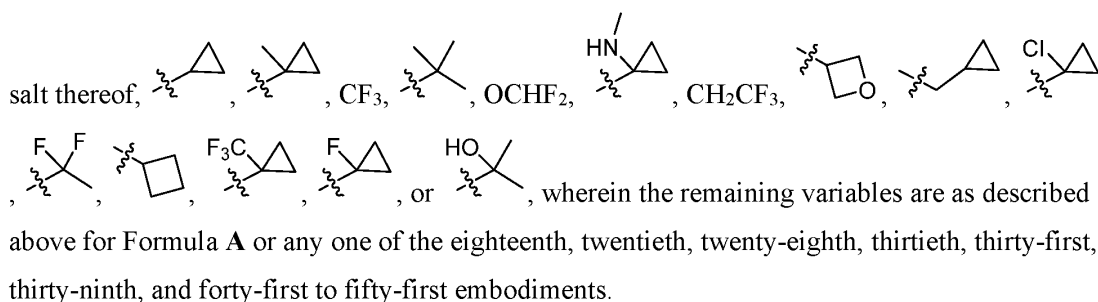
and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is , wherein the remaining variables are as described above for Formula **A**.

[0082] In a fifty-second embodiment, R⁴ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-first embodiments. Alternatively, as a part of a fifty-second embodiment, R⁴ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said (C₃-C₆)cycloalkyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl, wherein the remaining variables are as described above for Formula **A** or any

one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-first embodiments. In another alternative, as a part of a fifty-second embodiment, R^4 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt

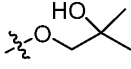


described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-first embodiments. In yet another alternative, as a part of a fifty-second embodiment, R^4 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is (C₂-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-first embodiments. In yet another alternative, as a part of a fifty-second embodiment, R^4 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is C₂-C₄alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said cyclopropyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-first embodiments. In yet another alternative, as a part of a fifty-second embodiment, R^4 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable

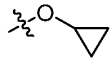


[0083] In a fifty-third embodiment, R^7 in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is hydrogen, halo, -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl], or cyano, wherein the remaining variables are as described

above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-second embodiments. Alternatively, as a part of a fifty-third

embodiment, is hydrogen, fluoro, bromo, chloro, , or cyano, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-second embodiments. In another alternative, as a part of a fifty-third embodiment, is hydrogen, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-second embodiments. In yet another alternative, as a part of a fifty-third embodiment, is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, cyano, hydroxy, or halo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-second embodiments. In yet another alternative, as a part of a fifty-third embodiment, is CH₃, CF₃, cyano, hydroxy, fluoro, chloro, or bromo, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-second embodiments.

[0084] In a fifty-fourth embodiment, R⁶ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-third embodiments. Alternatively, as a part of a fifty-fourth embodiment, R⁶ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt

thereof, is cyano, CHF₂, hydroxy, acetyl, OCH₃, OEt, fluoro, OCHF₂, OCF₃, , or OCD₃, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-third embodiments. In another alternative, as a part of a fifty-fourth embodiment, R⁶ in the compound of any one of Formulae **A** and **A-I** to **A-XV**, or a pharmaceutically acceptable salt thereof, is fluoro, wherein the remaining variables are as described above for Formula **A** or any one of the eighteenth, twentieth, twenty-eighth, thirtieth, thirty-first, thirty-ninth, and forty-first to fifty-third embodiments.

[0085] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-

dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0086] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide, wherein the compound has a negative specific optical rotation.

[0087] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0088] In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0089] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-

(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0090] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0091] In some embodiments, the compound of Formula **A** is N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0092] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0093] In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-

4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthylloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0094] In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-4-quinazolinylloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-4-quinazolinylloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[4-(6,7-dimethoxy-4-quinazolinylloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0095] In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylthio)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylthio)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylthio)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0096] In some embodiments, the compound of Formula **A** is 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide. In some embodiments, the compound of Formula **A** is 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula **A** is 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0097] In some embodiments, the compound of Formula **A** is N-[6-(3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-quinolylamino)phenyl]-6'-ethoxymethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide. In some embodiments, the compound of Formula **A** is N-[6-(3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-quinolylamino)phenyl]-6'-

ethoxymethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a positive specific optical rotation. In some embodiments, the compound of Formula A is N-[6-(3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl)-6-cyclopropyl-quinolylamino)phenyl]-6'-ethoxymethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide, wherein the compound has a negative specific optical rotation.

[0098] In some embodiments, the disclosure provides a compound selected from any one of those in Table 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the disclosure provides a compound selected from any one of those in Table 2, or a pharmaceutically acceptable salt thereof.

[0099] In some embodiments, compounds described herein (e.g., as in any one of the first to fifty-fourth embodiments) are a single atropisomer.

[0100] Compounds having the disclosed formulae are further disclosed in the Exemplification and are included in the present disclosure. Pharmaceutically acceptable salts thereof as well as the neutral forms are included.

4. Uses, Formulation and Administration

[0101] The compounds and compositions described herein are generally useful for modulating the activity of PLK4. In some aspects, the compounds and pharmaceutical compositions described herein inhibit the activity PLK4.

[0102] In some aspects, the compounds and pharmaceutical compositions described herein are useful in treating a condition associated with PLK4. Thus, provided herein are methods of treating a condition associated with PLK4, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof. Also provided is the use of a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a condition associated with PLK4. Also provided is a compound described herein, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a disclosed compound or pharmaceutically acceptable salt thereof, for use in treating a condition associated with protein PLK4.

[0103] In some embodiments, the present disclosure provides a pharmaceutical composition, the pharmaceutical composition comprising a population of molecules with a structure according

to a compound provided herein, wherein at least about 60%, 70%, 80%, 90%, 97%, 98%, 99%, or 99.9% of the molecules of the population have the same atropisomeric configuration.

[0104] In some aspects, the compounds and pharmaceutical compositions described herein are useful in treating cancer. Such cancers include, but are not limited to, lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiforme, ovarian cancer, lymphoma, leukemia, melanoma, sarcoma, paraneoplasia, osteosarcoma, germinoma, glioma and mesothelioma. In one embodiment, the cancer is lung cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiforme or ovarian cancer. In another embodiment, the cancer is lung cancer, breast cancer, colon cancer, brain cancer, neuroblastoma, prostate cancer, melanoma, glioblastoma multiforme or ovarian cancer. In yet another specific embodiment, the cancer is a breast cancer. In another embodiment, the cancer is a basal sub-type breast cancer or a luminal B sub-type breast cancer. In one embodiment, the basal sub-type breast cancer is ER (estrogen receptor), HER2 and PR (progesterone receptor) negative breast cancer. In another embodiment, the cancer is a soft tissue cancer. A “soft tissue cancer” is an art-recognized term that encompasses tumors derived from any soft tissue of the body. Such soft tissue connects, supports, or surrounds various structures and organs of the body, including, but not limited to, smooth muscle, skeletal muscle, tendons, fibrous tissues, fatty tissue, blood and lymph vessels, perivascular tissue, nerves, mesenchymal cells and synovial tissues. Thus, soft tissue cancers can be of fat tissue, muscle tissue, nerve tissue, joint tissue, blood vessels, lymph vessels, and fibrous tissues. Soft tissue cancers can be benign or malignant. Generally, malignant soft tissue cancers are referred to as sarcomas, or soft tissue sarcomas. There are many types of soft tissue tumors, including lipoma, lipoblastoma, hibernoma, liposarcoma, leiomyoma, leiomyosarcoma, rhabdomyoma, rhabdomyosarcoma, neurofibroma, schwannoma (neurilemoma), neuroma, malignant schwannoma, neurofibrosarcoma, neurogenic sarcoma, nodular tenosynovitis, synovial sarcoma, hemangioma, glomus tumor, hemangiopericytoma, hemangioendothelioma, angiosarcoma, Kaposi sarcoma, lymphangioma, fibroma, elastofibroma, superficial fibromatosis, fibrous histiocytoma, fibrosarcoma, fibromatosis, dermatofibrosarcoma protuberans (DFSP), malignant fibrous histiocytoma (MFH), myxoma, granular cell tumor, malignant mesenchymomas, alveolar soft-part sarcoma, epithelioid sarcoma, clear cell sarcoma, and desmoplastic small cell tumor. In one embodiment, the soft tissue cancer is a sarcoma selected from the group consisting of a fibrosarcoma, a gastrointestinal sarcoma, a leiomyosarcoma, a dedifferentiated liposarcoma, a pleomorphic liposarcoma, a malignant fibrous histiocytoma, a round cell sarcoma, and a synovial sarcoma. In some embodiments, the cancer is acute myeloid leukemia, a myelodysplastic syndrome, chronic myelomonocytic leukemia, triple negative breast cancer,

advanced breast cancer, metastatic breast cancer, or prostate cancer. In some embodiments, the cancer is acute myeloid leukemia. In some embodiments, the cancer is a myelodysplastic syndrome. In some embodiments, the cancer is chronic myelomonocytic leukemia. In some embodiments, the cancer is triple negative breast cancer. In some embodiments, the cancer is advanced breast cancer. In some embodiments, the cancer is metastatic breast cancer. In some embodiments, the cancer is prostate cancer.

[0105] In certain aspects, a pharmaceutical composition described herein is formulated for administration to a patient in need of such composition. Pharmaceutical compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the pharmaceutical compositions described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents.

[0106] A pharmaceutical composition of the disclosure can be used, for example, before, during, or after treatment of a subject with, for example, another pharmaceutical agent.

[0107] Subjects can be, for example, elderly adults, adults, adolescents, pre-adolescents, children, toddlers, infants, neonates, and non-human animals. In some embodiments, a subject is a patient.

[0108] A pharmaceutical composition of the disclosure can be a combination of any pharmaceutical compounds described herein with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. The pharmaceutical composition facilitates administration of the compound to an organism. Pharmaceutical compositions can be administered in therapeutically-effective amounts as pharmaceutical compositions by various forms and routes including, for example, intravenous, subcutaneous, intramuscular, oral, parenteral, ophthalmic, subcutaneous, transdermal, nasal, vaginal, and topical administration.

[0109] A pharmaceutical composition can be administered in a local manner, for example, via injection of the compound directly into an organ, optionally in a depot or sustained release formulation or implant. Pharmaceutical compositions can be provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. A rapid release form can provide an immediate release. An extended release formulation can provide a controlled release or a sustained delayed release.

[0110] For oral administration, pharmaceutical compositions can be formulated by combining the active compounds with pharmaceutically-acceptable carriers or excipients. Such carriers can be used to formulate liquids, gels, syrups, elixirs, slurries, or suspensions, for oral ingestion by a subject. Non-limiting examples of solvents used in an oral dissolvable formulation can include water, ethanol, isopropanol, saline, physiological saline, DMSO, dimethylformamide, potassium phosphate buffer, phosphate buffer saline (PBS), sodium phosphate buffer, 4-2-hydroxyethyl-1-piperazineethanesulfonic acid buffer (HEPES), 3-(N-morpholino)propanesulfonic acid buffer (MOPS), piperazine-N,N'-bis(2-ethanesulfonic acid) buffer (PIPES), and saline sodium citrate buffer (SSC). Non-limiting examples of co-solvents used in an oral dissolvable formulation can include sucrose, urea, cremaphor, DMSO, and potassium phosphate buffer.

[0111] Pharmaceutical preparations can be formulated for intravenous administration. The pharmaceutical compositions can be in a form suitable for parenteral injection as a sterile suspension, solution or emulsion in oily or aqueous vehicles, and can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water soluble form. Suspensions of the active compounds can be prepared as oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. The suspension can also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient can be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0112] The active compounds can be administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams, and ointments. Such pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0113] The compounds of the disclosure can be applied topically to the skin, or a body cavity, for example, oral, vaginal, bladder, cranial, spinal, thoracic, or pelvic cavity of a subject. The compounds of the disclosure can be applied to an accessible body cavity.

[0114] The compounds can also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, and PEG. In suppository forms of the compositions, a low-melting wax such as a mixture of fatty acid glycerides, optionally in combination with cocoa butter, can be melted.

[0115] In practicing the methods of treatment or use provided herein, therapeutically-effective amounts of the compounds described herein are administered in pharmaceutical compositions to a subject having a disease or condition to be treated. In some embodiments, the subject is a mammal such as a human. A therapeutically-effective amount can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compounds used, and other factors. The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures.

[0116] Pharmaceutical compositions can be formulated using one or more physiologically-acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations that can be used pharmaceutically. Formulations can be modified depending upon the route of administration chosen. Pharmaceutical compositions comprising a compound described herein can be manufactured, for example, by mixing, dissolving, emulsifying, encapsulating, entrapping, or compression processes.

[0117] The pharmaceutical compositions can include at least one pharmaceutically-acceptable carrier, diluent, or excipient and compounds described herein as free-base or pharmaceutically-acceptable salt form. Pharmaceutical compositions can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[0118] Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically-acceptable excipients or carriers to form a solid, semi-solid, or liquid composition. Solid compositions include, for example, powders, tablets, dispersible granules, capsules, and cachets. Liquid compositions include, for example, solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, for example, gels, suspensions and creams. The compositions can be in liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions can also contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and other pharmaceutically-acceptable additives.

[0119] Non-limiting examples of dosage forms suitable for use in the disclosure include liquid, powder, gel, nanosuspension, nanoparticle, microgel, aqueous or oily suspensions, emulsion, and any combination thereof.

[0120] Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the disclosure include binding agents, disintegrating agents, anti-adherents, anti-static agents, surfactants, anti-oxidants, coating agents, coloring agents, plasticizers, preservatives, suspending

agents, emulsifying agents, anti-microbial agents, spheronization agents, and any combination thereof.

[0121] A composition of the disclosure can be, for example, an immediate release form or a controlled release formulation. An immediate release formulation can be formulated to allow the compounds to act rapidly. Non-limiting examples of immediate release formulations include readily dissolvable formulations. A controlled release formulation can be a pharmaceutical formulation that has been adapted such that release rates and release profiles of the active agent can be matched to physiological and chronotherapeutic requirements or, alternatively, has been formulated to effect release of an active agent at a programmed rate. Non-limiting examples of controlled release formulations include granules, delayed release granules, hydrogels (e.g., of synthetic or natural origin), other gelling agents (e.g., gel-forming dietary fibers), matrix-based formulations (e.g., formulations comprising a polymeric material having at least one active ingredient dispersed through), granules within a matrix, polymeric mixtures, and granular masses.

[0122] In some, a controlled release formulation is a delayed release form. A delayed release form can be formulated to delay a compound's action for an extended period of time. A delayed release form can be formulated to delay the release of an effective dose of one or more compounds, for example, for about 4, about 8, about 12, about 16, or about 24 hours.

[0123] A controlled release formulation can be a sustained release form. A sustained release form can be formulated to sustain, for example, the compound's action over an extended period of time. A sustained release form can be formulated to provide an effective dose of any compound described herein (e.g., provide a physiologically-effective blood profile) over about 4, about 8, about 12, about 16 or about 24 hours.

[0124] Non-limiting examples of pharmaceutically-acceptable excipients can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams and Wilkins 1999), each of which is incorporated by reference in its entirety.

[0125] Multiple therapeutic agents can be administered in any order or simultaneously. In some embodiments, a compound of the disclosure is administered in combination with, before, or after treatment with another therapeutic agent. If simultaneously, the multiple therapeutic agents can be provided in a single, unified form, or in multiple forms, for example, as multiple separate pills. The agents can be packed together or separately, in a single package or in a

plurality of packages. One or all of the therapeutic agents can be given in multiple doses. If not simultaneous, the timing between the multiple doses can vary to as much as about a month.

[0126] Therapeutic agents described herein can be administered before, during, or after the occurrence of a disease or condition, and the timing of administering the composition containing a therapeutic agent can vary. For example, the compositions can be used as a prophylactic and can be administered continuously to subjects with a propensity to conditions or diseases in order to lessen a likelihood of the occurrence of the disease or condition. The compositions can be administered to a subject during or as soon as possible after the onset of the symptoms. The administration of the therapeutic agents can be initiated within the first 48 hours of the onset of the symptoms, within the first 24 hours of the onset of the symptoms, within the first 6 hours of the onset of the symptoms, or within 3 hours of the onset of the symptoms. The initial administration can be via any route practical, such as by any route described herein using any formulation described herein.

[0127] A compound can be administered as soon as is practical after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease, such as, for example, from about 1 month to about 3 months. In some embodiments, the length of time a compound can be administered can be about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 1 month, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 2 months, about 9 weeks, about 10 weeks, about 11 weeks, about 12 weeks, about 3 months, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 4 months, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 5 months, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 1 year, about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 19 months, about 20 months, about 21 months, about 22 months about 23 months, about 2 years, about 2.5 years, about 3 years, about 3.5 years, about 4 years, about 4.5 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, or about 10 years. The length of treatment can vary for each subject.

[0128] Pharmaceutical compositions described herein can be in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compounds. The unit dosage can be in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged injectables, vials, or ampoules. Aqueous suspension compositions can be packaged in single-dose non-reclosable containers. Multiple-dose reclosable containers can be used, for

example, in combination with or without a preservative. Formulations for injection can be presented in unit dosage form, for example, in ampoules, or in multi dose containers with a preservative.

[0129] Pharmaceutical compositions provided herein, can be administered in conjunction with other therapies, for example, chemotherapy, radiation, surgery, anti-inflammatory agents, and selected vitamins. The other agents can be administered prior to, after, or concomitantly with the pharmaceutical compositions.

[0130] Depending on the intended mode of administration, the pharmaceutical compositions can be in the form of solid, semi solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, or gels, for example, in unit dosage form suitable for single administration of a precise dosage.

[0131] For solid compositions, nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, and magnesium carbonate.

[0132] Non-limiting examples of pharmaceutically active agents suitable for combination with compositions of the disclosure include anti-infectives, i.e., aminoglycosides, antiviral agents, antimicrobials, anticholinergics/antispasmodics, antidiabetic agents, antihypertensive agents, antineoplastics, cardiovascular agents, central nervous system agents, coagulation modifiers, hormones, immunologic agents, immunosuppressive agents, and ophthalmic preparations.

[0133] Compounds can be delivered via liposomal technology. The use of liposomes as drug carriers can increase the therapeutic index of the compounds. Liposomes are composed of natural phospholipids and can contain mixed lipid chains with surfactant properties (e.g., egg phosphatidylethanolamine). A liposome design can employ surface ligands for attaching to unhealthy tissue. Non-limiting examples of liposomes include the multilamellar vesicle (MLV), the small unilamellar vesicle (SUV), and the large unilamellar vesicle (LUV). Liposomal physicochemical properties can be modulated to optimize penetration through biological barriers and retention at the site of administration, and to reduce a likelihood of developing premature degradation and toxicity to non-target tissues. Optimal liposomal properties depend on the administration route: large-sized liposomes show good retention upon local injection, small-sized liposomes are better suited to achieve passive targeting. PEGylation reduces the uptake of the liposomes by the liver and spleen, and increases the circulation time, resulting in increased localization at the inflamed site due to the enhanced permeability and retention (EPR) effect. Additionally, liposomal surfaces can be modified to achieve selective delivery of the encapsulated drug to specific target cells. Non-limiting examples of targeting ligands include

monoclonal antibodies, vitamins, peptides, and polysaccharides specific for receptors concentrated on the surface of cells associated with the disease.

[0134] Non-limiting examples of dosage forms suitable for use in the disclosure include liquid, elixir, nanosuspension, aqueous or oily suspensions, drops, syrups, and any combination thereof. Non-limiting examples of pharmaceutically-acceptable excipients suitable for use in the disclosure include granulating agents, binding agents, lubricating agents, disintegrating agents, sweetening agents, glidants, anti-adherents, anti-static agents, surfactants, anti-oxidants, gums, coating agents, coloring agents, flavoring agents, coating agents, plasticizers, preservatives, suspending agents, emulsifying agents, plant cellulosic material and spheronization agents, and any combination thereof.

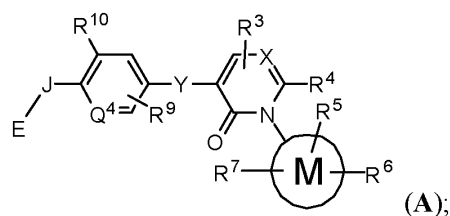
[0135] Compositions of the disclosure can be packaged as a kit. In some embodiments, a kit includes written instructions on the administration/use of the composition. The written material can be, for example, a label. The written material can suggest conditions methods of administration. The instructions provide the subject and the supervising physician with the best guidance for achieving the optimal clinical outcome from the administration of the therapy. The written material can be a label. In some embodiments, the label can be approved by a regulatory agency, for example the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), or other regulatory agencies.

[0136] In some aspects, the pharmaceutical compositions are administered orally.

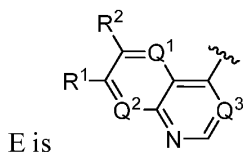
[0137] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the pharmaceutical composition.

NUMBERED EMBODIMENTS

[0138] Embodiment 1. A compound of the Formula A:



or a pharmaceutically acceptable salt thereof, wherein



E is or a bicyclic heterocyclic ring system comprising a 5-membered ring ortho-fused to a 6-membered ring, wherein the bicyclic heterocyclic ring system is optionally substituted by 1 to 3 groups independently selected from halo, oxo, and (C₁-C₄)alkyl;

R¹ and R² are each independently -OR^a or -NR^bR^c; or R¹ and R², together with the carbon atoms to which R¹ and R² are bound, form a 5- to 7-membered heterocyclyl;

R^a is selected from (C₁-C₄)alkyl, 4- to 6-membered heterocyclyl, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), and -(C₁-C₄)alkyl[4- to 6-membered heterocyclyl], wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups independently selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C₁-C₄)alkyl, or R^b and R^c taken together with the nitrogen atom to which R^b and R^c are attached form a 4- to 6-membered heterocyclyl;

R³ is hydrogen or (C₁-C₄)alkoxy;

R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups independently selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, cyano, and -NH(C₁-C₄)alkyl;

Ring M is a 6-membered aryl or 6-membered heteroaryl;

R⁵ and R⁷ are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, hydroxy, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R⁶ is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy;

R⁸ and R⁹ are each independently hydrogen or halo;

J is O, NR¹¹, S, or CH₂;

R¹⁰ is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, or deuterated(C₁-C₄)alkyl, and R¹¹ is hydrogen; or R¹⁰ and R¹¹, together with the atoms to which R¹⁰ and R¹¹ are bound, form a 5-membered heterocyclyl;

each of Q¹ and Q² is independently CH or N;

Q³ is CR⁸ or N;

Q^4 is N, CH, or a carbon atom attached to R^9 ;

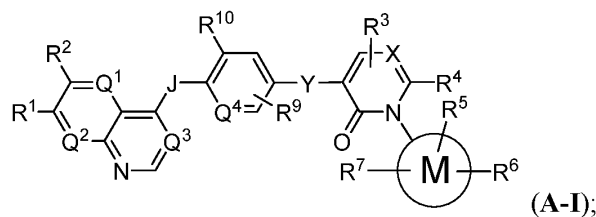
X is N, CH, or a carbon atom attached to R^3 ; and

Y is $-NHC(O)-$ or $-C(O)NH-$.

[0139] Embodiment 2. The compound of Embodiment 1, provided that if R^4 is CH_3 , then: (a) R^5 is not hydrogen or (b) Q^3 is CR^8 wherein R^8 is halo.

[0140] Embodiment 3. The compound of Embodiment 1 or Embodiment 2, provided that if Q^1 is N, Q^2 is CH, Q^3 is CR^8 , and R^4 is CH_3 or CH_2OH , then R^8 is halo.

[0141] Embodiment 4. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula A-I:



or a pharmaceutically acceptable salt thereof.

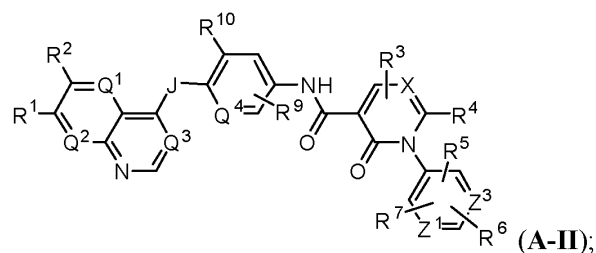
[0142] Embodiment 5. The compound of any one of Embodiments 1 to 4, or a

pharmaceutically-acceptable salt thereof, wherein

is

, wherein Z^1 , Z^2 , and Z^3 are each independently N, CH, or a carbon atom bound to one of R^5 , R^6 , and R^7 .

[0143] Embodiment 6. The compound of Embodiment 5, wherein the compound is of the Formula A-II:



or a pharmaceutically acceptable salt thereof.

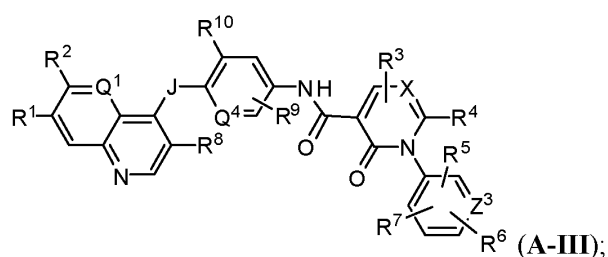
[0144] Embodiment 7. The compound of Embodiment 5 or Embodiment 6, or a pharmaceutically acceptable salt thereof, wherein Z^1 and Z^3 are each independently CH or a carbon atom bound to one of R^5 and R^7 .

[0145] Embodiment 8. The compound of Embodiment 5 or Embodiment 6, or a pharmaceutically acceptable salt thereof, wherein Z^1 and Z^3 are each N.

[0146] Embodiment 9. The compound of Embodiment 5 or Embodiment 6, or a pharmaceutically acceptable salt thereof, wherein Z^1 is CH or a carbon atom bound to R^7 , and Z^3 is N.

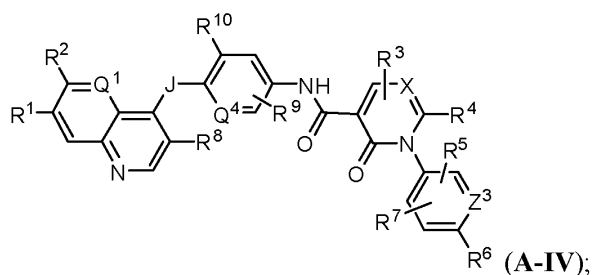
[0147] Embodiment 10. The compound of Embodiment 5 or Embodiment 6, or a pharmaceutically acceptable salt thereof, wherein Z^1 is N and Z^3 is CH or a carbon atom bound to R^5 .

[0148] Embodiment 11. The compound of Embodiment 5, wherein the compound is of the Formula A-III:



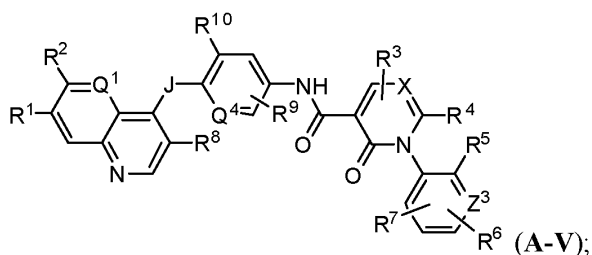
or a pharmaceutically acceptable salt thereof.

[0149] Embodiment 12. The compound of Embodiment 5, wherein the compound is of the Formula A-IV:



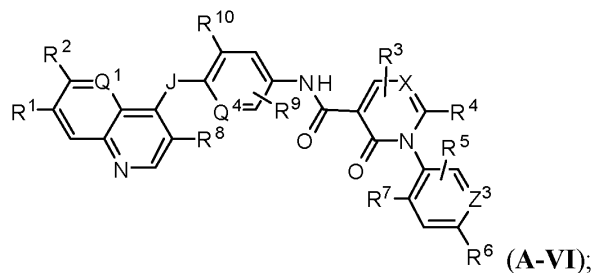
or a pharmaceutically acceptable salt thereof.

[0150] Embodiment 13. The compound of Embodiment 5, wherein the compound is of the Formula A-V:



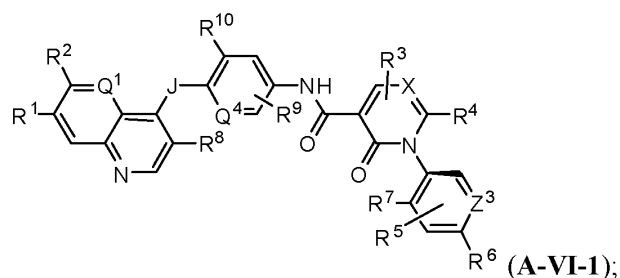
or a pharmaceutically acceptable salt thereof.

[0151] Embodiment 14. The compound of Embodiment 5, wherein the compound is of the Formula A-VI:



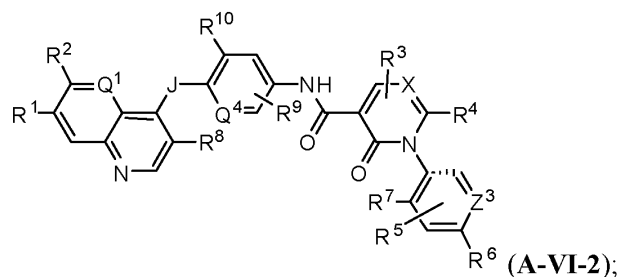
or a pharmaceutically acceptable salt thereof.

[0152] Embodiment 15. The compound of Embodiment 5, wherein the compound is of the Formula **A-VI-1**:



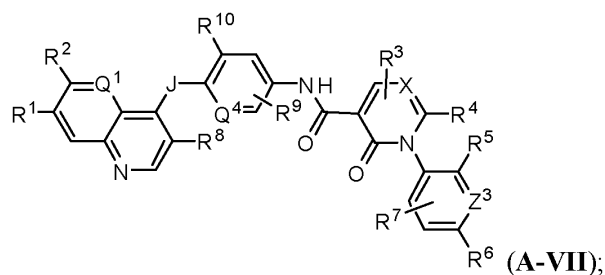
or a pharmaceutically acceptable salt thereof.

[0153] Embodiment 16. The compound of Embodiment 5, wherein the compound is of the Formula **A-VI-2**:



or a pharmaceutically acceptable salt thereof.

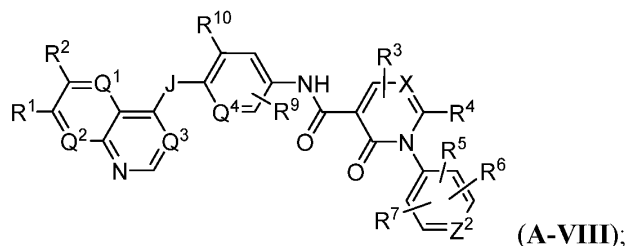
[0154] Embodiment 17. The compound of Embodiment 5, wherein the compound is of the Formula **A-VII**:



or a pharmaceutically acceptable salt thereof.

[0155] Embodiment 18. The compound of any one of Embodiments 5 and 11 to 17, or a pharmaceutically acceptable salt thereof, wherein Z³ is N.

[0156] Embodiment 19. The compound of Embodiment 5, wherein the compound is of the Formula **A-VIII**:



or a pharmaceutically acceptable salt thereof.

[0157] Embodiment 20. The compound of any one of Embodiments 5 and 19, or a pharmaceutically acceptable salt thereof, wherein Z^2 is N.

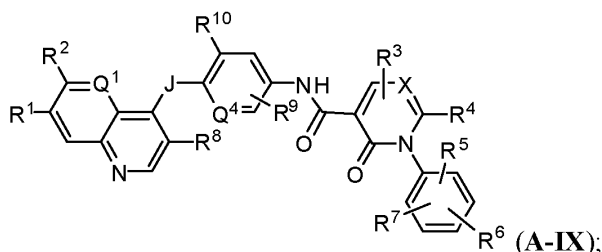
[0158] Embodiment 21. The compound of any one of Embodiments 1 to 10, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein Q^1 and Q^2 each are CH, and Q^3 is CR^8 .

[0159] Embodiment 22. The compound of any one of Embodiments 1 to 10, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein Q^1 and Q^2 each are CH, and Q^3 is N.

[0160] Embodiment 23. The compound of any one of Embodiments 1 to 10, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein Q^1 is N, Q^2 is CH, and Q^3 is CR^8 .

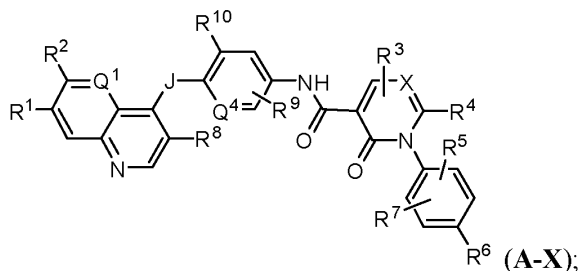
[0161] Embodiment 24. The compound of any one of Embodiments 1 to 10, 19, and 20, or a pharmaceutically acceptable salt thereof, wherein Q^1 is CH, Q^2 is N, and Q^3 is CR^8 .

[0162] Embodiment 25. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-IX**:



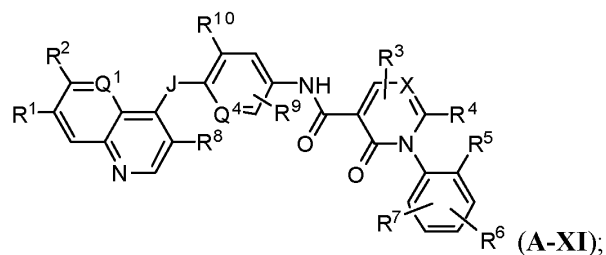
or a pharmaceutically acceptable salt thereof.

[0163] Embodiment 26. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-X**:



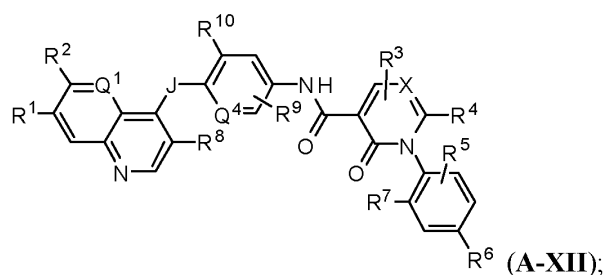
or a pharmaceutically acceptable salt thereof.

[0164] Embodiment 27. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-XI**:



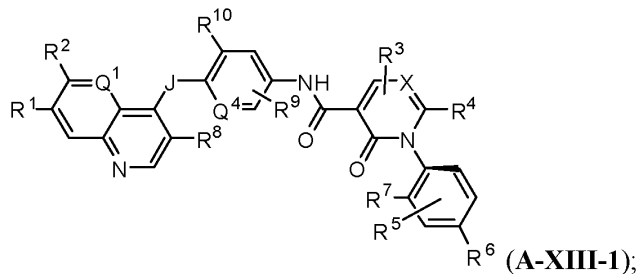
or a pharmaceutically acceptable salt thereof.

[0165] Embodiment 28. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-XII**:



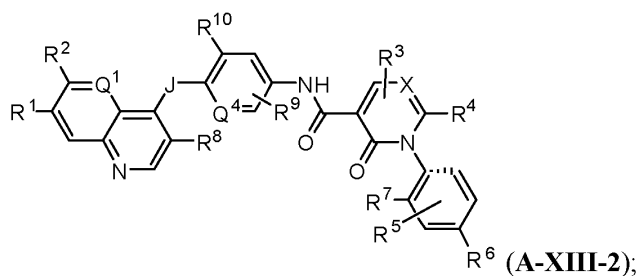
or a pharmaceutically acceptable salt thereof.

[0166] Embodiment 29. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-XIII-1**:



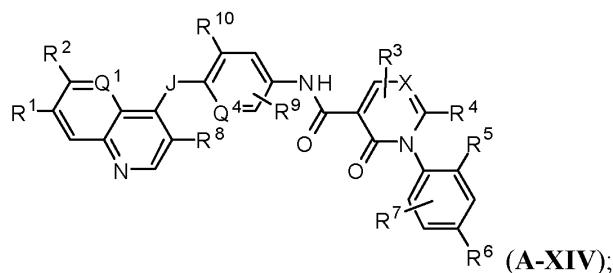
or a pharmaceutically acceptable salt thereof.

[0167] Embodiment 30. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-XIII-2**:



or a pharmaceutically acceptable salt thereof.

[0168] Embodiment 31. The compound of any one of Embodiments 1 to 3, wherein the compound is of the Formula **A-XIV**:



or a pharmaceutically acceptable salt thereof.

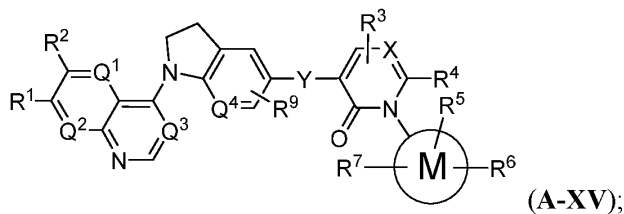
[0169] Embodiment 32. The compound of any one of Embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein J is O.

[0170] Embodiment 33. The compound of any one of Embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein J is S.

[0171] Embodiment 34. The compound of any one of Embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein J is CH₂.

[0172] Embodiment 35. The compound of any one of Embodiments 1 to 31, or a pharmaceutically acceptable salt thereof, wherein J is NR¹¹.

[0173] Embodiment 36. The compound of any one of Embodiments 1 to 5, wherein the compound is of the Formula **A-XV**:



or a pharmaceutically acceptable salt thereof.

[0174] Embodiment 37. The compound of any one of Embodiments 1-35, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is halo.

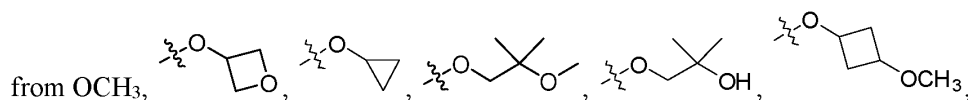
[0175] Embodiment 38. The compound of any one of Embodiments 1-35, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is fluoro.

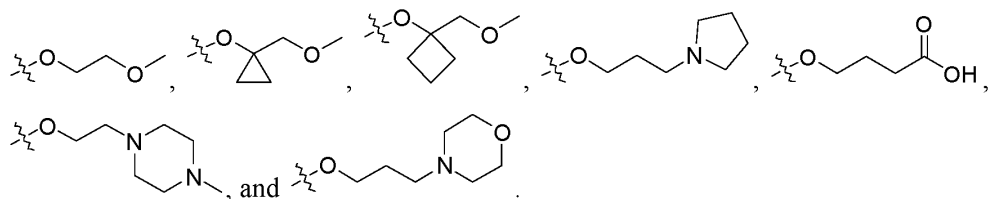
[0176] Embodiment 39. The compound of any one of Embodiments 1 to 20, 25 to 31, and 36, or a pharmaceutically acceptable salt thereof, wherein Q¹ is N.

[0177] Embodiment 40. The compound of any one of Embodiments 1 to 20, 25 to 31, and 36, or a pharmaceutically acceptable salt thereof, wherein Q¹ is CH.

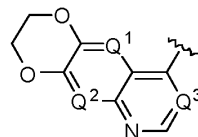
[0178] Embodiment 41. The compound of any one of Embodiments 1 to 40, or a pharmaceutically acceptable salt thereof, wherein Q⁴ is N.

- [0179] Embodiment 42. The compound of any one of Embodiments 1 to 40, or a pharmaceutically acceptable salt thereof, wherein Q^4 is a carbon atom bound to R^9 .
- [0180] Embodiment 43. The compound of any one of Embodiments 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^9 is hydrogen.
- [0181] Embodiment 44. The compound of any one of Embodiments 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R^9 is fluoro.
- [0182] Embodiment 45. The compound of any one of Embodiments 1 to 44, or a pharmaceutically acceptable salt thereof, wherein R^5 is hydrogen, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.
- [0183] Embodiment 46. The compound of any one of Embodiments 1 to 45, or a pharmaceutically acceptable salt thereof, wherein R^5 is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, cyano, hydroxy, or halo.
- [0184] Embodiment 47. The compound of any one of Embodiments 1 to 46, or a pharmaceutically acceptable salt thereof, wherein R^5 is CH₃, CF₃, cyano, hydroxy, fluoro, chloro, or bromo.
- [0185] Embodiment 48. The compound of any one of Embodiments 1 to 47, or a pharmaceutically acceptable salt thereof, wherein X is CH.
- [0186] Embodiment 49. The compound of any one of Embodiments 1 to 47, or a pharmaceutically acceptable salt thereof, wherein X is N.
- [0187] Embodiment 50. The compound of any one of Embodiments 1 to 49, or a pharmaceutically acceptable salt thereof, wherein R^3 is hydrogen.
- [0188] Embodiment 51. The compound of any one of Embodiments 1 to 21, 23 to 31, 36, 39, and 40, or a pharmaceutically acceptable salt thereof, wherein R^8 is fluoro.
- [0189] Embodiment 52. The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt thereof, wherein each R^a is independently selected from (C₁-C₄)alkyl, oxetanyl, cyclopropyl, cyclobutyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), -(C₁-C₄)alkyl[pyrrolidinyl], -(C₁-C₄)alkyl[piperizinyl], and -(C₁-C₄)alkyl[morpholinyl], wherein said cyclopropyl, cyclobutyl, piperazinyl, pyrrolidinyl, and oxetanyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy.
- [0190] Embodiment 53. The compound of any one of Embodiments 1 to 51, or a pharmaceutically acceptable salt thereof, wherein R^1 and R^2 are each independently selected



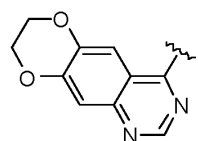


[0191] Embodiment 54. The compound of any one of Embodiments 1 to 51, or a



pharmaceutically-acceptable salt thereof, wherein E is

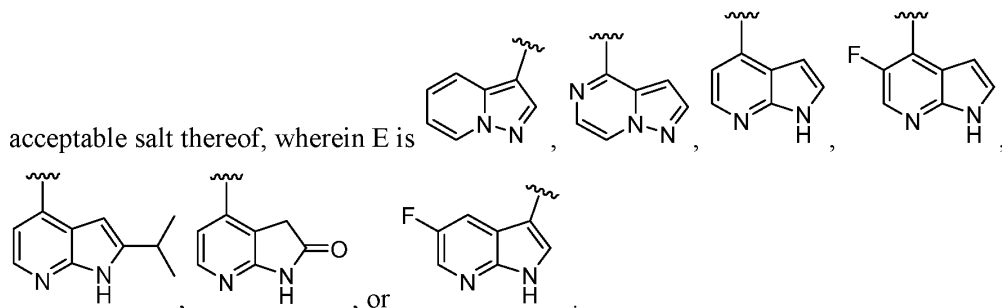
[0192] Embodiment 55. The compound of any one of Embodiments 1 to 51, or a



pharmaceutically-acceptable salt thereof, wherein E is

[0193] Embodiment 56. The compound any one of Embodiments 1 to 3, or a pharmaceutically-acceptable salt thereof, wherein E is pyrazolo[1,5-a]pyridyl, pyrazolo[1,5-a]pyrazolyl, 1H-pyrrolo[2,3-b]pyridyl, 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one, each of which is optionally substituted with 1 to 3 groups independently selected from halo and (C₁-C₄)alkyl.

[0194] Embodiment 57. The compound any one of Embodiments 1 to 3, or a pharmaceutically



[0195] Embodiment 58. The compound of any one of Embodiments 1 to 57, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

[0196] Embodiment 59. The compound of any one of Embodiments 1 to 57, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl,

wherein said (C₃-C₆)cycloalkyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

[0197] Embodiment 60. The compound of any one of Embodiments 1 to 57, or a

pharmaceutically acceptable salt thereof, wherein R⁴ is , , CF₃, CH₃, , OCHF₂, , CH₂CF₃, , , , , , , , or .

[0198] Embodiment 61. The compound of any one of Embodiments 1 to 57, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₂-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

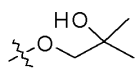
[0199] Embodiment 62. The compound of any one of Embodiments 1 to 57, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₂-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said cyclopropyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

[0200] Embodiment 63. The compound of any one of Embodiments 1 to 57, or a

pharmaceutically acceptable salt thereof, wherein R⁴ is , , CF₃, , OCHF₂, , CH₂CF₃, , , , , , , , or .

[0201] Embodiment 64. The compound of any one of Embodiments 1 to 63, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, halo, -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl], or cyano.

[0202] Embodiment 65. The compound of any one of Embodiments 1 to 63, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, bromo, chloro,

, or cyano.

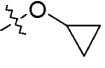
[0203] Embodiment 66. The compound of any one of Embodiments 1 to 63, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.

[0204] Embodiment 67. The compound of any one of Embodiments 1 to 63, or a pharmaceutically acceptable salt thereof, wherein R^7 is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, cyano, hydroxy, or halo.

[0205] Embodiment 68. The compound of any one of Embodiments 1 to 63, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH₃, CF₃, cyano, hydroxy, fluoro, chloro, or bromo.

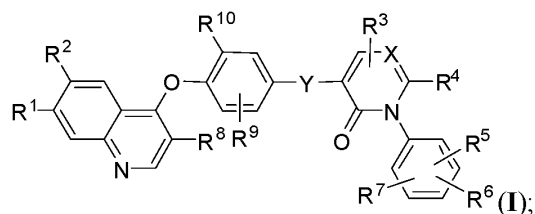
[0206] Embodiment 69. The compound of any one of Embodiments 1 to 68, or a pharmaceutically acceptable salt thereof, wherein R^6 is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy.

[0207] Embodiment 70. The compound of any one of Embodiments 1 to 68, or a pharmaceutically acceptable salt thereof, wherein R^6 is cyano, CHF₂, hydroxy, acetyl, OCH₃,

OEt, fluoro, OCHF₂, OCF₃, , or OCD₃.

[0208] Embodiment 71. The compound of any one of Embodiments 1 to 68, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro.

[0209] Embodiment 72. The compound of embodiment 1, wherein the compound is of the Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are each independently -OR^a or -NR^bR^c;

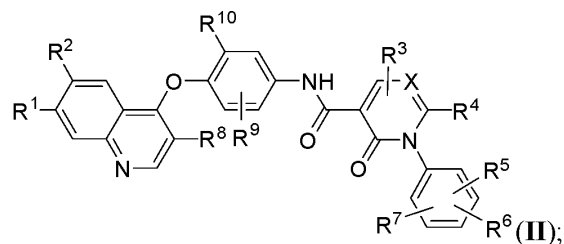
R^5 and R^7 are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R^6 is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy;

R^8 and R^9 are each independently hydrogen or fluoro;

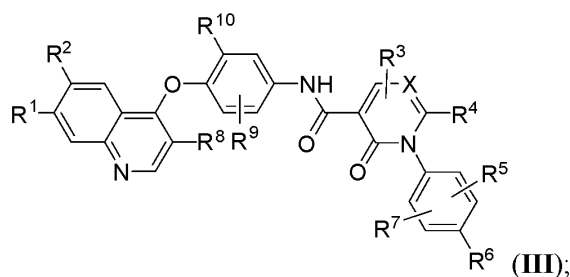
provided that if R^4 is CH₃, then R^5 is not hydrogen.

[0210] Embodiment 73. The compound of Embodiment 72, wherein the compound is of the Formula II:



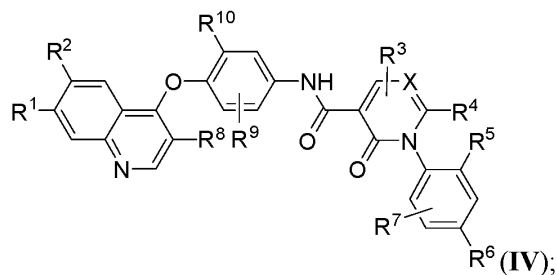
or a pharmaceutically acceptable salt thereof.

[0211] Embodiment 74. The compound of Embodiment 72 or Embodiment 73, wherein the compound is of the Formula **III**:



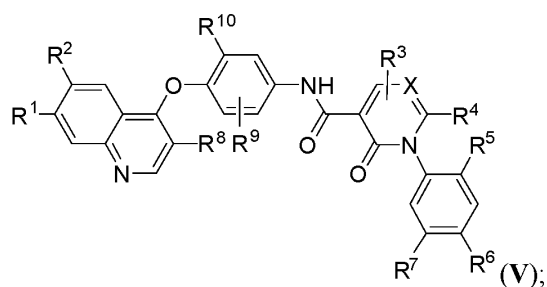
or a pharmaceutically acceptable salt thereof.

[0212] Embodiment 75. The compound of any one of Embodiments 72 to 74, wherein the compound is of Formula **IV**:



or a pharmaceutically acceptable salt thereof.

[0213] Embodiment 76. The compound of any one of Embodiments 72 to 75, wherein the compound is of Formula **V**:



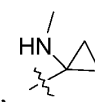
or a pharmaceutically acceptable salt thereof.

[0214] Embodiment 77. The compound of any one of Embodiments 72 to 76, or a pharmaceutically acceptable salt thereof, wherein R^{10} is halo.

hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

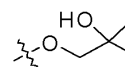
[0226] Embodiment 89. The compound of any one of Embodiments 72 to 88, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said cyclopropyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

[0227] Embodiment 90. The compound of any one of Embodiments 72 to 89, or a

pharmaceutically acceptable salt thereof, wherein R⁴ is , , CF₃, CH₃, , OCHF₂, , CH₂CF₃, , , , , , , , or .

[0228] Embodiment 91. The compound of any one of Embodiments 72 to 90, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, halo, -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl], or cyano.

[0229] Embodiment 92. The compound of any one of Embodiments 72 to 91, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, fluoro, bromo, chloro,

, or cyano.

[0230] Embodiment 93. The compound of any one of Embodiments 72 to 92, or a

pharmaceutically acceptable salt thereof, wherein R⁶ is OCH₃, fluoro, OCHF₂, OCF₃, , OCD₃.

[0231] Embodiment 94. The compound of any one of Embodiments 72 to 93, or a pharmaceutically acceptable salt thereof, wherein R⁶ is fluoro.

[0232] Embodiment 95. The compound of Embodiment 1, wherein the compound is selected from any of those in Table 1; or a pharmaceutically acceptable salt thereof.

[0233] Embodiment 96. The compound of Embodiment 1, wherein the compound is selected from any of those in Table 2; or a pharmaceutically acceptable salt thereof.

[0234] Embodiment 97. The compound of any one of Embodiments 1 to 94, or a pharmaceutically acceptable salt thereof, wherein the compound is a single atropisomer.

[0235] Embodiment 98. The compound of Embodiment 97, or a pharmaceutically acceptable salt thereof, wherein the single atropisomer has a negative specific optical rotation.

[0236] Embodiment 99. The compound of Embodiment 97, or a pharmaceutically acceptable salt thereof, wherein the single atropisomer has a positive specific optical rotation.

[0237] Embodiment 100. A pharmaceutical composition comprising a compound of any one of Embodiments 1 to 99, or a pharmaceutically acceptable salt thereof.

[0238] Embodiment 101. A pharmaceutical composition, the pharmaceutical composition comprising a population of molecules with a structure according to a compound of any one of Embodiments 1 to 96, wherein at least about 97% of the molecules of the population have the same atropisomeric configuration.

[0239] Embodiment 102. The pharmaceutical composition of Embodiment 101, further comprising a pharmaceutically acceptable carrier.

[0240] Embodiment 103. A method of treating a condition, comprising administering to a subject in need a therapeutically effective amount of a compound of any one of Embodiments 1 to 99, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of any one of Embodiments 100 to 102.

[0241] Embodiment 104. The method of Embodiment 103, wherein the condition is responsive to the modulation of PLK4.

[0242] Embodiment 105. The method of Embodiment 103, wherein the condition is cancer.

EXEMPLIFICATION

[0243] The described compounds can be prepared according to the following examples. As used below, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

ACN or MeCN: acetonitrile

C: degrees Celsius

d: chemical shift in parts per million downfield from tetramethylsilane dichloromethane (CH_2Cl_2)

DCM: dichloromethane

DIPEA: N,N-Diisopropylethylamine

DMF: dimethylformamide

DMSO: dimethylsulfoxide

Et_2O : diethyl ether

EtOAc: ethyl acetate

ES^+ : electrospray ionization

Et: ethyl
g: gram(s)
HATU: Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
Hex: hexanes
h: hour(s)
HOBt: Hydroxybenzotriazole
HPLC: high performance liquid chromatography
Hz: hertz
J: coupling constant (in NMR spectrometry)
LCMS: liquid chromatography mass spectrometry
m: micro
m: multiplet (spectral); meter(s); milli
M: molar
M⁺: parent molecular ion
Me: methyl
MeOH: methanol
MHz: megahertz
min: minute(s)
mol: mole(s); molecular (as in mol wt)
mL: milliliter
NIS: *N*-iodosuccinimide
NMI: N-methylimidazole
MS: mass spectrometry
nm: nanometer(s)
NMR: nuclear magnetic resonance
pH: potential of hydrogen; a measure of the acidity or basicity of an aqueous solution
PE: petroleum ether
rt: room temperature
s: singlet (spectral)
T3P: propanephosphonic acid anhydride
t: triplet (spectral)
T: temperature
TCHF: tetramethylchloroformamidinium hexafluorophosphate
TEA: triethylamine
TFA: trifluoroacetic acid

THF: tetrahydrofuran

EDC.HCl: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

SOR: Specific Optical Rotation

ee: enantiomeric excess

TLC: thin layer chromatography

ES: Electrospray

ANALYTICAL TECHNIQUES

LCMS

Method A

[0244] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	0	2
2.0	2	98
3.0	2	98
3.2	98	2
4	98	2

[0245] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0246] Solvent B: 0.05% formic acid in acetonitrile

[0247] Injection volume: 2.0uL

[0248] Column: Waters X-Select CSH (3.0 × 50) mm, 2.5 μm.

Method B

[0249] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following

parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
6.0	2	98
8.0	2	98
9.0	100	0
10.0	100	0

[0250] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0251] Solvent B: 0.05% formic acid in acetonitrile

[0252] Injection volume: 2.0uL

[0253] Columns: Waters X-Bridge CSH (3.0 × 50 mm) 2.5 µm.

Method C

[0254] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	98	2
0.2	98	2
2.2	2	98
3.0	2	98
3.2	98	2
4.0	98	2

[0255] Solvent A: 0.05% formic acid in water

[0256] Solvent B: 0.05% formic acid in acetonitrile

[0257] Injection volume: 2.0uL

[0258] Column: Waters XSelect-C18(3.0 × 50) mm, 2.5 µm.

Method D

[0259] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.00	100	0
1.5	0	100
2.2	0	100
2.6	100	0
3.0	93	7

[0260] Solvent A: 2.5mM Ammonium Bicarbonate + 5% ACN in H₂O

[0261] Solvent B: Acetonitrile.

[0262] Injection volume: 2.0 µL

[0263] Column: X Select CSH C18 (3.0*50) mm 2.5 µ

Method E

[0264] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
1.5	0	100
2.0	0	100
2.2	100	0
3.0	100	0

[0265] Solvent A: 2.5mM Ammonium Bicarbonate + 5% ACN in H₂O

[0266] Solvent B: Acetonitrile.

[0267] Injection volume: 2.0 µL

[0268] Column: X-Bridge BEH C18 (3.0 × 50) mm 2.5 µm

Method F

[0269] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
6.0	2	98
8.0	2	98
9.0	100	0
10.0	100	0

[0270] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0271] Solvent B: 0.05% formic acid in acetonitrile

[0272] Injection volume: 2.0 µL

[0273] Column: X-Select CSH C18 (3.0 × 50) mm 2.5 µm

Method G

[0274] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
2.0	2	98
3.0	2	98
3.2	100	0
4.0	100	0

[0275] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0276] Solvent B: 0.05% formic acid in acetonitrile

[0277] Injection volume: 2.0 μ L

[0278] Column: X-Select CSH C18 (3.0 $\times$ 50) mm 2.5 μ m

Method H

[0279] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 $^{\circ}$ C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
1.5	0	100
2.2	0	100
2.6	100	0
3.0	100	0

[0280] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0281] Solvent B: 0.05% formic acid in acetonitrile

[0282] Injection volume: 2.0 μ L

[0283] Column: X-Select CSH C18 (3.0 $\times$ 50) mm 2.5 μ m

Method I

[0284] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser,

SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
2.0	2	98
3.0	2	98
3.2	100	0
4.0	100	0

[0285] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0286] Solvent B: 0.05% formic acid in acetonitrile

[0287] Injection volume: 2.0 µL

[0288] Column: X-Bridge CSH C18 (3.0 × 50) mm 2.5 µm

Method J

[0289] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
6.0	2	98
8.0	2	98
9.0	98	2
10.0	98	2

[0290] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0291] Solvent B: 0.05% formic acid in acetonitrile

[0292] Injection volume: 2.0 µL

[0293] Column: X-Select CSH (3.0 × 50) mm 2.5 μm

Method K

[0294] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
1.5	0	100
2.2	0	100
2.6	100	0
3.0	100	0

[0295] Solvent A: 2.5mM Ammonium Bicarbonate + 50 mL ACN

[0296] Solvent B: Acetonitrile

[0297] Injection volume: 2.0 μL

[0298] Column: X-Bridge BEH C18 (3.0 × 50) mm 2.5 μm

Method L

[0299] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (Dual gradient run)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
6.0	0	100

[0300] Solvent A: 0.1% TFA in H₂O

[0301] Solvent B: 0.1% TFA in ACN

[0302] Injection volume: 2.0 μ L

[0303] Column: Merck Milipore Chromolith SpeedROD C18 (50 $\times$ 4.6 mm)

Method M

[0304] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.5 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
0.4	0	100
1.5	95	5

[0305] Solvent A: 0.1% TFA in H₂O

[0306] Solvent B: 0.1% TFA in ACN

[0307] Injection volume: 2.0 μ L

[0308] Column: Water Cortex C18 (3 $\times$ 50 mm) 2.7 μ m

Method N

[0309] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	98	2
0.3	98	2
2.0	2	98
2.8	2	98
3.0	98	2

3.7	98	2
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[0310] Solvent A: 0.05% formic acid in water

[0311] Solvent B: 0.05% formic acid in acetonitrile

[0312] Injection volume: 2.0 μ L

[0313] Column: X-Select CSH C18 (3.0 $\times$ 50) mm 2.5 μ m

Method P

[0314] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	100	0
1.5	0	100
2.2	0	100
2.6	100	0
3.0	100	0

[0315] Solvent A: 0.05 mM Ammonium Bicarbonate

[0316] Solvent B: 100% FA in Acetonitrile

[0317] Injection volume: 2.0 μ L

[0318] Column: X-Select CSH C18 (3.0 $\times$ 50) mm 2.5 μ m

Method Q

[0319] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	0	2
1.5	98	2
6.0	2	98
8.0	2	98
9.0	98	2
10.0	98	2

[0320] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0321] Solvent B: 0.05% formic acid in acetonitrile

[0322] Injection volume: 2.0uL

[0323] Column: Waters X-Select CSH (3.0 × 50) mm, 2.5 μm.

Method R

[0324] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler coupled with a Shimadzu LCMS (SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	0	2
1.5	2	98
2.2	2	98
2.6	98	2
3.0	98	2

[0325] Solvent A: 0.05% formic acid in water (95%): ACN (5%)

[0326] Solvent B: 0.05% formic acid in acetonitrile

[0327] Injection volume: 2.0uL

[0328] Column: Waters X-Select CSH C18 (3.0 × 50) mm, 2.5 μm.

Method S

[0329] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.2 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
6.0	2	98
8.0	2	98
9.0	2	98
10.0	98	2

[0330] Solvent A: 0.1% TFA in H₂O

[0331] Solvent B: Acetonitrile

[0332] Injection volume: 2.0 µL

[0333] Column: X-Select CSH C18 (3 × 50) mm, 2.5 µm

Method T

[0334] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 45 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (0.85 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	97	3
0.1	97	3
1.4	3	97
2.0	3	97
2.05	97	3
2.5	97	3

[0335] Solvent A: 0.05% TFA in Water

[0336] Solvent B: 0.05% TFA in Acetonitrile

[0337] Injection volume: 2.0 μ L

[0338] Column: CORTECS UPLC C18 (3 $\times$ 30) mm, 1.6 μ m

Method U

[0339] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
1.5	98	2
6.0	2	98
9.0	98	2
10.0	98	2

[0340] Solvent A: 0.05% Formic Acid in Water

[0341] Solvent B: 0.05% Formic Acid in Acetonitrile

[0342] Injection volume: 2.0 μ L

[0343] Column: XTERA MS C18, (50 mm $\times$ 2.1 mm, 3.5 μ m)

Method V

[0344] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
1.5	98	2

6.0	2	98
8.0	2	98
9.0	98	2
10.0	98	2

[0345] Solvent A: 2.5 mM Ammonium bicarbonate in water

[0346] Solvent B: Acetonitrile

[0347] Injection volume: 2.0 μ L

[0348] Column: XSelect CSH-C18 (3.0 $\times$ 50mm, 2.5 μ m)

Method W

[0349] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
1.5	98	2
6.0	2	98
8.0	2	98
9.0	98	2
10.0	98	2

[0350] Solvent A: 0.05% Formic Acid in Water

[0351] Solvent B: 0.05% Formic Acid in Acetonitrile

[0352] Injection volume: 2.0 μ L

[0353] Column: XSelect CSH-C18 (3.0 $\times$ 50mm, 2.5 μ m)

Method AC

[0354] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software

under the following parameters: Column temp: 40 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
1.5	98	2
6.0	2	98
8.0	2	98
9.0	98	2
10.0	98	2

[0355] Solvent A: 2.5 mM NH_4HCO_3 in water +5% Acetonitrile

[0356] Solvent B: Acetonitrile

[0357] Injection volume: 2.0 μL

[0358] Column: XSelect CSH-C18(3.0X50mm,2.5 μm)

Method AD

[0359] Liquid Chromatography Mass Spectrometry (LCMS) was performed on a Shimadzu LCMS system consisting of consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC auto sampler coupled with a Shimadzu LCMS(SQD) mass spectrometer using Lab Solutions, v.3.70.390 software under the following parameters: Column temp: 45 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LCMS Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	97	3
1.5	97	3
6.0	3	97
8.0	3	97
9.0	97	3
10.0	97	3

[0360] Solvent A: 0.05% TFA in Water

[0361] Solvent B: 0.05% TFA in Acetonitrile

[0362] Injection volume: 2.0 μL

[0363] Column: CORTECS UPLC C18 (3.0 x 30mm, 1.6 µm)

Analytical HPLC

Method A

[0364] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.2 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0365] Solvent A: 0.1% TFA in water

[0366] Solvent B: 0.1% TFA in acetonitrile

[0367] Inj Volume: 5.0uL

[0368] Column: Waters X-Select CSH C18 (4.6*150) mm 5 µm.

Method B

[0369] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.0 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.01	90	10
6.0	10	90
10.0	0	100
12.0	0	100
14.0	90	10
18.0	90	10

[0370] Solvent A: 0.1% Formic acid in water: Acetonitrile (95:05)

[0371] Solvent B: Acetonitrile

[0372] Injection Volume- 5.0uL

[0373] Column: Waters X-Select CSH C18 (4.6*150) mm 5 µm.

Method C

[0374] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.0 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.01	90	10
6.0	10	90
10.0	0	100
12.0	0	100
14.0	90	10
18.0	90	10

[0375] Solvent A: 5mM Ammonium Bicarbonate in water

[0376] Solvent B: Acetonitrile

[0377] Injection Volume: 5.0uL

[0378] Column: Waters X-Bridge CSH C18 (4.6*150) mm 5 µm.

Method D

[0379] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.2 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0380] Solvent A: 0.1% TFA in water

[0381] Solvent B: Acetonitrile

[0382] Injection Volume- 5.0uL

[0383] Column: Waters X-Select CSH C18 (4.6*150) mm 5µm.

Method E

[0384] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.01	90	10
5.0	95	80
12.0	0	90
16.0	0	90
14.0	95	5
18.0	95	5

[0385] Mobile Phase A: 0.05% TFA; ACN (95;05)

[0386] Mobile Phase B: 0.05% TFA; ACN (05;95)

[0387] Injection Volume: 5.0uL

[0388] Column: Waters X SELECT CSH C18 (150 X 4.6mm, 3.5μ)

Method F

[0389] HPLC analyses were obtained on a AMC-UPLC-04 HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 30 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0	95	05
0.05	95	5
4.0	5	95
8	5	95
10	95	5

[0390] Mobile Phase A: 0.1% FA in (Water:ACN)(95:5)

[0391] Mobile Phase B: Acetonitrile

[0392] Injection Volume: 5.0uL

[0393] Column: X-Select CSH C18, (50mm*3.0mm,2.5μ)

Method G

[0394] HPLC analyses were obtained on a AMC-UPLC-04 HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 50 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.2 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	0
6.0	02	98
8.0	02	98
9.0	98	02
10	98	02

[0395] Mobile Phase A: 0.05% Formic Acid in Water:Acetonitrile (95:5)

[0396] Mobile Phase B: 0.05% Formic Acid in Acetonitrile

[0397] Injection Volume- 5.0uL

[0398] Column: X-Select CSH C18, (50mm*3.0mm,2.5μ)

[0399] Gradient Program (B%) :0.0/2, 6.0/98, 8.0/98, 9.0/2, 10.0/2.

Method H

[0400] HPLC analyses were obtained on a AMC-UPLC-04 HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 30 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.2 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0	95	05
0.05	95	5
4.0	5	95
8	5	95
10	95	5

[0401] Mobile Phase A: 0.1% FA in water

[0402] Mobile Phase B: Acetonitrile

[0403] Inj Volume: 5.0uL

[0404] Column: X-select CSH C18 (4.6*150mmx5μm)

Preparative HPLC***Method A***

[0405] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0406] Solvent A: 0.1% TFA in water

[0407] Solvent B: Acetonitrile

[0408] Injection Volume: 5.0uL

[0409] Column: X-SELECT (250*30 mm), 5.0 µm.

Method B

[0410] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	85	15
3	85	15
12	75	25
17	40	60
22	35	65
27	30	70
32	25	75
37	20	80
42	10	90
47	0	100
52	0	100

[0411] Solubility: ACN: H₂O: DMSO: TFA

[0412] Solvent A: 0.1% TFA in water

[0413] Solvent B: Acetonitrile

[0414] Injection Volume: 5.0uL

[0415] Column: X-select: C-18 (30 x 250 mm), 5nm.

Method C

[0416] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0417] Solvent A: 5mM ammonium bicarbonate in Water

[0418] Solvent B: acetonitrile

[0419] Inj Volume: 5.0μL

[0420] Column: X-SELECT (250*30 mm), 5.0 μm.

Method D

[0421] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0422] Solvent A: 5mM ammonium bicarbonate in Water

[0423] Solvent B: acetonitrile

[0424] Injection Volume: 5.0 μ L

[0425] Column: X-Bridge C18 (4.6*150) mm 5 μ

Method E

[0426] HPLC analyses were obtained on a Shimadzu HPLC 2010CHT HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	5
1.0	95	5
8.0	0	100
12.0	0	100
14.0	95	5
18.0	95	5

[0427] Solvent A: 0.1% formic acid in water

[0428] Solvent B: Acetonitrile

[0429] Injection Volume: 5.0 μ L

[0430] Column: X-SELECT (250*30 mm), 5.0 μ m.

Method F

[0431] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
3.0	95	5
10.0	75	25
15.0	60	40
20.0	55	45
25.0	50	50
25.0	40	60
30.0	30	70
40.0	5	95
47.0	05	95

48.0	95	05
55.0	95	05

[0432] Solvent A: 10mM Ammonium Bicarbonate in water

[0433] Solvent B: Acetonitrile

[0434] Injection Volume: 5.0uL

[0435] Column: X-SELECT CSH (250*30 mm), 5.0 µm.

Method G

[0436] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.0mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	90	10
5.0	95	80
12.0	0	90
16.0	0	90
14.0	95	5
18.0	95	5

[0437] Solvent A: 0.1% FA in (ACN:Water)(50:950)

[0438] Solvent B: Acetonitrile

[0439] Injection Volume: 5.0uL

[0440] Column: X-SELECT CSH (250*30 mm), 5.0 µm.

Method H

[0441] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	95	05
3	95	05
10	75	25
15	60	40
20	95	45

25	50	50
25	40	60
30	30	70
40	05	95
47	05	95
48	95	05
55	95	05

[0442] Solvent A: 0.01% FA in Water

[0443] Solvent B: Acetonitrile

[0444] Injection Volume: 5.0uL

[0445] Column: X-SELECT CSH (250*30 mm), 5.0 µm.

Method I

[0446] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.1	95	05
5	95	05
15	60	40
20	50	50
25	45	55
30	40	60
35	25	75
40	02	98

[0447] Solvent A: 0.1% formic acid in water: 0.01% FA in water

[0448] Solvent B: Acetonitrile

[0449] Injection Volume: 5.0uL

[0450] Column: X-select (250*30mm, 5u).

Method J

[0451] HPLC analyses were obtained on a Shimatzu Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (35 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	95	05
3	95	05
10	75	25
15	60	40
20	55	45
25	50	50
25	40	60
30	30	70
40	05	95
47	05	95
48	95	05
55	95	05

[0452] Solvent A: 0.1% Formic acid in water

[0453] Solvent B: Acetonitrile

[0454] Injection Volume: 5.0uL

[0455] Column: YMS Trait C18 (250*30mm) 5u.

Method K

[0456] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters:

Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	90	10
2	90	10
8	80	20
20	25	75
30	10	90
32	05	95
37	05	95
38	90	10

[0457] Solvent A: 0.1% Ammonium carbonate in water

[0458] Solvent B: Acetonitrile

[0459] Injection Volume: 5.0uL

[0460] Column: YMC trait C18 (250*30mm) 5um.

Method L

[0461] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0	90	10
2	90	10
8	80	20
20	25	75
30	10	90
32	05	95
37	05	95
38	90	10

[0462] Solvent A: 0.1% Ammonium bicarbonate in water

[0463] Solvent B: Acetonitrile

[0464] Injection Volume: 5.0uL

[0465] Column: YMC trait C18 (250*30mm) 5um.

[0466] Method N Prep-purification method: Instrument: Gilson autoprep HPLC, Column: X-select 30mm, Mobile phase: A: 10mm Formic acid in water, B: Acetonitrile, Flow rate: 25 mL/min, Gradient time/% of B: 0.01/1,3/10,10/20,20/35,30/55,40/70,45/85,45.1/98,49/98, RT-35 min.

Method M

[0467] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
3.0	95	5
10.0	75	25
15.0	60	40
20.0	55	45
25.0	50	50
25.0	40	60

30.0	30	70
40.0	5	95
47.0	05	95
48.0	95	05
55.0	95	05

[0468] Solvent A: 0.1% Ammonium Bicarbonate in water

[0469] Solvent B: Acetonitrile

[0470] Injection Volume: 5.0uL

[0471] Column: X-SELECT CSH (250*30 mm), 5.0 µm.

Method N

[0472] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)		
Time (min)	Solvent A (%)	Solvent B (%)
0.0	95	5
3.0	95	5
10.0	75	25
15.0	60	40
20.0	55	45
25.0	50	50
25.0	40	60
30.0	30	70
40.0	5	95
47.0	05	95
48.0	95	05
55.0	95	05

[0473] Solvent A: 10 mM Formic acid in water

[0474] Solvent B: Acetonitrile

[0475] Injection Volume: 5.0uL

[0476] Column: X-SELECT CSH (250*30 mm), 5.0 µm.

Method O

[0477] HPLC analyses were obtained on a TELEDYNE-02 HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	98	2
0.3	98	2
2.0	02	98
2.8	02	98
3.0	98	02
3.7	98	02

[0478] Solvent A: 2.5 mM Ammonium Bicarbonate + 5% ACN

[0479] Solvent B: Acetonitrile

[0480] Injection Volume: 5.0uL

[0481] Column: X-Select CSH C18 (3.0 × 50) mm, 2.5 µm.

Method P

[0482] HPLC analyses were obtained on a Gilson Autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35°C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	80	20
2.0	80	20
10.0	55	45
30.0	05	95
30.0	00	100

[0483] Solvent A: 10 mM Formic acid in H₂O

[0484] Solvent B: 100% Acetonitrile

[0485] Injection Volume: 5.0uL

[0486] Column: X BRIDGE C18 (30 × 250) mm, 5µ.

Method Q

[0487] HPLC analyses were obtained on a Shimatzu autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (1.0 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.01	95	05
1.0	95	05
8.0	00	100
12.0	00	100
14.0	95	05
18.0	95	05

[0488] Solvent A: 0.1% Formic acid in water: Acetonitrile(95:05)

[0489] Solvent B: Acetonitrile

[0490] Injection Volume: 5.0uL

[0491] Column: X-Select CSH C18 (4.6 × 150) mm 5u.

Method R

[0492] HPLC analyses were obtained on a TELEDYNE autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 35 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (25 mL/min flow)

Time (min)	Solvent A (%)	Solvent B (%)
0.0	70	30
3.0	70	30
10.0	40	60
15.0	30	70
20.0	25	75
30.0	15	85
40.0	05	95

[0493] Solvent A: 10mm ABC in water

[0494] Solvent B: Acetonitrile

[0495] Injection Volume: 5.0uL

[0496] Column: GOLD C-18 50 g.

Method S

[0497] HPLC analyses were obtained on a TFA CORTECS 2.5 Min autoprep HPLC consisting of a LC 20 AD prominence pump, DGU-20 A3 prominence degasser, SPD-M20A prominence DAD detector, SIL-HTC autosampler using LC Solutions, v.1.25 software under the following parameters: Column temp: 45 °C. Gradient elution methods, mobile phase eluents, PDA detection and columns are shown below.

LC Gradient (0.85 mL/min flow) 0.0/3, 0.1/3, 1.4/97, 2.0/97, 2.05/3, 2.5/3

Time (min)	Solvent A (%)	Solvent B (%)
0.0	97	03
0.1	97	03
1.4	03	97
2.0	03	97
2.05	97	03
2.5	97	03

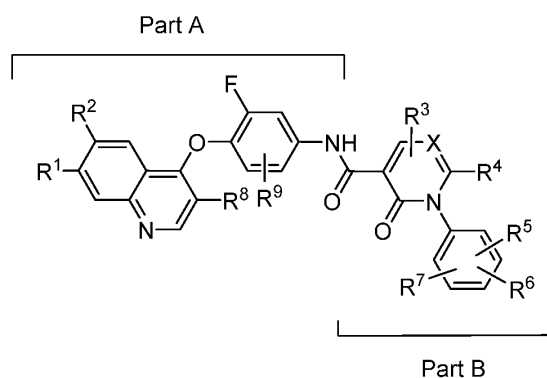
[0498] Solvent A: 0.05% TFA in Water

[0499] Solvent B: 0.05% TFA in Acetonitrile

[0500] Injection Volume: 5.0uL

[0501] Column: CORTECS UPLC C18 (3 × 30)mm, 1.6um.

General Procedure employed for the preparation of Compounds:



Method A

[0502] To a stirred solution of PART B (1.20 eq.) in DMF (0.50 mL) was added TEA (3.00 eq.) and T3P (1.50 eq.) followed by PART A (1.00 eq.). Reaction was stirred at room temperature for 16 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was poured into ice water (5 mL) after which precipitation was observed. The obtained precipitate was filtered, washed with water (3 × 10 mL) and dried to obtain the crude. The crude was purified by prep-HPLC. The pure fraction was evaporated under reduced pressure to afford the title compound.

Method B

[0503] To a stirred solution of PART B (1-1.5 eq.) in DMF (2.0-5.0 mL) under inert (N₂/Ar) atmosphere was added DIPEA (3-5 eq.) and HATU (1.3-1.5 eq.) at room temperature followed by PART A (1-1.5 eq.). The reaction mixture was stirred for 16 h. The reaction progress was monitored by TLC. After the consumption of starting materials, the reaction was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL). Combined organic layer was washed

with brine (10 mL), then dried over sodium sulfate and concentrated under reduced pressure to get crude. The crude was purified by prep-HPLC. The pure fraction was evaporated under reduced pressure to afford the title compound.

Method C

[0504] To a stirred solution of PART B (1.20 eq.) in MeCN (0.50 mL,) was added NMI (5.00 eq.) and TCFH (2.00 eq.) followed by PART A (1.00 eq.). The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, as monitored by TLC, the mixture was poured into ice –water (5 mL) mixture leading to precipitation. The obtained precipitates were filtered, washed with water (3 x 10 mL) and dried to obtain the crude. The crude was purified by prep-HPLC. The pure fractions were evaporated under reduced pressure to afford the title compound.

Method D

[0505] To a stirred solution of PART B (1.20 eq.), in pyridine (5 mL) was added TEA (3.00 eq.), HOBt (1.50 eq.) and EDC.HCl (1.50 eq.) at room temperature followed by PART A (1.00 eq.) under nitrogen atmosphere. The reaction mixture was stirred at 70°C for 16 h. The crude compound was purified, and pure fractions were evaporated under reduced pressure to afford the title compound.

Method E

[0506] To a stirred solution of PART A (1.00 eq) in Ethanol (2 mL) was added PART B (1.20 eq) and Zinc triflate (1.00 eq). Then the reaction was stirred at 90°C for 16 h.

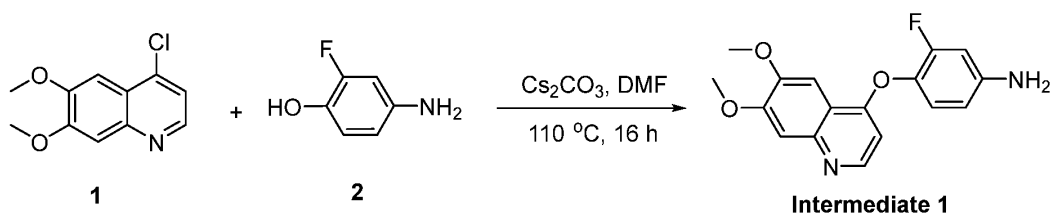
Method F

[0507] To a stirred solution of PART B (1.00 to 1.02 eq.) in DCM (2 mL) was added oxalyl chloride (3.00 eq) followed by catalytic amount of DMF (0.300 eq) at room temperature. The reaction mixture was stirred for 1 h. The reaction mixture was evaporated under nitrogen atmosphere to remove excess amount of oxalyl chloride to obtain acid chloride. The acid chloride was dissolved in DCM (1 mL) and was added to a stirred solution of PART A (1.00 to 1.2 eq) and TEA (5.00 eq) in DCM (3 mL) at room temperature. The reaction mixture was stirred for 16 h. The reaction mixture was diluted with DCM (20 mL) and washed with saturated sodium bicarbonate solution (3 x 20 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure.

Examples:

Part A Intermediate Synthesis:

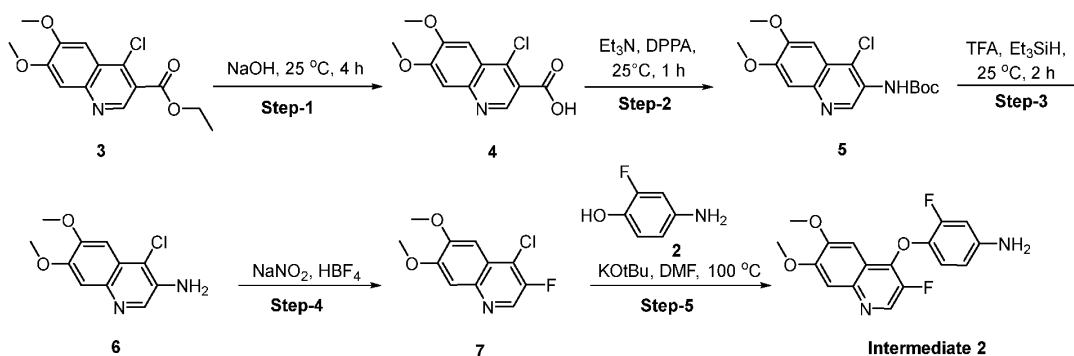
[0508] Synthesis of 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-aniline [Intermediate 1]:



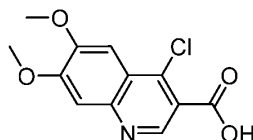
[0509] A stirred solution of 4-chloro-6,7-dimethoxyquinoline (15.00 g, 67.1 mmol, 1.00 eq) and 4-amino-2-fluorophenol (12.79 g, 101 mmol, 1.50 eq) in DMF (200 mL, 0.3353 M) was charged with cesium carbonate (65.55 g, 201 mmol, 3.00 eq) at rt. The reaction mixture was heated to 110 °C stirred for 16 h. The reaction mixture was treated with water (100 mL) and extracted with ethyl acetate (3 × 500 mL) and the combined organic layers were washed with cold water (2 × 300 mL), brine solution (300 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude compound. The crude was purified by combi flash column chromatography eluting 90% EtOAc in hexane resulting in 8.50 g, 36.21% yield of Intermediate 1 as a pale brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.45 (d, *J* = 5.3 Hz, 1H), 7.50 (s, 1H), 7.44 - 7.32 (m, 1H), 7.07 (t, *J* = 9.1 Hz, 1H), 6.55 (dd, *J* = 2.5, 13.3 Hz, 1H), 6.50 - 6.43 (m, 1H), 6.43 - 6.35 (m, 1H), 5.50 (s, 2H), 3.94 (s, 6H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₇H₁₅FN₂O₃+H]⁺: 315.32, found: 315.0, *t_R* = 1.22 min, [Method N].

[0510] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline

[Intermediate 2]:



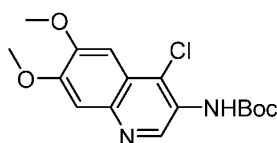
[0511] Synthesis of 4-chloro-6,7-dimethoxy-quinoline-3-carboxylic acid [4]:



[0512] A stirred solution of ethyl 4-chloro-6,7-dimethoxy-quinoline-3-carboxylate (4.00 g, 13.5 mmol, 1.00 eq) in ethanol (32 mL, 0.2818 M) at rt was dropwise charged with a solution of NaOH (1.62 g, 40.6 mmol, 3.00 eq) in water (16 mL, 0.2818 M). The reaction mixture was

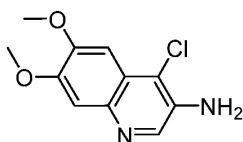
stirred at rt for 4 h. The reaction mixture was concentrated under reduced pressure to remove ethanol and the resulting aqueous layer was washed with dichloromethane (2×200 mL) and separated. The aqueous layer was acidified with 1N HCl (100 mL) to pH 3-6 resulting in a white precipitate that was filtered and washed with water (2×200 mL), dried under reduced pressure to afford 4-chloro-6,7-dimethoxy-quinoline-3-carboxylic acid (3.2 g, 88% yield) as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 13.66 (br s, 1H), 8.94 (s, 1H), 7.49 (d, J = 18.1 Hz, 2H), 3.97 (s, 6H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{10}\text{ClNO}_4+\text{H}]^+$: 268.04, found: 267.90, t_R = 1.040 min, [Method G].

[0513] Synthesis of *tert*-butyl *N*-(4-chloro-6,7-dimethoxy-3-quinolyl)carbamate [5]:



[0514] A stirred solution of 4-chloro-6,7-dimethoxy-quinoline-3-carboxylic acid (7.30 g, 27.3 mmol, 1.00 eq) in DMF (150 mL, 0.1818 M) was cooled to 0 °C and charged with triethyl amine (15 mL, 81.8 mmol, 3.00 eq) and diphenylphosphoryl azide (12 mL, 54.5 mmol, 2.00 eq). The reaction mixture was slowly warm to rt and stirred for 1 h. Then *tert*-butanol (52 mL, 545 mmol, 20.0 eq) was dropwise added to the reaction mixture and heated to 100 °C for 16 h, under nitrogen atmosphere. The reaction mixture was cooled to rt and water was added and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude as a brown solid. The crude was purified by combi flash by using 80 g cartridge and eluting with 20-50% ethyl acetate in heptane to afford 1.2 g, 12% yield of *tert*-butyl *N*-(4-chloro-6,7-dimethoxy-3-quinolyl)carbamate as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 9.13 (br s, 1H), 8.71 (s, 1H), 7.44 (s, 1H), 7.36 (s, 1H), 3.96 (d, J = 7.9 Hz, 6H), 1.48 (s, 9H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{19}\text{ClN}_2\text{O}_4+\text{H}]^+$: 339.06, found: 339.00, t_R = 1.730 min, [Method A].

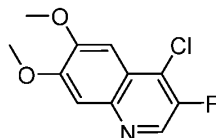
[0515] Synthesis of 4-chloro-6,7-dimethoxy-quinolin-3-amine [6]:



[0516] A stirred solution of *tert*-butyl *N*-(4-chloro-6,7-dimethoxy-3-quinolyl)carbamate (1.20 g, 3.54 mmol, 1.00 eq) in DCM (10 mL, 0.3542 M) was cooled to 0 °C. and charged with trifluoroacetic acid (20 mL, 10.6 mmol, 3.00 eq). The reaction mixture was slowly allowed to warm to rt and stirred for 2 h. The reaction mixture was evaporated under reduced pressure to

get crude. The crude was triturated with ether (50 ML) and the resultant solid was filtered and dried under vacuum to afford 4-chloro-6,7-dimethoxy-quinolin-3-amine (660 mg, 67% yield) as an off white solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₁H₁₁ClN₂O₂+H]⁺: 239.06, found: 238.80, *t*_R = 0.960 min, [Method A].

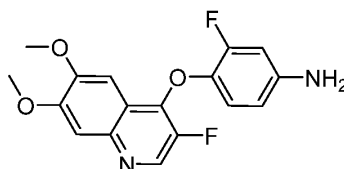
[0517] Synthesis of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline [7]:



[0518] A stirred solution of 4-chloro-6,7-dimethoxy-quinolin-3-amine (2.40 g, 10.1 mmol, 1.00 eq) in THF (50 mL, 0.1915 M) was cooled 0 °C and charged with HBF₄ (5.5 mL, 40.2 mmol, 4.00 eq) (note: reaction was conducted in a plastic reaction vessel). The reaction mixture was stirred for 5 min and charged with NaNO₂ (1.04 g, 15.1 mmol, 1.50 eq) in water (2.5 mL, 0.1915 M) and stirred for 30 min. and the resultant yellow solid was filtered, washed with THF (2 x 5 mL) and dried under reduced pressure to get yellow solid (1.2 g). The solid was carefully heated to 160 °C until a gas evolution was observed this was heated at 160 °C until no gas evolution was observed. The resulted black crude was purified by combi flash eluting 20-30% EtOAc in heptane to afford 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (600 mg, 23% yield) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.81 (d, *J* = 0.8 Hz, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₁H₉ClFNO₂+H]⁺: 242.04, found: 241.80, *t*_R = 1.730 min, [Method A].

[0519] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline

[Intermediate 2]:

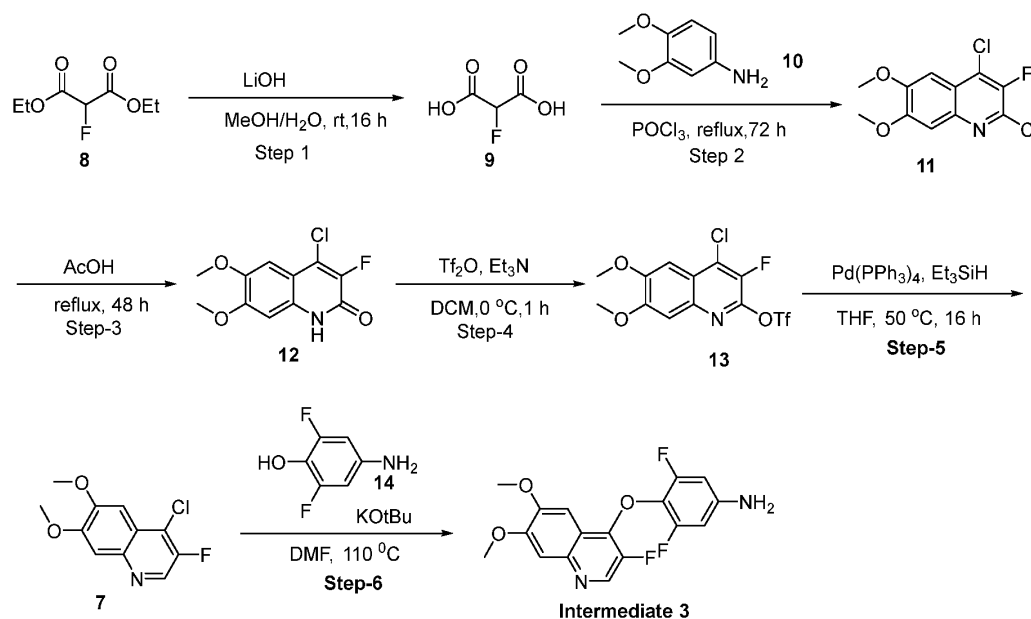


[0520] A stirred solution of 4-amino-2-fluorophenol (810 mg, 6.37 mmol, 2.00 eq) in DMF (20 mL, 0.1593 M) at rt was charged with potassium *tert*-butoxide (1.07 g, 9.56 mmol, 3.00 eq) and stirred for 20 min. The reaction was then charged with 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (770 mg, 3.19 mmol, 1.00 eq) and the reaction mixture was heated to 100 °C for 16 h. The reaction mixture was cooled to rt, filtered through pad of celite and washed with ethyl acetate (100 mL). Then filtrate was washed with brine (100 mL) and dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude was purified by combi flash by using 24 g cartridge and eluting with 40-50% ethyl acetate in heptane and concentrated under reduced pressure. The resulting material was triturated with diethyl ether (10 mL) to

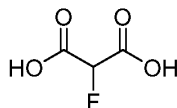
afford 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (110 mg, 10% yield) as a brown solid. ^1H NMR (400 MHz, DMSO- d_6): δ 8.66 (d, J = 3.5 Hz, 1H), 7.41 (s, 1H), 7.36 (s, 1H), 6.87 (t, J = 9.2 Hz, 1H), 6.48 (d, J = 13.6 Hz, 1H), 6.30 (d, J = 8.8 Hz, 1H), 5.28 (s, 2H), 3.94 (s, 3H), 3.89 (s, 3H); MS(es^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_3+\text{H}]^+$: 333.11, found: 332.90, t_R = 1.50 min and 1.61 min, [Method A].

[0521] Synthesis of 3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline

[Intermediate 3]:

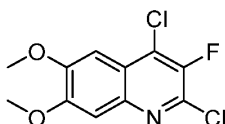


[0522] Synthesis of 2-fluoropropanedioic acid [9]:



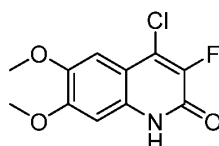
[0523] A stirred solution of diethyl 2-fluoropropanedioate (100.00 g, 561 mmol, 1.00 eq), in methanol and water (1000 mL) was charged with LiOH.H₂O (72.24 g, 1684 mmol, 3.00 eq) and stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure to get a residue which was acidified with an aqueous solution of 1N HCl (200 mL) and the resultant precipitate was filtered and washed with water (100 mL), dried under reduced pressure to afford 60 g, 82% yield of the title compound as a white solid; MS(ES)⁺ m/z calc'd for $[\text{M}-\text{H}]^+$ $[\text{C}_3\text{H}_3\text{FO}_4-\text{H}]^+$: 123.05, found: 121.1, t_R = 1.02 mins. [Method N].

[0524] Synthesis of 2,4-dichloro-3-fluoro-6,7-dimethoxyquinoline [11]:



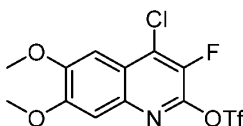
[0525] A stirred solution of 2-fluoropropanedioic acid (100.00 g, 819 mmol, 1.00 eq) in POCl₃ (1200 mL, 819 mmol, 1.00 eq) was heated at 120 °C for 30 mins, then the reaction mixture was cooled to 60 °C and portion wise charged with 3,4-Dimethoxyaniline (125.51 g, 819 mmol, 1.00 eq) and heated to 120 °C for 72 h. Excess POCl₃ was removed from the reaction mixture by downward distillation to remove almost 1L of POCl₃. The reaction mixture was poured into ice cold water (2 L), stirred at room temperature for 20 min. and the resultant precipitate was filtered, washed with water (2 × 200 mL), dried under vacuum to get crude. The crude was purified by column chromatography using 60-120 silica gel and eluted with 10-20% ethyl acetate in *n*-heptane to afford 13.00 g, 6% yield as a light yellow solid; MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₁H₈Cl₂FNO₂+H]⁺: 277.09, found: 275.8, *t_R*= 2.14 mins, [Method N].

[0526] Synthesis of 4-chloro-3-fluoro-6,7-dimethoxy-1H-quinolin-2-one [12]:



[0527] A stirred solution of 2,4-dichloro-3-fluoro-6,7-dimethoxy-quinoline (27.00 g, 97.8 mmol, 1.00 eq) in acetic acid (420 mL, 0.2328 M) was heated to reflux at 130 °C for 48 h. The reaction mixture was allowed to cool to rt and charged with water upon which a solid was precipitated. The precipitate was filtered and the resulting solid was washed with acetone (50 mL) and diethyl ether (50 mL), and co-distilled with toluene, dried under reduced pressure to afford 22 g, 84% yield of 12 as an off-white solid; MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₁H₉ClFNO₃+H]⁺: 258.65, found: 257.9, *t_R*= 1.58 min, [Method N].

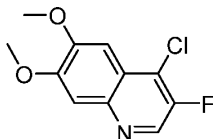
[0528] Synthesis of (4-chloro-3-fluoro-6,7-dimethoxy-2-quinolyl) trifluoromethanesulfonate [13]:



[0529] A stirred solution of 4-chloro-3-fluoro-6,7-dimethoxy-1H-quinolin-2-one (22.00 g, 85.4 mmol, 1.00 eq) in DCM (400 mL, 0.2135 M) was cooled to 0 °C and charged with TEA (18 mL, 128 mmol, 1.50 eq) and triflic anhydride (17 mL, 102 mmol, 1.20 eq). The reaction was stirred at 0 °C for 1 h. The reaction mixture was diluted with DCM (300 mL) and washed with water (100 mL) and the combined organic layers were washed with brine (100 mL) and dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to get crude. The crude was purified flash column chromatography using 100-200 g silica gel and eluted with 100% DCM to afford 24.00 g, 68% yield of 13 as an off-white solid. ¹H NMR (400 MHz,

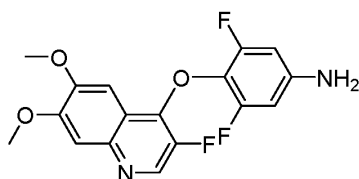
DMSO-*d*₆): δ 7.42 (s, 1H), 7.34 (s, 1H), 4.01 (s, 3H), 3.98 (s, 3H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₂H₈ClF₄NO₅S+H]⁺: 390.7, found: 389.80, *t*_R = 2.23 min, [Method N].

[0530] Synthesis of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline [7]:



[0531] A stirred solution of (4-chloro-3-fluoro-6,7-dimethoxy-2-quinolyl) trifluoromethanesulfonate (24.00 g, 61.6 mmol, 1.00 eq) in THF (200 mL, 0.3079 M) was degassed with Nitrogen for 10 min and charged with Pd tetrakis (1.17 g, 1.02 mmol, 0.0165 eq) under a nitrogen atmosphere. The reaction mixture was stirred at 50 °C for 10 min and charged with pyridine (50 mL, 616 mmol, 10.0 eq) and triethylsilane (98 mL, 616 mmol, 10.0 eq). The reaction was stirred at rt for 5 h then concentrated under reduced pressure resulting in a residue. The residue was dissolved in ethyl acetate (400 mL) and washed with water (100 mL). The aqueous layer was extracted with ethyl acetate (2 × 200 mL) and the combined organic layers were washed with brine (2 × 200 mL) and dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to get crude. The crude was purified by comb flash using 120 g column cartridge and eluted with 20-30% ethyl acetate/heptane to get product. The product was further triturated with MeOH (100 mL), Et₂O (2 × 100 mL). The resulting precipitate was filtered, dried under reduced pressure to afford 9.50 g, 61% yield as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.81 (s, 1H), 7.47 (s, 1H), 7.32 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₁H₉ClFNO₂+H]⁺: 242.04, found: 241.90, *t*_R = 1.850 min, [Method N].

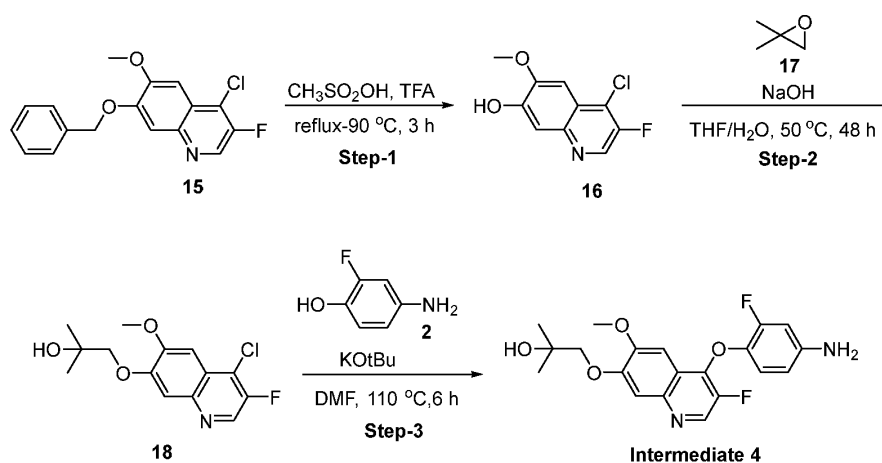
[0532] Synthesis of 3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline [Intermediate 3]:



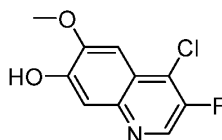
[0533] A stirred solution of 4-amino-2,6-difluorophenol (7.21 g, 49.7 mmol, 2.00 eq) in DMF (60 mL, 0.4138 M) at rt was charged with potassium *tert*-butoxide (8.36 g, 74.5 mmol, 3.00 eq) and stirred for 10 min followed by the addition of 4-chloro-3-fluoro-6,7-dimethoxyquinoline (6.00 g, 24.8 mmol, 1.00 eq) and heated to 120 °C for 6 h. The reaction mixture was cooled to rt, then filtered through a pad of celite. The celite was washed with ethyl acetate (500 mL) and the filtrate was washed with brine (200 mL) and cold water (200 mL), dried over anhydrous sodium sulfate, filtered, evaporated under reduced pressure to get crude. The crude was purified by

comb flash using YMC-80 g column cartridge and eluted with 40-60% ethyl acetate in heptane to get titled product. The product was triturated with methanol (100 mL) and acetonitrile (3×50 mL), and the resulting precipitate was filtered, dried under vacuum to afford 4.30 g, 48% yield as an off-white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.63 (d, $J = 4.0$ Hz, 1H), 7.46 (s, 1H), 7.40 (s, 1H), 6.31 (d, $J = 11.0$ Hz, 2H), 5.68 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H); $\text{MS}(\text{ES})^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3+\text{H}]^+$: 351.3, found: 351.4, $t_R = 2.003$ min, [Method H'].

[0534] Synthesis of 1-[[4-(4-amino-2-fluorophenoxy)-3-fluoro-6-methoxy-7-quinolyl]oxy]-2-methylpropan-2-ol [Intermediate 4]:

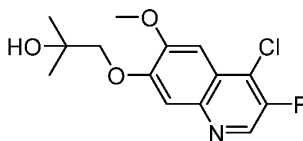


[0535] Synthesis of 4-chloro-3-fluoro-6-methoxyquinolin-7-ol [16]:



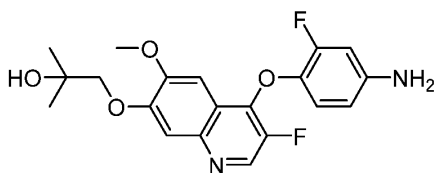
[0536] A solution of 7-benzyloxy-4-chloro-3-fluoro-6-methoxyquinoline (4.50 g, 14.2 mmol, 1.00 eq) in TFA (30 mL, 14.2 mmol, 1.00 eq) at rt was charged with methanesulfonic acid (1.7 mL, 26.9 mmol, 1.90 eq). The reaction mixture was heated to 90 °C for 3 h. The reaction mixture was allowed to cool to rt and was evaporated under reduced pressure to get a residue. The residue was dissolved in sat. NaHCO_3 solution (50 mL) and adjusted to pH 7-9 and extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine solution (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated under reduced pressure to get crude. The crude was triturated with DCM and diethyl ether and the resulting precipitate was filtered, washed with diethyl ether to afford 3.10 g, 90% yield as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.56 (br s, 1H), 7.17 (s, 1H), 7.07 (br s, 1H), 3.93 (s, 3H); $\text{MS}(\text{ES})^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{10}\text{H}_7\text{ClFNO}_2+\text{H}]^+$: 228.12, found: 227.90, $t_R = 1.690$ min, [Method N].

[0537] **Synthesis of 1-[(4-chloro-3-fluoro-6-methoxy-7-quinolyl)oxy]-2-methyl-propan-2-ol [18]:**



[0538] A solution of 4-chloro-3-fluoro-6-methoxy-quinolin-7-ol (2.80 g, 12.3 mmol, 1.00 eq) in 1:1 mixture THF/water (30 mL) at rt was charged with NaOH (1.48 g, 36.9 mmol, 3.00 eq), followed by 1,2-Epoxy-2-methylpropane (13 mL, 123 mmol, 10.0 eq). The reaction mixture was heated to 50 °C for 16 h. The reaction mixture was treated with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine solution (50 mL) dried over anhydrous sodium sulfate filtered and concentrated under reduced pressure to get crude. The crude compound was purified by comb flash column chromatography using 40 g column cartridge and eluted with 30-80% ethyl acetate in n-heptane to afford 2.10 g, 53% as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.81 (d, *J* = 0.8 Hz, 1H), 7.47 (s, 1H), 7.35 (s, 1H), 4.68 (br s, 1H), 4.01 (s, 3H), 3.91 (s, 2H), 1.26 (s, 6H); MS(ES⁺) calc'd for [M+H]⁺ [C₁₄H₁₅ClFNO₃+H]⁺: 300.08, found: 299.90, *t*_R = 1.810 min, [Method N].

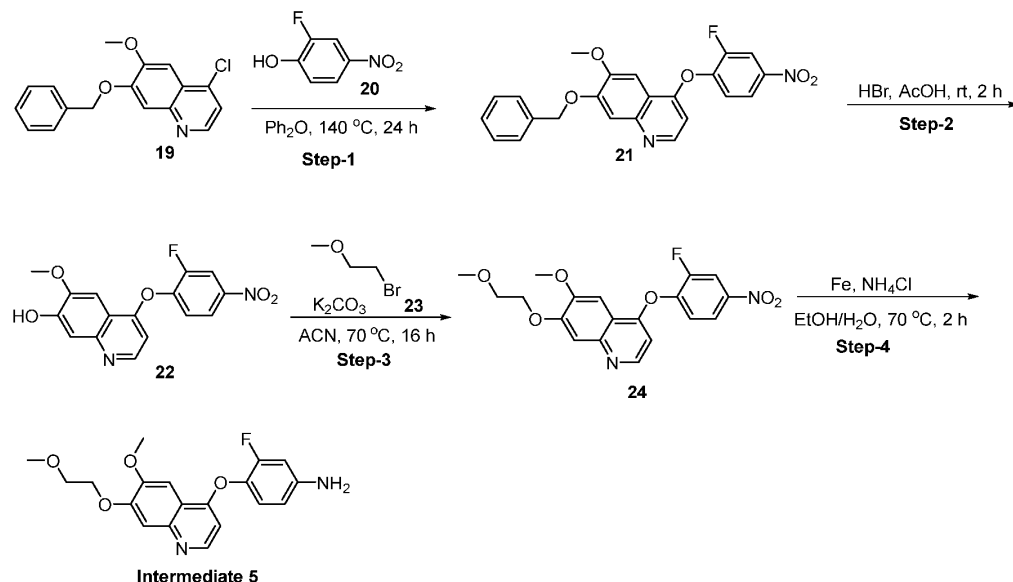
[0539] **Synthesis of 1-[[4-(4-amino-2-fluoro-phenoxy)-3-fluoro-6-methoxy-7-quinolyl]oxy]-2-methyl-propan-2-ol [Intermediate 4]:**



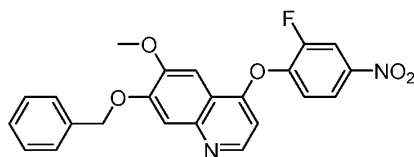
[0540] A stirred solution of 4-amino-2-fluorophenol (679 mg, 5.34 mmol, 2.00 eq) in DMF (10 mL, 0.2669 M) at rt was charged with potassium *tert*-butoxide (898 mg, 8.01 mmol, 3.00 eq) and stirred for 10 min then charged with 1-[(4-chloro-3-fluoro-6-methoxy-7-quinolyl)oxy]-2-methyl-propan-2-ol (800 mg, 2.67 mmol, 1.00 eq). The reaction mixture was heated to 110 °C for 4 h. The reaction mixture was cooled to rt, filtered through pad of celite, washed with ethyl acetate (100 mL). The filtrate was washed with brine (100 mL) and dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to get crude. The crude was purified by comb flash using YMC-40 g column cartridge and eluted with 40-60% ethyl acetate in heptane to get product. The product was further purified by prep-HPLC purification, collected fractions were evaporated under vacuum to afford 300 mg, 28% yield as a light brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.65 (d, *J* = 3.6 Hz, 1H), 7.39 (s, 1H), 7.36 (s, 1H), 6.86 (t, *J* = 9.2 Hz, 1H), 6.47 (dd, *J* = 13.6, 2.8 Hz, 1H), 6.32-6.27 (m, 1H), 5.28 (s, 2H), 4.66 (s, 1H), 3.91

(s, 3H), 3.88 (s, 2H), 1.25 (s, 6H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₂₀H₂₀F₂N₂O₄+H]⁺: 391.15, found: 390.90, *t*_R= 3.970 min, [Method N].

[0541] Synthesis of 3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl] oxy] aniline [Intermediate 5]:

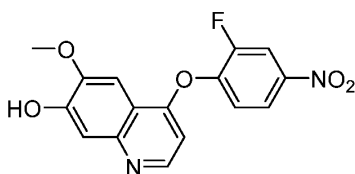


[0542] Synthesis of 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline [21]:



[0543] A stirred solution of 7-benzyloxy-4-chloro-6-methoxy-quinoline (20.00 g, 66.7 mmol, 1.00 eq) in diphenyl ether (350 mL, 2224 mmol, 33.3 eq) at rt was charged 2-fluoro-4-nitrophenol (20.96 g, 133 mmol, 2.00 eq) and the reaction mixture was heated to 140 °C for 24 h. The reaction mixture was diluted with diethyl ether (200 mL) and the resultant precipitate was filtered and washed with heptane (200 mL), dried under vacuum to afford 26.00 g, 76% yield of title compound as a pale brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₂₃H₁₇FN₂O+H]⁺: 421.4, found: 421.0, *t*_R= 1.71min, [Method N].

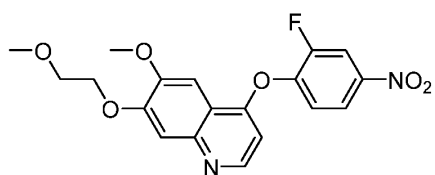
[0544] Synthesis of 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol [22]:



[0545] 7-benzyloxy-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (15.00 g, 35.7 mmol, 1.00 eq) was cooled to 0 °C and was dropwise charge with a solution of 33% hydrogen bromide

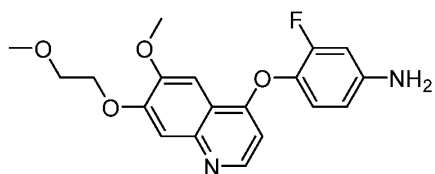
in acetic acid (150 mL, 922 mmol, 25.8 eq) after addition, the reaction mixture was heated to 60 °C for 2h. The reaction mixture was cooled to 0 °C and diluted with diethyl ether (150 mL) and stirred for 30 min. The resultant precipitate was filtered and washed with diethyl ether (2 × 50 mL), dried under reduced pressure to afford 7.00 g of titled compound, 55% yield as an off white solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₆H₁₁FN₂O₅+H]⁺: 331.27, found: 331.0, *t*_R= 1.38 min, [Method N].

[0546] Synthesis of 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methoxyethoxy) quinoline [24]:



[0547] A stirred solution of 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (5.00 g, 15.1 mmol, 1.00 eq) in acetonitrile (50 mL, 0.3028 M) at rt was charged with 2-bromoethyl methyl ether (2.8 mL, 30.3 mmol, 2.00 eq) followed by K₂CO₃ (6.27 g, 45.4 mmol, 3.00 eq) nitrogen atmosphere. After addition, the reaction mixture was heated to 70 °C for 16 h. The reaction mixture was treated with water (150 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine solution (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude compound. The crude was purified by comb flash chromatography by 80 g column cartridge, eluted with 30-50% ethyl acetate in heptane to afford 3.50 g, 52% yield of the title compound as a pale-yellow solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₉H₁₇FN₂O₆+H]⁺: 389.35, found: 389.0, *t*_R= 1.50 min, [Method N].

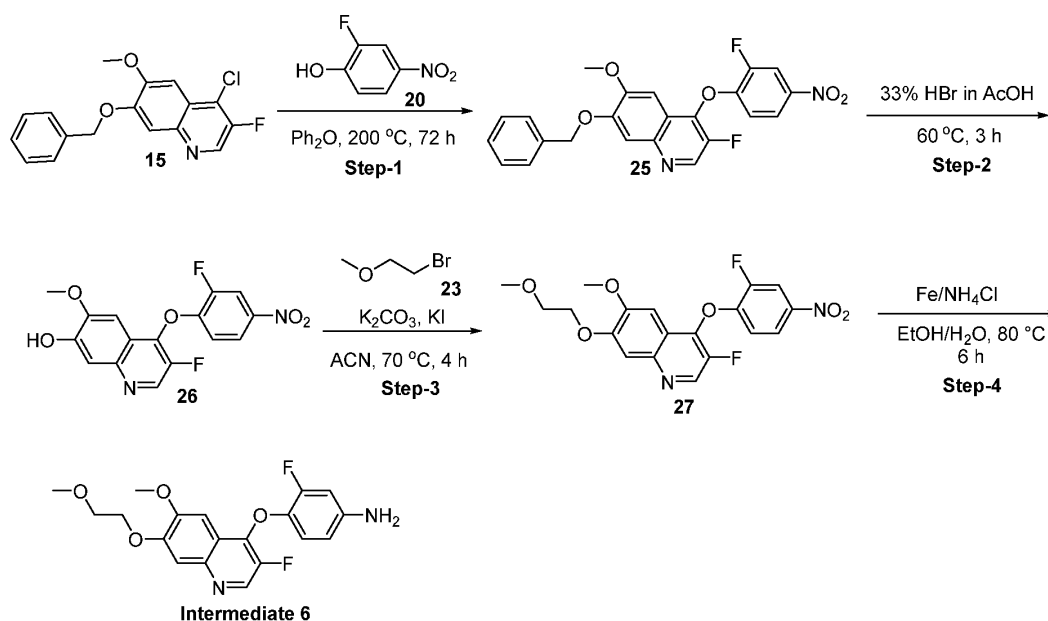
[0548] Synthesis of 3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl] oxy] aniline [Intermediate 5]:



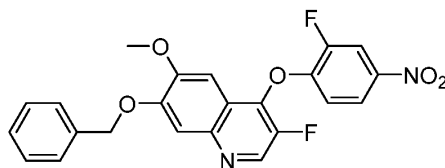
[0549] A stirred solution of 4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methoxyethoxy) quinoline (3.50 g, 9.01 mmol, 1.00 eq) in 5:1 ethanol/water (50 mL) at rt was charged with NH₄Cl (2.41 g, 45.1 mmol, 5.00 eq) and Fe (2.52 g, 45.1 mmol, 5.00 eq). The reaction mixture was heated to 70 °C for 2 h. Upon cooling, the reaction mixture was filtered through a pad of celite and washed with ethanol (70 mL) and 10% methanol in DCM (3 × 100 mL). The filtrate was concentrated to get crude. The crude was purified by comb flash with 70 g cartridge and 4-5% MeOH in DCM, followed by triturated with Et₂O (50 mL) to afford 1.70 g, 50% yield as a

pale-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.45 (d, $J = 5.4$ Hz, 1H), 7.51 (s, 1H), 7.45–7.33 (m, 1H), 7.07 (t, $J = 9.0$ Hz, 1H), 6.59–6.51 (m, 1H), 6.50–6.43 (m, 1H), 6.39 (d, $J = 4.9$ Hz, 1H), 5.47 (s, 2H), 4.34–4.20 (m, 2H), 3.95 (s, 3H), 3.80–3.71 (m, 2H), 3.35 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{19}\text{H}_{19}\text{FN}_2\text{O}_4+\text{H}]^+$: 359.37, found: 359.0 $t_R = 1.31$ min, [Method N].

[0550] Synthesis of 3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol [V117540] and 3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline [Intermediate 6]:

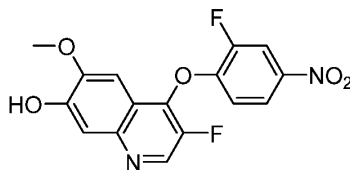


[0551] Synthesis of 7-benzyloxy-3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline [25]:



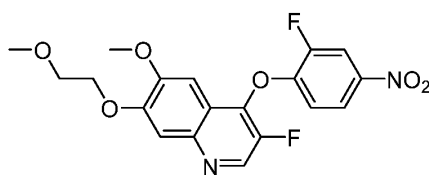
[0552] In a sealed tube, a solution of 7-benzyloxy-4-chloro-3-fluoro-6-methoxy-quinoline (4.00 g, 8.81 mmol, 1.00 eq) in diphenyl ether (36 mL, 224 mmol, 25.4 eq) at rt was charged with 2-Fluoro-4-nitrophenol (3.46 g, 22.0 mmol, 2.50 eq) under a nitrogen atmosphere. The reaction mixture heated to 200 °C for 72 h. The reaction mixture was allowed to cool to rt and was charged with DCM (50 mL). The reaction was concentrated using reduced pressure and the crude mixture was purified by comb flash using YMC-40 g column cartridge and eluted with 25–30% ethyl acetate/heptane to afford 2.80 g, 32% yield of the title compound as a pale yellow solid. MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{23}\text{H}_{16}\text{F}_2\text{N}_2\text{O}_5+\text{H}]^+$: 439.39, found: 438.9, $t_R = 2.18$ min, [Method N].

[0553] Synthesis of 3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol hydrogen bromide salt [26]:



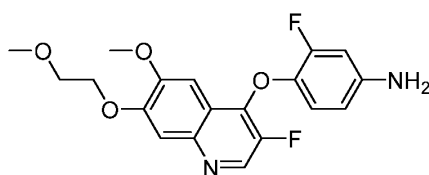
[0554] A solid sample of 7-benzyloxy-3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinoline (2.80 g, 3.19 mmol, 1.00 eq) was cooled to 0 °C and dropwise charged with 33% solution of hydrogen bromide in acetic acid (30 mL, 184 mmol, 57.7 eq) under nitrogen atmosphere. The reaction mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to 0 °C and diluted with Et₂O (10 mL) and stirred for 30 min. and the resulting precipitate was filtered and washed with Et₂O (3 × 5 mL) and dried under reduced pressure to get the HBr salt 1.20 g, 81% yield of the title compound as an off white solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₆H₁₀F₂N₂O₅+H]⁺: 349.26, found: 348.8, *t*_R= 1.85 min, [Method N].

[0555] Synthesis of 3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methoxyethoxy)quinoline [27]:



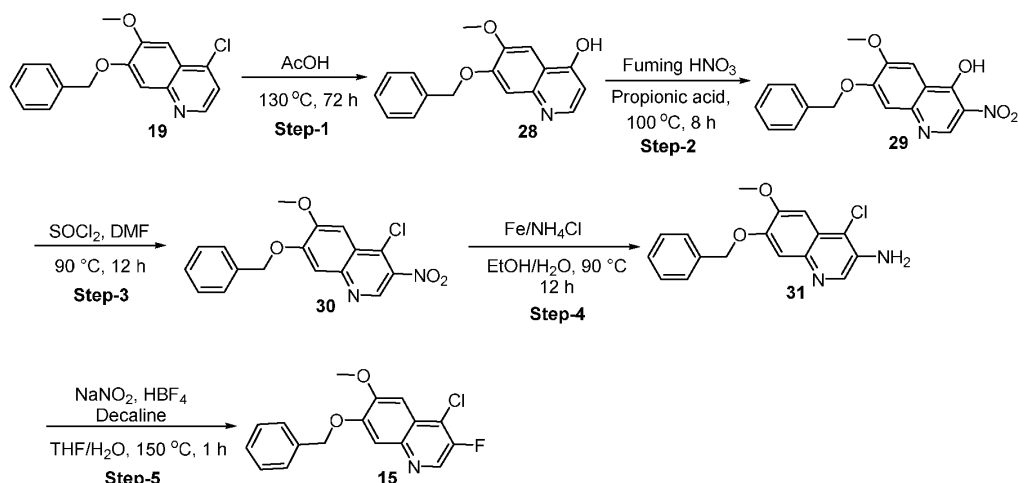
[0556] A solution of 3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-quinolin-7-ol (600 mg, 1.14 mmol, 1.00 eq) in acetonitrile (8 mL, 0.1421 M) at rt was charged with K₂CO₃ (785 mg, 5.69 mmol, 5.00 eq) and KI (94 mg, 0.569 mmol, 0.500 eq) under a nitrogen atmosphere and stirred for 30 min. The reaction was then charged with 2-Bromoethyl methyl ether (1.1 mL, 11.4 mmol, 10.0 eq) and stirred at 90 °C for 12 h. The reaction mixture was evaporated under reduced pressure to get residue which was treated with water (10 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine solution (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 230 mg, 40% yield of the title compound as pale brown solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₉H₁₆F₂N₂O₆+H]⁺: 407.34, found: 406.9, *t*_R= 1.96 min, [Method N].

[0557] Synthesis of 3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline [Intermediate 6]:

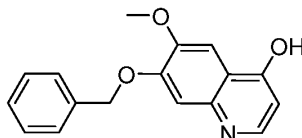


[0558] A stirred solution of 3-fluoro-4-(2-fluoro-4-nitro-phenoxy)-6-methoxy-7-(2-methoxyethoxy)quinoline (230 mg, 0.566 mmol, 1.00 eq) in ethanol (8 mL, 0.0566 M) and water (2 mL, 0.0566 M) at rt was charged with NH_4Cl (151 mg, 2.83 mmol, 5.00 eq) followed by Fe (158 mg, 2.83 mmol, 5.00 eq). The reaction mixture was heated 80 °C for 6 h. The reaction mixture was filtered through a pad of celite and washed with ethanol (10 mL) and 20% methanol/DCM (2×10 mL). The filtrate was concentrated under reduced pressure to get a residue which was diluted in water (5 mL) and 10% methanol and extracted with DCM (50 mL) and separated. The organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude. The crude compound was triturated with Et_2O (3×5 mL) resulting precipitate that was filtered and dried under reduced pressure to afford 150 mg, 56% yield of the title compound as a pale brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.66 (d, $J = 3.4$ Hz, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 6.87 (t, $J = 9.0$ Hz, 1H), 6.48 (dd, $J = 2.4, 13.7$ Hz, 1H), 6.33 - 6.27 (m, 1H), 5.30 (s, 2H), 4.29 - 4.24 (m, 2H), 3.90 (s, 3H), 3.77 - 3.72 (m, 2H), 3.34 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{19}\text{H}_{18}\text{F}_2\text{N}_2\text{O}_4+\text{H}]^+$: 377.36, found: 376.9, $t_R = 1.68$ min, [Method N].

[0559] Synthesis of 7-benzyloxy-4-chloro-3-fluoro-6-methoxy-quinoline [15]:



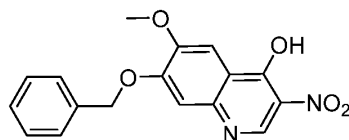
[0560] Synthesis of 7-benzyloxy-6-methoxy-quinolin-4-ol [28]:



[0561] A solution of 7-(Benzyloxy)-4-chloro-6-methoxyquinoline (80.00 g, 267 mmol, 1.00 eq) was charged with acetic acid (350 mL, 0.7625 M) and heated at 130 °C for 72 h. The reaction mixture was cooled to rt and was poured into crushed ice (2000 mL) and basified with solid NaHCO_3 . The resulting precipitate was filtered, washed with water (1000 mL) and acetone (500 mL) dried under reduced pressure to afford 60.00 g, 73.62% yield of the title compound as

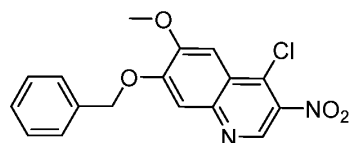
a pale brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.53 (br s, 1H), 7.78 (d, $J = 7.5$ Hz, 1H), 7.58 - 7.34 (m, 6H), 7.08 (s, 1H), 5.95 (d, $J = 7.0$ Hz, 1H), 5.21 (s, 2H), 3.86 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{15}\text{NO}_3+\text{H}]^+$: 282.11, found: 281.9, $t_R = 1.54$ min, [Method N].

[0562] Synthesis of 7-benzyloxy-6-methoxy-3-nitro-quinolin-4-ol [29]:



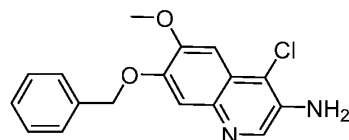
[0563] A solution of 7-benzyloxy-6-methoxy-quinolin-4-ol (30.00 g, 107 mmol, 1.00 eq) in propionic acid (400 mL, 107 mmol, 1.00 eq) at rt was charged with HNO_3 (9.3 mL, 224 mmol, 2.10 eq) and reaction mixture was heated to 100 °C for 8 h. The reaction mixture was allowed to cool at rt and the resulting precipitate was filtered, washed with heptane (200 mL), and 1:5 methanol:MTBE (500 mL), dried under reduced pressure to afford 27.00 g, 55.09% yield of the title compound as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 12.76 (s, 1H), 9.06 (s, 1H), 7.62 (s, 1H), 7.52 - 7.47 (m, 2H), 7.45 - 7.41 (m, 3H), 7.24 (s, 1H), 5.24 (s, 2H), 3.89 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_5+\text{H}]^+$: 327.09, found: 326.9, $t_R = 1.65$ min, [Method N].

[0564] Synthesis of 7-benzyloxy-4-chloro-6-methoxy-3-nitro-quinoline [30]:



[0565] A solution of 7-benzyloxy-6-methoxy-3-nitro-quinolin-4-ol (54.00 g, 165 mmol, 1.00 eq) in SOCl_2 (600 mL, 8274 mmol, 50.0 eq) at rt was charged with DMF (1.3 mL, 16.5 mmol, 0.100 eq) and the resulting reaction mixture was heated to 90 °C for 6 h. The reaction mixture was evaporated under reduced pressure to get crude as 50.00 g, 77.12% yield of the title compound as a brown solid. MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_4+\text{H}]^+$: 345.06, found: 344.9, $t_R = 2.25$ min, [Method N].

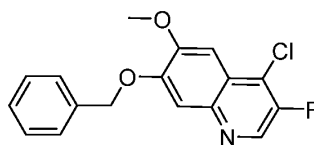
[0566] Synthesis of 7-benzyloxy-4-chloro-6-methoxy-quinolin-3-amine [31]:



[0567] A solution of 7-benzyloxy-4-chloro-6-methoxy-3-nitro-quinoline (30.00 g, 87.0 mmol, 1.00 eq) in ethanol (700 mL, 0.0989 M) and water (180 mL, 0.0989 M) at rt was charged with Fe powder (14.36 g, 261 mmol, 3.00 eq) and NH_4Cl (14.04 g, 261 mmol, 3.00 eq) under a nitrogen atmosphere. The resulting reaction mixture was heated to 90 °C for 12 h. The reaction mixture

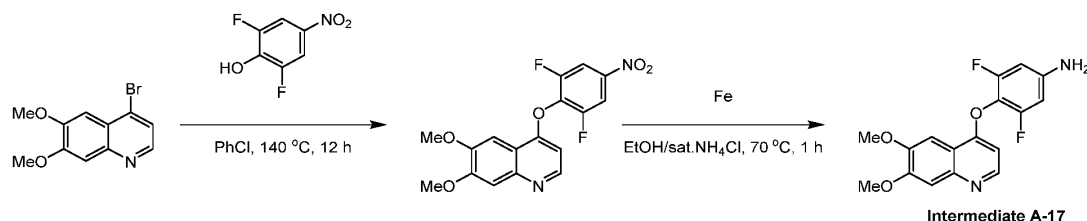
was filtered through a pad of celite washed with ethyl acetate (100 mL). The filtrate was evaporated under reduced pressure to get crude. The crude was diluted with water (50 mL) and 10% methanol in DCM (2×500 mL) and separated. The organic layer was washed with brine solution (100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. The crude was triturated with diethyl ether stirring for 30 min, resulting solid that was filtered and dried under reduced pressure to afford 25.00 g, 76.67% yield of the title compound as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.36 (s, 1H), 7.50 - 7.48 (m, 2H), 7.43 - 7.40 (m, 2H), 7.37 (s, 2H), 7.18 (s, 1H), 5.21 (s, 2H), 3.94 (s, 3H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+ [\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}_2+\text{H}]^+$: 315.08, found: 314.9, t_R = 1.71 min, [Method N].

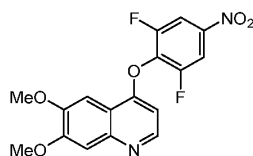
[0568] Synthesis of 7-benzyloxy-4-chloro-3-fluoro-6-methoxy-quinoline [15]:



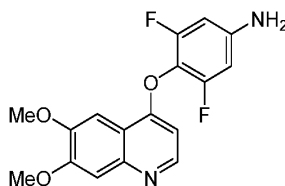
[0569] A stirred solution of 7-benzyloxy-4-chloro-6-methoxy-quinolin-3-amine (15.00 g, 47.7 mmol, 1.00 eq) in THF (150 mL, 0.3177 M) at rt was charged with HBF_4 (18 mL, 143 mmol, 3.00 eq) and stirred at rt for 30 min. The reaction mixture was cooled to 0 °C and charged with NaNO_2 (4.93 g, 71.5 mmol, 1.50 eq) in water 15 mL. The reaction mixture was stirred at 0 °C for another 30 min. The resulting precipitate was filtered and washed with THF (5 mL), dried under reduced pressure for 5 h to get diazonium tetrafluoro borate. The diazonium tetrafluoro borate was dissolved in decaline (150 mL) and heated to 150 °C for 30 min. The reaction mixture was dissolved in DCM and directly purified by combi flash column using YMC-80 g and 60-90% DCM in heptane to afford 4.00 g, 17.17% yield of the title compound as an off white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.60 (d, J = 1.0 Hz, 1H), 7.50 (d, J = 7.0 Hz, 2H), 7.45 (s, 1H), 7.41 - 7.36 (m, 4H), 5.30 (s, 2H), 4.07 (s, 3H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+ [\text{C}_{17}\text{H}_{13}\text{ClFNO}_2]^+$: 318.09, found: 317.8, t_R = 2.15 min, [Method N].

[0570] Synthesis of 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3,5-difluoro-aniline [Intermediate A-17]:



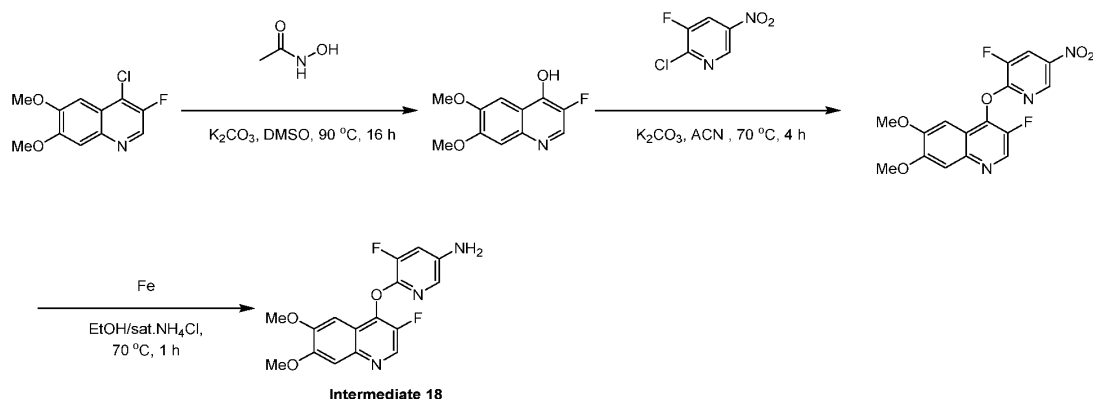
[0571] Synthesis of 4-(2,6-difluoro-4-nitro-phenoxy)-6,7-dimethoxy-quinoline

[0572] To a mixture of 4-bromo-6,7-dimethoxy-quinoline (2.00 g, 7.46 mmol, 1.00 eq) and 2,6-difluoro-4-nitro-phenol (2.61 g, 14.92 mmol, 2.00 eq) in chlorobenzene (30 mL) in one portion under N₂. The mixture was stirred at 140 °C for 12 hrs. LCMS showed the reaction was completed. The reaction mixture was concentrated under reduced pressure to remove solvent, treated with CH₂Cl₂ (100 mL) and washed with 10% NaOH aqueous solution (3×20 mL) and water (20 mL). The organic layers were dried over anhydrous Na₂SO₄ and filtered. The crude product was triturated with pet. ether (100 mL) at 25 °C for 0.5 h, filtered and the filter cake was dried to afford 4-(2,6-difluoro-4-nitro-phenoxy)-6,7-dimethoxy-quinoline (2.2 g, 81.40% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.53 (d, J=5.25 Hz, 1 H) 8.43 (d, J=7.50 Hz, 2 H) 7.55 (s, 1 H) 7.45 (s, 1 H) 6.76 (d, J=5.25 Hz, 1 H) 3.96 (d, J=1.63 Hz, 6 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₇H₁₂F₂N₂O₅+H]⁺: 363.07, found: 363.1, *t*_R= 1.346 min.

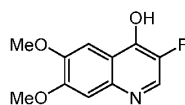
[0573] Synthesis of 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3,5-difluoro-aniline [Intermediate A-17]:

[0574] To a mixture of 4-(2,6-difluoro-4-nitro-phenoxy)-6,7-dimethoxy-quinoline (1.10 g, 3.04 mmol, 1.00 eq) in EtOH (12 mL) was added saturated NH₄Cl (3.04 mmol, 3 mL, 1.00 eq) in one portion, then Fe (847.81 mg, 15.18 mmol, 5.00 eq) was added at 70 °C. The mixture was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. The residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with brine (3×20 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3,5-difluoro-aniline (330 mg) as light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.48 (d, J=5.13 Hz, 1 H) 7.50 (s, 1 H) 7.40 (s, 1 H) 6.50 (d, J=5.25 Hz, 1 H) 6.41 - 6.44 (m, 1 H) 6.38 - 6.41 (m, 1 H) 5.82 (s, 2 H) 3.94 (s, 6 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₇H₁₄F₂N₂O₃+H]⁺: 333.09, found: 333.2, *t*_R= 1.256 min.

[0575] Synthesis of 5-fluoro-6-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]pyridin-3-amine [Intermediate 18]:

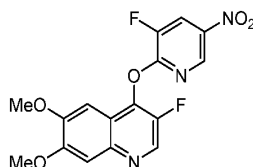


[0576] Synthesis of 3-fluoro-6,7-dimethoxy-quinolin-4-ol



[0577] To a solution of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (1.50 g, 6.21 mmol, 1.00 *eq*) in DMSO (30.00 mL) was added ethanehydroxamic acid (1.86 g, 24.83 mmol, 4.00 *eq*) and K_2CO_3 (4.29 g, 31.04 mmol, 5.00 *eq*), and then the mixture was stirred at 90 °C for 16 hr under N_2 . LCMS showed the reaction was completed. The mixture was diluted with H_2O (150 mL) and extracted with EtOAc (2×40 mL). The aqueous phase was adjusted to pH=2 with 2 N HCl. The precipitated solid was collected and washed with water (2 × 20 mL), dried in vacuo to afford 3-fluoro-6,7-dimethoxy-quinolin-4-ol (1.1 g, 78.64% yield) as yellow solid. MS(ES⁺) m/z calc'd for $[M+H]^+$ $[C_{11}H_{10}FNO_3 + H]^+$: 224.06, found: 224.0, t_R = 0.646 min

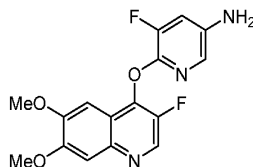
[0578] Synthesis of 3-fluoro-4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline



[0579] To a solution of 3-fluoro-6,7-dimethoxy-quinolin-4-ol (0.25 g, 1.12 mmol, 1.00 *eq*) in MeCN (7.50 mL) was added K_2CO_3 (309.60 mg, 2.24 mmol, 2.00 *eq*) and 2-chloro-3-fluoro-5-nitro-pyridine (296.59 mg, 1.68 mmol, 1.50 *eq*), then the mixture was stirred at 70 °C for 4 hr under N_2 . LCMS showed little starting material had remained and the major peak was the desired product. The mixture was diluted with EtOAc (30 mL) and washed with water (10 mL) and brine (10 mL), the organic layer was separated, dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-TLC (SiO_2 , pet. ether/EtOAc = 3/1, R_f = 0.35) to afford 3-fluoro-4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline (0.115 g, 25.44% yield) as yellow solid. 1H NMR (400 MHz, DMSO- d_6): δ 8.94 (dd, J = 9.51, 2.38 Hz, 1 H) 8.88 (d, J = 1.75 Hz, 1 H) 8.85 (d, J = 2.38 Hz, 1 H) 7.49 (s, 1 H) 7.26 (s, 1 H) 3.95 (s, 3 H) 3.87 (s, 3

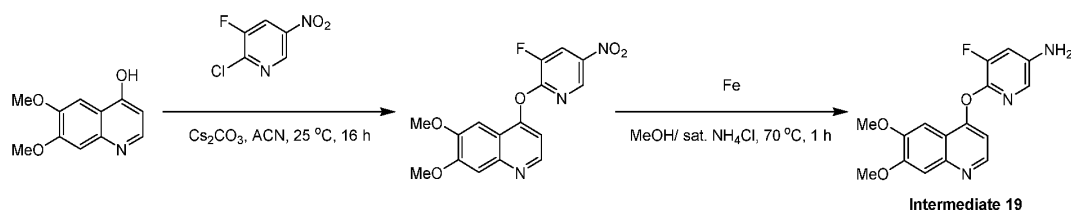
H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₁F₂N₃O₅ +H]⁺: 364.07, found: 363.9, t_R= 1.228 min.

[0580] Synthesis of 5-fluoro-6-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]pyridin-3-amine [Intermediate 18]:

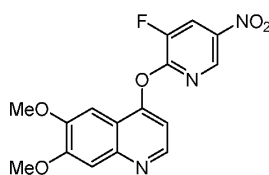


[0581] To a mixture of 3-fluoro-4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline (115.00 mg, 316.57 μ mol, 1.00 *eq*) in EtOH (4.50 mL) and saturated NH₄Cl (1.50 mL) was added Fe (88.39 mg, 1.58 mmol, 5.00 *eq*) in portions at 70 °C, and then the mixture was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. The mixture was filtered through celite and washed with EtOAc (50 mL), the filtrate was diluted with H₂O (20 mL), the organic layer was separated, and the aqueous phase was extracted with EtOAc (3 $\times$ 15 mL), the organic layers was washed with brine (20 mL), dried over Na₂SO₄ to afford 5-fluoro-6-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]pyridin-3-amine (0.07 g) as yellow crude solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₃F₂N₃O₃ +H]⁺: 334.09, found: 334.0, t_R= 1.044 min

[0582] Synthesis of 6-[(6,7-dimethoxy-4-quinolyl)oxy]-5-fluoro-pyridin-3-amine [Intermediate 19]:



[0583] Synthesis of 4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline

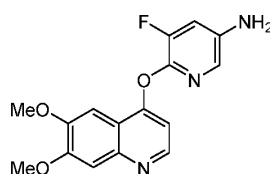


[0584] A mixture of 6,7-dimethoxyquinolin-4-ol (1.00 g, 4.87 mmol, 1.00 *eq*) in MeCN (20 mL) was added Cs₂CO₃ (2.86 g, 8.77 mmol, 1.80 *eq*) and 2-chloro-3-fluoro-5-nitro-pyridine (946.28 mg, 5.36 mmol, 1.10 *eq*), the mixture was stirred at 25 °C for 16 hours. LCMS showed 22% of starting material remained and two peaks with desired MS was formed. The reaction mixture was poured into 100 ml H₂O, then extracted by EtOAc (3 $\times$ 40 mL), the combined organic layer was washed with brine (2 $\times$ 40 mL), dried over Na₂SO₄, filtered and concentrated to

give crude. The residue was purified by column chromatography (SiO₂, pet. ether/EtOAc=50/50 to 20/80) to afford 4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline (0.62 g, 34.93% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.91 (d, J=2.38 Hz, 1 H) 8.87 - 8.93 (m, 1 H) 8.88 (t, J=2.20 Hz, 1 H) 8.72 (d, J=5.02 Hz, 1 H) 7.47 (s, 1 H) 7.31 (d, J=5.02 Hz, 1 H) 7.24 (s, 1 H) 3.96 (s, 3 H) 3.85 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₂FN₃O₅ +H]⁺: 346.08, found: 346.0, t_R= 0.360 min.

[0585] Synthesis of 6-[(6,7-dimethoxy-4-quinolyl)oxy]-5-fluoro-pyridin-3-amine

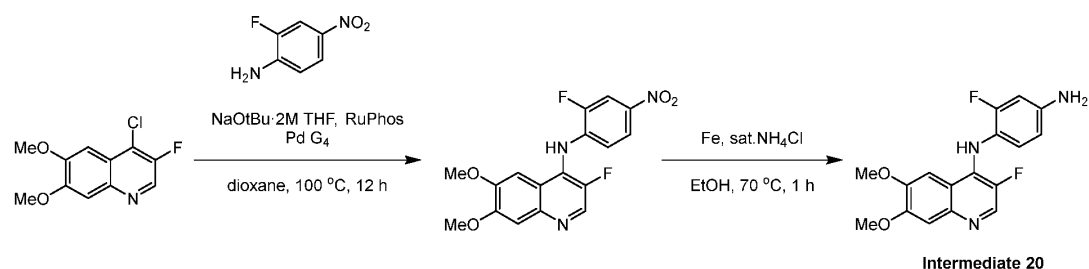
[Intermediate 19]:



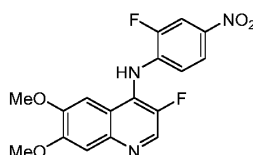
[0586] To a solution of 4-[(3-fluoro-5-nitro-2-pyridyl)oxy]-6,7-dimethoxy-quinoline (600.00 mg, 1.74 mmol, 1.00 eq) in MeOH (12 mL) and saturated NH₄Cl (6 mL) was added Fe (776.34 mg, 13.90 mmol, 8.00 eq) at 70 °C. The mixture was stirred at 70 °C for 1 hours. LCMS showed the reaction was completed. The reaction mixture was filtered, and the filtrate was concentrated to remove MeOH, then poured into 60 mL H₂O, extracted by EtOAc (3×30 mL), the combined organic layer was washed with brine (2×30 mL), dried over Na₂SO₄, filtered and concentrated to give 6-[(6,7-dimethoxy-4-quinolyl)oxy]-5-fluoro-pyridin-3-amine (500.00 mg) crude as a brown solid. MS (ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₄FN₃O₃ +H]⁺: 316.10, found: 316.2, t_R= 0.318 min.

[0587] Synthesis of 2-fluoro-N1-(3-fluoro-6,7-dimethoxy-4-quinolyl)benzene-1,4-diamine

[Intermediate 20]:



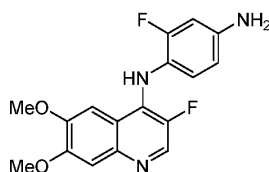
[0588] Synthesis of 3-fluoro-N-(2-fluoro-4-nitro-phenyl)-6,7-dimethoxy-quinolin-4-amine



[0589] A mixture of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (200.00 mg, 827.66 μmol, 1.00 eq), 2-fluoro-4-nitro-aniline (155.05 mg, 993.19 μmol, 1.20 eq), NaOtBu (2 M in THF,

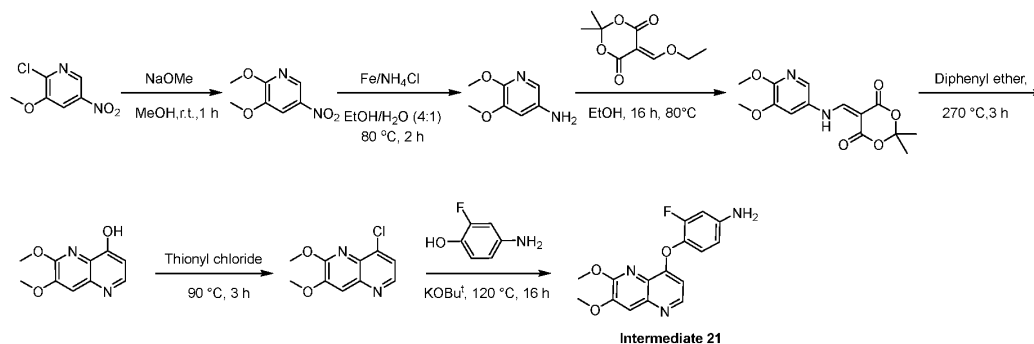
827.66 μL , 2.00 eq), RuPhos Pd G₄ (70.38 mg, 82.77 μmol , 0.10 eq) in dioxane (3 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 12 h under N₂ atmosphere. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O 20 mL, and then extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/EtOAc=1/0 to 60/40) to afford 3-fluoro-N-(2-fluoro-4-nitro-phenyl)-6,7-dimethoxy-quinolin-4-amine (150.00 mg, 50.16% yield) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₃N₃F₂O₄+H]⁺: 362.08, found: 362.2, *t*_R= 0.393 min.

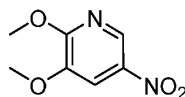
[0590] Synthesis of 2-fluoro-N1-(3-fluoro-6,7-dimethoxy-4-quinolyl)benzene-1,4-diamine [Intermediate 20]:



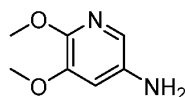
[0591] To a solution of 3-fluoro-N-(2-fluoro-4-nitro-phenyl)-6,7-dimethoxy-quinolin-4-amine (120.00 mg, 332.13 μmol , 1.00 eq) in EtOH (2 mL) was added sat. NH₄Cl (0.5 mL) and Fe (92.74 mg, 1.66 mmol, 5.00 eq). The mixture was stirred at 70 °C for 1 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc (2×20 mL). The resulting filtrate was extracted with EtOAc (2×20 mL). The combined organic layer was washed successively with water (2×20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 2-fluoro-N1-(3-fluoro-6,7-dimethoxy-4-quinolyl)benzene-1,4-diamine (130.00 mg) as yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₅N₃F₂O₂+H]⁺: 332.11, found: 332.1, *t*_R= 0.299 min.

[0592] Synthesis of 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-aniline [Intermediate 21]:

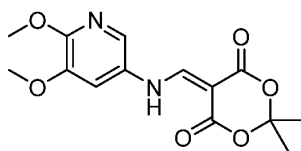


[0593] Synthesis of 2,3-dimethoxy-5-nitro-pyridine

[0594] To a stirred solution of NaOMe (28.56 g, 255 mmol, 2.00 eq) in Methanol (150 mL, 0.8485 M) was added 2-chloro-3-methoxy-5-nitro-pyridine (24.00 g, 127 mmol, 1.00 eq) portion wise at room temperature and stirred for 1 h. The reaction progress was monitored by LCMS. The reaction was concentrated to dryness to get residue. The residue was treated with water (200 mL) and the resulting solid was filtered and dried in vacuo to afford 2,3-dimethoxy-5-nitro-pyridine (15.00 g, 62% yield) as an off white solid; MS(ES+) m/z calc'd for $[M+H]^+$ $[C_7H_8N_2O_4+H]^+$: 185.06, found: 184.90, t_R = 1.690 min.

[0595] Synthesis of 5,6-dimethoxypyridin-3-amine

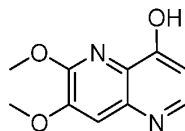
[0596] To a stirred solution of 2,3-dimethoxy-5-nitro-pyridine (15.00 g, 81.5 mmol, 1.00 eq) in ethanol (100 mL, 0.6516 M) and water (25 mL, 0.6516 M) was added Iron powder (22.75 g, 407 mmol, 5.00 eq) and ammonium chloride (21.79 g, 407 mmol, 5.00 eq) at room temperature. The reaction mixture was stirred for 2 h at 80 °C. The reaction progress was monitored by LCMS. The reaction mixture was filtered through a celite pad and washed with methanol. The filtrate was concentrated under vacuum to get crude. The crude was diluted with ethyl acetate (500 mL) and water (100 mL). The combined organic layer was washed with brine solution (120 mL), dried over Na₂SO₄, filtered, and concentrated to afford 5,6-dimethoxypyridin-3-amine (11.00 g, 81% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.05 (d, *J* = 2.5 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 4.89 (br s, 2H), 3.71 (s, 3H), 3.69 (s, 3H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_7H_{10}N_2O_2+H]^+$: 155.08, found :155.00, t_R = 0.690 min and t_R = 0.80 min.

[0597] Synthesis of 5-[(5,6-dimethoxy-3-pyridyl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione

[0598] To a stirred solution of 5,6-dimethoxypyridin-3-amine (10.00 g, 64.9 mmol, 1.00 eq) and 5-(ethoxy methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (14.28 g, 71.3 mmol, 1.10 eq) in ethanol (200 mL, 0.3243 M) was stirred for 16 h at 80 °C. The reaction progress was monitored by LCMS. The reaction mixture was filtered and washed with methanol and dried

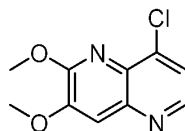
under vacuum to afford 5-[[[(5,6-dimethoxy-3-pyridyl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (15.00 g, 81% yield) as a Pale brown solid. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{14}H_{16}N_2O_6+H]^+$: 309.11, found: 308.90, t_R = 1.640 min.

[0599] Synthesis of 6,7-dimethoxy-1,5-naphthyridin-4-ol



[0600] To a stirred solution of diphenyl ether (100 mL, 1622 mmol, 50.0 eq) at 270 °C was added 5-[[[(5,6-dimethoxy-3-pyridyl)amino]methylene]-2,2-dimethyl-1,3-dioxane-4,6-dione (10.00 g, 32.4 mmol, 1.00 eq) portion wise over a period of 0.5 h continued for stirred 3 h at 270°C. The reaction progress was monitored by LCMS. Upon cooling, the reaction mixture was treated with heptane (100 mL) and the resulting precipitate was filtered and washed with heptane (100 mL) to afford 6,7-dimethoxy-1,5-naphthyridin-4-ol (4.00 g, 38% yield) as a Pale yellow solid. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{10}H_{10}N_2O_3+H]^+$: 207.08, found: 206.09, t_R = 1.130 min.

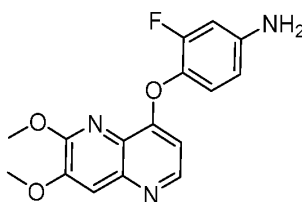
[0601] Synthesis of 8-chloro-2,3-dimethoxy-1,5-naphthyridine



[0602] To a stirred solution of 6,7-dimethoxy-1,5-naphthyridin-4-ol (3.60 g, 17.5 mmol, 1.00 eq) in thionyl chloride (90 mL, 1241 mmol, 71.1 eq) was added catalytic amount of N,N-dimethylformamide (1.8 mL, 23.2 mmol, 1.33 eq) at room temperature. The resulting reaction mixture was heated at 90 °C for 3 h. The reaction progress was monitored by LCMS, the reaction mixture was concentrated under reduced pressure obtained crude. The crude was triturated with ethyl acetate (100 mL) for 10 min. The resulting solid was filtered and dried under vacuum to obtain 8-chloro-2,3-dimethoxy-1,5-naphthyridine (2.20 g, 51% yield) as a pale yellow solid. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{10}H_9ClN_2O_2+H]^+$: 225.05, found: 224.80, t_R = 1.750 min.

[0603] Synthesis of 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-aniline

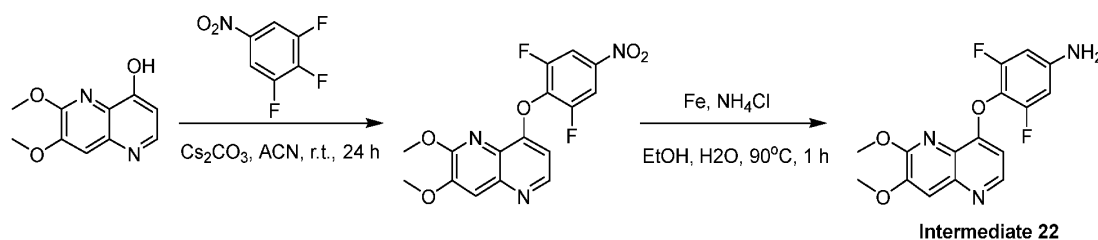
[Intermediate 21]:



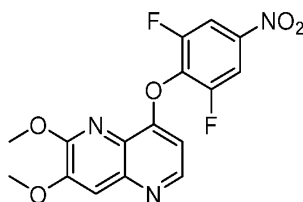
[0604] To a stirred solution of 4-amino-2-fluorophenol (1.92 g, 15.1 mmol, 2.00 eq) in N,N-dimethylformamide (60 mL, 0.1261 M) was added potassium *tert* butoxide (2548 mg, 22.7 mmol, 3.00 eq) at room temperature and stirred for 10 min and added 8-chloro-2,3-dimethoxy-1,5-naphthyridine (1.70 g, 7.57 mmol, 1.00 eq). The reaction was heated to 120 °C for 16 h. The reaction mixture was cooled to room temperature, filtered through celite pad and washed with ethyl acetate (300 mL). The filtrate was washed with brine (100 mL) and dried over Na₂SO₄, filtered and concentrated under reduced pressure to get crude. The crude was purified by combi flash using YMC 40 g column and eluted with 60-100% ethyl acetate in heptane to get the desired product. The product was triturated with diethyl ether (2x50 mL) and n-pentane (2x50 mL). The resulting precipitate was filtered, dried under vacuum to afford 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-aniline (950 mg, 38% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.48 (d, *J* = 5.3 Hz, 1H), 7.62 (s, 1H), 7.04 (t, *J* = 9.0 Hz, 1H), 6.60 (d, *J* = 5.3 Hz, 1H), 6.54 (dd, *J* = 2.3, 13.3 Hz, 1H), 6.45 (dd, *J* = 2.0, 8.8 Hz, 1H), 5.45 (s, 2H), 4.03 (s, 3H), 3.96 (s, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₄FN₃O₃+H]⁺: 316.3, found: 316.00, *t*_R = 1.35 min.

[0605] Synthesis of 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3,5-difluoroaniline

[Intermediate 22]:



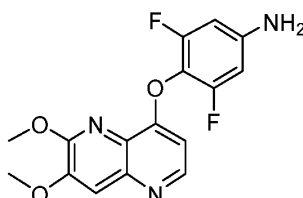
[0606] Synthesis of 8-(2,6-difluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine



[0607] To a stirred solution of 6,7-dimethoxy-1,5-naphthyridin-4-ol (1.5 g, 7.3 mmol) in acetonitrile (15 mL) were added cesium carbonate (4.8 g, 2 equiv., 15 mmol), 1,2,3-trifluoro-5-nitro-benzene (1.9 g, 1.5 equiv., 11 mmol) and stirred for 24 h at room temperature. After completion of the reaction by TLC, reaction mass was diluted with EtOAc (50 mL), filtrated the reaction mass through celite bed, washed with ethyl acetate (40 mL) and concentrated the organic layer to get crude 2.17 g as brown color liquid which was purified by 100-200 silica mesh, compound elutes with 21-23% EtOAc in heptane to afford 8-(2,6-difluoro-4-

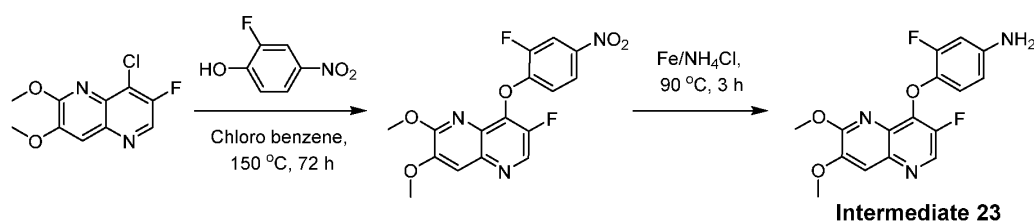
nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine (680 mg, 1.823 mmol, 25% yield) as pale yellow solid. MS(ES⁺) m/z calc'd for M+H]⁺ [C₁₆H₁₁F₂N₃O₅+H]⁺: 363.07, found: 334, *t*_R= 1.945 min.

[0608] Synthesis of 4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3,5-difluoroaniline
[Intermediate 22]:

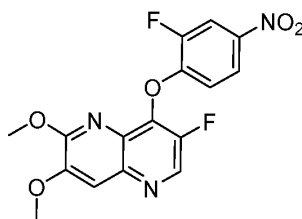


[0609] To a stirred solution of 8-(2,6-difluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine (830 mg, 2.285 mmol) in ethanol (80 mL) and water (8 mL) at room temperature, were added Iron (638 mg, 5 equiv., 11.42 mmol), ammonium chloride (612 mg, 5 equiv., 11.42 mmol) and stirred at 90°C for 60 min. The reaction mixture was monitored by TLC. After cooling, the reaction mixture was filtrated through celite bed, bed washed with EtOAc (50 mL) and concentrated as crude (230 mg), added 20 mL of water, stirred for 10 min and filtrated, dried to afford 4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3,5-difluoroaniline (700 mg, 2.058 mmol, 90.09% yield) as off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) = 8.51 (d, *J* = 5.2 Hz, 1H), 7.63 (s, 1H), 6.40 (dd, *J* = 10.8 Hz, 1H), 5.78 (brs, 2H), 4.02 (s, 3H), 3.97 (s, 2H). MS(ES⁺) m/z calc'd for M+H]⁺ [C₁₆H₁₃F₂N₃O₃+H]⁺: 333.09, found: 334, *t*_R = 1.531 min.

[0610] Synthesis of 3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline
[Intermediate 23]:

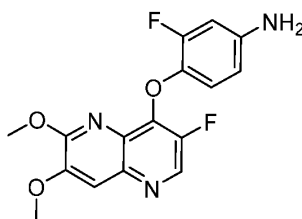


[0611] Synthesis of 7-fluoro-8-(2-fluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine



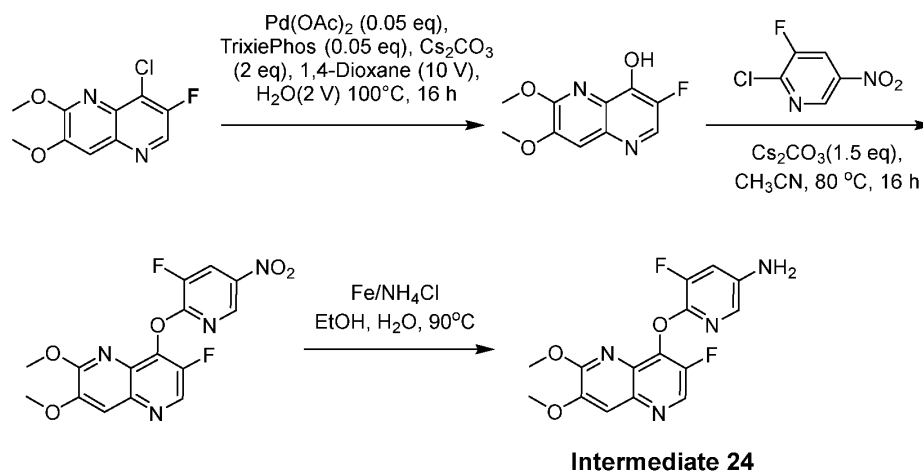
[0612] To a solution of 2-fluoro-4-nitro-phenol (0.971 g, 6.1822 mmol, 1.5 eq) in chlorobenzene (10 mL,) at room temperature were added DIEA (2.2 mL, 13 mmol, 10 eq) and 8-chloro-7-fluoro-2,3-dimethoxy-1,5-naphthyridine (1 g, 4.1215 mmol, 1 eq). The resulting mixture was stirred at 150 °C for 72 h. After completion of reaction, the mixture evaporated under vacuum to get crude product which was purified by combiflash using 24 g column cartridge and eluted with 0-50% EtOAc/heptane to afford 7-fluoro-8-(2-fluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine (200 mg, 0.4349 mmol, 10.55% yield) as a pale-yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₁F₂N₃O₅+H]⁺: 364.08, found 364.0, t_R=2.08 min.

[0613] Synthesis of 3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline [Intermediate 23]:

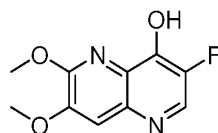


[0614] To a solution of 7-fluoro-8-(2-fluoro-4-nitro-phenoxy)-2,3-dimethoxy-1,5-naphthyridine (200 mg, 0.5505 mmol), in EtOH: H₂O (10 mL), were added NH₄Cl (0.146 g, 2.75 mmol, 5 eq) and Fe (0.152 g, 2.75 mmol, 5 eq) at room temperature under nitrogen atmosphere. The resulting reaction was stirred at 90 °C for 3 h. After completion of reaction, the mixture was filtered on celite, washed with ethyl acetate (20 mL) and filtrate was dried under vacuum to get crude residue. Further the crude was treated with water and extracted with ethyl acetate (2x50 mL). The combined organic layer was washed with brine solution (10 mL), dried over Na₂SO₄, filtered and concentrated under vacuum and then purified by combiflash using 12 g column cartridge and eluted with 50-70% ethyl acetate in heptane to afford 3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline (0.15 g, 0.35 mmol, 64% yield) as pale brown solid. ¹H NMR (400 MHz, DMSO-d₆): 8.83 (d, *J* = 2.4 Hz, 1H), 7.65 (s, 1H), 6.84 (t, *J* = 8.8 Hz, 1H), 6.44 (dd, *J* = 2.8 Hz, *J* = 13.6 Hz, 1H), 6.26 (dd *J* = 2.0 Hz, *J* = 8.8 Hz, 1H), 5.21 (s, 2H), 3.93 (s, 3H), 3.72 (s, 3H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₁F₂N₃O₅+H]⁺: 364.08, found 364.0, t_R=2.08 min.

[0615] Synthesis of 5-fluoro-6-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)pyridin-3-amine [Intermediate 24]:

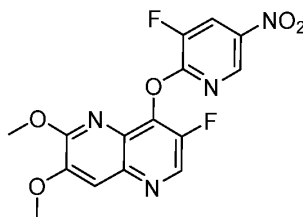


[0616] Synthesis of 3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-ol



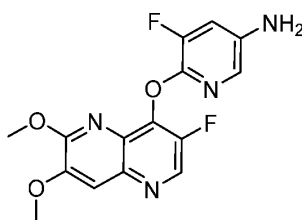
[0617] To a solution of 8-chloro-7-fluoro-2,3-dimethoxy-1,5-naphthyridine (2 g, 8.2430 mmol, 1 eq), in 1,4 -dioxane and water (100 mL [1:1]) was added K_2CO_3 (2.29 g, 16.5 mmol, 2 eq) at room temperature under nitrogen atmosphere. The reaction was degassed for 10 min under nitrogen atmosphere and added Trixie Phos (0.492 g, 1.2365 mmol, 0.15 eq) and $PdCl_2(dppf)DCM$ (1.35 g, 1.65 mmol, 0.2 eq). The resulting mixture was stirred at 100 °C for 16 h and filtered on celite, washed with ethyl acetate (100 mL) followed by 15% MeOH in DCM (2x50 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 , filtered and concentrated under vacuum to afford 3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-ol (1.4 g, 6.1 mmol, 74% yield) as a white solid. 1H NMR (400 MHz, DMSO- d_6): 8.05 (d, $J = 5.2$ Hz, 1H), 7.23 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{10}H_9FN_2O_3]^+$: 225.01, found: 225.1, t_R = 1.23 min.

[0618] Synthesis of 7-fluoro-8-((3-fluoro-5-nitropyridin-2-yl)oxy)-2,3-dimethoxy-1,5-naphthyridine



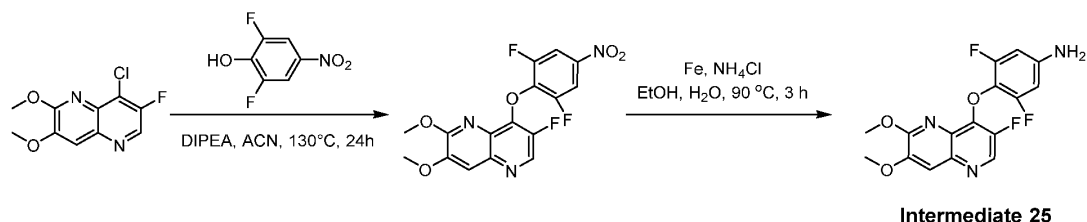
[0619] To a solution of 2-chloro-3-fluoro-5-nitro-pyridine (1.3 g, 7.4 mmol, 1.18 eq) in ACN (70 mL), were added Cs₂CO₃ (2.2 g, 6.8 mmol, 1.08 eq) and 3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-ol (1.4 g, 6.2 mmol, 1 eq) at room temperature. The resulting mixture was stirred at room temperature for 16 h. After completion of reaction the mixture was evaporated under vacuum to get crude which was purified by combiflash using 24 g column cartridge and eluted with 40-50% EtOAc/heptane to afford 7-fluoro-8-[(3-fluoro-5-nitro-2-pyridyl)oxy]-2,3-dimethoxy-1,5-naphthyridine (1.4 g, 2.8 mmol, 44% yield). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₁₀F₂N₄O₅]⁺: 365.06, found: 365.2, t_R = 2.28 min.

[0620] Synthesis of 5-fluoro-6-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)pyridin-3-amine [Intermediate 24]:

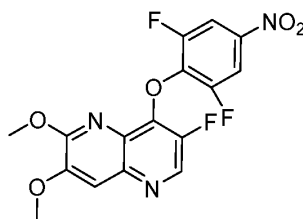


[0621] To a solution of 7-fluoro-8-[(3-fluoro-5-nitro-2-pyridyl)oxy]-2,3-dimethoxy-1,5-naphthyridine (1.4 g, 3.8 mmol, 100 mass%) in EtOH and water (50 mL[1:1]) was added NH₄Cl (1.0 g, 19 mmol, 15 eq) and Fe (1.1 g, 20 mmol, 5 eq) at room temperature under nitrogen atmosphere. The resulting reaction was stirred at 90 °C, 1 h. After completion of the reaction, the mixture was filtered on celite and washed with ethyl acetate (100 mL), dried under vacuum to get residue. The residue was treated with water (50 mL), stirred for 5 min and the resulting precipitate was filtered and washed with water (30 mL), dried under vacuum to afford 5-fluoro-6-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]pyridin-3-amine (900 mg, 66% yield). ¹HNMR (400 MHz, DMSO-d₆): 8.88 (d, *J* = 1.6 Hz, 1H), 7.67 (s, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 2.4 Hz, *J* = 12.4 Hz, 1H), 5.38 (s, 2H), 3.93 (s, 3H), 3.64 (s, 3H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₁₂F₂N₄O₃ + H]⁺: 335.10, found: 335.0, t_R = 1.75 min.

[0622] Synthesis of 3,5-difluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline [Intermediate 25]:

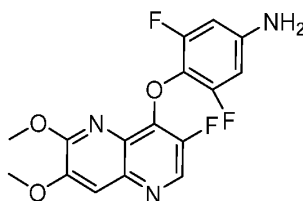


[0623] Synthesis of 8-(2,6-difluoro-4-nitrophenoxy)-7-fluoro-2,3-dimethoxy-1,5-naphthyridine

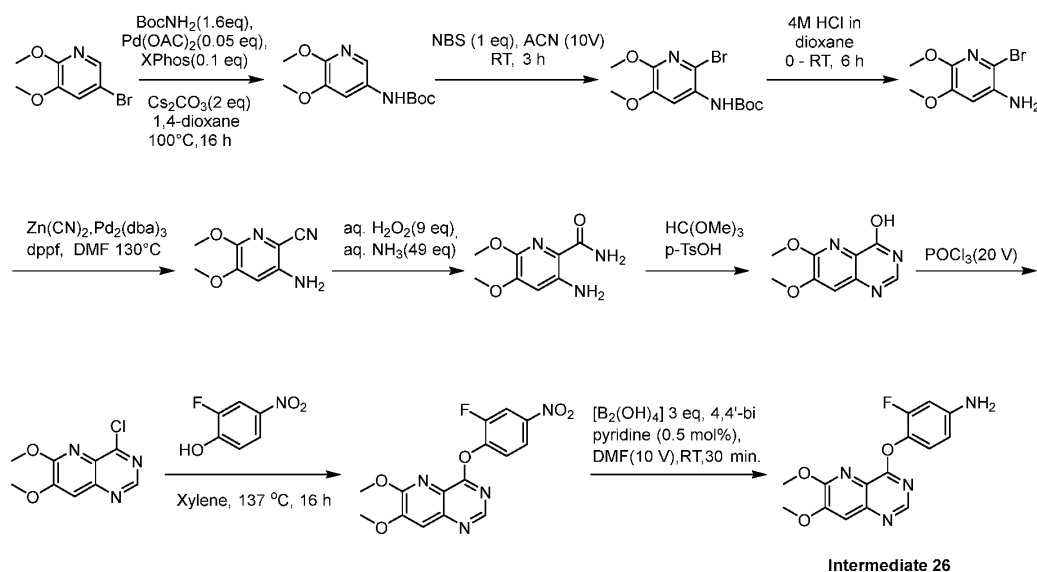
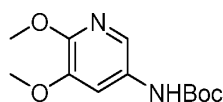


[0624] To a stirred solution of 8-chloro-7-fluoro-2,3-dimethoxy-1,5-naphthyridine (500 mg, 2.0608 mmol) in acetonitrile (10 mL) at room temperature was added 2,6-difluoro-4-nitrophenol (541 mg, 1.5 equiv., 3.09 mmol) followed by N,N-diisopropylethylamine (3.6 mL, 10 equiv., 20.61 mmol). The resulting mixture was stirred at 130 °C for 24 h. The reaction progress was monitored by LCMS. After completion, the reaction mixture was concentrated and purified by combi flash column using 230-400 mesh silica gel and eluted with 30-40% ethyl acetate in heptane to afford 8-(2,6-difluoro-4-nitro-phenoxy)-7-fluoro-2,3-dimethoxy-1,5-naphthyridine (450.00 mg, 41.23% yield) as off white solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₀F₃N₃O₅]⁺: 381.3, found: 382.0, t_R = 2.10 min.

[0625] Synthesis of 3,5-difluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline [Intermediate 25]:

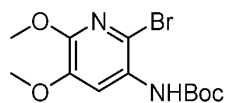


[0626] To a stirred solution of mixture of two compounds [20% of 7-chloro-8-(2,6-difluoro-4-nitrophenoxy)-2,3-dimethoxy-1,5-naphthyridine and 72% of 8-(2,6-difluoro-4-nitrophenoxy)-7-fluoro-2,3-dimethoxy-1,5-naphthyridine (450.00 mg, 0.8497 mmol)] in a mixture of ethanol (16 mL, 270 mmol) and water (4 mL) was added Iron (237 mg, 5 equiv., 4.249 mmol) followed by ammonium chloride (228 mg, 5 equiv., 4.249 mmol) at 0°C under nitrogen atmosphere and stirred for 12 h at 80°C. The progress of the reaction was monitored by LCMS. After completion, the reaction mixture was filtered through a celite pad and washed with methanol (100 mL) and concentrated to get the residue. The residue was treated with 20% MeOH/DCM (50 mL), filtered and concentrated to get crude. The crude was purified by combi flash column using 230-400 mesh silica gel and eluted with 40-50% ethyl acetate in heptane to afford 3,5-difluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)aniline (310 mg, 16% yield) as pale brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.82 (d, J = 2.4 Hz, 1H), 7.64 (s, 1H), 6.26 (d, J=11.2Hz, 2H), 5.55 (s, 2H), 3.93 (s, 3H), 3.71 (s, 3H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₀H₁₀ClN₃O₂+H]⁺: 239.66, found: 239.8, t_R = 1.63 min.

[0627] Synthesis of 4-((6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluoroaniline**[Intermediate 26]:****[0628] Synthesis of *tert*-butyl (5,6-dimethoxypyridin-3-yl)carbamate**

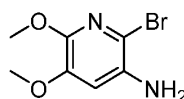
[0629] To a stirred solution of 5-bromo-2,3-dimethoxy-pyridine (6 g, 27.517 mmol, 1eq) in 1,4-dioxane (60 mL) were added *tert*-butyl carbamate (5.209 g, 44.02 mmol, 1.6eq), cesium carbonate (18.8 g, 57.6 mmol, 2.09 eq) and XPhos (1.59 g, 3.30 mmol, 0.12eq) under argon. The mixture was degassed with argon for 5 min and then Palladium(II)acetate (309 mg, 1.376 mmol, 0.05eq) was added. The resulting mixture was stirred at 120°C for 16h. After completion, the reaction mass was quenched with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum get crude product. The crude product was purified by combi flash by using a 40 g YMC cartridge and 20-25% ethyl acetate in heptane as an eluent to afford *tert*-butyl (5,6-dimethoxypyridin-3-yl)carbamate (4.30 g, 59.8% yield) as an off white solid. MS(ES+) m/z calc'd for

$[M+H]^+$ $[C_{12}H_{18}N_2O_4 + H]^+$: 255.28, found:255.1, t_R = 1.81 min. Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5 μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[0630] Synthesis of *tert*-butyl (2-bromo-5,6-dimethoxypyridin-3-yl)carbamate

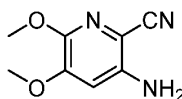
[0631] To a stirred solution of ~{*tert*}-butyl ~{N}-(5,6-dimethoxy-3-pyridyl)carbamate (8 g, 31.461 mmol, 1eq) in MeCN (160 mL) was added NBS (6.0568 g, 33.349 mmol, 1.06eq) in portions at 25 °C. The resulting reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, the mixture was quenched with water (100 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with brine solution (100 mL), dried over sodium sulphate and concentrated under vacuum to get crude product and purified by combi flash by using 40g YMC cartridge 20-25% ethyl acetate in heptane as an eluent to afford *tert*-butyl (2-bromo-5,6-dimethoxypyridin-3-yl)carbamate (7.6 g, 69% yield) as white solid. ¹H NMR (401 MHz, DMSO-*d*₆) δ ppm 8.65 (s, 1 H) 7.39 (s, 1 H) 3.84 (s, 3 H) 3.78 (s, 3 H) 1.45 (s, 9 H). MS(ES+) *m/z* calc'd for [M+H]⁺ [C₁₂H₁₇BrN₂O₄+H]⁺: 334.18, found: 332.7, *t_R*= 5.11min.

Method Details: TFA 10 MINS Column : Acquity UPLC BEH C18 (2.1*50)mm, 1.7um Flow rate: 0.5 mL/min. Mobile Phase A: 0.05%TFA in Water Mobile Phase B: 0.05%TFA in Acetonitrile Column Temp.: 40°C Gradient Program Time/B: 0.0/3, 1.5/3, 6/97, 8/97, 9.0/3,10/3.

[0632] Synthesis of 2-bromo-5,6-dimethoxypyridin-3-amine

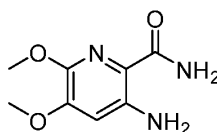
[0633] To a stirred solution of *tert*-butyl N-(2-bromo-5,6-dimethoxy-3-pyridyl)carbamate (7.50 g, 22.5 mmol, 1eq) in DCM (73 mL) was added 4M HCl in dioxane (50 mL, 200 mmol, 8.89eq) at 0°C. The reaction mixture was stirred at room temperature for 6 h and progress of the reaction was monitored by TLC. After completion, reaction mass was basified with sat. K₂CO₃ solution, extracted with DCM (110 mL) and organic layer was washed with brine solution (200 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford 2-bromo-5,6-dimethoxypyridin-3-amine (5.3 g, 100% yield) as brown semi solid. MS(ES+) *m/z* calc'd for [M+H]⁺ [C₇H₉BrN₂O₂+H]⁺: 234.06, found: 234.7, *t_R*= 1.67 min.

[0634] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[0635] Synthesis of 3-amino-5,6-dimethoxypicolinonitrile

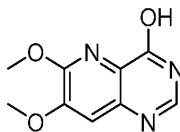
[0636] To a stirred solution of 2-bromo-5,6-dimethoxy-pyridin-3-amine (5.3 g, 23 mmol, 1 eq) in N,N-dimethylformamide (53 mL) was added zinc cyanide (1.9 g, 16 mmol, 0.7 eq) under argon. Then, 1,1'-bis(diphenylphosphino)ferrocene (650 mg, 0.1154 mmol, 0.05 eq) was added and degassed for 5 min. and then added tris(dibenzylideneacetone)dipalladium(0) (640 mg, 0.699 mmol, 0.035 eq). The mixture was stirred at 130 °C for 16h. After completion, the reaction mass was quenched with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum to get crude 3-amino-5,6-dimethoxypicolinonitrile (4.1 g, 90% yield) as pale brown liquid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₈H₉N₃O₂+H]⁺: 180.19, found: 179.9, *t_R* = 1.59 min.

[0637] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%): 0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[0638] Synthesis of 3-amino-5,6-dimethoxypicolinamide

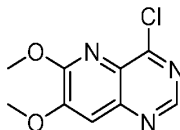
[0639] To a 3-amino-5,6-dimethoxy-pyridine-2-carbonitrile (4.10 g, 22.9 mmol, 1 eq) in mixture of ammonium hydroxide solution in water (157 mL, 1119.97 mmol, 49 eq), hydrogen peroxide in water (23.6 mL, 208 mmol, 9.1eq) was added at 0°C. The reaction mixture was stirred at room temperature for 1 h and progress of the reaction was monitored by TLC and LCMS. After completion, the solids were filtered under vacuum and washed with water (20 mL). Collect the filtrate and extracted with ethyl acetate (200 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum to afford 3-amino-5,6-dimethoxy-pyridine-2-carboxamide (3.2 g, 68% yield) as pale brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₈H₁₁N₃O₃+H]⁺: 198.19, found: 197.9, *t_R* = 1.36 min.

[0640] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%): 0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[0641] Synthesis of 3-amino-5,6-dimethoxypicolinamide

[0642] To a stirred solution of 3-amino-5,6-dimethoxy-pyridine-2-carboxamide (3.2 g, 16 mmol, 1 eq) in toluene (64 ml) was added triethyl orthoformate (14 ml, 81.6 mmol, 5.03 eq) and *p*-toluenesulfonic acid (280 mg, 1.46 mmol, 0.09 eq) at room temperature. The reaction mixture was stirred at 120 °C for 6 h. Progress of the reaction was monitored by LCMS and TLC. After completion of reaction, the mixture was concentrated under vacuum get crude product. The crude product was triturated with 20% ethyl acetate in heptane, filtered the solids under vacuum and dried to afford 3-amino-5,6-dimethoxypicolinamide (2.60 g, 70% yield) as an pale brown solid. MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₉H₉N₃O₃+H]⁺: 208.19, found: 207.8, *t_R* = 1.26 min.

[0643] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

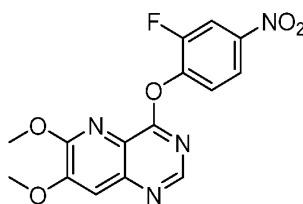
[0644] Synthesis of 4-chloro-6,7-dimethoxypyrido[3,2-d]pyrimidine

[0645] A solution of phosphoryl chloride (53 mL, 562.9 mmol, 47 eq) in 6,7-dimethoxypyrido[3,2-d]pyrimidin-4-ol (2.5 g, 12 mmol, 1 eq) was added at room temperature and later stirred at 120°C for 3h. Progress of the reaction was monitored by LCMS and TLC. After completion, the reaction mixture was concentrated under reduced pressure get a crude residue. The residue was dissolved in DCM (200 mL) and added slowly sat. NaHCO₃ solution (200 mL) and stirred for 5 min then separated the layers. Organic layer was again washed with brine solution (300 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum to afford 4-chloro-6,7-dimethoxypyrido[3,2-d]pyrimidine (2.3 g, 77% yield) as brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.93 (s, 1 H) 7.70 (s, 1 H) 4.11 (s, 3 H) 4.04 (s, 3 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₉H₈ClN₃O₂+H]⁺: 226.63, found: 225.8, *t_R* = 1.75 min.

[0646] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate:

1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[0647] Synthesis of 4-(2-fluoro-4-nitrophenoxy)-6,7-dimethoxypyrido[3,2-d]pyrimidine

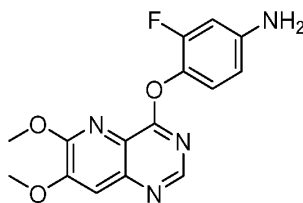


[0648] To a stirred solution of 4-chloro-6,7-dimethoxy-pyrido[3,2-d]pyrimidine (2.5 g, 11 mmol, 1 eq) in O-xylene (62.50 mL, 510 mmol) was added 2-fluoro-4-nitro-phenol (1.9g, 12 mmol, 1.1 eq) at room temperature. The resulting mixture was stirred at 130°C for 16 h and progress of the reaction was monitored by LCMS and TLC. After completion, the reaction mixture was concentrated under reduced pressure to get the crude residue which was purified by combi flash using 24 g YMC cartridge 50-60% ethyl acetate in heptane as an eluent to afford 4-(2-fluoro-4-nitrophenoxy)-6,7-dimethoxypyrido[3,2-d]pyrimidine (1.4 g, 33% yield) as white solid. ¹H NMR (401 MHz, DMSO-*d*₆) δ ppm: 8.65 (s, 1 H) 8.43 (dd, *J*=10.21, 2.63 Hz, 1 H) 8.22 - 8.28 (m, 1 H) 7.85 (dd, *J*=8.86, 7.89 Hz, 1 H) 7.70 (s, 1 H) 4.09 (s, 3 H) 4.04 (s, 3 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₁FN₄O₅+H]⁺: 347.3, found 347.6 *t_R*: 4.40 min.

[0649] Method Details: Column: XSelect CSH-C18(3.0X50mm,2.5μm) Mobile Phase: A: 0.05% Formic acid in water Mobile Phase: B: 0.05% Formic acid in MeCN (Gradient) T/B%:0.0/2,0.3/2,2.0/98,2.8/98,3.0/2,3.7/2. Flow rate:1 ml/min. Column Temp.:40°C.

[0650] Synthesis of 4-((6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluoroaniline

[Intermediate 26]:

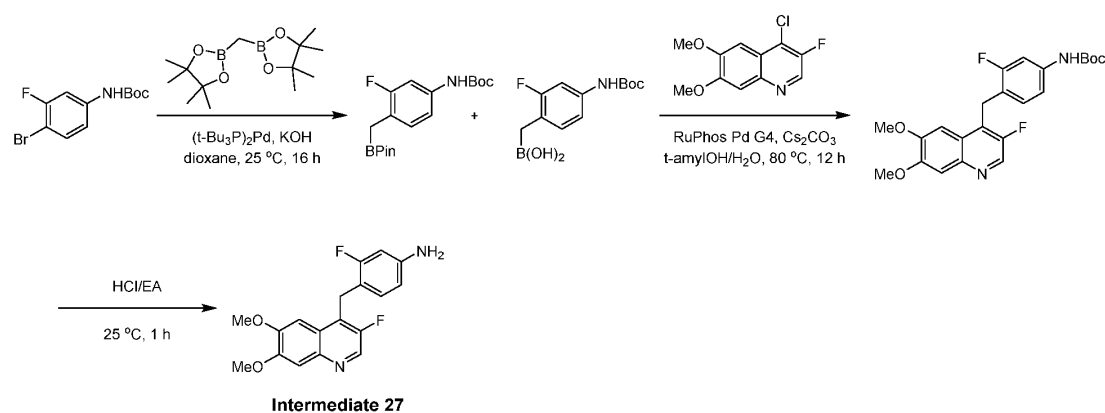


[0651] To a stirred solution of 4-(2-fluoro-4-nitrophenoxy)-6,7-dimethoxypyrido[3,2-d]pyrimidine (1.3 g, 3.5 mmol, 1 eq) in N,N-dimethylformamide (15.00 mL,) were added tetrahydroxydiboron (980 mg, 10 mmol, 3 eq) at room temperature and 4,4'-bipyridine (9 mg, 0.052 mmol, 0.015 eq). The resulting mixture was stirred at room temperature for 30 min. After completion, the reaction mixture was poured into a chilled water and precipitated solids were filtered under vacuum and dried. The obtained solids were triturated with methanol (10 mL) and filtered and dried under vacuum to afford 4-((6,7-dimethoxypyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluoroaniline (820 mg, 73% yield) as pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm:

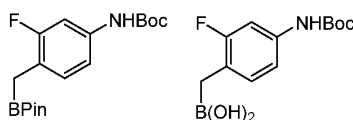
8.57 (s, 1 H) 7.62 (s, 1 H) 7.03 (t, $J=8.82$ Hz, 1 H) 6.50 (dd, $J=13.07$, 2.19 Hz, 1 H) 6.42 (dd, $J=8.76$, 1.75 Hz, 1 H) 5.38 (s, 2 H) 4.08 (s, 3 H) 4.01 (s, 3 H). MS(ES⁺) m/z calc'd for $[M+H]^+$ $[C_{15}H_{13}FN_4O_3+H]^+$: 317.3, found 317.37 t_R : 3.85 min.

[0652] Method Details: FA 10 MINS Column : Acquity UPLC BEH C18 (2.1*50)mm, 1.7um Flow rate: 0.5 mL/min. Mobile Phase A: 0.05%Formic acid in Water Mobile Phase B: 0.05%Formic acid in Acetonitrile Column Temp.: 45°C Gradient Program Time/B%: 0.0/3, 1.5/3, 6/97, 8/97, 9.0/3,10/3.

[0653] Synthesis of N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide
[Intermediate 27]:



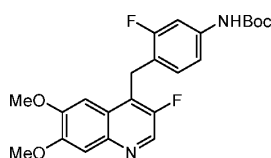
[0654] Synthesis of *tert*-butyl N-[3-fluoro-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]phenyl]carbamate and [4-(*tert*-butoxycarbonylamino)-2-fluorophenyl]methylboronic acid



[0655] To a solution of *tert*-butyl N-(4-bromo-3-fluorophenyl)carbamate (550.00 mg, 1.90 mmol, 1.00 eq) and 4,4,5,5-tetramethyl-2-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]-1,3,2-dioxaborolane (1.52 g, 5.69 mmol, 3.00 eq) in dioxane (5.5 mL) was added palladium;tritylphosphane (96.88 mg, 189.57 μ mol, 0.10 eq) and KOH (8 M, 348.34 μ L, 1.47 eq). The mixture was stirred at 25 °C for 16 hr. LC-MS showed ~10% of starting material remained and ~60% of product was detected. The mixture was quenched with water (100 mL) and extracted with EtOAc (3 $\times$ 50 mL). The combined organic phase was washed with brine (2 $\times$ 50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (neutral condition; column: WePure Biotech XP tC18 150*40*7um; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient:50%-80% B over 8.0 min) to afford *tert*-butyl N-[3-

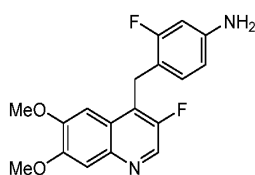
fluoro-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]phenyl]carbamate and [4-(*tert*-butoxycarbonylamino)-2-fluoro-phenyl]methylboronic acid (250 mg, 18.77% yield) as a mixture of yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 9.29 - 9.44 (m, 2 H) 7.64 (s, 2 H) 7.16 - 7.21 (m, 2 H) 7.00 - 7.08 (m, 4 H) 2.03 - 2.07 (m, 2 H) 1.94 - 2.08 (m, 1 H) 1.96 (s, 1 H) 1.46 (s, 18 H) 1.16 (s, 12 H). MS(ES⁺) *m/z* calc'd for [M-H]⁺ [C₁₈H₂₇BFNO₄+H]⁺: 352.20, found: 350.1, *t*_R = 1.485 min.

[0656] Synthesis of *tert*-butyl N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]carbamate



[0657] To a solution of mixture of *tert*-butyl N-[3-fluoro-4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl]phenyl]carbamate and [4-(*tert*-butoxycarbonylamino)-2-fluoro-phenyl]methylboronic acid (188.95 mg, 537.98 μmol, 1.00 eq) and 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (130.00 mg, 537.98 μmol, 1.00 eq) in 2-methylbutan-2-ol (2 mL) and H₂O (0.5 mL) was added Cs₂CO₃ (350.57 mg, 1.08 mmol, 2.00 eq) and RuPhos Pd G4 (45.75 mg, 53.80 μmol, 0.10 eq). The mixture was stirred at 80 °C for 12 hr. LCMS showed both starting materials were consumed completely and one main peak with desired *m/z* was detected. The mixture was quenched with water (50 mL) and extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (2×30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (Formic acid condition; column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.2% Formic acid)-MeCN]; gradient: 35%-70% B over 8.0 min to afford 35 mg, 13.91% yield of 1_3 as a white solid. MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₂₃H₂₄F₂N₂O₄+H]⁺: 431.17, found: 431.3, *t*_R = 1.974 min.

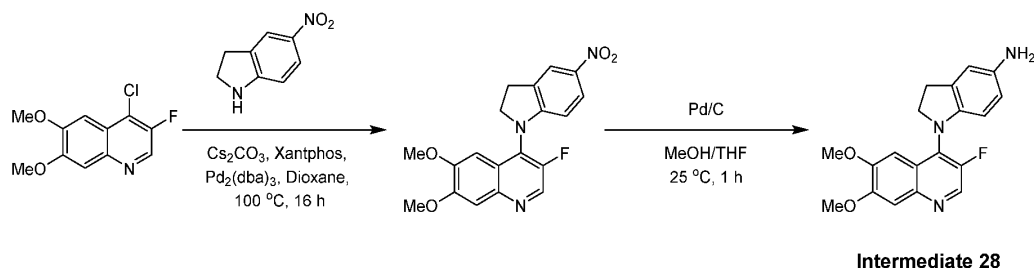
[0658] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]aniline [Intermediate 27]:



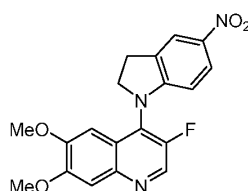
[0659] To *tert*-butyl N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]carbamate (25.00 mg, 58.08 μmol, 1.00 eq) was added in HCl/EtOAc (4 M, 2.50 mL). The mixture was stirred at 25 °C for 1 hr. LCMS showed starting material was consumed completely and one main peak with desired *m/z* was detected. The mixture was

concentrated to afford 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]aniline (19 mg, crude) as a white solid which was directly used for the amide coupling reaction. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{18}H_{16}F_2N_2O_2+H]^+$: 331.11, found: 331.3, t_R = 0.539 min.

[0660] Synthesis of N-[1-(3-fluoro-6,7-dimethoxy-4-quinolyl)indolin-5-yl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Intermediate 28]:

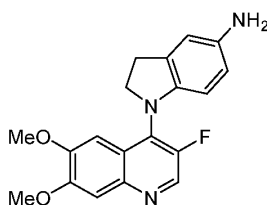


[0661] Synthesis of 3-fluoro-6,7-dimethoxy-4-(5-nitroindolin-1-yl)quinoline



[0662] To a solution of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (100.00 mg, 413.83 μ mol, 1.00 eq) in dioxane (2 mL) was added 5-nitroindoline (81.52 mg, 496.59 μ mol, 1.20 eq), CS_2CO_3 (404.50 mg, 1.24 mmol, 3.00 eq), Xantphos (47.89 mg, 82.77 μ mol, 0.20 eq), $Pd_2(dba)_3$ (37.89 mg, 41.38 μ mol, 0.10 eq) under N_2 . The mixture was stirred at 100 °C for 16 hr. LCMS showed the reaction was completed. The reaction mixture was poured into H_2O (50 mL), then the aqueous phase was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phase was washed with brine (2 $\times$ 100 mL), dried with anhydrous Na_2SO_4 , and concentrated by filtration and vacuum. The residue was purified by prep-TLC (SiO_2 , pet. ether: EtOAc = 4:1) to afford 3-fluoro-6,7-dimethoxy-4-(5-nitroindolin-1-yl)quinoline (120.00 mg, 78.51% yield) as yellow solid. MS (ES+) m/z calc'd for $[M+H]^+$ $[C_{19}H_{16}N_3FO_4+H]^+$: 370.11, found: 369.8, t_R = 0.567 min.

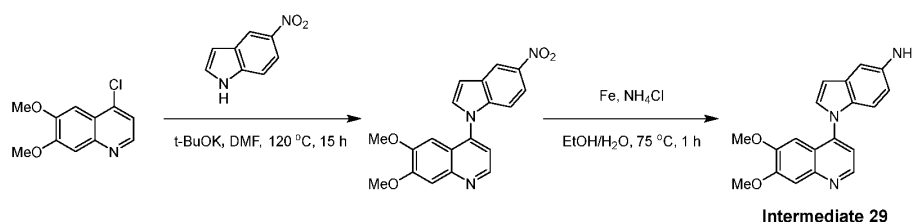
[0663] Synthesis of 1-(3-fluoro-6,7-dimethoxy-4-quinolyl)indolin-5-amine



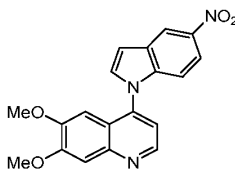
[0664] To a mixture of 3-fluoro-6,7-dimethoxy-4-(5-nitroindolin-1-yl)quinoline (90.00 mg, 243.67 μ mol, 1.00 eq) in MeOH (1 mL), THF (1 mL) was added Pd/C (259.32 mg, 243.67 μ mol,

10% purity, 1.00 eq) under H₂. The mixture was stirred at 25 °C for 1 h. LCMS showed no starting material remained, and a new peak was detected. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc (2×10 mL). The reaction mixture was poured into water (20 mL) and the aqueous phase was extracted with EtOAc (3×10 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue to afford 1-(3-fluoro-6,7-dimethoxy-4-quinolyl)indolin-5-amine (70.00 mg, 84.65% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.62 (d, J=3.75 Hz, 1 H) 7.38 (s, 1 H) 7.17 (s, 1 H) 6.56 (s, 1 H) 6.25 (dd, J=8.19, 1.81 Hz, 1 H) 6.00 (dd, J=8.25, 1.50 Hz, 1 H) 4.57 (br s, 2 H) 4.10 (br d, J=4.13 Hz, 1 H) 3.92 (s, 4 H) 3.75 (s, 3 H) 3.08 - 3.20 (m, 2 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₉H₁₈N₃FO₂+H]⁺: 340.14, found: 339.8, *t*_R= 0.485 min.

[0665] Synthesis of 1-(6,7-dimethoxy-4-quinolyl)indol-5-amine[Intermediate 29]:



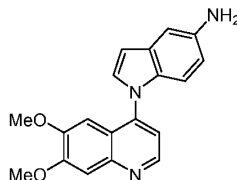
[0666] Synthesis of 6,7-dimethoxy-4-(5-nitroindol-1-yl)quinoline



[0667] To a mixture of 5-nitro-1H-indole (1.45 g, 8.94 mmol, 1.00 eq), 4-chloro-6,7-dimethoxy-quinoline (2.00 g, 8.94 mmol, 1.00 eq) in DMA (20 mL) was added *t*-BuOK (3.01 g, 26.83 mmol, 3.00 eq) and the mixture was stirred at 120 °C for 15 h. LCMS showed 30% of starting material was remained and 25% product was detected. The reaction mixture was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height: 250 mm, diameter: 100 mm, 100-200 mesh silica gel, pet. ether/ethyl acetate=3/1, 0/1) to afford 6,7-dimethoxy-4-(5-nitroindol-1-yl)quinoline (1.1 g, 29.33% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.87 (d, J=4.75 Hz, 1 H) 8.75 (d, J=2.25 Hz, 1 H) 8.01 - 8.10 (m, 2 H) 7.57 - 7.59 (m, 1 H) 7.54 - 7.57 (m, 1 H) 7.32 (d, J=9.13 Hz, 1 H) 7.15

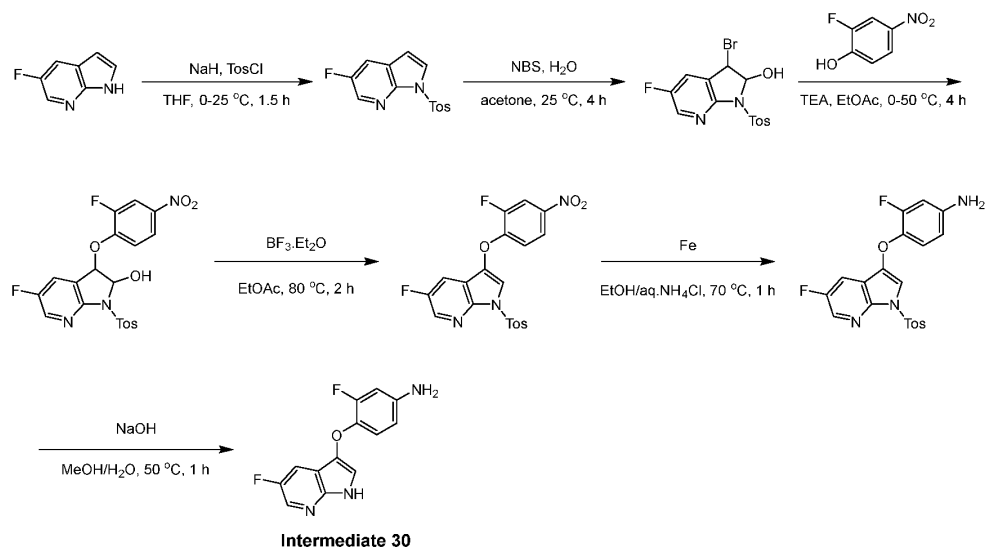
(d, J=2.75 Hz, 1 H) 6.72 (s, 1 H) 3.99 (s, 3 H) 3.64 (s, 3 H) 1.95 (s, 4 H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{19}H_{15}N_3O_4+H]^+$: 350.10, found: 349.8, t_R = 0.564 min.

[0668] Synthesis of 1-(6,7-dimethoxy-4-quinolyl)indol-5-amine [Intermediate 29]:

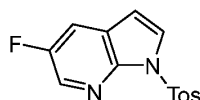


[0669] To a mixture of 6,7-dimethoxy-4-(5-nitroindol-1-yl)quinoline (0.50 g, 1.43 mmol, 1.00 *eq*) in EtOH (10 mL), saturated NH_4Cl (2.5 mL) was added Fe (399.65 mg, 7.16 mmol, 5.00 *eq*) at 75 °C and the mixture was stirred at 75 °C for 1 h. LCMS showed the reaction was completed. The residue was poured into Na_2CO_3 (100 mL) and EtOAc (50 mL) was added. The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum to afford 1-(6,7-dimethoxy-4-quinolyl)indol-5-amine (0.4 g, crude) as brown solid which was directly used for the amide coupling reaction. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{19}H_{17}N_3O_2+H]^+$: 320.13, found: 319.8, t_R = 0.463 min.

[0670] Synthesis of 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)oxy]aniline [Intermediate 30]:

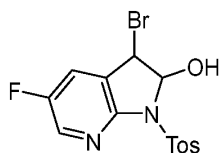


[0671] Synthesis of 5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



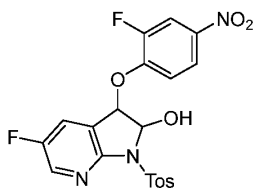
[0672] To a mixture of 5-fluoro-1H-pyrrolo[2,3-b]pyridine (2.00 g, 14.69 mmol, 1.00 eq) in THF (40 mL) was added NaH (705.16 mg, 17.63 mmol, 60% purity, 1.20 eq) in portions at 0 °C under N₂. The mixture was stirred at 0 °C for 30 min, then 4-methylbenzenesulfonyl chloride (3.08 g, 16.16 mmol, 1.10 eq) in THF (10 mL) was added. The mixture was stirred at 25 °C for 1 h. LCMS showed the reaction completed. The reaction mixture was poured into 80 mL saturated NH₄Cl. The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford 5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (3 g crude) as yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₄H₁₁FN₂O₂S+H]⁺: 291.05, found: 291.1, *t_R*= 0.522 min.

[0673] Synthesis of 3-bromo-5-fluoro-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol



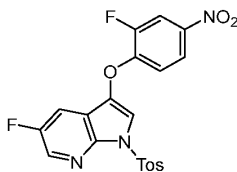
[0674] To a mixture of 5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (2.50 g, 8.61 mmol, 1.00 eq) in acetone (50 mL) was added NBS (1.69 g, 9.47 mmol, 1.10 eq) and H₂O (1.55 g, 86.11 mmol, 1.55 mL, 10.00 eq) in one portion at 25 °C under N₂. The mixture was stirred at 25 °C for 4 hr. LCMS showed the reaction completed. The residue was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/pet. ether gradient @ 80 mL/min) to afford 3-bromo-5-fluoro-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol (2.5 g, 74.97% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.21 (dd, J=2.75, 1.25 Hz, 1 H) 7.96 (d, J=8.38 Hz, 2 H) 7.89 (dd, J=8.00, 2.75 Hz, 1 H) 7.77 (br d, J=5.00 Hz, 1 H) 7.40 (d, J=8.00 Hz, 2 H) 5.98 (br s, 1 H) 5.32 (s, 1 H) 2.36 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₄H₁₂BrFN₂O₃S+H]⁺: 386.97, found: 387.1, 389.1, *t_R*= 1.751 min.

[0675] Synthesis of 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol



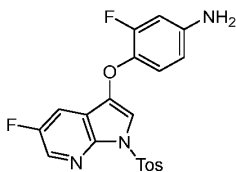
[0676] To a mixture of 3-bromo-5-fluoro-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol (2.00 g, 5.16 mmol, 1.00 eq) in EtOAc (100 mL) was added TEA (2.61 g, 25.82 mmol, 3.59 mL, 5.00 eq) in one portion at 0 °C under N₂. The mixture was stirred at 25 °C for 10 min, then 2-fluoro-4-nitro-phenol (1.62 g, 10.33 mmol, 2.00 eq) was added. The mixture was stirred at 0 °C for 1 h 50 min. Then heated to 50 °C and stirred for 2 hours. LCMS showed the reaction was completed. The residue was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/pet. ether gradient @ 120 mL/min) to afford 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol (2 g, 83.56% yield) as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.34 (d, J=1.75 Hz, 1 H) 8.16 - 8.31 (m, 2 H) 7.94 - 8.02 (m, 1 H) 7.88 - 8.02 (m, 1 H) 7.91 (dd, J=7.69, 4.44 Hz, 2 H) 7.65 (d, J=8.75 Hz, 1 H) 7.38 (d, J=8.25 Hz, 2 H) 5.88 (d, J=7.38 Hz, 1 H) 5.75 (s, 1 H) 2.37 (s, 3 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₂₀H₁₅F₂N₃O₆S+H]⁺: 464.06, found: 463.9, *t*_R= 1.286 min.

[0677] Synthesis of 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine



[0678] To a mixture of 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)-2,3-dihydropyrrolo[2,3-b]pyridin-2-ol (1.00 g, 2.16 mmol, 1.00 eq) in EtOAc (60 mL) was added BF₃.Et₂O (1.53 g, 10.79 mmol, 1.33 mL, 5.00 eq) in portions under N₂. The mixture was stirred at 80 °C for 2 hr. LCMS showed the reaction was completed. The residue was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% ethyl acetate/pet. ether gradient @ 80 mL/min) to afford 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (460 mg, 47.86% yield) as red solid. MS(ES+) m/z calc'd for [M+H]⁺ [C₂₀H₁₃F₂N₃O₅S+H]⁺: 446.05, found: 445.9, *t*_R= 0.663 min.

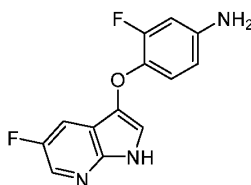
[0679] Synthesis of 3-fluoro-4-[5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridin-3-yl]oxy-aniline



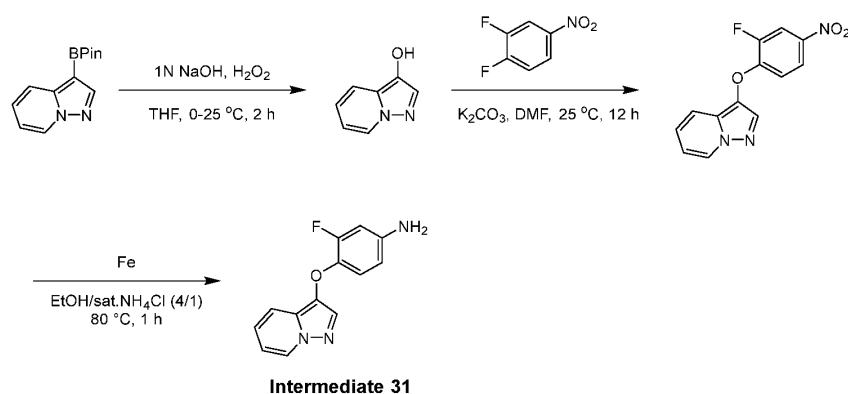
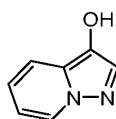
[0680] To a mixture of 5-fluoro-3-(2-fluoro-4-nitro-phenoxy)-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridine (460.00 mg, 1.03 mmol, 1.00 eq) in EtOH (8 mL) was added saturated NH_4Cl (2 mL), then Fe (288.38 mg, 5.16 mmol, 5.00 eq) was added at 70 °C. The mixture was stirred at 70 °C for 1 h. LCMS showed the reaction completed. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc (2×20 mL). The filtrate was poured into water (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO_2 , pet. ether:EtOAc = 2:1) to afford 3-fluoro-4-[5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridin-3-yl]oxy-aniline (256 mg, 59.67% yield) as brown oil. MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{20}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_3\text{S}+\text{H}]^+$: 416.08, found: 415.9, t_R = 0.606 min.

[0681] Synthesis of 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)oxy]aniline

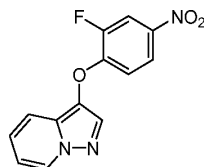
[Intermediate 30]:



[0682] To a mixture of 3-fluoro-4-[5-fluoro-1-(p-tolylsulfonyl)pyrrolo[2,3-b]pyridin-3-yl]oxy-aniline (150.00 mg, 361.09 μmol , 1.00 eq) in H_2O (0.6 mL) and MeOH (1.8 mL) was added NaOH (57.77 mg, 1.44 mmol, 4.00 eq) in one portion under N_2 . The mixture was stirred at 50 °C for 1 hr. LCMS showed the reaction was completed. The residue was poured into water (50 mL). The aqueous phase was extracted with DCM (3×30 mL). The combined organic phase was washed with brine (3×20 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The crude product was triturated with DCM (5 mL) at 25 °C for 0.5 h. The Filter cake was contained the desired product of 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-3-yl)oxy]aniline (50 mg, 53.01% yield) as white solid. MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{13}\text{H}_9\text{F}_2\text{N}_3\text{O}+\text{H}]^+$: 261.07, found: 261.8, t_R = 0.461 min.

[0683] Synthesis of 3-fluoro-4-pyrazolo[1,5-a]pyridin-3-yloxy-aniline [Intermediate 31]:**[0684] Synthesis of pyrazolo[1,5-a]pyridin-3-ol**

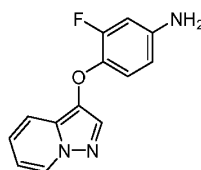
[0685] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (780.00 mg, 3.20 mmol, 1.00 eq) in THF (35 mL) was added NaOH (1 M, 7.09 mL, 2.22 eq) and H₂O₂ (836.73 mg, 7.38 mmol, 709.09 μ L, 30% purity, 2.31 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hr. LCMS showed no starting material remained and ~69% of desired compound was detected. The reaction mixture was poured into ice water (60 mL) and then adjusting then pH to 2 with 6 N HCl. The aqueous phase was extracted with DCM (3 $\times$ 30 mL). The combined organic phase was washed with brine (30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~100% ethyl acetate/pet. ether gradient @ 100 mL/min) to afford pyrazolo[1,5-a]pyridin-3-ol (150.00 mg, 35.00% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.83 (s, 1 H) 8.36 (d, *J*=7.13 Hz, 1 H) 7.56 (s, 1 H) 7.51 (d, *J*=9.01 Hz, 1 H) 6.92 (ddd, *J*=8.97, 6.53, 0.75 Hz, 1 H) 6.60 - 6.69 (m, 1 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₇H₆N₂O+H]⁺: 135.05, found: 135.2, *t*_R= 0.215 min.

[0686] Synthesis of 3-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyridine

[0687] To a solution of pyrazolo[1,5-a]pyridin-3-ol (150.00 mg, 1.12 mmol, 1.00 eq) in DMF (3 mL) was added K₂CO₃ (154.56 mg, 1.12 mmol, 1.00 eq) and 1,2-difluoro-4-nitro-benzene (177.91 mg, 1.12 mmol, 123.80 μ L, 1.00 eq) was added. The mixture was stirred at 25 °C for 12 hr. LCMS showed no starting material remained and ~65% of desired compound was detected.

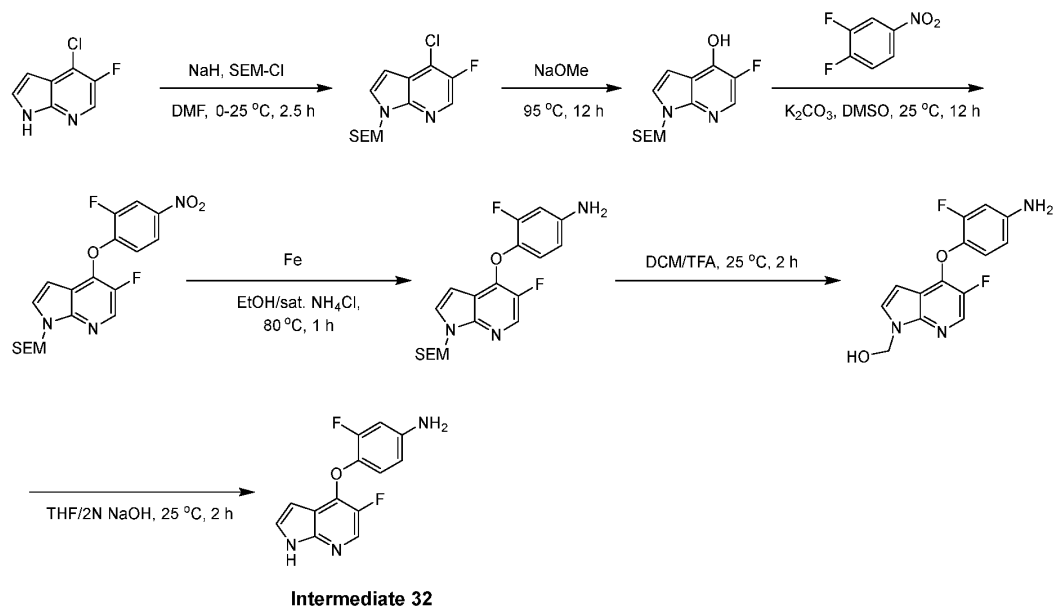
The reaction mixture was poured into water (30 mL). The aqueous phase was extracted with ethyl acetate (3×15 mL). The combined organic phase was washed with brine (15 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-TLC (SiO₂, pet. ether:ethyl acetate=1:1) to afford 3-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyridine (170.00 mg, 55.64% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.71 (d, J=7.00 Hz, 1 H) 8.35 (dd, J=10.88, 2.75 Hz, 1 H) 8.20 (s, 1 H) 7.99 - 8.06 (m, 1 H) 7.52 (d, J=9.01 Hz, 1 H) 7.21 - 7.29 (m, 1 H) 7.07 (t, J=8.82 Hz, 1 H) 6.92 - 7.01 (m, 1 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₈FN₃O₃+H]⁺: 274.05, found: 274.1, *t*_R= 0.492 min.

[0688] Synthesis of 3-fluoro-4-pyrazolo[1,5-a]pyridin-3-yloxy-aniline [Intermediate 31]:

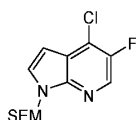


[0689] To a solution of 3-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyridine (150.00 mg, 549.01 μmol, 1.00 eq) in EtOH (2.4 mL) and saturated NH₄Cl (0.60 g, 0.6 mL) was added Fe (153.30 mg, 2.75 mmol, 5.00 eq) was added. The mixture was stirred at 80 °C for 1 hr. LCMS showed no starting material remained and ~89% of desired compound was detected. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc (2×20 mL). The resulting filtrate was extracted with EtOAc (2×20 mL). The combined organic layer was washed successively with water (2×20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-TLC (SiO₂, pet. ether:ethyl acetate=1:1) to afford 3-fluoro-4-pyrazolo[1,5-a]pyridin-3-yloxy-aniline (120.00 mg, 89.86% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.55 (d, J=7.13 Hz, 1 H) 7.85 (s, 1 H) 7.41 (d, J=9.01 Hz, 1 H) 7.09 - 7.16 (m, 1 H) 6.79 - 6.89 (m, 2 H) 6.46 (dd, J=13.51, 2.50 Hz, 1 H) 6.28 (dt, J=8.69, 1.22 Hz, 1 H) 5.20 (s, 2 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₁₀FN₃O+H]⁺: 244.08, found: 244.2, *t*_R= 0.330 min.

[0690] Synthesis of 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]aniline [Intermediate 32]:

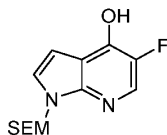


[0691] Synthesis of 2-[(4-chloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane



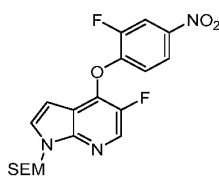
[0692] To a solution of 4-chloro-5-fluoro-1H-pyrrolo[2,3-b]pyridine (2.00 g, 11.73 mmol, 1.00 *eq*) in DMF (40 mL) was added NaH (2.34 g, 58.63 mmol, 60% purity, 5.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1 hr, and then SEM-Cl (2.35 g, 14.07 mmol, 2.49 mL, 1.20 *eq*) was added at 0 °C. The resulting mixture was stirred at 25 °C for 1.5 hr. LCMS showed ~95% of desired compound was detected. The reaction mixture was poured into saturated NH₄Cl (100 mL). The aqueous phase was extracted with ethyl acetate (3×60 mL). The combined organic phase was washed with brine (2×90 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=4/1) to afford 2-[(4-chloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (3.30 g, 90.75% yield) as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 (d, J=2.00 Hz, 1 H) 7.87 (d, J=3.63 Hz, 1 H) 6.62 (d, J=3.63 Hz, 1 H) 5.62 (s, 2 H) 3.50 (t, J=8.00 Hz, 2 H) 0.80 (t, J=8.00 Hz, 2 H) -0.12 (s, 9 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₃H₁₈ClFN₂OSi+H]⁺: 301.09, found: 301.1, *t*_R= 0.669 min.

[0693] Synthesis of 5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol



[0694] To a solution of NaOMe (60 mL, 30% solution in MeOH) was added 2-[(4-chloro-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (1.50 g, 4.99 mmol, 1.00 *eq*). The mixture was stirred at 95 °C for 12 hr. LCMS showed ~75% of desired compound was detected. The reaction mixture was poured into water (150 mL). Then the aqueous phase was then adjusted to PH=5~6 with 6N HCl solution. The aqueous phase was extracted with ethyl acetate (3×90 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=4/1) to afford 5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol (1.00 g, 71.02% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.20 (br s, 1 H) 8.10 (br d, J=3.50 Hz, 1 H) 7.46 (br d, J=2.88 Hz, 1 H) 6.65 (br d, J=3.25 Hz, 1 H) 5.52 (s, 2 H) 3.47 (t, J=8.00 Hz, 2 H) 0.76 - 0.82 (m, 2 H) -0.11 (s, 9 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₃H₁₉FN₂O₂Si+H]⁺: 283.12, found: 283.1, *t*_R= 0.459 min.

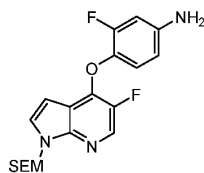
[0695] Synthesis of 2-[[5-fluoro-4-(2-fluoro-4-nitro-phenoxy)pyrrolo[2,3-b]pyridin-1-yl]methoxy] ethyl-trimethyl-silane



[0696] To a solution of 5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol (1.20 g, 4.25 mmol, 1.00 *eq*) in DMSO (12 mL) was added K₂CO₃ (2.35 g, 17.00 mmol, 4.00 *eq*) and 1,2-difluoro-4-nitro-benzene (1.28 g, 8.07 mmol, 893.88 μL, 1.90 *eq*). The mixture was stirred at 25 °C for 12 hr. LCMS showed ~60% of desired compound was detected. The reaction mixture was poured into water (90 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (2×70 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=4/1) to afford 2-[[5-fluoro-4-(2-fluoro-4-nitro-phenoxy)pyrrolo[2,3-b]pyridin-1-yl]methoxy] ethyl-trimethyl-silane (1.50 g, 83.75% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.47 (d, J=3.13 Hz, 1 H) 8.39 (dd, J=10.69, 2.44 Hz, 1 H) 8.08 (br dd, J=9.13, 1.25 Hz, 1 H) 7.73 (d, J=3.63 Hz, 1 H) 7.31 (t, J=8.63 Hz, 1 H) 6.20 (d, J=3.50 Hz, 1 H) 5.62 (s, 2 H) 3.53 (br t, J=7.94 Hz, 2 H) 0.82 (br t, J=7.94 Hz, 2 H) -

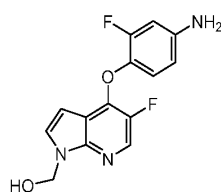
0.10 (s, 9 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₉H₂₁F₂N₃O₄Si+H]⁺: 422.13, found: 422.2, *t*_R= 0.655 min.

[0697] Synthesis of 3-fluoro-4-[5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline



[0698] To a solution of 2-[[5-fluoro-4-(2-fluoro-4-nitro-phenoxy)pyrrolo[2,3-b]pyridin-1-yl]methoxy] ethyl-trimethyl-silane (700.00 mg, 1.66 mmol, 1.00 *eq*) in EtOH (4 mL), saturated NH₄Cl (2 mL) was added Fe (927.51 mg, 16.61 mmol, 10.00 *eq*) at 80 °C. The mixture was stirred at 80 °C for 1 hr. LCMS showed ~94% of desired compound was detected. The mixture was filtered in vacuum. The filtrate mixture was poured into water (80 mL). The aqueous phase was extracted with ethyl acetate (3×40 mL). The combined organic phase was washed with brine (2×90 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum, to afford 3-fluoro-4-[5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline (600.00 mg, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 (d, *J*=3.75 Hz, 1 H) 7.48 (d, *J*=3.63 Hz, 1 H) 7.08 (t, *J*=9.13 Hz, 1 H) 6.50 (dd, *J*=13.38, 2.50 Hz, 1 H) 6.42 (dt, *J*=8.69, 1.22 Hz, 1 H) 5.52 - 5.54 (m, 1 H) 5.53 (s, 1 H) 5.48 (s, 2 H) 5.44 (d, *J*=3.75 Hz, 1 H) 3.47 (t, *J*=8.00 Hz, 2 H) 0.71 - 0.83 (m, 2 H) -0.13 - -0.10 (m, 9 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₉H₂₃F₂N₃O₂Si+H]⁺: 392.15, found: 391.6, *t*_R= 0.577 min.

[0699] Synthesis of [4-(4-amino-2-fluoro-phenoxy)-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl]methanol

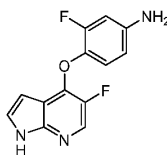


[0700] To a solution of DCM (5.4 mL), TFA (1.8 mL) was added 3-fluoro-4-[5-fluoro-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline (300.00 mg, 766.31 μmol, 1.00 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed ~76% of desired compound was detected. The reaction mixture was poured into water (40 mL), then adjust to PH=11~12 with sat. Na₂CO₃. The aqueous phase was extracted with ethyl acetate (3×20 mL). The combined organic phase was washed with brine (40 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford [4-(4-amino-2-fluoro-phenoxy)-5-fluoro-pyrrolo[2,3-b]

b]pyridin-1-yl]methanol (290.00 mg, crude) as a yellow oil. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{14}H_{11}F_2N_3O_2+H]^+$: 292.08, found: 292.1, t_R = 0.350 min.

[0701] Synthesis of 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]aniline

[Intermediate 32]:

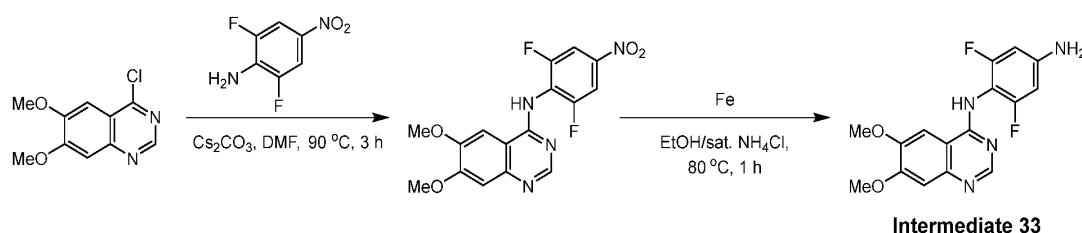


[0702] To a solution of THF (2 mL), NaOH (4 M, 1.82 mL, 11.00 *eq*) was added [4-(4-amino-2-fluoro-phenoxy)-5-fluoro-pyrrolo[2,3-b]pyridin-1-yl]methanol (280.00 mg, 663.34 μ mol, 1.00 *eq*). The mixture was stirred at 25 °C for 2 hr. LCMS showed ~72% of desired compound was detected. The reaction mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phase was washed with brine (2×60 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum to afford 3-fluoro-4-[(5-fluoro-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]aniline (200.00 mg, crude) as a yellow solid.

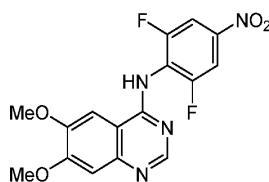
MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{13}H_9F_2N_3O+H]^+$: 262.07, found: 262.1, t_R = 0.356 min.

[0703] Synthesis of N1-(6,7-dimethoxyquinazolin-4-yl)-2,6-difluoro-benzene-1,4-diamine

[Intermediate 33]:



[0704] Synthesis of N-(2,6-difluoro-4-nitro-phenyl)-6,7-dimethoxy-quinazolin-4-amine

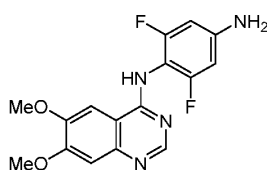


[0705] To a solution of 4-chloro-6,7-dimethoxy-quinazoline (500.00 mg, 2.23 mmol, 1.00 *eq*), 2,6-difluoro-4-nitro-aniline (426.27 mg, 2.45 mmol, 1.10 *eq*) in DMF (5 mL) was added Cs_2CO_3 (2.18 g, 6.68 mmol, 3.00 *eq*). The mixture was stirred at 90 °C for 3 hr. LCMS showed ~75% of desired compound was detected. The reaction mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phase was washed with brine (3×50 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in

vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=1/1) to give N-(2,6-difluoro-4-nitro-phenyl)-6,7-dimethoxy-quinazolin-4-amine (750 mg, purity 78%) as a yellow solid, which was further purified by prep-TLC (SiO₂, pet. ether:EtOAc=1:1) to afford N-(2,6-difluoro-4-nitro-phenyl)-6,7-dimethoxy-quinazolin-4-amine (570.00 mg, 70.69% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.92 (br s, 1 H) 8.42 (br s, 1 H) 8.23 (br d, J=7.25 Hz, 2 H) 7.86 (br s, 1 H) 7.26 (br s, 1 H) 3.95 (br s, 6 H) 2.89 (s, 1 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₂F₂N₄O₄+H]⁺: 363.08, found: 362.8, *t*_R= 0.520 min.

Synthesis of N1-(6,7-dimethoxyquinazolin-4-yl)-2,6-difluoro-benzene-1,4-diamine

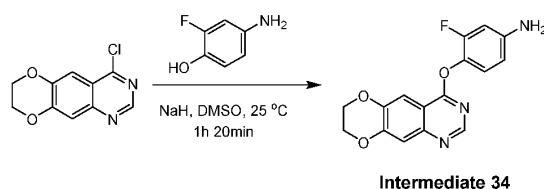
[Intermediate 33]:



[0706] To a solution of N-(2,6-difluoro-4-nitro-phenyl)-6,7-dimethoxy-quinazolin-4-amine (300.00 mg, 828.07 μmol, 1.00 *eq*) in EtOH (4 mL), saturated NH₄Cl (2 mL) was added Fe (462.44 mg, 8.28 mmol, 10.00 *eq*). The mixture was stirred at 80 °C for 1 hr. LC-MS showed ~99% of desired compound was detected. The reaction mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phase was washed with brine (2×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford N1-(6,7-dimethoxyquinazolin-4-yl)-2,6-difluoro-benzene-1,4-diamine (270.00 mg, crude) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1 H) 8.28 (s, 1 H) 7.78 (s, 1 H) 7.16 (s, 1 H) 6.31 (d, J=10.38 Hz, 2 H) 5.73 (s, 2 H) 3.92 (d, J=3.00 Hz, 6 H) 1.99 (s, 4 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₄F₂N₄O₂+H]⁺: 333.11, found: 332.9, *t*_R= 0.442 min.

[0707] Synthesis of 3-fluoro-4-(2-fluoro-4-nitro-phenyl)sulfanyl-6,7-dimethoxy-quinoline

[Intermediate 34]:

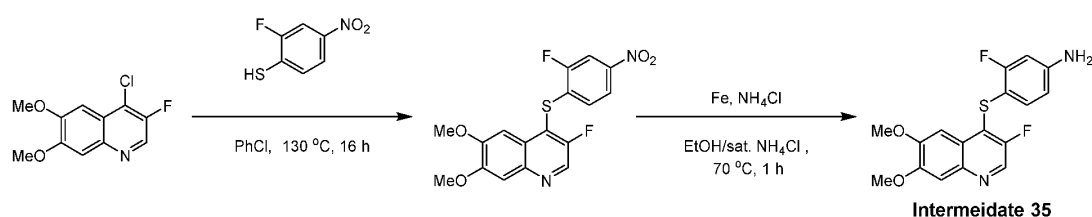


[0708] To DMSO (10 mL) was added NaH (98.81 mg, 2.47 mmol, 60% purity, 1.10 *eq*) at 25 °C, and the reaction mixture was stirred at 25 °C for 10 min, then 4-amino-2-fluorophenol (314.04 mg, 2.47 mmol, 1.10 *eq*) was added and stirred for 10 min. 4-chloro-7,8-dihydro-

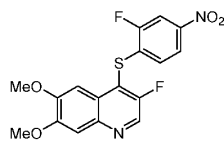
[1,4]dioxino[2,3-g]quinazoline (0.50 g, 2.25 mmol, 1.00 eq) was added and then stirred at 25 °C for 1 h. LCMS showed the reaction was completed. The mixture was quenched with H₂O (10 mL) and extracted with EtOAc (3×100 mL), the organic layers was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated to afford 3-fluoro-4-(2-fluoro-4-nitro-phenyl)sulfanyl-6,7-dimethoxy-quinoline (0.53 g, crude) as brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (s, 1 H) 7.63 (s, 1 H) 7.37 (s, 1 H) 7.02 (t, J=8.82 Hz, 1 H) 6.38 - 6.52 (m, 2 H) 5.40 (s, 2 H) 4.43 (br dd, J=12.88, 5.13 Hz, 4 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₂FN₃O₃ +H]⁺: 314.09, found: 314.0, t_R= 1.038 min.

[0709] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)sulfanyl]aniline

[Intermediate 35]:



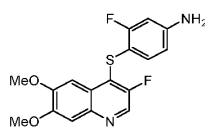
[0710] Synthesis of 3-fluoro-4-(2-fluoro-4-nitro-phenyl)sulfanyl-6,7-dimethoxy-quinoline



[0711] To a solution of 4-chloro-3-fluoro-6,7-dimethoxy-quinoline (0.10 g, 413.83 μmol, 1.00 eq) in chlorobenzene (4.00 mL) was added 2-fluoro-4-nitro-benzenethiol (107.49 mg, 620.74 μmol, 1.50 eq), and then the mixture was stirred at 130 °C for 16 hrs under N₂. LCMS showed little starting material remained and ~70% desired was detected. The mixture was concentrated to remove chlorobenzene. To the residue was added 4 mL of MeOH and stirred for 1 hr. The precipitated solid was collected by filtration. The filter cake was collected and dried in vacuo to afford 3-fluoro-4-(2-fluoro-4-nitro-phenyl)sulfanyl-6,7-dimethoxy-quinoline (0.11 g, 63.23% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.90 (s, 1 H) 8.24 (dd, J=9.88, 2.38 Hz, 1 H) 7.92 (dd, J=8.76, 2.13 Hz, 1 H) 7.55 (s, 1 H) 7.42 (s, 1 H) 7.12 (t, J=8.25 Hz, 1 H) 3.96 (s, 3 H) 3.85 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₂F₂N₂O₄S +H]⁺: 379.05, found: 378.9, t_R= 1.367 min.

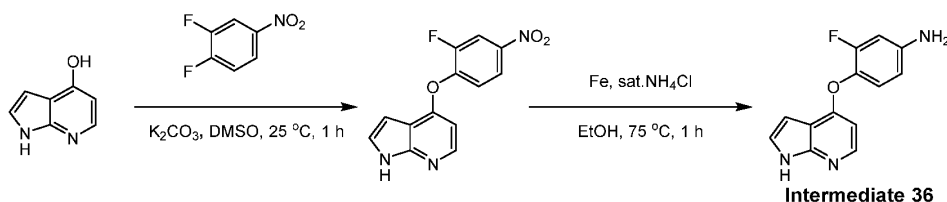
[0712] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)sulfanyl]aniline

[Intermediate 35]:

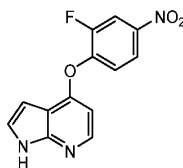


[0713] To a mixture of 3-fluoro-4-(2-fluoro-4-nitro-phenyl)sulfanyl-6,7-dimethoxy-quinoline (0.11 g, 290.74 μmol , 1.00 eq) in EtOH (4.50 mL) and saturated NH_4Cl (1.50 mL) was added Fe (81.18 mg, 1.45 mmol, 5.00 eq) in portions at 70 °C, and then the mixture was stirred at 70 °C for 1 hr. LCMS showed the reaction was completed. The mixture was filtered through celite and washed with EtOAc (50 mL), the filtrate was diluted with H_2O (20 mL), the organic layer was separated, and the aqueous phase was extracted with EtOAc (3 $\times$ 15 mL), the organic layers were washed with brine (20 mL), dried over Na_2SO_4 to afford 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)sulfanyl]aniline (0.075 g) as yellow solid. MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{14}\text{F}_2\text{N}_2\text{O}_2\text{S}+\text{H}]^+$: 349.07, found: 348.9, t_R = 1.201 min

[0714] **Synthesis of 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)aniline [Intermediate 36]:**

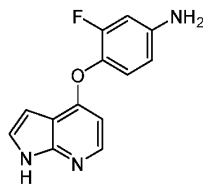


[0715] **Synthesis of 4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridine**



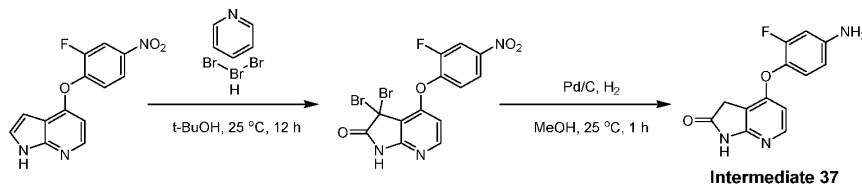
[0716] To a mixture of 1H-pyrrolo[2,3-b]pyridin-4-ol (2.00 g, 14.91 mmol, 1.00 eq), 1,2-difluoro-4-nitro-benzene (2.61 g, 16.40 mmol, 1.82 mL, 1.10 eq) in DMSO (20 mL) was added K_2CO_3 (8.24 g, 59.64 mmol, 4.00 eq) at 25 °C and the mixture was stirred at 25 °C for 1 h. TLC (pet. ether:EtOAc=1:1, SM_2/R_f =0.41, TM/R_f =0.27) showed the reaction was completed. The residue was poured into H_2O (100 mL). A lot of solids were formed, then filtered and collected. The aqueous phase was extracted with ethyl acetate (3 $\times$ 40 mL). The combined organic phase was washed with brine (3 $\times$ 40 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated under vacuum. The solid was washed with MeOH (2 $\times$ 10 mL) and concentrated under vacuum to afford 4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridine (1 g, 24.36% yield) as light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.05 - 12.69 (m, 1 H) 8.41 (dd, J =10.57, 2.69 Hz, 1 H) 8.20 (d, J =5.38 Hz, 1 H) 8.09 - 8.15 (m, 1 H) 7.36 - 7.49 (m, 2 H) 6.72 (d, J =5.38 Hz, 1 H) 6.24 (d, J =3.50 Hz, 1 H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{13}\text{H}_8\text{FN}_3\text{O}_3+\text{H}]^+$: 274.05, found: 274.0, t_R = 1.155 min.

[0717] Synthesis of 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)aniline [Intermediate 36]

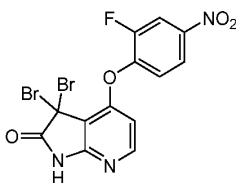


[0718] To a mixture of 4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridine (1.00 g, 3.66 mmol, 1.00 *eq*) in EtOH (10 mL), saturated NH₄Cl (2.5 mL) was added Fe (1.02 g, 18.30 mmol, 5.00 *eq*) at 75 °C and the mixture was stirred at 75 °C for 1 h. TLC (pet. ether:EtOAc=2:1, *S_M*/*R_f*=0.42, *T_M*/*R_f*=0.28) showed the reaction was completed. The reaction mixture was poured into sat. Na₂CO₃ (100 mL) and EtOAc (50 mL) was added. The aqueous phase was extracted with ethyl acetate (3x50 mL). The combined organic phase was washed with brine (3x50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford 3-fluoro-4-(1H-pyrrolo[2,3-b]pyridin-4-yloxy)aniline (0.8 g) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.68 (br s, 1 H) 8.02 (d, *J*=5.50 Hz, 1 H) 7.26 - 7.35 (m, 1 H) 7.02 (t, *J*=9.01 Hz, 1 H) 6.51 (dd, *J*=13.20, 2.44 Hz, 1 H) 6.43 (dd, *J*=8.69, 2.19 Hz, 1 H) 6.26 - 6.32 (m, 1 H) 6.19 - 6.25 (m, 1 H) 5.31 - 5.49 (m, 2 H).

[0719] Synthesis of 4-(4-amino-2-fluoro-phenoxy)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one [Intermediate 37]:



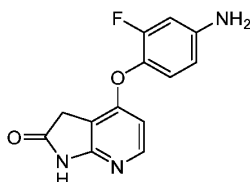
[0720] Synthesis of 3,3-dibromo-4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridine-2-one



[0721] To a solution of 4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridine (500.00 mg, 1.83 mmol, 1.00 *eq*) in *t*-BuOH (32.5 mL) was added BLAH;pyridin-1-ium (2.05 g, 6.41 mmol, 3.50 *eq*). The mixture was stirred at 25 °C for 12 hr. TLC (pet. ether:EtOAc=1:1, *S_M*/*R_f*=0.44, *T_M*/*R_f*=0.57) indicated starting material was consumed completely and one new spot formed. The reaction mixture was poured into H₂O (50 mL). The aqueous phase was extracted with ethyl acetate (3x25 mL). The combined organic phase was washed with brine (20 mL), dried with

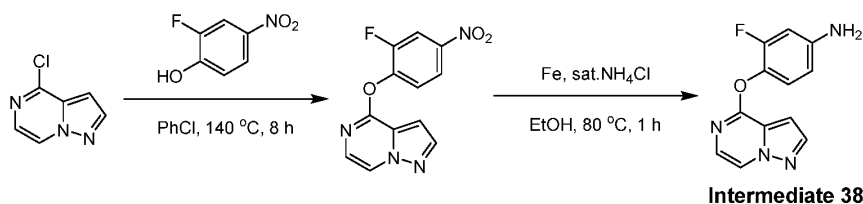
anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The crude product was triturated with $\text{DCM}:\text{MeOH}=10:1$ (10 mL) at 25°C for 20 min, filtered to afford 3,3-dibromo-4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridin-2-one (450 mg, 55.01% yield) as a light yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 12.19 (s, 1 H) 8.48 (dd, $J=10.38$, 2.63 Hz, 1 H) 8.14 - 8.27 (m, 2 H) 7.70 (t, $J=8.50$ Hz, 1 H) 6.69 (d, $J=6.13$ Hz, 1 H).

[0722] Synthesis of 4-(4-amino-2-fluoro-phenoxy)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one [Intermediate 37]:

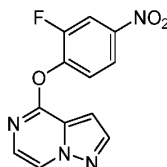


[0723] To a solution of 3,3-dibromo-4-(2-fluoro-4-nitro-phenoxy)-1H-pyrrolo[2,3-b]pyridin-2-one (200.00 mg, 447.42 μmol , 1.00 eq) in MeOH (15 mL) was added Pd/C (1 g, 939.67 μmol , 10% purity, 2.10 eq). The mixture was stirred at 25°C for 1 hr under H_2 . LCMS showed starting material consumed and ~57% of desired compound was detected. The reaction solution filtered through celite. The celite pad was rinsed with MeOH (100 mL) and concentrated in vacuo to get the crude product. The residue was purified by prep-TLC (SiO_2 , pet. ether:ethyl acetate=1:1) to afford 4-(4-amino-2-fluoro-phenoxy)-1,3-dihydropyrrolo[2,3-b]pyridin-2-one (25 mg, 21.55% yield) as a yellow solid. ^1H NMR (400 MHz, $\text{METHANOL}-d_4$): δ 7.92 (d, $J=6.13$ Hz, 1 H) 6.97 (t, $J=8.82$ Hz, 1 H) 6.56 (dd, $J=12.63$, 2.50 Hz, 1 H) 6.49 - 6.53 (m, 1 H) 6.41 (d, $J=6.25$ Hz, 1 H) 3.42 (s, 2 H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{13}\text{H}_{10}\text{FN}_3\text{O}_2+\text{H}]^+$: 260.08, found: 260.0, t_R =0.837 min.

[0724] Synthesis of 3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-aniline [Intermediate 38]:



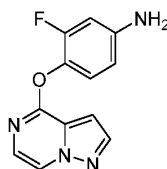
[0725] Synthesis of 4-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyrazine



[0726] To a solution of 4-chloropyrazolo [1, 5-a] pyrazine (200.00 mg, 1.30 mmol, 1.00 eq) in chlorobenzene (2 mL) was added 2-fluoro-4-nitro-phenol (204.60 mg, 1.30 mmol, 1.00 eq). The mixture was stirred at 140°C for 8 hrs. LCMS showed the reaction was completed. The reaction

mixture was poured into H₂O (50 mL), then the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na₂SO₄, filtration and concentrated under vacuum. The residue was purified by prep-TLC (SiO₂, pet. ether:EtOAc = 4:1) to afford 4-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyrazine (100 mg, 28.00% yield) as yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₇FO₃N₄+H]⁺: 275.05, found: 274.6, *t_R* = 0.534 min.

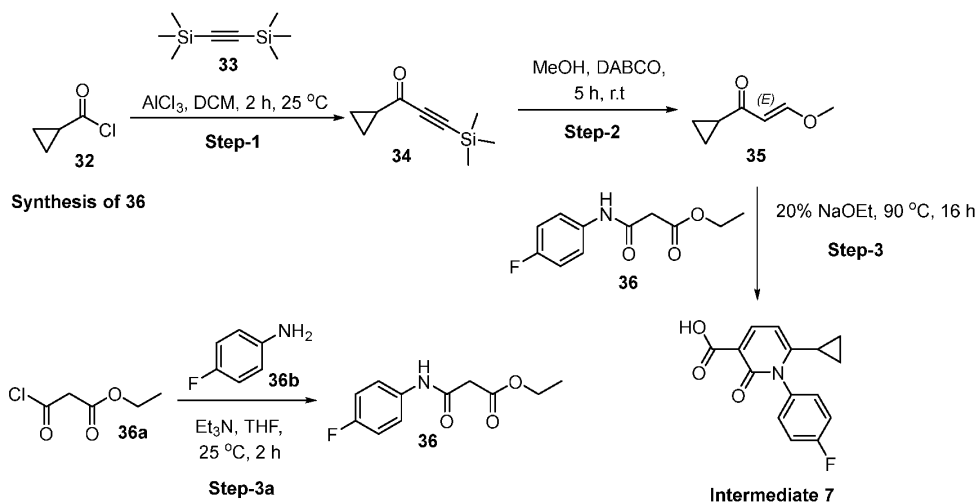
[0727] Synthesis of 3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-aniline [Intermediate 38]:



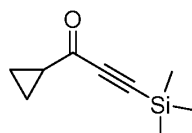
[0728] To a mixture of 4-(2-fluoro-4-nitro-phenoxy)pyrazolo[1,5-a]pyrazine (100.00 mg, 364.69 μmol, 1.00 eq) in EtOH (2 mL) was added saturated NH₄Cl (0.5 mL), then Fe (101.84 mg, 1.82 mmol, 5.00 eq) was added at 80 °C. The mixture was stirred at 80 °C for 1 h. LCMS showed no starting material remained and 90% product was detected. The reaction mixture was filtered through a pad of celite and the filter cake was washed with EtOAc (2×50 mL). The reaction mixture was poured into water (50 mL) and the aqueous phase was extracted with EtOAc (3×50 mL). The organic layer was washed with brine (2×50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford 3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-aniline (100.00 mg) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.49 (dd, *J*=4.75, 0.63 Hz, 1 H) 8.17 (d, *J*=2.25 Hz, 1 H) 7.35 (d, *J*=4.75 Hz, 1 H) 7.07 (d, *J*=1.63 Hz, 1 H) 7.03 (t, *J*=8.88 Hz, 1 H) 6.49 (dd, *J*=13.07, 2.44 Hz, 1 H) 6.41 (dd, *J*=8.63, 1.88 Hz, 1 H) 5.40 (s, 2 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₉FN₄O+H]⁺: 245.07 found: 244.9, *t_R* = 0.534 min.

Part B Synthesis:

[0729] Synthesis of Synthesis of 6-cyclopropyl-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 7]:

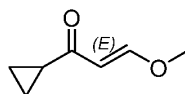


[0730] Synthesis of 1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one [34]:



[0731] A stirred solution of trimethyl(2-trimethylsilyl)ethynylsilane (31 mL, 143 mmol, 1.00 eq) in DCM (300 mL, 0.4783 M) at 0 °C was charged with cyclopropanecarbonyl chloride (13 mL, 143 mmol, 1.00 eq) and aluminium chloride (22.95 g, 172 mmol, 1.20 eq) and stirred for 2 h. Stirring was continued for another 6 h, then the reaction mixture was poured into a 10% HCl (300 mL) solution in ice-water and stirred for another 20 min. After the separation of two phases, the aqueous phase was extracted with DCM (3 × 200 mL) and separated. The combined organic layers were evaporated under reduced pressure to afford 22 g, 92.19% yield of the titled compound as a brown oil product, which was directly used in the next reaction. ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.10 - 2.01 (m, 1H), 1.14 - 1.04 (m, 4H), 0.23 (s, 9H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₉H₁₄OSi+H]⁺: 167.29, found: 167.0, *t*_R = 2.07 min, [Method N].

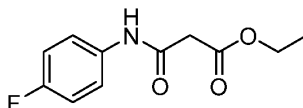
[0732] Synthesis of (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one [35]:



[0733] A stirred solution of 1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one (22.00 g, 132 mmol, 1.00 eq) in methanol (300 mL, 0.441 M) at rt was slowly charged with 1,4-Diazabicyclo[2.2.2]octane (22.26 g, 198 mmol, 1.50 eq) and resulting reaction mixture was stirred at room temperature for 5 h and concentrated. The crude was diluted with ethyl acetate (300 mL), washed with saturated brine (2 × 50 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to get crude. The crude compound was further purified by combi flash using YMC 80 g cartridge, eluting with 0-20% Ethyl acetate/Heptane to afford 7 g, 36.81% yield of the titled compound as a brown

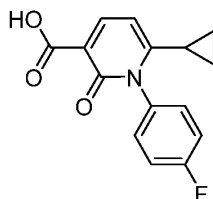
liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 7.75 (d, $J = 12.7$ Hz, 1H), 5.78 (d, $J = 12.7$ Hz, 1H), 3.72 (s, 3H), 2.21 - 2.10 (m, 1H), 0.85 - 0.79 (m, 4H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_7\text{H}_{10}\text{O}_2+\text{H}]^+$: 127.07, found: 127.0, $t_R = 1.43$ min, [Method N].

[0734] Synthesis of ethyl 3-(4-fluoroanilino)-3-oxo-propanoate [36]:



[0735] A stirred solution of 4-fluoroaniline (4.4 mL, 45.0 mmol, 1.00 eq) in THF (50 mL, 0.8999 M) and triethylamine (19 mL, 135 mmol, 3.00 eq) was cooled to 0 °C and charged with ethyl 3-chloro-3-oxo-propanoate (8.1 mL, 54.0 mmol, 1.20 eq) the mixture was stirred at rt for 2 hours. Then resulting mixture was filtered and was washed with heptane (50 mL) to obtain crude which was purified by combi flash using YMC 40 g cartridge, eluting with 0-70% Ethyl acetate/Heptane to afford 5.5 g, 42.12% yield of the titled compound as a pale-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 10.21 (br s, 1H), 7.61 - 7.55 (m, 2H), 7.20 - 7.11 (m, 2H), 4.15 - 4.08 (m, 2H), 3.44 (s, 2H), 1.20 (t, $J = 7.0$ Hz, 3H); MS(ES) $^+$ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{11}\text{H}_{12}\text{FNO}_3+\text{H}]^+$: 226.05, found: 226.0, $t_R = 1.62$ min, [Method N].

[0736] Synthesis of 6-cyclopropyl-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 7]:

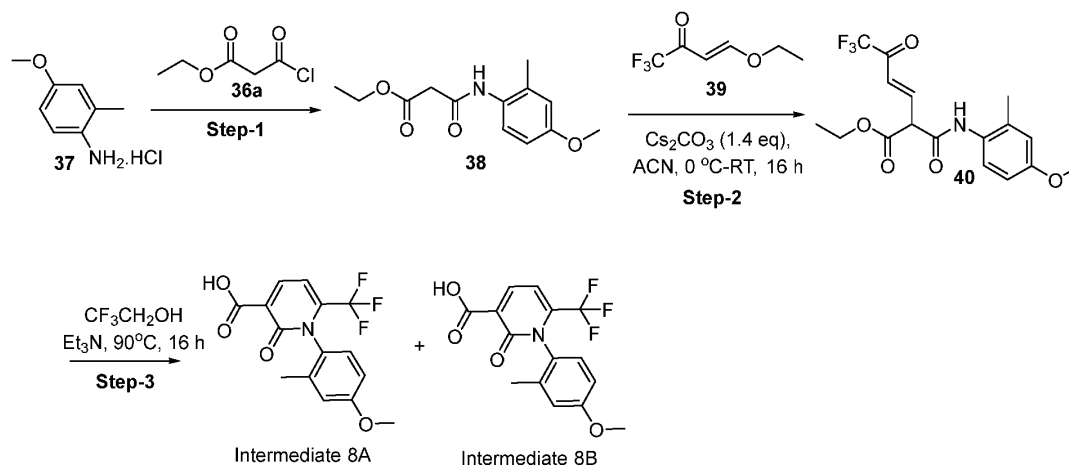


[0737] A stirred solution of ethyl 3-(4-fluoroanilino)-3-oxo-propanoate (2.00 g, 7.99 mmol, 1.00 eq) in ethanol (10 mL, 0.7992 M) at rt was charged with (*E*)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (1.512 g, 12.0 mmol, 1.50 eq) and 20% sodium ethoxide in ethanol (9.3 mL, 24.0 mmol, 3.00 eq). The reaction mixture was stirred for 16 h, at 90 °C. and the reaction mixture was concentrated to dryness and diluted with water (10 mL), and then cooled to 0 °C and the pH was adjusted to 1-2 using 2 N HCl (5 mL). The reaction mixture was extracted with EtOAc (100 mL), the combined organic layers were washed with water (20 mL) and saturated brine solution (20 mL). The combined organic layers were then separated and dried over anhydrous sodium sulfate, filtered, and concentrated to dryness under reduced pressure. Crude was purified by combi flash using YMC 24 g cartridge, eluting with 0-70% ethyl acetate/heptane to afford 550 mg, 24.92% yield of the titled compound as a pale-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 14.21 (br s, 1H), 8.36 (d, $J = 7.8$ Hz, 1H), 7.59 - 7.53 (m, 2H), 7.47 - 7.41 (m, 2H), 6.53 (d, $J = 7.8$ Hz, 1H), 1.40 - 1.32 (m, 1H), 0.99 - 0.91 (m, 2H), 0.90 - 0.83 (m, 2H),

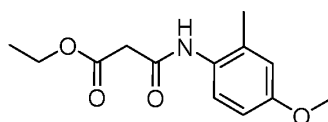
MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₅H₁₂FNO₃+H]⁺: 274.08, found: 274.0, *t*_R = 1.16 min,

[Method N]

[0738] Synthesis of 1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid [Intermediate 8A and Intermediate 8B mixture]:

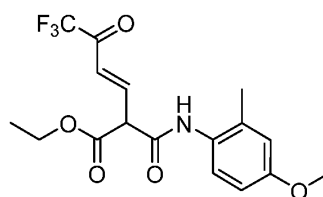


[0739] Synthesis of ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxo-propanoate [38]:



[0740] A stirred solution of 4-methoxy-2-methyl-aniline hydrochloride (17 mL, 115 mmol, 1.00 eq) in THF (250 mL, 0.4607 M) was cooled to 0 °C then charged with triethylamine (48 mL, 346 mmol, 3.00 eq) and stirred at 0 °C for 10 min. Then ethyl 3-chloro-3-oxo-propanoate (22 mL, 173 mmol, 1.50 eq) was added at 0 °C and the resulting reaction mixture was stirred at rt for 1 hour. The mixture was diluted with a Na₂CO₃ solution (100 mL) and extracted by ethyl acetate (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated in at reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography, using 10-15% ethyl acetate-hexane as a gradient to afford 17.00 g, 53.15% yield of the titled compound as pale brown solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₃H₁₇NO₄+H]⁺: 252.01, found: 262.1, *t*_R = 1.639 min, [Method N].

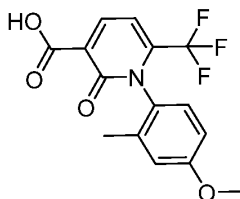
[0741] Synthesis of ethyl (*E*)-6,6,6-trifluoro-2-[(4-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate [40]:



[0742] A stirred solution of ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxo-propanoate (2.00 g, 7.16 mmol, 1.00 eq) and cesium carbonate (3.27 g, 10.0 mmol, 1.40 eq) in MeCN (20 mL, 0.3582 M) at rt was dropwise charged with (*E*)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (1.2 mL, 8.60 mmol, 1.20 eq) and the reaction mixture was stirred at rt for 16 hours. The reaction mixture was concentrated under reduced pressure to afford 2.00 g, 53.85 % yield of the title compound as brown solid. (no further purification was done) MS(ES⁺) m/z calc'd for

[M+H]⁺ [C₁₇H₁₈F₃NO₅+H]⁺: 373.0, found: 372.0, *t*_R= 1.825 min and *t*_R= 1.92 min, [Method N].

[0743] Synthesis of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 8A & 8B mixture]:



[0744] A stirred solution of ethyl (*E*)-6,6,6-trifluoro-2-[(4-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate (8.00 g, 17.1 mmol, 1.00 eq) in trifluoroethanol (80 mL, 1113 mmol, 64.9 eq) and triethylamine (7.2 mL, 51.4 mmol, 3.00 eq) was heated at 90 °C for 16 hours. After consumption of starting material, reaction was concentrated under reduced pressure to obtain a crude residue. The crude was dissolved in water and washed with ethyl acetate and the aqueous layer was acidified to pH 2-3 with 2 N HCl and extracted with ethyl acetate (2 × 100 mL) and separated. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to afford 1.60 g, 27.95% yield of the title compound as pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.65 (s, 1H), 8.44 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 3.0 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.81 (s, 3H), 1.98 (s, 3H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄+H]⁺: 328.01, found: 327.9, *t*_R= 1.917 min, [Method N].

[0745] Purification of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 8A & Intermediate 8B mixture]:

[0746] A mixture of Intermediate 8A and 8B (1.66g) was separated by chiral SFC (Instrument name: Waters-2767, prep-SFC 100) method to afford 670 mg yield of the titled compound 8A as a brown solid. SFC purification Method: No. of Injections 30 inj (50 mg/inj), Column Chiral pack IC (30 × 250 mm, 5u), Mobile phase A: 0.10% TFA in hexane, Mobile phase B: Ethanol:Methanol (1:1), Eluent A: B: 80-20, Total Flow rate (mL/min) 46, Diluent MP+DCM-MEOH, Mobile Phase Detection 330 nm.

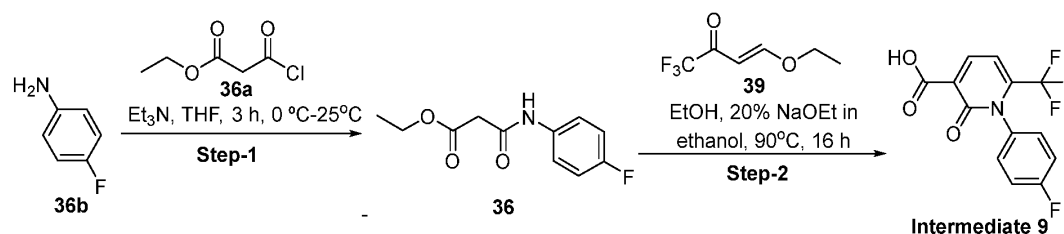
[0747] 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 8A]:

[0748] Chiral separation resulted in 670 mg of Pure Intermediate 8A. ¹H NMR (400 MHz, DMSO-d₆): δ 8.44 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.81 (s, 3H), 1.98 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄+H]⁺: 328.1, found: 327.9, *t*_R = 4.35 min, [Method W]. Chiral HPLC purity: 99.67%, *t*_R = 9.86 min, ee = 99.40%. Specific optical rotation (SOR): 127.68, Method: Light Source WI, Monitor wavelength 589 nm, D.I.T. 5 sec, No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture (L) Auto, Mode Specific O.R, Path Length 50 mm, Concentration 0.05 w/v%.

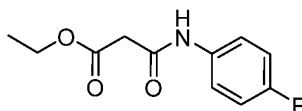
[0749] 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 8B]:

[0750] Chiral separation resulted in 760 mg of Intermediate 8B. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.44 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.81 (s, 3H), 1.98 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄+H]⁺: 328.1, found: 328.2, *t*_R = 3.50 min, [Method V]. Chiral HPLC purity: 97.27%, *t*_R = 11.37, ee = 94.54%. Specific optical rotation (SOR): -91.32, Method: Light Source WI, Monitor wavelength 589 nm, D.I.T. 5 sec, No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture (L) Auto, Mode Specific O.R, Path Length 50 mm, Concentration 0.05 w/v%.

[0751] Synthesis of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 9]:



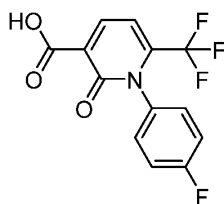
[0752] Synthesis of ethyl 3-(4-fluorophenyl)-3-oxopropanoate [36]:



[0753] A stirred solution of 4-fluoroaniline (43 mL, 450 mmol, 1.00 eq) in THF (550 mL, 0.8181 M) was cooled 0 °C and charged with triethylamine (188 mL, 1350 mmol, 3.00 eq) stirred for 10 min at 0 °C then charged with ethyl 3-chloro-3-oxopropanoate (69 mL, 540 mmol, 1.20 eq) and the resulting reaction mixture was stirred at rt for 1 hour. The reaction mixture was

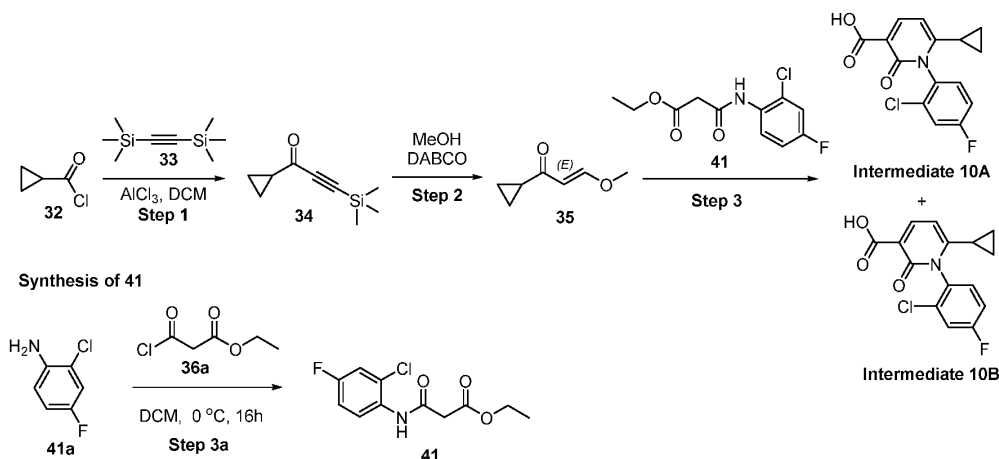
diluted with water and extracted with ethyl acetate and separated. The combined organic layers were washed with brine solution and separated and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated at a reduce pressure to get crude product. The crude product was purified by silica gel column chromatography, using 10-15% ethyl acetate-hexane as a gradient, to afford 23.00 g, 15.66% yield of the titled compound as a pale yellow solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₁H₁₂FNO₃+H]⁺: 226.22, found: 226.0, *t*_R= 1.66 min, [Method N].

[0754] Synthesis of 1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 9]:

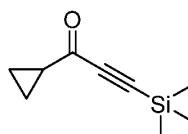


[0755] A stirred solution of ethyl 3-(4-fluoroanilino)-3-oxo-propanoate (12.00 g, 36.8 mmol, 1.00 eq) in ethanol (120 mL, 0.3064 M) at rt was charged with (*E*)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (7.9 mL, 55.1 mmol, 1.50 eq) followed by the addition of 20% sodium ethoxide (43 mL, 110 mmol, 3.00 eq) and the reaction mixture was then stirred for 16 h, at 90 °C. The reaction mixture was concentrated under reduced pressure, diluted with water and the pH was adjusted to 2-3 using 2 N HCl and extracted with ethyl acetate (2 × 120 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain crude product which was then recrystallized with 2-propanol (2 × 50 mL) to afford 4.10 g, 35.44% yield of the titled compound as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.60 (br s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 7.58 - 7.52 (m, 2H), 7.45 - 7.37 (m, 2H), 7.24 (d, *J* = 7.5 Hz, 1H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₃H₇F₄NO₃+H]⁺: 302.04, found: 301.9, *t*_R= 1.84 min, [Method N].

[0756] Synthesis of 1-(2-chloro-4-fluorophenyl)-6-cyclopropyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid [Intermediate 10A & Intermediate 10B mixture]:

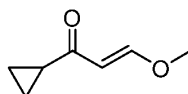


[0757] Synthesis of 1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one [34]:



[0758] A stirred solution trimethyl(2-trimethylsilyl)ethynyl)silane (62 mL, 287 mmol, 1.20 eq) in DCM (500 mL, 0.4783 M) was cooled 0 °C and charged with cyclopropanecarbonyl chloride (22 mL, 239 mmol, 1.00 eq) and aluminium chloride (38.26 g, 287 mmol, 1.20 eq) and stirred at 0 °C for 2 hours, then allowed warmed to rt and stirred for an additional 16 hours. The reaction mixture was poured into a solution of 10% hydrochloric acid in ice-water (300 mL) and stirred for 20 minutes. The aqueous phase was extracted with dichloromethane (2 x 200 mL) and separated. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford 35 g, 83.86% yield of the titled compound as brown oil. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₉H₁₄OSi+H]⁺: 167.29, found: 167.0, *t_R* = 2.08 min, [Method N].

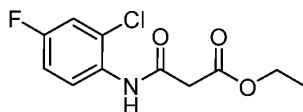
[0759] Synthesis of (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one [35]:



[0760] A stirred solution of 1-cyclopropyl-3-trimethylsilyl-prop-2-yn-1-one (35.00 g, 210 mmol, 1.00 eq) in methanol (350 mL, 0.6014 M) at rt was slowly charged with 1,4-Diazabicyclo [2.2.2]octane (35.41 g, 316 mmol, 1.50 eq) and stirred at rt for 16 h. After completion, reaction mixture was concentrated, and diluted with ethyl acetate (300 mL), washed with saturated brine (2 x 100 mL), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude compound was purified by combi flash using YMC 80 g cartridge, eluting with 0-20% ethyl acetate/heptane to afford 16.00 g, 57.00% yield of title compound as brown liquid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.59 (d, *J* = 12.6 Hz, 1H), 5.62 (d, *J* = 12.6 Hz, 1H), 3.56 (s,

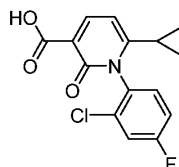
3H), 2.03 - 1.96 (m, 1H), 0.69 - 0.63 (m, 4H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₇H₁₀O₂+H]⁺: 127.07, found: 127.0, *t*_R = 1.46 min, [Method N].

[0761] Synthesis of ethyl 3-(2-chloro-4-fluoro-anilino)-3-oxo-propanoate [41]:



[0762] A stirred solution of 2-chloro-4-fluoroaniline (15 mL, 124 mmol, 1.00 eq) in THF (150 mL, 0.8244 M) was cooled to 0 °C then charged with triethylamine (52 mL, 371 mmol, 3.00 eq) and was stirred at 0 °C for 10 min. Then charged with ethyl 3-chloro-3-oxo-propanoate (24 mL, 185 mmol, 1.50 eq) at 0 °C and the resulting reaction mixture was stirred at rt for 1 hour. After completion of reaction, the mixture was diluted by solution of Na₂CO₃ (100 mL) and extracted by ethyl acetate (2 × 100 L). The combined organic layers were washed with brine (100 L), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude product. The crude product was purified by silica gel column chromatography, eluted at 5-10% ethyl acetate-hexane, to afford 15.00 g, 43.68% yield of the title compound as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.83 (s, 1H), 7.73 (dd, *J* = 5.5, 9.0 Hz, 1H), 7.51 (dd, *J* = 3.0, 8.5 Hz, 1H), 7.28 - 7.20 (m, 1H), 4.17 - 4.07 (m, 2H), 3.54 (s, 2H), 1.21 (t, *J* = 7.3 Hz, 3H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₁H₁₁ClFNO₃]⁺: 259.6, found: 259.9, *t*_R = 1.80 min, [Method N].

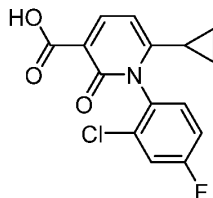
[0763] Synthesis of 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 10A & 10B mixture]:



[0764] A stirred solution of ethyl 3-(2-chloro-4-fluoro-anilino)-3-oxo-propanoate (13.00 g, 50.1 mmol, 1.00 eq) in ethanol (130 mL, 0.3851 M) at rt was charged with (*E*)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (9.47 g, 75.1 mmol, 1.50 eq) and 20% sodium ethoxide in ethanol (97 mL, 250 mmol, 5.00 eq) and the reaction mixture was stirred for 48 h at 50 °C. The reaction mixture was cooled to 0 °C and acidified to pH 1-2 with 2N HCl (100 mL). The resulting precipitate was filtered, washed with water (20 mL), and then dried under reduced pressure to obtain crude product. The crude compound was washed with IPA (2 x 30 mL) to afford 8.50 g, 52.04% yield of a mixture of Intermediate 10A & Intermediate 10B as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.83 (s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 7.85 - 7.82 (m, 1H), 7.81 - 7.78 (m, 1H), 7.54 - 7.49 (m, *J* = 8.5, 8.5 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 1.38 - 1.30 (m,

1H), 0.95 - 0.85 (m, 4H); MS (ES)⁺ m/z calc'd for [M+H]⁺ [C₁₅H₁₁ClFNO₃+H]⁺: 308.04, found: 307.9, *t*_R = 4.20 min, [Method W].

[0765] Purification of 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 10A and Intermediate 10B mixture]:



[0766] A mixture of Intermediate 10A and Intermediate 10B (8.5g) was separated by chiral SFC (instrument name: waters-2767, prep-SFC 100) method to afford 2.95 g of Intermediate 10A as an off-white solid and 3.1 g of Intermediate 10B. SFC purification method: No. of Injections 85 inj (100 mg/inj) Column Chiral pack IC (30 × 250mm, 5u), Mobile phase A: n-Hexane, Mobile phase B: ETOH:MEOH (1:1), Eluent A:B: 50-50, Total Flow rate (mL/min) 45 Diluent DCM:MEOH(1:1), Detection 330 nm.

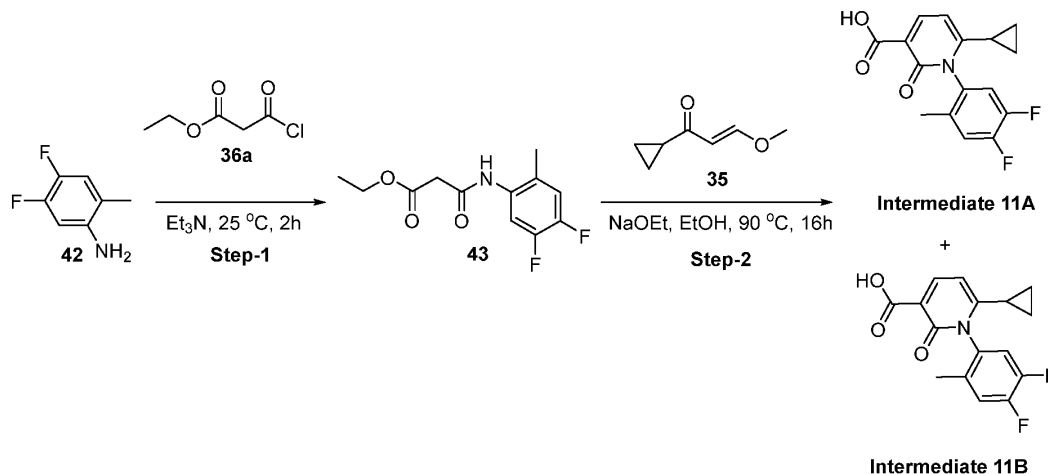
[0767] 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid

[Intermediate 10A]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.41 (d, *J* = 8.0 Hz, 1H), 7.85 - 7.78 (m, 2H), 7.55 - 7.49 (m, *J* = 8.5, 8.5 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 1.40 - 1.28 (m, 1H), 0.97 - 0.85 (m, 4H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₁₁ClFNO₃+H]⁺: 308.81, found: 307.9, *t*_R = 4.20, [Method O]. Chiral HPLC purity: 99.51%, *t*_R = 10.96 min, ee = 99.02%. Specific Optical Rotation (SOR): 156.96, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

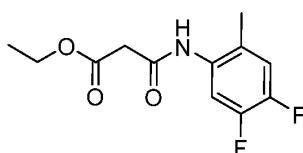
[0768] 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid

[Intermediate 10B]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.41 (d, *J* = 8.0 Hz, 1H), 7.86 - 7.77 (m, 2H), 7.55 - 7.49 (m, *J* = 8.6, 8.6 Hz, 1H), 6.57 (d, *J* = 7.5 Hz, 1H), 1.38 - 1.29 (m, 1H), 0.98 - 0.83 (m, 4H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₁₁ClFNO₃+H]⁺: 308.04, found: 307.9, *t*_R = 4.20 min, [Method O]. Chiral HPLC purity: 99.95%, *t*_R = 14.721 min, ee = 99.90%. Specific Optical Rotation (SOR): -136.800, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

[0769] Synthesis of 6-cyclopropyl-1-(4,5-difluoro-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid [Intermediate 11A and Intermediate 11B mixture]:

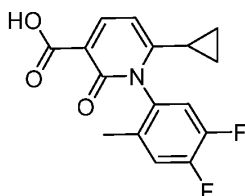


[0770] Synthesis of ethyl 3-(4,5-difluoro-2-methyl-anilino)-3-oxo-propanoate [43]:



[0771] A stirred solution of 4,5-difluoro-2-methyl-aniline (4.4 mL, 34.9 mmol, 1.00 eq) in THF (50 mL, 0.6986 M) was cooled to 0 °C and charged with triethylamine (15 mL, 105 mmol, 3.00 eq) followed by the addition of ethyl 3-chloro-3-oxopropanoate (6.3 mL, 41.9 mmol, 1.20 eq). The reaction mixture was allowed to warm to rt and stirred for 2 h. The resulting mixture was poured into ethyl acetate (500 mL) and washed with saturated sodium bicarbonate (100 mL) and water (2x100 mL), dried over sodium sulfate filtered, and concentrated under reduced pressure to give crude product. The crude compound was purified by combi flash using YMC 40 g cartridge, eluting with 0-70% Ethyl acetate/Heptane to give pure product which was further washed with diethyl ether (50 mL) to afford 5.00 g, 55.38% yield of the titled compound as an off white solid. ¹H NMR (400 MHz, CHLOROFORM-*d*): δ 9.43 (br s, 1H), 7.98 (dd, *J* = 7.9, 12.0 Hz, 1H), 7.01 - 6.92 (m, 1H), 4.32 - 4.22 (m, 2H), 3.49 (s, 2H), 2.27 (s, 3H), 1.33 (t, *J* = 7.0 Hz, 3H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₂H₁₃F₂NO₃+H]⁺:258.15.05, found: 257.9, *t_R* = 1.62 min. [Method N].

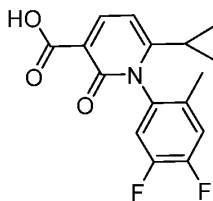
[0772] Synthesis of 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 11A & Intermediate 11B mixture]:



[0773] A stirred solution of (*E*)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (2.16 g, 17.1 mmol, 1.10 eq) in ethanol (40 mL, 2.2214 M) at rt was charged with ethyl 3-(4,5-difluoro-2-

methyl-anilino)-3-oxo-propanoate (4.00 g, 15.5 mmol, 1.00 eq) and 20% sodium ethoxide in ethanol (10.58 g, 31.1 mmol, 2.00 eq) then heated to 90 °C for 72 h, at 90 °C. The reaction mixture was allowed to cool to rt and solvent was evaporated under reduced pressure to give crude product. The crude was dissolved in water (100 mL), and the aqueous layer was washed with diethyl ether (3x20 mL). The combined organic layers were washed with water (10 mL) and the combined aqueous layer was acidified to pH 1-2 using a solution of 1N HCl (25 mL). The product was extracted in ethyl acetate (50 mL × 2), dried over sodium sulfate, filtered and concentrated under reduced pressure to give crude product. Crude product was purified using combi-flash column chromatography using 40g sepa-flash column and product eluted in 75% ethyl acetate in heptane to give pure product as yellow solid which and washed with Acetonitrile (10 mL) to afford 3.30 g, 68.36% yield of a mixture of Intermediate 11A and Intermediate 11B as a yellow solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₆H₁₃F₂NO₃+H]⁺: 306.18, found: 306.0, *t*_R= 1.80 min, [Method N].

[0774] Purification of 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 11A and Intermediate 11B mixture]:



[0775] 3.3 g mixture of Intermediate 11A and Intermediate 11B was separated was separated by preparative np-chiral prep meth SFC Purification Method: No. of injections 40 inj (25 mg/inj) Column chiralpak IK (30 × 250 mm, 5u), Mobile phase A: EtOH:MeOH (1:1), Mobile phase B: ACN, Eluent A:B-80-20, Total flow rate (mL/min) 42 Diluent MP Detection 335 nm; Nature - Off-white solid to afford 1.10 g of Intermediate 11A as an off white solid and 1.2 g of Intermediate 11B as an off white solid

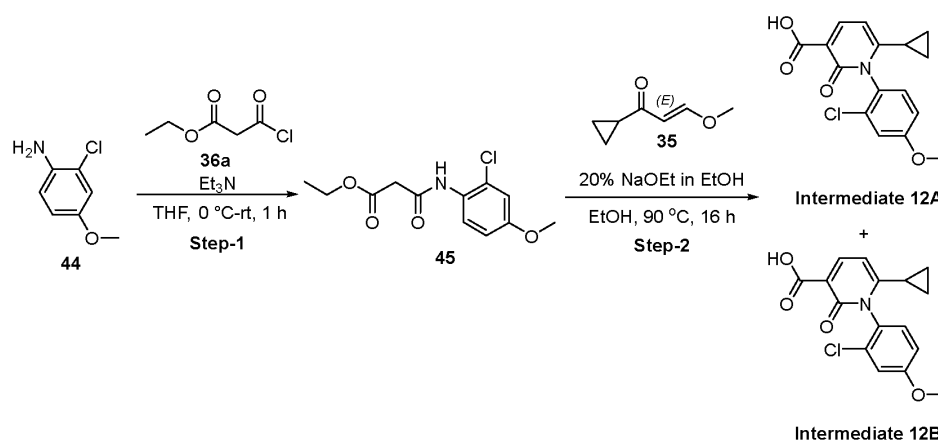
[0776] 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 11A]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.99 (s, 1H), 8.39 (d, *J* = 8.0 Hz, 1H), 7.75 (dd, *J* = 7.8, 11.0 Hz, 1H), 7.64 (dd, *J* = 8.6, 11.4 Hz, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 2.00 (s, 3H), 1.40 - 1.30 (m, 1H), 1.02 - 0.87 (m, 4H); MS (ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₃F₂NO₃+H]⁺: 306.09, found: 305.9, *t*_R= 4.23 min, [Method W]. Chiral HPLC: ee: 100%, Method file: Chiral_met -VIB_B 1mL.lcm, Column: CHIRALPAK IK (250 × 4.6mm, 5μm), Mobile Phase A: EtOH:MeOH, Mobile Phase B: ACN, A/B: 80:20, Flow: 1.5 mL/min. Specific Optical Rotation (SOR): 64.08, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. corr. factor None

Aperture(s) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

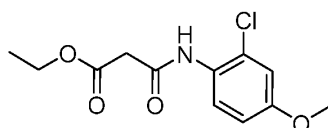
[0777] 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid

[Intermediate 11B]: ^1H NMR (400 MHz, DMSO- d_6): δ 13.99 (br s, 1H), 8.39 (d, $J = 7.5$ Hz, 1H), 7.75 (dd, $J = 7.5, 11.0$ Hz, 1H), 7.64 (dd, $J = 9.0, 11.5$ Hz, 1H), 6.54 (d, $J = 7.5$ Hz, 1H), 1.99 (s, 3H), 1.43 - 1.31 (m, 1H), 0.99 - 0.86 (m, 4H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{13}\text{F}_2\text{NO}_3+\text{H}]^+$: 306.09, found: 305.9, $t_R = 1.80$ min, [Method N] Specific Optical Rotation (SOR): -78.68, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. corr. factor None Aperture(s) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

[0778] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 12A and Intermediate 12B mixture]:

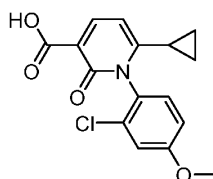


[0779] Synthesis of ethyl 3-(2-chloro-4-methoxy-anilino)-3-oxo-propanoate [45]:



[0780] A stirred solution of 2-chloro-4-methoxy-aniline (3.9 mL, 31.7 mmol, 1.00 eq) in THF (50 mL, 0.6345 M) was cooled to 0 °C and charged with triethylamine (13 mL, 95.2 mmol, 3.00 eq) and was stirred at 0 °C for 10 min, followed by the addition of ethyl 3-chloro-3-oxo-propanoate (4.9 mL, 38.1 mmol, 1.20 eq) at 0 °C and the resulting reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted by water (20 mL), and extracted by ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure get crude product. The crude product was purified by silica gel column chromatography, using 10-15% ethyl acetate-hexane as a gradient, to afford 3.40 g, 38.82% yield of the title compound as a brown solid. MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{14}\text{ClNO}_4+\text{H}]^+$: 272.1, found: 271.9, $t_R = 1.719$ min, [Method N].

[0781] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 12A and Intermediate 12B mixture]:



[0782] A solution of ethyl 3-(2-chloro-4-methoxy-anilino)-3-oxo-propanoate (2 g, 7.21 mmol, 1 eq) in ethanol (20 mL, 0.3607 M) in a seal tube were added (*E*)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (1.11 g, 8.66 mmol, 1.20 eq) and 20% sodium ethoxide in ethanol (14 mL, 36.1 mmol, 5.00 eq) at rt. The reaction mixture was stirred at 90 °C for 16 h. Then, the reaction mixture was concentrated and diluted with water (20 mL) and extracted with ethyl acetate (2 × 40 mL) and separated. The aqueous layer was acidified to pH ~3 using 2N HCl and precipitated solid was filtered to get crude. The crude was triturated with diethyl ether (3 × 20 mL) to afford 1.1 g, 45.38% yield of the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.01 (br s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 2.8 Hz, 1H), 7.15 (dd, *J* = 2.8, 9.0 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 3.87 (s, 3H), 1.39 - 1.31 (m, 1H), 1.01 - 0.83 (m, 4H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₄ClNO₄+H]⁺: 320.01, found: 320.4, *t*_R = 3.256 min, [Method AC].

[0783] Note: Obtained 1.1 g of product was further submitted for prep purification for atropisomer separation.

[0784] Purification of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 12A and Intermediate 12B mixture]:

[0785] 1.1 g of racemic compound was separated by chiral SFC (Instrument name: Waters-2767, PREP-SFC 100). SFC purification Method: No. of Injections 16 inj (68 mg/inj 12 min), Column: Chiral pack IK (20 × 250 mm, 5 u), Mobile phase A: 00.1% of TFA in n-Hexane, Mobile phase B: EtOH:MeOH (1:1), Eluent A:B:-20-80, Total Flow rate (mL/min) 50, Diluent Mobile MP+DCM, Phase Detection 340 nm to afford 530 mg of Intermediate 12A as a brown gummy semi-solid and 525mg of Intermediate 12B as a brown gummy semi-solid.

[0786] 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 12A]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.97 (br s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.35 (d, *J* = 2.5 Hz, 1H), 7.15 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 1.39 - 1.31 (m, 1H), 0.98 - 0.85 (m, 4H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₄ClNO₄+H]⁺: 320.01, found: 319.9, *t*_R = 4.28 min, [Method W]. Chiral HPLC purity: 99.99%, *t*_R = 9.88 min, ee = 99.99%. Specific optical rotation (SOR): 62.64, Method:

Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec
Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto
Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

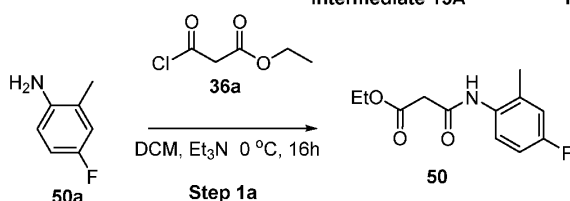
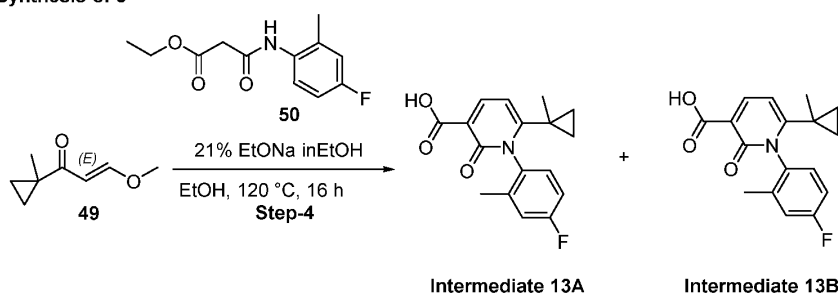
[0787] 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid

[Intermediate 12B]: ^1H NMR (400 MHz, DMSO- d_6): δ 13.93 (br s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 9.0 Hz, 1H), 7.35 (d, J = 2.5 Hz, 1H), 7.15 (dd, J = 2.8, 8.8 Hz, 1H), 6.54 (d, J = 7.5 Hz, 1H), 3.87 (s, 3H), 1.38 - 1.33 (m, 1H), 1.00 - 0.83 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{14}\text{ClNO}_4+\text{H}]^+$: 320.01, found: 319.9, t_R = 4.24 min, [Method W]. Chiral HPLC-Purity: 99.96%, t_R = 14.82 min, ee = 95.96 %. Specific optical rotation (SOR): -102.96, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec
Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto
Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

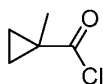
[0788] Synthesis of 1-(4-fluoro-2-methylphenyl)-6-(1-methylcyclopropyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid [Intermediate 13A and Intermediate 13B mixture]:



Synthesis of 5



[0789] Synthesis of 1-methylcyclopropanecarbonyl chloride [47]:

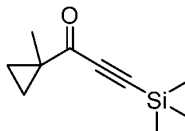


[0790] A suspension of the 1-methylcyclopropanecarboxylic acid (10.00 g, 99.9 mmol, 1.00 eq) and DMF (1 mL, 0.9889 M) in DCM (100 mL, 0.9889 M) was cooled to 0 °C and was dropwise charged with oxalyl chloride (10 mL, 120 mmol, 1.20 eq). The resulting mixture was stirred at rt for 2 h. Excess oxalyl chloride and solvent were removed under reduced pressure (at

< rt) resulting in 11.00 g, 92.89% yield of the title compound as oily compound which was taken to the next step without further purification.

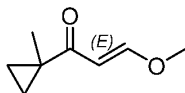
[0791]

Synthesis of 1-(1-methylcyclopropyl)-3-trimethylsilyl-prop-2-yn-1-one [48]:



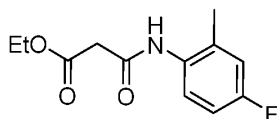
[0792] A solution trimethyl(2-trimethylsilylethynyl)silane (25 mL, 111 mmol, 1.20 eq) in DCM (20 mL, 4.639 M) was cooled to 0 °C and charged with 1-methylcyclopropanecarbonyl chloride (11.00 g, 92.8 mmol, 1.00 eq) followed by the slow addition of aluminum chloride (14.84 g, 111 mmol, 1.20 eq). The reaction mixture was stirred at 0 °C for 2 h then allowed to warm to rt and stirred for another 16 h. The reaction mixture was poured in to a 10% HCl (300 mL) solution in ice water and stirred for 10 min. After the two phases were separated, the aqueous phase was extracted three times with DCM (500 mL × 2), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to afford 16.00 g, 87.03% yield of the title compound as a brown oil product, which was directly used in the next step of reaction. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₀H₁₆OSi+H]⁺: 180.32, found: 181.1, [Method N].

[0793] **Synthesis of (E)-3-methoxy-1-(1-methylcyclopropyl)prop-2-en-1-one [49]:**



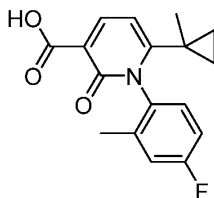
[0794] A solution of 1-(1-methylcyclopropyl)-3-trimethylsilyl-prop-2-yn-1-one (17.58 g, 88.7 mmol, 1.00 eq) in methanol (160 mL, 0.5546 M) was cooled to 0 °C then slowly charged with DABCO (14.93 g, 133 mmol, 1.50 eq) the reaction mixture was stirred for 2 h. After 2 h reaction mixture was concentrated under reduced pressure. The crude compound was purified by combi flash using YMC 40 g cartridge, eluting with 0-10% ethyl acetate/heptane to afford 4.70 g, 34.01% yield of the titled compound as a brown liquid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.50 (d, *J* = 12.0 Hz, 1H), 5.76 (d, *J* = 12.0 Hz, 1H), 3.70 (s, 3H), 1.25 (s, 3H), 1.16 - 1.12 (m, 2H), 0.76 - 0.70 (m, 2H); MS (ES)⁺ m/z calc'd for [M+H]⁺ [C₈H₁₂O₂+H]⁺: 140.18, found: 141.1, *t*_R = 1.60 min, [Method N].

[0795] **Synthesis of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate [50]:**



[0796] A stirred solution of 4-fluoro-2-methyl-aniline (22 mL, 200 mmol, 1.00 eq) in DCM (500 mL, 0.3995 M) was cooled to 0 °C then charged with triethylamine (83 mL, 599 mmol, 3.00 eq). After 10 min reaction was charged with ethyl 3-chloro-3-oxo-propanoate (30 mL, 240 mmol, 1.20 eq) the reaction mixture was stirred for 3 h, at rt. The reaction mixture was poured into ice water (400 mL), extracted with DCM (2 × 500 mL) and the combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude was purified by combi flash using 120 g column cartridge, eluting with 30-40% ethyl acetate in heptane to afford 22.00 g, 45.94% yield of the title compound as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.55 (s, 1H), 7.37 - 7.33 (m, 1H), 7.10 - 7.07 (m, 1H), 7.02 - 6.97 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.46 (s, 2H), 2.20 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₂H₁₄FNO₃]⁺: 239.2, found: 240.0, *t*_R = 3.78 min, [Method W].

[0797] Synthesis of 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 13A and Intermediate 13B mixture]:



[0798] A stirred solution of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate (1.70 g, 7.11 mmol, 1.00 eq) in ethanol (5 mL, 1.42 M) was charged 21% sodium ethoxide in ethanol (5.4 mL, 14.2 mmol, 2.00 eq) and the mixture was stirred at 120 °C for 90 h. The reaction solution was concentrated under reduced pressure and the crude was diluted with water (200 mL) and cooled to 0 °C acidified to pH 4-5 with 1N HCl (20 mL). The aqueous was extracted with ethyl acetate (3 × 100 mL) and separated, the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get crude. The crude compound was purified by combi flash using 40 g column cartridge, eluting with 50-60% ethyl acetate in heptane afford 600 mg, 27.45% yield of Intermediate 13A and Intermediate 13B mixture as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.18 (br s, 1H), 8.45 (d, *J* = 7.5 Hz, 1H), 7.58 (dd, *J* = 5.3, 8.8 Hz, 1H), 7.34 (dd, *J* = 3.0, 9.5 Hz, 1H), 7.28 - 7.23 (m, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 1.99 (s, 3H), 1.08 - 1.05 (m, 1H), 0.97 - 0.92 (m, 4H), 0.54 - 0.52 (m, 2H); MS(ES)⁺ *m/z* calc'd for [M+H]⁺ [C₁₇H₁₆FNO₃+H]⁺: 301.32, found: 301.9, *t*_R = 1.86 min, [Method N].

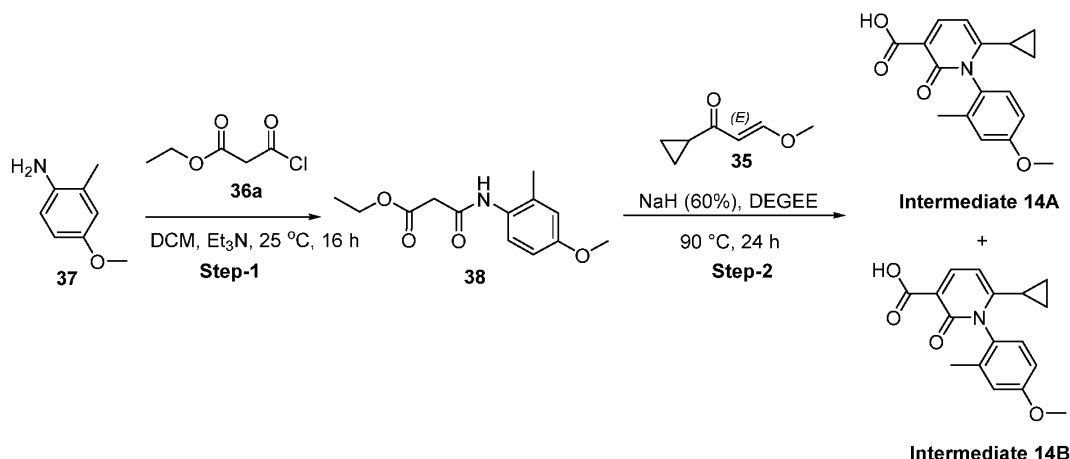
[0799] Chiral separation of 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 13A and Intermediate 13B mixture]:

[0800] 2.0 g of Intermediate 13A and Intermediate 13B mixture was separated by Chiral Preparative SFC Method. SFC purification method: No. of Injections 32 inj (60 mg/inj) Column Chiral Pak IK (30 × 250 mm, 5u), Mobile phase A: 0.1% TFA in n-Hexane, Mobile Phase B: EtOH:MeOH (1:1), Total Flow rate 1.0 mL/min, Detection 340 nm resulting in 560 mg of Intermediate 13A and 880 mg of Intermediate 13B as a light yellow solid recovered of P1 = 560 mg.

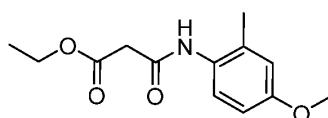
[0801] 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 13A]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.18 (br s, 1H), 8.45 (d, *J* = 7.5 Hz, 1H), 7.58 (dd, *J* = 5.5, 8.8 Hz, 1H), 7.34 (dd, *J* = 2.8, 9.5 Hz, 1H), 7.31 - 7.21 (m, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 1.99 (s, 3H), 1.10 - 1.00 (m, 1H), 0.96 (s, 3H), 0.95 - 0.90 (m, 1H), 0.57 - 0.48 (m, 2H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₇H₁₆FNO₃+H]⁺: 301.32, found: 301.9, *t*_R = 4.389, [Method W]. Chiral HPLC-Purity: 99.6%, *t*_R = 9.06 min, ee = 99.2 %. Specific Optical Rotation (SOR): 141.6800, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. corr. factor 0 at 20 C Aperture(s) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

[0802] 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 13B]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 14.18 (br s, 1H), 8.45 (d, *J* = 7.5 Hz, 1H), 7.59 (dd, *J* = 5.5, 8.8 Hz, 1H), 7.34 (dd, *J* = 2.8, 9.5 Hz, 1H), 7.29 - 7.23 (m, 1H), 6.87 (d, *J* = 7.5 Hz, 1H), 1.99 (s, 3H), 1.09 - 1.03 (m, 1H), 0.96 (s, 3H), 0.95 - 0.90 (m, 1H), 0.57 - 0.49 (m, 2H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₇H₁₆FNO₃+H]⁺: 301.32, found: 301.9, *t*_R = 4.392 min, [Method W]. Chiral HPLC-Purity: 99.69 %, *t*_R = 11.354 min, ee = 99.38%. Specific Optical Rotation (SOR): -148.2400, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%.

[0803] Synthesis of 6-cyclopropyl-1-(4-methoxy-2-methylphenyl)-2-oxo-1,2-dihydropyridine-3-carboxylic acid [Intermediate 14A and Intermediate 14B mixture]:

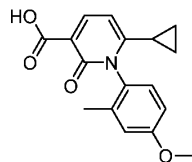


[0804] Synthesis of ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxopropanoate [38]:



[0805] A solution of 4-methoxy-2-methyl-aniline (5.00 g, 36.4 mmol, 1.00 eq) in DCM (50 mL, 0.729 M) at rt was charged with TEA (13 mL, 91.1 mmol, 2.50 eq) followed by dropwise addition of ethyl 3-chloro-3-oxopropanoate (6.1 mL, 47.4 mmol, 1.30 eq) mixture was stirred at rt for 16 h. The reaction mixture was diluted with DCM (100 mL) and washed with water (100 mL $\times$ 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to dryness at reduced pressure. The crude was then purified by triturating with diethyl ether (100 mL) and pentane (100 mL) to afford 5.50 g, 51.49% yield of the title compound as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ 9.42 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 6.79 (d, J = 2.9 Hz, 1H), 6.73 (dd, J = 2.9, 8.8 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.72 (s, 3H), 3.42 (s, 2H), 2.16 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H), MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{13}\text{H}_{17}\text{NO}_4+\text{H}]^+$: 252.28, found: 252.0, t_R = 1.60 min, [Method N].

[0806] Synthesis of 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 14A and Intermediate 14B mixture]:



[0807] A suspension of sodium hydride (60%) (1.03 g, 25.7 mmol, 1.50 eq) in diethylene glycol monoethyl ether (20 mL, 17.1 mmol, 1.00 eq) was charged with ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxopropanoate (4.30 g, 17.1 mmol, 1.00 eq) and (*E*)-1-cyclopropyl-3-methoxyprop-2-en-1-one (3.24 g, 25.7 mmol, 1.50 eq) and stirred at 90 °C for 24 h. The

reaction was not complete after 24 h so it was heated for an additional 48 h. Volatiles were removed under reduced pressure and diluted into water and extracted with diethyl ether (30 mL $\times$ 3). The aqueous layer was acidified with 3 N HCl and extracted with ethyl acetate (3 $\times$ 30 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to get crude. Crude was purified by flash column chromatography eluting with 30% ethyl acetate: Heptane as an eluent to afford 800 mg, 15.53% yield a mixture of Intermediate 14A and Intermediate 14B as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6): δ 14.27 (br s, 1H), 8.34 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 7.03 - 6.89 (m, 2H), 6.46 (d, J = 7.5 Hz, 1H), 3.78 (s, 3H), 1.95 (s, 3H), 1.32 - 1.25 (m, 1H), 0.95 - 0.86 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{17}\text{NO}_4+\text{H}]^+$: 300.33, found: 299.90, t_R = 1.77 min, [Method N].

[0808] Separation of 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 14A and Intermediate 14B mixture]:

[0809] The mixture of Intermediate 14A and Intermediate 14B (0.800 g) was separated by preparative np-chiral prep method to afford 320 mg of Intermediate 14A and 290 mg of Intermediate 14B of the titled compound as a pale yellow solid. Chiral purification method: No. of Injections 16 inj (50 mg/inj /7 min) Column IK (30 $\times$ 250 mm, 5 μ), Mobile phase A: 0.1% TFA in EtOH, Mobile phase B: MeOH (50:50), Eluent A:B: 0-100, Total Flow rate: 55 mL/min, Diluent MP Detection 345 nm.

[0810] 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid

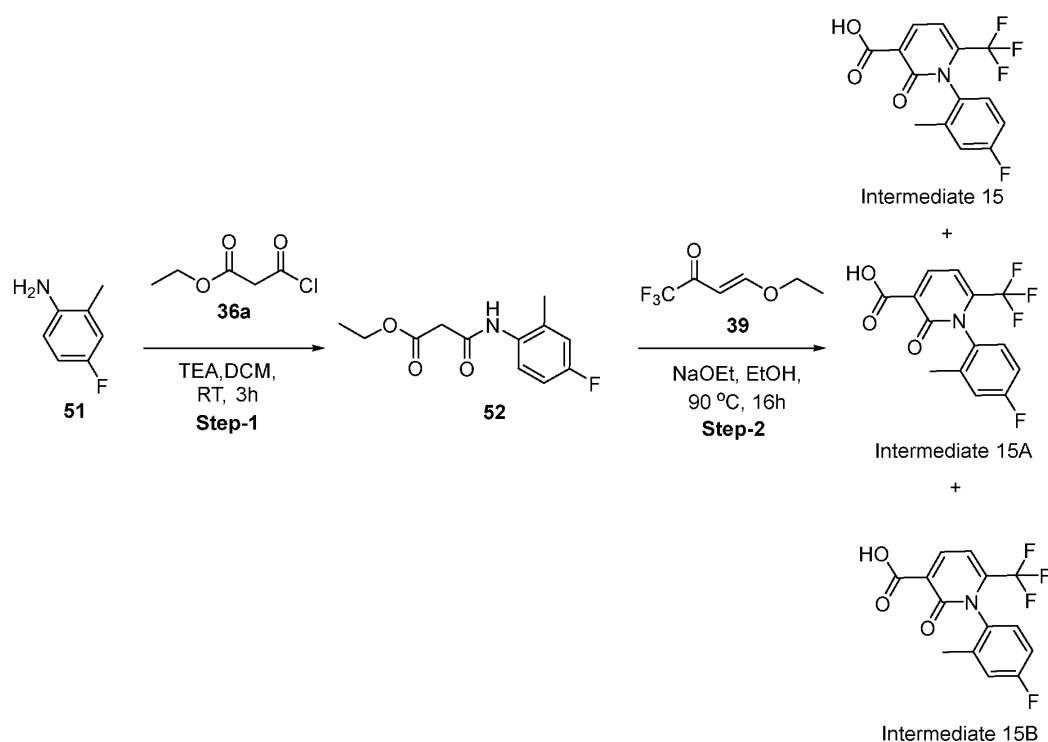
[Intermediate 14A]: ^1H NMR (400 MHz, DMSO- d_6): δ 14.30 (br s, 1H), 8.37 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.04 (s, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 7.6 Hz, 1H), 3.82 (s, 3H), 1.99 (s, 3H), 1.40 - 1.24 (m, 1H), 1.04 - 0.85 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{17}\text{H}_{17}\text{NO}_4+\text{H}]^+$: 300.33, found: 300.04, t_R = 4.349 min, [Method W]. Chiral HPLC purity: 99.99%, t_R = 8.540 min, ee = 99.98%, Method: Column: CHIRALPAK IK (250 $\times$ 4.6 mm, 5 μ m), Mobile Phase A: EtOH:MeOH (1:1), Mobile Phase B: ACN, A/B: 80:20 Flow: 1.0 mL/min, COLUMN ID:M-ARD-CAL/OLD-028. Specific Optical Rotation (SOR): 88.4400, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[0811] 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 14B]:

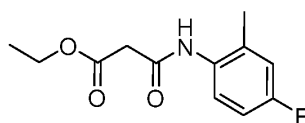
^1H NMR (400 MHz, DMSO- d_6): δ 14.32 (br s, 1H), 8.37 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.04 (d, J = 2.9 Hz, 1H), 6.96 (dd, J = 2.8, 8.7 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 1.98 (s, 3H), 1.36 - 1.28 (m, 1H), 1.00 - 0.87 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$

[C₁₇H₁₇NO₄+H]⁺: 300.33, found: 300.04, *t_R* = 4.348 min, [Method W]. Chiral HPLC purity: 98.90%, *t_R* = 12.830, ee = 97.80%, Method: Column: CHIRALPAK IK (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH:MeOH (1:1), Mobile Phase B: ACN, A/B: 80:20, Flow: 1.0 mL/min, COLUMN ID: M-ARD-CAL/OLD-028. Specific Optical Rotation (SOR): -67.0400, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[0812] Synthesis of 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 15 mixture]:



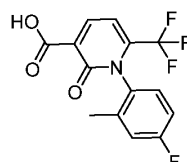
[0813] Synthesis of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate [52]:



[0814] A stirred solution of 4-fluoro-2-methyl-aniline (22 mL, 200 mmol, 1.00 eq) in DCM (200 mL, 0.9988 M) was cooled to 0 °C then charged with triethylamine (86 mL, 599 mmol, 3.00 eq) and ethyl 3-chloro-3-oxo-propanoate (36 mL, 240 mmol, 1.20 eq). Reaction mixture was allowed to warm to rt and stirred for 3 hours. The reaction was then concentrated under reduced pressure and the residue was dissolved in DCM (2 x 200 mL) and the organics were washed with water (100 mL) then saturated brine solution (100 mL). The combined organic

layers were dried over anhydrous sodium sulfate, filtered, and concentrated to obtain crude, which was purified by combi flash using YMC 120 g cartridge, eluting with 0-30% ethyl acetate/heptane to afford 14.0 g, 27.79% yield of the titled compound as an off-white solid. MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₁₂H₁₄FNO₃+H]⁺: 240.10, found: 240.0, *t*_R= 1.70 min, [Method N].

[0815] Synthesis of 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 15]:



[0816] A stirred solution of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate (13.00 g, 53.0 mmol, 1.00 eq) in ethanol (130 mL, 0.4079 M) at rt was charged with (*E*)-4-Ethoxy-1,1,1-trifluorobut-3-en-2-one (10.70 g, 63.6 mmol, 1.20 eq) and 20% sodium ethoxide in ethanol (62 mL, 159 mmol, 3.00 eq) and reaction mixture was heated to 90 °C for 16 h. After completion of reaction, reaction was concentrated to dryness to get crude. The crude was acidified with 2N HCl solution (50 mL), and then reaction mixture was extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with water (50 mL), then saturated brine solution (50 mL) and separated. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to get crude. The crude was triturated with IPA (2 x 20 mL) to afford 4.20 g, 24.49% yield of a mixture of Intermediate 15A and Intermediate 15B as an off-white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 13.51 (s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 7.50 - 7.43 (m, 1H), 7.35 - 7.30 (m, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.25 - 7.19 (m, 1H), 2.02 (s, 3H); MS (ES)⁺ m/z calc'd for [M+H]⁺ [C₁₄H₉F₄NO₃+H]⁺: 316.05, found: 315.80, *t*_R= 4.40 min, [Method Q].

[0817] The Intermediate 15 atropisomer mixture (8.8 g) was separated by chiral SFC (instrument name: waters-2767, prep-sfc 100) method to afford 4 g of Intermediate 15A and 4 g of Intermediate 15B of the titled compound as a pale brown sticky semi solid. SFC purification method: No Of Injections 30 (300 mg/ inj / 5.2 min) Column Chiralpak IK (30X250mm,5μ) Co-Solvent % 20% (0.1 % FA in IPA+ACN) Total Flow rate (mL/min) 90g-20%-100 Bar Diluent MP Detection 330 nm

[0818] 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 15A]:

[0819] ¹H NMR (400 MHz, DMSO-d₆): δ 13.43 (s, 1H), 8.40 (d, *J* = 7.3 Hz, 1H), 7.46 (dd, *J* = 5.7, 7.9 Hz, 1H), 7.33 (dd, *J* = 2.9, 9.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.25 - 7.20 (m, 1H), 2.02 (s, 3H). LCMS: MS (ES)⁺ m/z calc'd for [M+H]⁺ [C₁₄H₉F₄NO₃+H]⁺: 316.05 found 315.9, *t*_R:4.41, Method Details: : Column: X-Select CSH C18, (50mm*3.0mm,2.5μ) Mobile

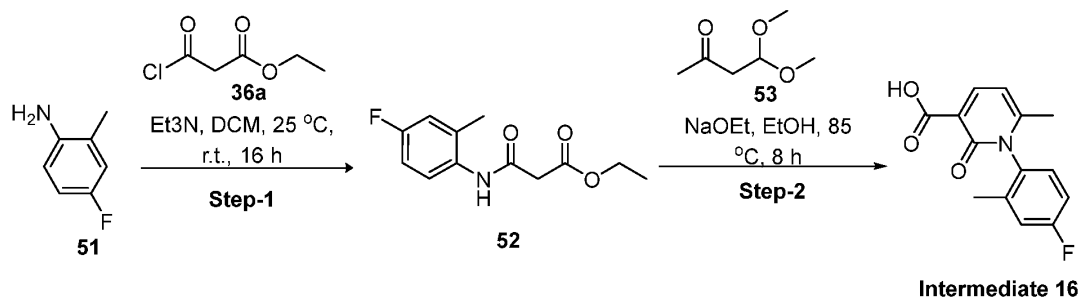
Phase A: 0.05% formic acid in water Mobile Phase B: 0.05% Formic Acid in Acetonitrile Flow rate: 1.0mL/min. Column temperature: 40°C Gradient Program (B%): 0.0/2, 1.5/2, 6.0/98, 8.0/98, 9.0/2, 10.0/2; Chiral HPLC purity: 98.16%, t_R = 6.57 min, ee = 97.51%; Specific Optical Rotation (SOR): 136.000, method: Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.1 w/v%

[0820] 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 15b]:

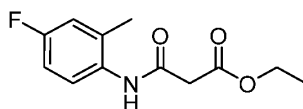
[0821] ^1H NMR (400 MHz, DMSO- d_6): δ 13.48 (s, 1H), 8.41 (d, J = 7.1 Hz, 1H), 7.47 (dd, J = 5.6, 7.8 Hz, 1H), 7.33 (dd, J = 2.9, 9.5 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.25 - 7.22 (m, 1H), 2.02 (s, 3H). LCMS: MS (ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{14}\text{H}_9\text{F}_4\text{NO}_3+\text{H}]^+$: 316.22 found 315.9, t_R : 4.38, Method Details: Column: XSelect CSH-18 (3.0X50mm, 2.5 μm) Mobile Phase: A: 10mM ammonium bicarbonate in water, Mobile Phase: B: MeCN (Gradient) T/B%: 0.0/2, 1/2, 5/98, 8/98, 8.1/2, 10/2. Flow rate: 1.0 ml/min. Column Temp.: 45°C

[0822] Chiral HPLC purity: 98.72%, t_R = 8.495 min, ee = 97.44%; Specific Optical Rotation (SOR): -105.00, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

[0823] Synthesis of 1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 16]:



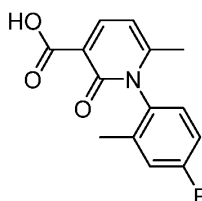
[0824] Synthesis of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate [52]:



[0825] A stirred solution of 4-fluoro-2-methyl-aniline (4.4 mL, 40.0 mmol, 1.00 eq) in DCM (50 mL, 0.799 M) was cooled to 0 °C then charged with TEA (17 mL, 120 mmol, 3.00 eq) followed by the addition of ethyl 3-chloro-3-oxo-propanoate (6.1 mL, 47.9 mmol, 1.20 eq) and was stirred for 16 h, at rt. The reaction mixture was diluted with water and extracted with DCM (70 mL), the combined organic layers were washed with brine solution (100 mL), dried over

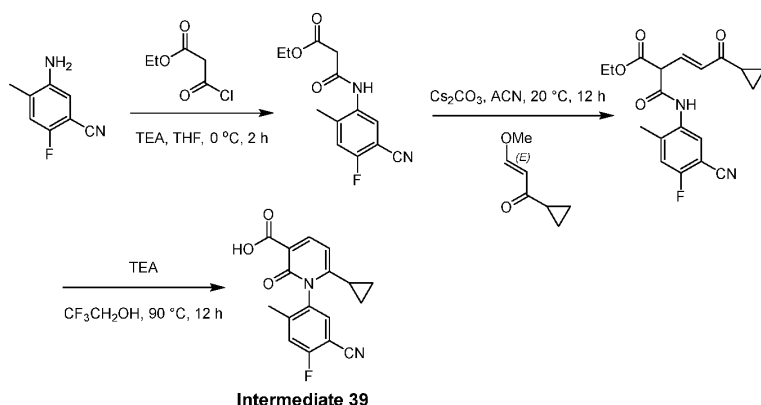
anhydrous sodium sulfate, filtered, and concentrated to get crude. Crude was purified by flash column chromatography eluting 50% ethyl acetate in heptane. The pure fractions were concentrated to afford 5 g, 47.07% yield of the titled compound as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.55 (s, 1H), 7.38 - 7.32 (m, 1H), 7.12 - 7.05 (m, 1H), 7.04 - 6.94 (m, 1H), 4.13 (q, $J = 7.2$ Hz, 2H), 3.46 (s, 2H), 2.20 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{14}\text{FNO}_3+\text{H}]^+$: 240.25, found : 240.00, $t_R = 1.67$ min, [Method W].

[0826] Synthesis of 1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxylic acid [16]:

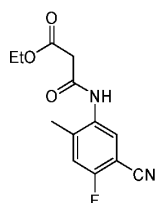


[0827] A stirred solution of ethyl 3-(4-fluoro-2-methyl-anilino)-3-oxo-propanoate (2.00 g, 8.36 mmol, 1.00 eq), 4,4-dimethoxybutan-2-one (1.3 mL, 10.0 mmol, 1.20 eq) in ethanol (10 mL, 0.8359 M) was charged with 20% sodium ethoxide in ethanol (8.53 g, 25.1 mmol, 3.00 eq). The flask was sealed and then heated at 85 °C for 8 hours. The reaction mixture was concentrated, and the residue was dissolved in water (20 mL), washed with ether (2×20 mL), and the aqueous layer was then acidified to pH 3 using 1 N HCl and extracted with EtOAc (3×50 mL) and separated. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness. The crude was purified by titrating with ethyl acetate, (3×20 mL) to afford 900 mg, 40.59% yield of the titled compound as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 14.12 (br s, 1H), 8.44 (d, $J = 7.5$ Hz, 1H), 7.44 (dd, $J = 8.8, 5.5$ Hz, 1H), 7.37 (dd, $J = 9.5, 2.7$ Hz, 1H), 7.27 (td, $J = 8.4, 2.8$ Hz, 1H), 6.84 (d, $J = 7.5$ Hz, 1H), 2.06 (s, 3H), 1.99 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{14}\text{H}_{12}\text{FNO}_3]^+$: 262.25, found: 262.00, $t_R = 1.66$ min, [Method W].

[0828] Synthesis of 1-(5-cyano-4-fluoro-2-methylphenyl)-6-cyclopropyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid [Intermediate 39]:

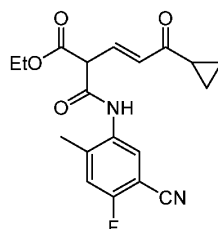


[0829] Synthesis of ethyl 3-(5-cyano-4-fluoro-2-methyl-anilino)-3-oxo-propanoate



[0830] To a solution of 5-amino-2-fluoro-4-methyl-benzonitrile (5.00 g, 33.30 mmol, 1.00 eq) in THF (50 mL) was added TETOAC (10.11 g, 99.90 mmol, 13.90 mL, 3.00 eq) and ethyl 3-chloro-3-oxo-propanoate (10.03 g, 66.60 mmol, 8.38 mL, 2.00 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O 100 mL and then extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine 100 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give residue. The residue was triturated with pet. ether:EtOAc=1:1 (60 mL) and stirred for 12 h. Then filtered and collected the solid to afford ethyl 3-(5-cyano-4-fluoro-2-methyl-anilino)-3-oxo-propanoate (4.00 g, 45.46% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.80 (s, 1 H) 7.89 (d, J=6.38 Hz, 1 H) 7.47 (d, J=10.13 Hz, 1 H) 4.13 (q, J=7.13 Hz, 2 H) 3.51 (s, 2 H) 2.31 (s, 3 H) 1.21 (t, J=7.13 Hz, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₁₃FN₂O₃+H]⁺: 265.09, found: 264.9, *t*_R= 0.402 min.

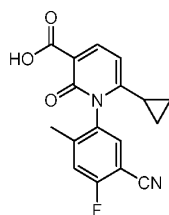
[0831] Synthesis of ethyl (E)-2-[(5-cyano-4-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate



[0832] To a solution of ethyl 3-(5-cyano-4-fluoro-2-methyl-anilino)-3-oxo-propanoate (1.00 g, 3.78 mmol, 1.00 eq) and (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (572.87 mg, 4.54 mmol,

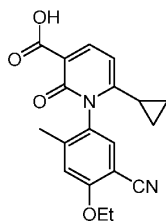
1.20 eq) in MeCN (10 mL) was added Cs₂CO₃ (1.73 g, 5.30 mmol, 1.40 eq). The mixture was stirred at 20 °C for 12 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford ethyl (E)-2-[(5-cyano-4-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate (1.20 g) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₉H₁₉FN₂O₄+H]⁺: 359.13, found: 359.1, *t*_R= 1.097 min.

[0833] Synthesis of 1-(5-cyano-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 39]



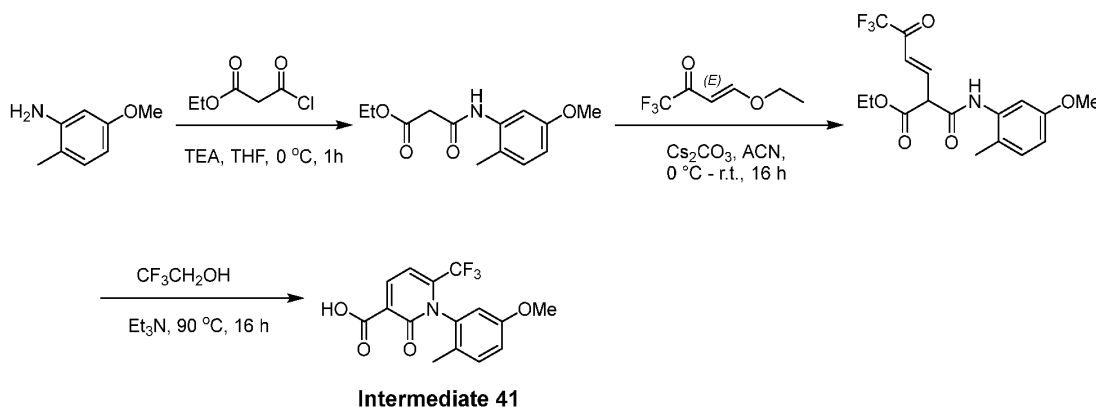
[0834] To a solution of ethyl (E)-2-[(5-cyano-4-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate (1.00 g, 2.79 mmol, 1.00 eq) in CF₃CH₂OH (10 mL) was added TEA (847.10 mg, 8.37 mmol, 1.17 mL, 3.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by H₂O (20 mL) and extracted with EtOAc (3×20 mL), then the aqueous phase was adjusted to PH=2 with 2N HCl. The resulting solution was extracted with EtOAc (2×20 mL). The combined organic layer was washed successively with water (2×20 mL) and brine (20 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-HPLC (Formic acid condition: column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.2% FA)-MeCN]; gradient: 20%-50% B over 8.0 min) to afford 1-(5-cyano-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid (30.00 mg 3.44% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.83 (br s, 1 H) 8.40 (d, J=7.88 Hz, 1 H) 8.18 (d, J=6.25 Hz, 1 H) 7.76 (d, J=10.01 Hz, 1 H) 6.56 (d, J=7.88 Hz, 1 H) 2.12 (s, 3 H) 1.31 - 1.40 (m, 1 H) 0.85 - 0.99 (m, 4 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₃FN₂O₃+H]⁺: 313.09, found: 313.3, *t*_R= 1.578 min.

[0835] Synthesis 1-(5-cyano-4-ethoxy-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 40]:

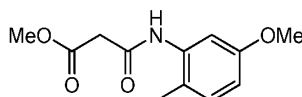
**Intermediate 40**

[0836] To a solution of ethyl 3-(5-cyano-4-fluoro-2-methyl-anilino)-3-oxo-propanoate (500.00 mg, 1.89 mmol, 1.00 eq) and (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (358.05 mg, 2.84 mmol, 1.50 eq) in EtOH (5 mL) was added EtONa (3.22 g, 9.46 mmol, 20% purity, 5.00 eq). The mixture was stirred at 50 °C for 48 h. LCMS showed the reaction was completed. The reaction mixture was cooled to 0 °C and acidified to pH 1-2 with 2N HCl (20 mL) and a lot of solid formed. The solid was filtered and washed with water (20 mL) and then dried to obtain the crude product. The crude was purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:30%-60% B over 8.0 min) to afford 1-(5-cyano-4-ethoxy-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid (200 mg, 31.24% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ14.03 (s, 1 H) 8.39 (d, J=7.88 Hz, 1 H) 7.91 (s, 1 H) 7.39 (s, 1 H) 6.53 (d, J=7.75 Hz, 1 H) 4.22 - 4.32 (m, 2 H) 2.08 (s, 3 H) 1.41 (t, J=6.94 Hz, 3 H) 1.35 (s, 1 H) 0.87 - 0.97 (m, 4 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₉H₁₈O₄N₂+H]⁺: 339.13, found: 339.0, *t*_R= 0.449 min.

[0837] Synthesis of Synthesis of 1-(5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 41]:

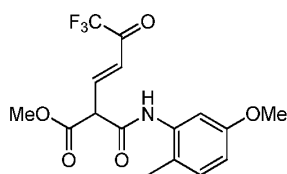
**Intermediate 41**

[0838] Synthesis of methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate



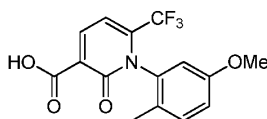
[0839] To a solution of 5-methoxy-2-methyl-aniline (1.00 g, 7.29 mmol, 1.00 eq) in THF (10 mL) was added TEA (2.21 g, 21.87 mmol, 3.04 mL, 3.00 eq) at 0 °C. Then methyl 3-chloro-3-oxo-propanoate (1.49 g, 10.93 mmol, 1.17 mL, 1.50 eq) was added and the mixture was stirred at 0 °C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was poured into H₂O 60 mL and then extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (2×30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=65/35 to 60/40). To afford methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate (0.75 g, 41.20% yield) as a gray solid. MS (ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₅NO₄+H]⁺: 238.10, found: 238.1, *t*_R= 0.384 min.

[0840] Synthesis of methyl (E)-6,6,6-trifluoro-2-[(5-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate



[0841] To a solution of methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate (650.00 mg, 2.60 mmol, 1.00 eq) in MeCN (13 mL) was added Cs₂CO₃ (1.19 g, 3.64 mmol, 1.40 eq) and (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (656.33 mg, 3.90 mmol, 556.21 μL, 1.50 eq) at 0 °C. The mixture was stirred at 25 °C for 16 hours. LCMS showed the reaction was completed. The reaction mixture was poured into 80 mL H₂O, and then extracted by EtOAc (2×30 mL), the combined organic layer was washed with brine (2×30 mL), dried over Na₂SO₄, filtered and concentrated to give the crude methyl (E)-6,6,6-trifluoro-2-[(5-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate (1.20 g) as a brown gum. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₆F₃NO₅+H]⁺: 360.10, found: 360.2, *t*_R= 0.444 min.

[0842] Synthesis of 1-(5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 41]

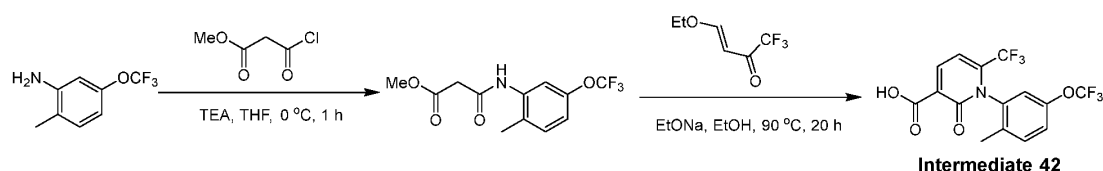


[0843] To a solution of methyl (E)-6,6,6-trifluoro-2-[(5-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate (1.00 g, 2.78 mmol, 1.00 eq) in 2,2,2-TRIFLUOROETHANOL (10 mL) was added TEA (844.90 mg, 8.35 mmol, 1.16 mL, 3.00 eq). The mixture was stirred at 90 °C

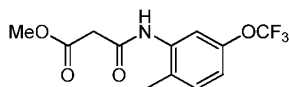
for 16 hours. LCMS showed the reaction was completed. The reaction mixture was poured into 70 mL H₂O, and then adjust to PH= 5~6 with 2N HCl solution, then extracted by EtOAc (3×30 mL), the combined organic layer was washed with brine (2×20 mL), dried over Na₂SO₄, filtered and concentrated to give crude. The crude was purified by prep-HPLC (FA condition;).

Phenomenex Luna C18 100*30mm*5um; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:40%-75% B over 8.0 min. to afford 1-(5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (410.00 mg, 42.76% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.29 - 13.85 (m, 1 H) 8.43 (d, J=7.38 Hz, 1 H) 7.22 - 7.35 (m, 2 H) 6.99 - 7.09 (m, 2 H) 3.73 (s, 3 H) 1.92 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄ +H]⁺: 328.07, found: 328.1, *t*_R= 0.496 min.

[0844] Synthesis of 1-[2-methyl-5-(trifluoromethoxy)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 42]:

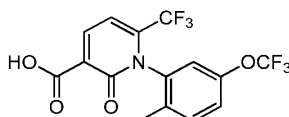


[0845] Synthesis of methyl 3-[2-methyl-5-(trifluoromethoxy)anilino]-3-oxo-propanoate



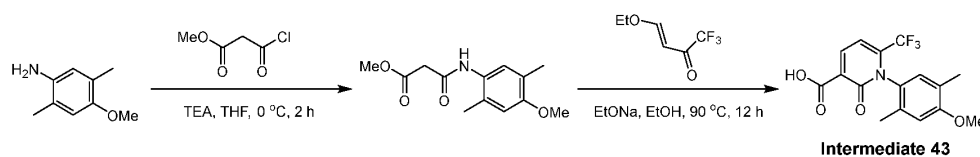
[0846] To a solution of 2-methyl-5-(trifluoromethoxy)aniline (1.00 g, 5.23 mmol, 1.00 eq) in THF (10 mL) was added TEE (1.59 g, 15.69 mmol, 2.18 mL, 3.00 eq) and methyl 3-chloro-3-oxo-propanoate (1.07 g, 7.85 mmol, 838.35 μL, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 1 hour. LCMS showed the reaction was completed. The reaction mixture was poured into H₂O 60 mL and then extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine (2×30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=50/50 to 45/55) to afford methyl 3-[2-methyl-5-(trifluoromethoxy)anilino]-3-oxo-propanoate (0.52 g, 32.42% yield) as a white solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₂F₃NO₄ +H]⁺: 292.07, found: 292.0, *t*_R= 0.493 min.

[0847] Synthesis of 1-[2-methyl-5-(trifluoromethoxy)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 42]

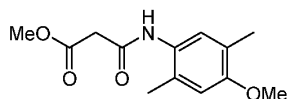


[0848] A mixture of methyl 3-[2-methyl-5-(trifluoromethoxy)anilino]-3-oxo-propanoate (400.00 mg, 1.30 mmol, 1.00 eq) in EtOH (8 mL) was added EtONa (443.97 mg, 6.52 mmol, 5.00 eq) and (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (329.04 mg, 1.96 mmol, 278.85 μ L, 1.50 eq), the reaction mixture stirred at 90 °C for 20 hours. LCMS showed the reaction was completed. The reaction mixture was poured into 60 mL H₂O, then adjust to PH=2~3 with 2N HCl solution, extracted by EtOAc (3 $\times$ 30 mL), the combined organic layer was washed with brine (2 $\times$ 30 mL), dried over Na₂SO₄, filtered and concentrated to give crude. The crude was purified by prep-HPLC (Formic acid condition;). Phenomenex Luna C18 100 $\times$ 30mm $\times$ 5 μ m; mobile phase: [H₂O (0.2% Formic acid)-MeCN];gradient:45%-75% B over 8.0 min. to afford 1-[2-methyl-5-(trifluoromethoxy)phenyl]-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (190.00 mg, 38.20% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.12 - 13.81 (m, 1 H) 8.40 (d, J=7.50 Hz, 1 H) 7.60 - 7.65 (m, 1 H) 7.55 - 7.59 (m, 1 H) 7.45 - 7.53 (m, 1 H) 7.27 (d, J=7.50 Hz, 1 H) 2.04 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₉F₆NO₄+H]⁺: 382.04, found: 382.1, *t*_R= 2.019 min.

[0849] Synthesis of Synthesis of 1-(4-methoxy-2,5-dimethyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 43]:

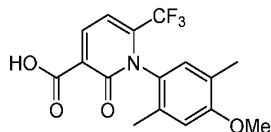


[0850] Synthesis of methyl 3-(4-methoxy-2,5-dimethyl-anilino)-3-oxo-propanoate



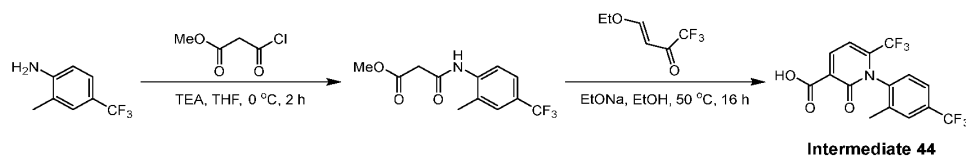
[0851] To a solution of 4-methoxy-2,5-dimethylaniline (500.00 mg, 3.31 mmol, 1.00 eq) in THF (5 mL) was added TEA (1.00 g, 9.92 mmol, 1.38 mL, 3.00 eq) and methyl 3-chloro-3-oxopropanoate (677.23 mg, 4.96 mmol, 529.91 μ L, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 2 hr. LCMS showed ~55% of desired compound was detected. The reaction mixture was poured into water (90 mL). The aqueous phase was extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic phase was washed with brine (3 $\times$ 60 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=4/1) to afford methyl 3-(4-methoxy-2,5-dimethyl-anilino)-3-oxo-propanoate (460.00 mg, 49.82% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.39 (s, 1 H) 7.04 (s, 1 H) 6.77 (s, 1 H) 3.75 (s, 3 H) 3.65 (s, 3 H) 3.43 (s, 2 H) 2.15 (s, 3 H) 2.07 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₁₇NO₄+H]⁺: 252.12, found: 252.2, *t*_R= 0.380 min.

[0852] Synthesis of 1-(4-methoxy-2,5-dimethyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 43]

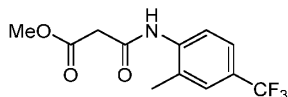


[0853] To a solution of methyl 3-(4-methoxy-2,5-dimethyl-anilino)-3-oxo-propanoate (360.00 mg, 1.43 mmol, 1.00 *eq*), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (361.28 mg, 2.15 mmol, 306.17 μ L, 1.50 *eq*) in EtOH (7.2 mL) was added EtONa (487.47 mg, 7.16 mmol, 5.00 *eq*). The mixture was stirred at 90 °C for 12 hr. LCMS showed ~66% of desired compound was detected. The reaction mixture was poured into water (80 mL), then adjusted to PH=1~2 with 2N HCl solution. The aqueous phase was extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic phase was washed with brine (60 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O (10 mM NH₄HCO₃)-MeCN]; gradient: 15%-45% B over 8.0 min) to afford 1-(4-methoxy-2,5-dimethyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (270.00 mg, 55.22% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.15 (d, *J*=7.25 Hz, 1 H) 7.16 (d, *J*=7.38 Hz, 1 H) 7.06 (s, 1 H) 6.96 (s, 1 H) 3.85 (s, 3 H) 2.12 (s, 3 H) 1.96 (s, 3 H). MS(ES+) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₄F₃NO₄+H]⁺: 342.09, found: 342.0, *t*_R= 0.893 min.

[0854] Synthesis of 1-[2-methyl-4-(trifluoromethyl)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 44]:



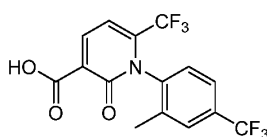
[0855] Synthesis of methyl 3-[2-methyl-4-(trifluoromethyl)anilino]-3-oxo-propanoate



[0856] To a solution of 2-methyl-4-(trifluoromethyl)aniline (1.00 g, 5.71 mmol, 1.00 *eq*) in THF (10 mL) was added TEA (1.73 g, 17.13 mmol, 2.38 mL, 3.00 *eq*) at 0 °C, and then methyl 3-chloro-3-oxopropanoate (1.17 g, 8.56 mmol, 914.93 μ L, 1.50 *eq*) was added. The resulting mixture was stirred at 0 °C for 2 hr. LCMS showed ~80% of desired compound was detected. The reaction mixture was poured into water (90 mL). The aqueous phase was extracted with ethyl acetate (3 $\times$ 50 mL). The combined organic phase was washed with brine (80 mL), dried

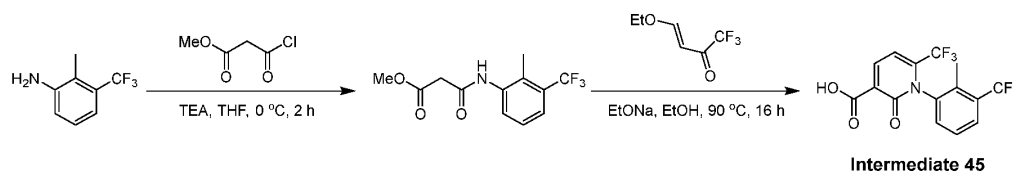
with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , pet. ether/ethyl acetate=4/1) to afford methyl 3-[2-methyl-4-(trifluoromethyl)anilino]-3-oxo-propanoate (790.00 mg, 50.28% yield) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 9.73 (s, 1 H) 7.78 (d, $J=8.38$ Hz, 1 H) 7.60 (s, 1 H) 7.54 (br d, $J=8.38$ Hz, 1 H) 3.67 (s, 3 H) 3.58 (s, 2 H) 2.31 (s, 3 H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{12}\text{F}_3\text{NO}_3+\text{H}]^+$: 276.08, found: 276.1, $t_R=0.457$ min.

[0857] Synthesis of 1-[2-methyl-4-(trifluoromethyl)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 44]

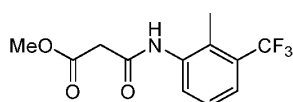


[0858] To a solution of methyl 3-[2-methyl-4-(trifluoromethyl)anilino]-3-oxo-propanoate (690.00 mg, 2.51 mmol, 1.00 *eq*), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (632.20 mg, 3.76 mmol, 535.77 μL , 1.50 *eq*) in EtOH (7 mL) was added EtONa (4.27 g, 12.54 mmol, 20% purity, 5.00 *eq*). The mixture was stirred at 50 $^\circ\text{C}$ for 16 hr. LCMS showed ~53% of desired compound was detected. The reaction mixture was poured into water (80 mL), then adjusted to $\text{pH}=1\sim 2$ with 2N HCl solution. The aqueous phase was extracted with ethyl acetate (3×50 mL). The combined organic phase was washed with brine (60 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by prep-HPLC (column: Welch Xtimate C18 180*70mm#10um; mobile phase: $[\text{H}_2\text{O}$ (10 mM NH_4HCO_3)-MeCN]; gradient: 1%-50% B over 17.0 min) to afford 1-[2-methyl-4-(trifluoromethyl)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (390.00 mg, 42.59% yield) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 8.03 (d, $J=7.25$ Hz, 1 H) 7.85 (s, 1 H) 7.75 (br d, $J=8.25$ Hz, 1 H) 7.61 (br d, $J=8.13$ Hz, 1 H) 7.15 (d, $J=7.38$ Hz, 1 H) 2.10 (s, 3 H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{15}\text{H}_9\text{F}_6\text{NO}_3+\text{H}]^+$: 366.05, found: 366.0, $t_R=0.953$ min.

[0859] Synthesis of 1-[2-methyl-3-(trifluoromethyl)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 45]:

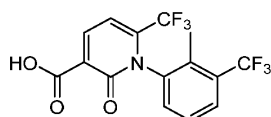


[0860] Synthesis of methyl 3-[2-methyl-3-(trifluoromethyl)anilino]-3-oxo-propanoate



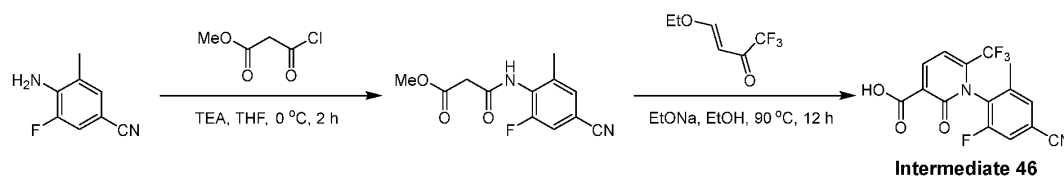
[0861] To a stirred solution of 2-methyl-3-(trifluoromethyl)aniline (3.00 g, 17.13 mmol, 1.00 eq), methyl 3-chloro-3-oxo-propanoate (3.51 g, 25.69 mmol, 2.74 mL, 1.50 eq), TEA (5.20 g, 51.38 mmol, 7.15 mL, 3.00 eq) in THF (30 mL), the mixture was stirred at 0 °C for 2 hr under N₂. LC-MS showed no starting material remained, and 70% desired compound was detected. The reaction mixture was poured into H₂O (100 mL), then the aqueous phase was extracted with EtOAc (3×30 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=10/1 to 4/1), after purification to afford methyl 3-[2-methyl-3-(trifluoromethyl)anilino]-3-oxo-propanoate (2.70 g, 57.28% yield) as a yellow solid. LC-MS (ES⁺, m/z): 276.1 [(M+H)⁺]. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.86 (br s, 1 H) 7.62 (br d, J=7.88 Hz, 1 H) 7.56 (br d, J=7.75 Hz, 1 H) 7.32 - 7.47 (m, 1 H) 3.68 (s, 3 H) 3.54 (s, 2 H) 2.30 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₂O₃NF₃+H]⁺: 276.07, found: 276.1, *t*_R= 0.434 min.

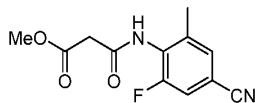
[0862] Synthesis of 1-[2-methyl-3-(trifluoromethyl) phenyl]-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 45]



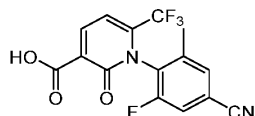
[0863] To a stirred solution of methyl 3-[2-methyl-3-(trifluoromethyl)anilino]-3-oxo-propanoate (1.00 g, 3.63 mmol, 1.00 eq), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (916.24 mg, 5.45 mmol, 776.47 μL, 1.50 eq), EtONa (1.24 g, 18.17 mmol, 5.00 eq) in EtOH (20 mL), the mixture was stirred at 90 °C for 16 hrs under N₂. LCMS showed the reaction was completed. The reaction mixture was poured into H₂O (50 mL), then the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by prep-HPLC: Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:35%-65% B over 8.0 min to afford 1-[2-methyl-3-(trifluoromethyl) phenyl]-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (500.00 mg, 37.68% yield) as yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₉O₃NF₆+H]⁺: 366.04 found: 365.8, *t*_R= 0.396 min.

[0864] Synthesis of 1-(4-cyano-2-fluoro-6-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 46]:



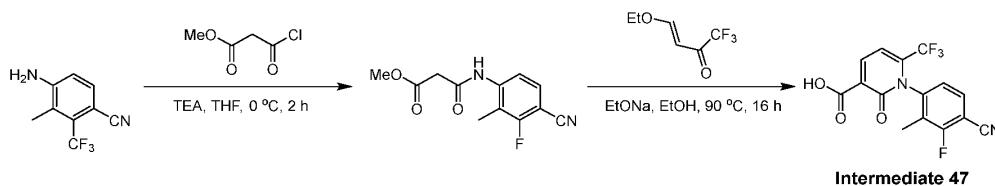
[0865] Synthesis of methyl 3-(4-cyano-2-fluoro-6-methyl-anilino)-3-oxo-propanoate

[0866] To a solution of 4-amino-3-fluoro-5-methyl-benzonitrile (500.00 mg, 3.33 mmol, 1.00 eq) in THF (5 mL) was added TEA (1.01 g, 9.99 mmol, 1.39 mL, 3.00 eq) and methyl 3-chloro-3-oxo-propanoate (681.97 mg, 4.99 mmol, 533.63 μ L, 1.50 eq) in portions at 0 °C. The mixture was stirred at 0 °C for 2 hr. LCMS showed the reaction was completed. The mixture was quenched with water (100 mL) and extracted with EtOAc (3 $\times$ 50 mL). The combined organic phase was washed with brine (2 $\times$ 50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=10/1 to 1/1, pet. ether/ EtOAc =1/1, TM/R_f=0.50). The product was triturated with MTBE (25 mL) at 25 °C for 12 hr to afford methyl 3-(4-cyano-2-fluoro-6-methyl-anilino)-3-oxo-propanoate (400.00 mg, 44.07% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.05 (s, 1 H) 7.75 (d, J=9.63 Hz, 1 H) 7.65 (s, 1 H) 3.67 (s, 3 H) 3.54 (s, 2 H) 2.24 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₁FN₂O₃+H]⁺: 251.07, found: 251.0, *t*_R = 0.835 min.

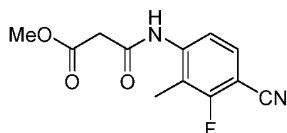
[0867] Synthesis of 1-(4-cyano-2-fluoro-6-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 46]

[0868] To a solution of methyl 3-(4-cyano-2-fluoro-6-methyl-anilino)-3-oxo-propanoate (350.00 mg, 1.40 mmol, 1.00 eq) in EtOH (7 mL) was added (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (352.72 mg, 2.10 mmol, 298.92 μ L, 1.50 eq) and EtONa (475.92 mg, 6.99 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 hr. LCMS showed the reaction was completed. The reaction mixture was poured into water (30 mL), then the aqueous phase was adjusted to pH=5~6 with sat. citric acid. The aqueous phase was extracted with ethyl acetate (2 $\times$ 40 mL), filtered and concentrated in vacuum. The residue was purified by prep-HPLC (Formic acid condition; column: Phenomenex luna C18 100 $\times$ 40mm $\times$ 5 μ m; mobile phase: [H₂O(0.2% Formic acid)-MeCN]; gradient: 35%-65% B over 8.0 min) to afford 1-(4-cyano-2-fluoro-6-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (205.00 mg, 38.77% yield) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₅H₈F₄N₂O₃+H]⁺: 341.04, found: 341.1, *t*_R = 1.698 min.

[0869] Synthesis of 1-(4-cyano-3-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 47]:

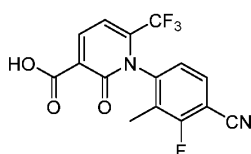


[0870] Synthesis of methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxopropanoate



[0871] To a stirred solution of 4-amino-2-fluoro-3-methyl-benzonitriles (500.00 mg, 3.33 mmol, 1.00 eq), TEA (1.01 g, 9.99 mmol, 1.39 mL, 3.00 eq) in THF (5 mL) was added methyl 3-chloro-3-oxo-propanoate (681.97 mg, 4.99 mmol, 533.63 μ L, 1.50 eq) at 0 °C, the mixture was stirred at 0 °C for 2 hrs under N₂. LCMS showed no starting material had remained and 70% desired compound was detected. The reaction mixture was poured into H₂O (100 mL), then the aqueous phase was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with brine (2 $\times$ 100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=10/1 to 4/1) to afford methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxo-propanoate (370.00 mg, 44.41% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.95 (s, 1 H) 7.65 - 7.76 (m, 2 H) 3.67 (s, 3 H) 3.61 (s, 2 H) 2.18 (d, J=2.25 Hz, 3 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₂H₁₁O₃N₂F+H]⁺: 251.07, found: 251.1, *t*_R= 0.401 min.

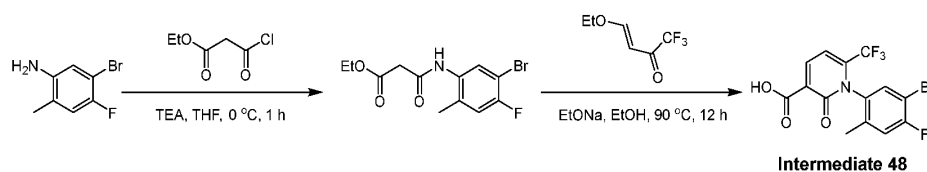
[0872] Synthesis of 1-(4-cyano-3-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 47]



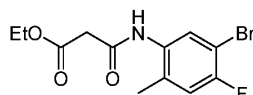
[0873] To a stirred solution of methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxo-propanoate (300.00 mg, 1.20 mmol, 1.00 eq), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (302.33 mg, 1.80 mmol, 256.21 μ L, 1.50 eq), EtONa (407.93 mg, 5.99 mmol, 5.00 eq) in EtOH (12 mL), the mixture was stirred at 90 °C for 16 hr under N₂. LCMS showed the reaction completed. The reaction mixture was poured into H₂O (50 mL), then the aqueous phase was extracted with EtOAc (3 $\times$ 20 mL). The combined organic phase was washed with brine (2 $\times$ 100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by prep-HPLC: column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase:

[H₂O(0.2% Formic acid)-MeCN];gradient:18%-58% B over 8.0 min to afford 1-(4-cyano-3-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (300.00 mg, 73.55% yield) as yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.49 - 14.11 (m, 1 H) 8.37 (br d, J=7.25 Hz, 1 H) 8.02 (br t, J=7.63 Hz, 1 H) 7.60 (br d, J=8.25 Hz, 1 H) 7.22 - 7.31 (m, 1 H) 2.02 (s, 3 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₅H₈O₃N₂F₄+H]⁺: 341.04, found: 341.0, *t*_R= 2.109 min.

[0874] Synthesis of 1-(5-bromo-4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 48]:

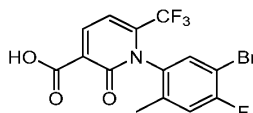


[0875] Synthesis of ethyl 3-(5-bromo-4-fluoro-2-methyl-anilino)-3-oxo-propanoate



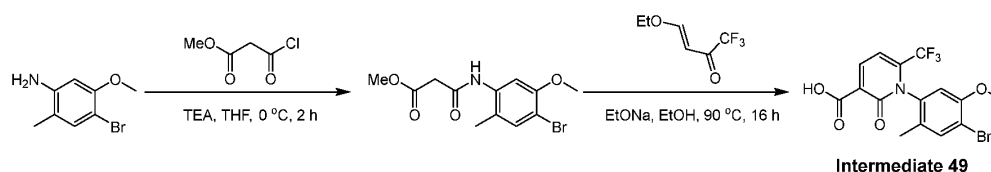
[0876] To a solution of 4-fluoro-2,5-dimethyl-aniline (5.00 g, 35.93 mmol, 1.00 eq) in THF (50 mL) was added TEA (10.91 g, 107.78 mmol, 15.00 mL, 3.00 eq) and ethyl 3-chloro-3-oxopropanoate (10.82 g, 71.85 mmol, 9.05 mL, 2.00 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. LCMS showed the reaction was completed. The reaction mixture was quenched by an addition of H₂O (100 mL), and then extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine 100 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with pet. ether: EtOAc =3:1 (60 mL) and stirred for 4 h. Then filtered and collected the solid to afford ethyl 3-(5-bromo-4-fluoro-2-methyl-anilino)-3-oxo-propanoate (3.80 g, 33.25% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.67 (s, 1 H) 7.72 (d, J=6.88 Hz, 1 H) 7.30 (d, J=9.63 Hz, 1 H) 4.13 (q, J=7.13 Hz, 2 H) 3.49 (s, 2 H) 2.19 (s, 3 H) 1.21 (t, J=7.13 Hz, 3 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₂H₁₃BrNO₃+H]⁺: 318.0/320.0, found: 317.8/319.7, *t*_R= 0.531 min.

[0877] Synthesis of 1-(5-bromo-4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 48]

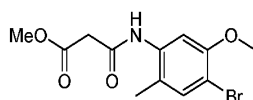


[0878] To a solution of ethyl 3-(5-bromo-4-fluoro-2-methyl-anilino)-3-oxo-propanoate (400.00 mg, 1.26 mmol, 1.00 eq) and (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (317.06 mg, 1.89 mmol, 268.69 μ L, 1.50 eq) in EtOH (5 mL) was added EtONa (427.80 mg, 6.29 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL) and then extracted with EtOAc (3 $\times$ 20 mL), then the aqueous phase adjusting the pH to 2 with 2N HCl. Then the resulting solution was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient: 10%-40% B over 8.0 min), after purification to afford 1-(5-bromo-4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (150.00 mg, 30.27% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.09 (d, J=7.38 Hz, 1 H) 7.87 (d, J=6.63 Hz, 1 H) 7.52 (d, J=9.51 Hz, 1 H) 7.14 (d, J=7.38 Hz, 1 H) 1.99 (s, 3 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₄H₈O₃NF₄Br+H]⁺: 393.96, found: 393.9/395.9, *t*_R= 0.902 min.

[0879] Synthesis of 1-(4-bromo-5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 49]:



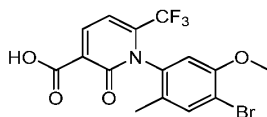
[0880] Synthesis of methyl 3-(4-bromo-5-methoxy-2-methyl-anilino)-3-oxo-propanoate



[0881] To a stirred solution of 4-bromo-5-methoxy-2-methyl-aniline (500.00 mg, 2.31 mmol, 1.00 eq), TEA (702.47 mg, 6.94 mmol, 966.25 μ L, 3.00 eq), methyl 3-chloro-3-oxopropanoate (473.91 mg, 3.47 mmol, 370.82 μ L, 1.50 eq) in THF (5 mL), the mixture was stirred at 0 °C for 2 hrs under N₂. LCMS showed no starting material remained and 70% desired compound was detected. The reaction mixture was poured into H₂O (100 mL), then the aqueous phase was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with brine (2 $\times$ 100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=10/1 to 4/1) to afford methyl 3-(4-bromo-5-methoxy-2-methyl-anilino)-3-oxo-propanoate (370.00 mg, 50.58% yield) as

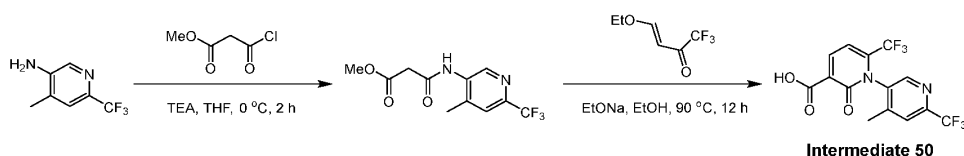
yellow solid; MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{12}H_{14}O_4NBr+H]^+$: 316.01&318.01, found: 315.6&317.6, t_R = 2.109 min.

[0882] Synthesis of 1-(4-bromo-5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 49]

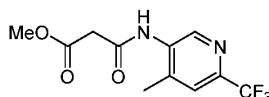


[0883] To a stirred solution of methyl 3-(4-bromo-5-methoxy-2-methyl-anilino)-3-oxo-propanoate (350.00 mg, 1.11 mmol, 1.00 eq), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (279.17 mg, 1.66 mmol, 236.59 μ L, 1.50 eq), EtONa (376.68 mg, 5.54 mmol, 5.00 eq) in EtOH (2 mL), the mixture was stirred at 90 °C for 16 hr under N_2 . LCMS showed the reaction completed. The reaction mixture was poured into H_2O (50 mL), then the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na_2SO_4 , and concentrated by filtration and vacuum. The residue was purified by prep-HPLC: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H_2O (0.2% Formic acid)-MeCN]; gradient: 18%-58% B over 8.0 min to afford 1-(4-bromo-5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (400 mg, 80% purity) as yellow solid. Then the residue was purified by prep-HPLC: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: [H_2O (0.2% Formic acid)-MeCN]; gradient: 40%-70% B over 8.0 min to afford 1-(4-bromo-5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (300.00 mg, 66.72% yield) as yellow solid. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{15}H_{11}O_4NBrF_3+H]^+$: 405.98&407.98, found: 405.8&407.6, t_R = 2.109 min.

[0884] Synthesis of 1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 50]:



[0885] Synthesis of methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxo-propanoate

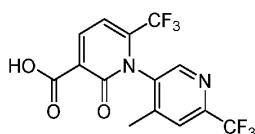


[0886] To a solution of 4-methyl-6-(trifluoromethyl)pyridin-3-amine (900.00 mg, 5.11 mmol, 1.00 eq) in THF (10 mL) was added TEA (1.55 g, 15.33 mmol, 2.13 mL, 3.00 eq) and methyl 3-

chloro-3-oxo-propanoate (1.05 g, 7.66 mmol, 818.82 μ L, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O (30 mL), and then extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine 30 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was triturated with pet. ether: EtOAc =1:1 (20 mL) and stirred for 4 h. Then filtered and collected the solid to afford methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxo-propanoate (450.00 mg) as a yellow solid.

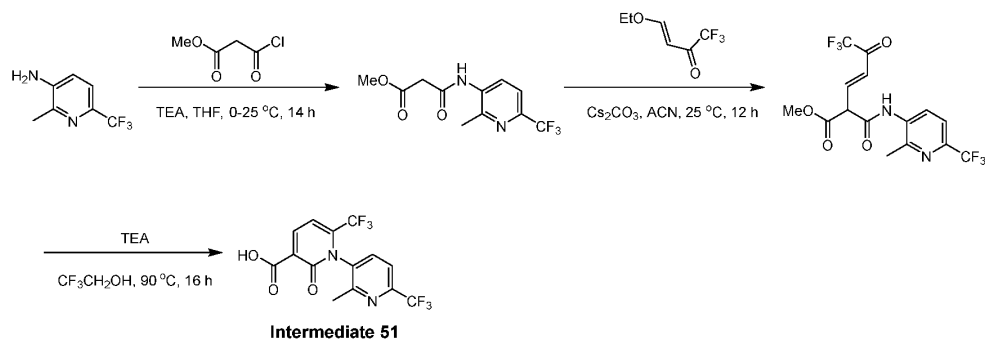
MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₁H₁₁O₃N₂F₃+H]⁺: 277.07, found: 277.1, *t*_R= 0.379 min.

[0887] Synthesis of 1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 51]

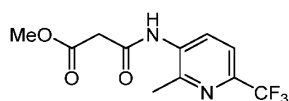


[0888] To a solution of methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxo-propanoate (400.00 mg, 1.45 mmol, 1.00 eq) and (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (292.15 mg, 1.74 mmol, 247.58 μ L, 1.20 eq) in EtOH (5 mL) was added EtONa (492.74 mg, 7.24 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O (20 mL), extracted with EtOAc (3 $\times$ 20 mL), then the aqueous phase was adjusted to pH to 2 with 2N HCl. Then the resulting solution was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient: 10%-50% B over 8.0 min) to afford 1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (140.00 mg, 26.40% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.72 (s, 1 H) 8.11 (s, 1 H) 7.77 (s, 1 H) 7.08 (d, J=7.25 Hz, 1 H) 2.18 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₄H₈O₃N₂F₆+H]⁺: 367.04, found: 367.0, *t*_R= 0.860 min.

[0889] Synthesis of 1-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 51]:

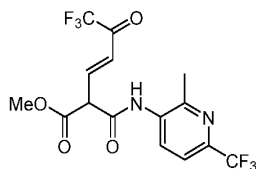


[0890] Synthesis of methyl 3-[[2-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxopropanoate



[0891] To a mixture of 2-methyl-6-(trifluoromethyl)pyridin-3-amine (0.50 g, 2.84 mmol, 1.00 *eq*) in THF (10 mL) was added TEA (861.74 mg, 8.52 mmol, 1.19 mL, 3.00 *eq*) at 0 °C, methyl 3-chloro-3-oxopropanoate (581.36 mg, 4.26 mmol, 454.90 μ L, 1.50 *eq*) was added dropwise and the mixture was stirred at 0 °C for 2 h. LCMS showed 40% starting material was remained and 53% product was detected. Then methyl 3-chloro-3-oxopropanoate (387.57 mg, 2.84 mmol, 303.27 μ L, 1.00 *eq*) was added and the reaction was stirred at 25 °C for 12 h. LCMS showed 14% of starting material remained and 70% product was detected. The mixture was poured into H₂O (100 mL). The aqueous phase was extracted with ethyl acetate (3x40 mL). The combined organic phase was washed with brine (3x40 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to afford methyl 3-[[2-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxopropanoate (0.7 g) as brown solid. MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₁H₁₁F₃N₂O₃+H]⁺: 277.07, found: 277.1, *t_R* = 0.968 min.

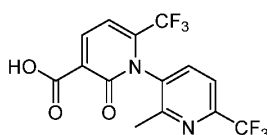
[0892] Synthesis of methyl (Z)-6,6,6-trifluoro-2-[[2-methyl-6-(trifluoromethyl)-3-pyridyl]carbamoyl]-5-oxo-hex-3-enoate



[0893] To a mixture of methyl 3-[[2-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxopropanoate (0.50 g, 1.81 mmol, 1.00 *eq*), (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (365.18 mg, 2.17 mmol, 309.48 μ L, 1.20 *eq*) in MeCN (5 mL) was added Cs₂CO₃ (825.72 mg, 2.53 mmol, 1.06 mL, 1.40 *eq*) and the mixture was stirred at 25 °C for 12 h. LCMS showed the

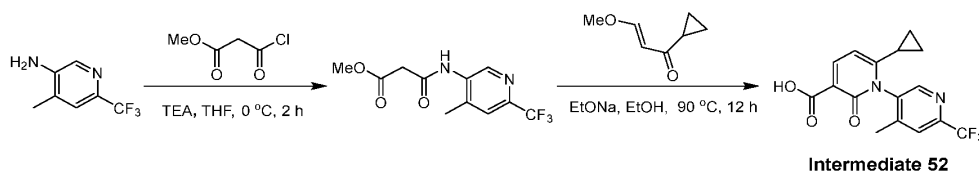
reaction was completed. The mixture was poured into H₂O (100 mL). The aqueous phase was extracted with ethyl acetate (3x50 mL). The combined organic phase was washed with brine (3x50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford methyl (Z)-6,6,6-trifluoro-2-[[2-methyl-6-(trifluoromethyl)-3-pyridyl] carbamoyl] -5-oxo-hex-3-enoate (0.7 g) as a brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₁H₁₁F₃N₂O₃+H]⁺: 399.07, found: 399.1, *t*_R = 1.134 min.

[0894] Synthesis of 1-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 51]

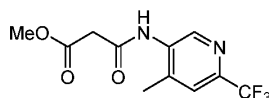


[0895] To a mixture of methyl (Z)-6,6,6-trifluoro-2-[[2-methyl-6-(trifluoromethyl)-3-pyridyl]carbamoyl]-5-oxo-hex-3-enoate (0.60 g, 1.51 mmol, 1.00 *eq*) in 2,2,2-trifluoroethanol (6 mL) was added TEA (457.35 mg, 4.52 mmol, 629.09 μ L, 3.00 *eq*) and the mixture was stirred at 90 °C for 16 h. LCMS showed the reaction was completed. The mixture was concentrated in vacuum. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 100*30mm*5 μ m; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:40%-80% B over 8.0 min) to afford 1-[2-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (0.3 g, 54.37% yield) as white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.38 (d, J=7.38 Hz, 1 H) 8.27 (d, J=8.13 Hz, 1 H) 8.03 (d, J=8.13 Hz, 1 H) 7.28 (d, J=7.38 Hz, 1 H) 2.32 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₄H₈F₆N₂O₃+H]⁺: 367.04, found: 367.1, *t*_R = 1.799 min.

[0896] Synthesis of 6-cyclopropyl-1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-pyridine-3-carboxylic acid [Intermediate 52]:



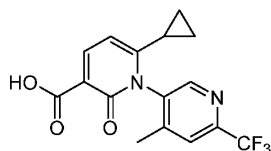
[0897] Synthesis of methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxopropanoate



[0898] To a solution of 4-methyl-6-(trifluoromethyl)pyridin-3-amine (1.00 g, 5.68 mmol, 1.00 *eq*) in THF (10 mL) was added TEA (1.72 g, 17.03 mmol, 2.37 mL, 3.00 *eq*) then was added

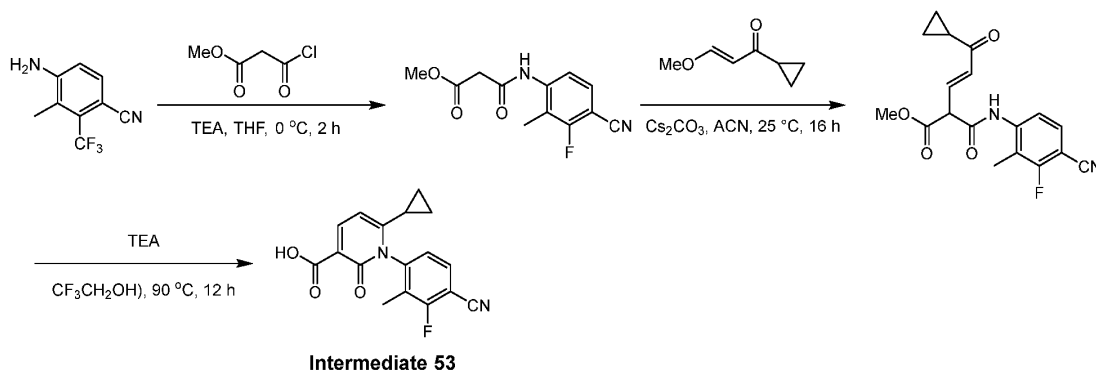
methyl 3-chloro-3-oxo-propanoate (1.16 g, 8.52 mmol, 909.80 μ L, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (30 mL), and then extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine 30 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=1/0 to 90/10, pet. ether/ EtOAc =3/1, TM/R_f=0.30) to afford methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxo-propanoate (600.00 mg, 38.26% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.02 (s, 1 H) 8.81 (s, 1 H) 7.84 (s, 1 H) 3.68 (s, 3 H) 3.61 (s, 2 H) 2.34 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₁H₁₁O₃N₂F₃+H]⁺: 277.07, found: 277.2, *t*_R= 0.379 min.

[0899] Synthesis of 6-cyclopropyl-1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-pyridine-3-carboxylic acid [Intermediate 52]

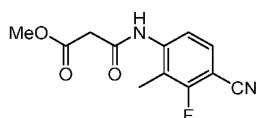


[0900] To a solution of methyl 3-[[4-methyl-6-(trifluoromethyl)-3-pyridyl]amino]-3-oxo-propanoate (250.00 mg, 905.10 μ mol, 1.00 eq) and (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (171.27 mg, 1.36 mmol, 1.50 eq) in EtOH (5 mL) was added EtONa (307.96 mg, 4.53 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3 $\times$ 20 mL), then the aqueous phase adjusted the pH to 2 with 2N HCl. Then the resulting solution was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 6-cyclopropyl-1-[4-methyl-6-(trifluoromethyl)-3-pyridyl]-2-oxo-pyridine-3-carboxylic acid (250.00 mg, crude) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₁₃O₃N₂F₃+H]⁺: 339.09, found: 339.1, *t*_R= 0.765 min.

[0901] Synthesis of 1-(4-cyano-3-fluoro-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 53]:

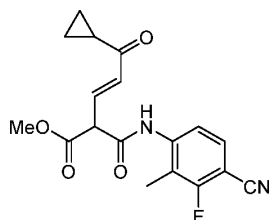


[0902] Synthesis of methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxo-propanoate



[0903] To a stirred solution of 4-amino-2-fluoro-3-methyl-benzonitrile (500.00 mg, 3.33 mmol, 1.00 eq), TEA (1.01 g, 9.99 mmol, 1.39 mL, 3.00 eq) in THF (5 mL) was added methyl 3-chloro-3-oxopropanoate (681.97 mg, 4.99 mmol, 533.63 μ L, 1.50 eq) at 0 °C, the mixture was stirred at 0 °C for 2 hrs under N₂. LCMS showed no starting material remained and 70% desired compound was detected. The reaction mixture was poured into H₂O (100 mL), then the aqueous phase was extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with brine (2 $\times$ 100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=10/1 to 4/1) to afford methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxopropanoate (370.00 mg, 44.41% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.95 (s, 1 H) 7.65 - 7.76 (m, 2 H) 3.67 (s, 3 H) 3.61 (s, 2 H) 2.18 (d, J=2.25 Hz, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₁O₃N₂F+H]⁺: 251.07, found: 251.1, *t*_R= 0.401 min.

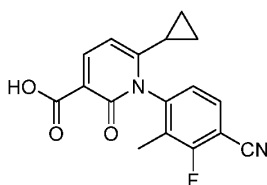
[0904] Synthesis of methyl (E)-2-[(4-cyano-3-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate



[0905] To a stirred solution of methyl 3-(4-cyano-3-fluoro-2-methyl-anilino)-3-oxopropanoate (300.00 mg, 1.20 mmol, 1.00 eq), (E)-1-cyclopropyl-3-ethoxyprop-2-en-1-one (252.10 mg, 1.80 mmol, 1.50 eq), Cs₂CO₃ (585.95 mg, 1.80 mmol, 1.50 eq) in MeCN (6 mL),

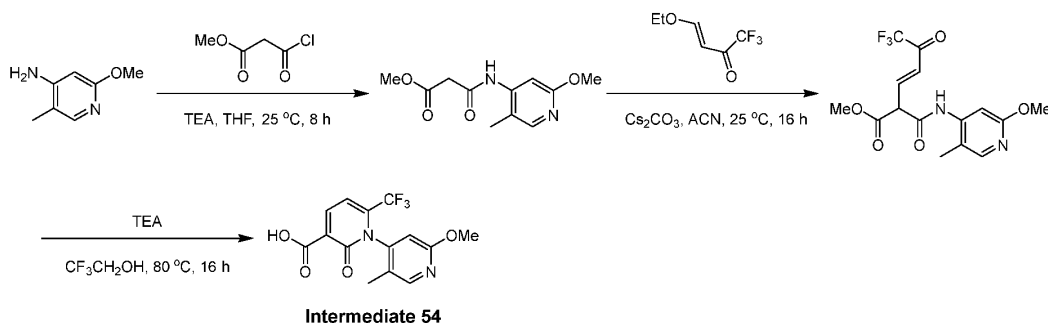
and then the mixture was stirred at 25 °C for 16 hr under N₂. LCMS showed the reaction was completed. The reaction mixture was poured into H₂O (50 mL), then the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration under vacuum to afford methyl (E)-2-[(4-cyano-3-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate (420.00 mg, crude) as yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₈H₁₇O₄FN₂+H]⁺: 345.34, found: 345.0, *t*_R= 1.030 min.

[0906] Synthesis of 1-(4-cyano-3-fluoro-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid [Intermediate 53]

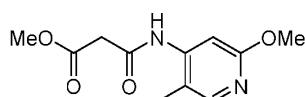


[0907] To a stirred solution of methyl (E)-2-[(4-cyano-3-fluoro-2-methyl-phenyl)carbamoyl]-5-cyclopropyl-5-oxo-pent-3-enoate (220.00 mg, 638.91 μmol, 1.00 eq), TEA (193.95 mg, 1.92 mmol, 266.79 μL, 3.00 eq) in CF₃CH₂OH (4 mL), and then the mixture was stirred at 90 °C for 12 hr under N₂. LCMS showed no starting material remained. Several new peaks were shown in LC-MS and ~20% of desired compound was detected. The reaction mixture was poured into H₂O (50 mL), then the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic phase was washed with brine (2×100 mL), dried with anhydrous Na₂SO₄, and concentrated by filtration and vacuum. The residue was purified by prep-HPLC: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.2% Formic acid)-MeCN]; gradient: 25%-55% B over 9.0 min to afford 1-(4-cyano-3-fluoro-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid (40.00 mg) as yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.33 - 14.17 (m, 1 H) 8.40 (d, J=7.75 Hz, 1 H) 8.05 (t, J=7.57 Hz, 1 H) 7.60 (d, J=8.25 Hz, 1 H) 6.56 (d, J=7.75 Hz, 1 H) 2.01 (d, J=1.75 Hz, 3 H) 1.29 - 1.37 (m, 1 H) 0.91 - 0.97 (m, 2 H) 0.81 - 0.91 (m, 2 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₃O₃N₂F+H]⁺: 313.30, found: 312.9, *t*_R= 0.781 min.

[0908] Synthesis of 1-(2-methoxy-5-methyl-4-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 54]:

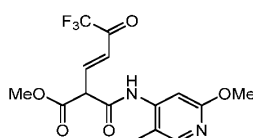


[0909] Synthesis of methyl 3-[(2-methoxy-5-methyl-4-pyridyl)amino]-3-oxo-propanoate



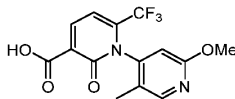
[0910] To a solution of 2-methoxy-5-methyl-pyridin-4-amine (1.50 g, 10.86 mmol, 1.00 eq) in THF (30.00 mL) was added TEA (5.49 g, 54.28 mmol, 7.56 mL, 5.00 eq), and then methyl 3-chloro-3-oxo-propanoate (4.45 g, 32.57 mmol, 3.48 mL, 3.00 eq) was added at 25 °C. The solution was stirred at 25 °C for 8 hr. LCMS showed the reaction was completed. The mixture was quenched with water (150 mL), and extracted with EtOAc (3×90 mL), the combined organic layers was washed with brine (90 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The crude product was triturated with EtOAc (60 mL) at 25 °C for 2 hr. The mixture was filtered and the filter cake was collected to afford methyl 3-[(2-methoxy-5-methyl-4-pyridyl)amino]-3-oxo-propanoate (0.75 g, 26.10% yield) as white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.52 (s, 1 H) 7.93 (s, 1 H) 7.33 (s, 1 H) 3.79 (s, 3 H) 3.67 (s, 3 H) 3.63 (s, 2 H) 2.14 (s, 3 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₁H₁₄N₂O₄ +H]⁺: 239.10, found: 239.0, *t*_R= 0.850 min.

[0911] Synthesis of methyl (E)-6,6,6-trifluoro-2-[(2-methoxy-5-methyl-4-pyridyl)carbamoyl]-5-oxo-hex-3-enoate



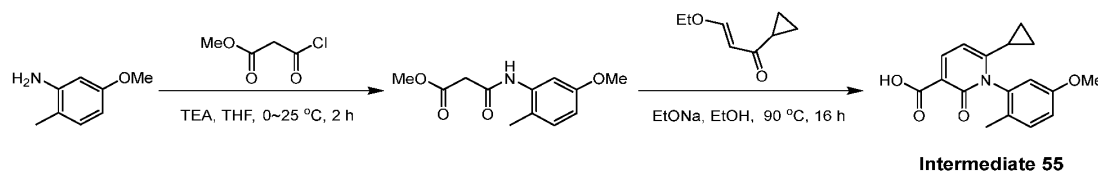
[0912] To a solution of methyl 3-[(2-methoxy-5-methyl-4-pyridyl)amino]-3-oxo-propanoate (0.20 g, 839.49 μmol, 1.00 eq) in MeCN (6 mL) was added Cs₂CO₃ (410.28 mg, 1.26 mmol, 1.50 eq) and (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (211.69 mg, 1.26 mmol, 179.40 μL, 1.50 eq), and then the mixture was stirred at 25 °C for 16 hr. LCMS showed the reaction was completed. The mixture was quenched with water (50 mL), and extracted with EtOAc (3×30 mL), the combined organic layers was washed with brine (30mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum to afford methyl (E)-6,6,6-trifluoro-2-[(2-methoxy-5-methyl-4-pyridyl)carbamoyl]-5-oxo-hex-3-enoate (0.3 g, crude) as yellow solid. MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₅F₃N₂O₅ +H]⁺: 361.09, found: 361.0, *t*_R= 0.994 min.

[0913] Synthesis of 1-(2-methoxy-5-methyl-4-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 54]

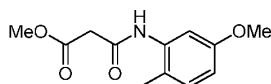


[0914] To a solution of methyl (E)-6,6,6-trifluoro-2-[(2-methoxy-5-methyl-4-pyridyl)carbamoyl]-5-oxo-hex-3-enoate (0.15 g, 416.34 μ mol, 1.00 eq) in $\text{CF}_3\text{CH}_2\text{OH}$ (1.50 mL) was added TEA (126.39 mg, 1.25 mmol, 173.85 μ L, 3.00 eq), and then the mixture was stirred at 80 °C for 16 hrs under N_2 . LCMS showed the reaction was completed. The reaction was concentrated to remove $\text{CF}_3\text{CH}_2\text{OH}$, and then 10 mL of water was added, and extracted with EtOAc (10 mL). The aqueous phase was adjusted to pH=2 with 1N HCl. The formed precipitation was collected by filtration to afford 1-(2-methoxy-5-methyl-4-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (55 mg, crude) as yellow solid. MS(ES⁺) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{14}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_4 + \text{H}]^+$: 329.07, found: 328.9, t_R = 0.755 min.

[0915] Synthesis of 1-(5-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 55]:

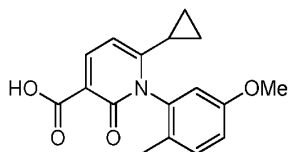


[0916] Synthesis of methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate



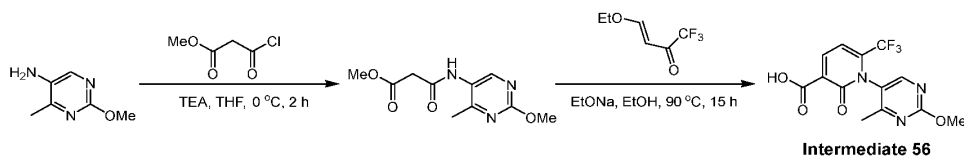
[0917] To a solution of 5-methoxy-2-methyl-aniline (2.00 g, 14.58 mmol, 1.00 eq) in THF (20 mL) was added TEA (4.43 g, 43.74 mmol, 6.09 mL, 3.00 eq) and methyl 3-chloro-3-oxo-propanoate (2.99 g, 21.87 mmol, 2.34 mL, 1.50 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hours. TLC (pet. ether: EtOAc =1:1, SM/ R_f =0.56, TM/ R_f =0.43) showed the reaction was completed. The reaction mixture was poured into H_2O (100 mL), and then extracted by EtOAc (3 $\times$ 50 mL), the combined organic layer was washed with brine (2 $\times$ 50 mL), dried over Na_2SO_4 , filtered and concentrated to give crude. The residue was purified by column chromatography (SiO_2 , pet. ether/ DCM=20/80 to 0/100) to afford methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate (1.00 g, 27.93% yield) as off-white solid. MS(ES⁺) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{15}\text{NO}_4 + \text{H}]^+$: 238.10, found: 238.2, t_R = 0.369 min.

[0918] Synthesis of methyl 6-cyclopropyl-1-(5-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 55]

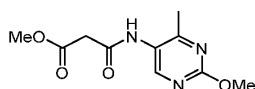


[0919] To a solution of methyl 3-(5-methoxy-2-methyl-anilino)-3-oxo-propanoate (750.00 mg, 3.16 mmol, 1.00 eq) and (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (598.19 mg, 4.74 mmol, 1.50 eq) in EtOH (15 mL) was added EtONa (1.08 g, 15.81 mmol, 5.00 eq). The mixture was stirred at 90 °C for 16 hours. LCMS showed ~47% of desired product. The reaction mixture was concentrated to remove EtOH, and then poured into 50 mL H₂O, adjusted to PH=5~6 with 2N. HCl solution, then extracted by EtOAc (3×30 mL), the combined organic layer was washed with brine (2×30 mL), dried over Na₂SO₄, filtered and concentrated to give a crude. The crude was purified by prep-HPLC (Formic acid condition). Phenomenex luna C18 100*40mm*5 um; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:20%-60% B over 8.0 min. The desired methyl 6-cyclopropyl-1-(5-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid afforded (430.00 mg, 44.90% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.23 (s, 1 H) 8.38 (d, J=7.88 Hz, 1 H) 7.38 (d, J=8.13 Hz, 1 H) 7.00 - 7.07 (m, 2 H) 6.50 (d, J=7.88 Hz, 1 H) 3.76 (s, 3 H) 1.93 (s, 3 H) 1.29 - 1.40 (m, 1 H) 0.90 - 1.05 (m, 4 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₁₇H₁₇NO₄+H]⁺: 300.12, found: 300.2, *t*_R= 1.635 min.

[0920] Synthesis of 1-(2-methoxy-4-methyl-pyrimidin-5-yl)-2-oxo-6-(trifluoromethyl)pyridine -3-carboxylic acid [Intermediate 56]:



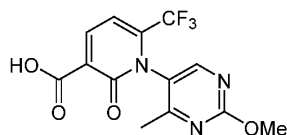
[0921] Synthesis of methyl 3-[(2-methoxy-4-methyl-pyrimidin-5-yl)amino]-3-oxo-propanoate



[0922] To a mixture of 2-methoxy-4-methyl-pyrimidin-5-amine (500.00 mg, 3.59 mmol, 1.00 eq) in THF (10 mL) was added TEA (1.09 g, 10.78 mmol, 1.50 mL, 3.00 eq) at 0 °C, then methyl 3-chloro-3-oxo-propanoate (735.87 mg, 5.39 mmol, 575.80 μL, 1.50 eq) was added dropwise and the mixture was stirred at 0 °C for 2 h. LCMS showed 18% of starting material was remained and 80% product was detected. The mixture was poured into saturated Na₂CO₃ (100 mL). The aqueous phase was extracted with ethyl acetate (3×40 mL). The combined organic phase was washed with brine (3×40 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (column height:

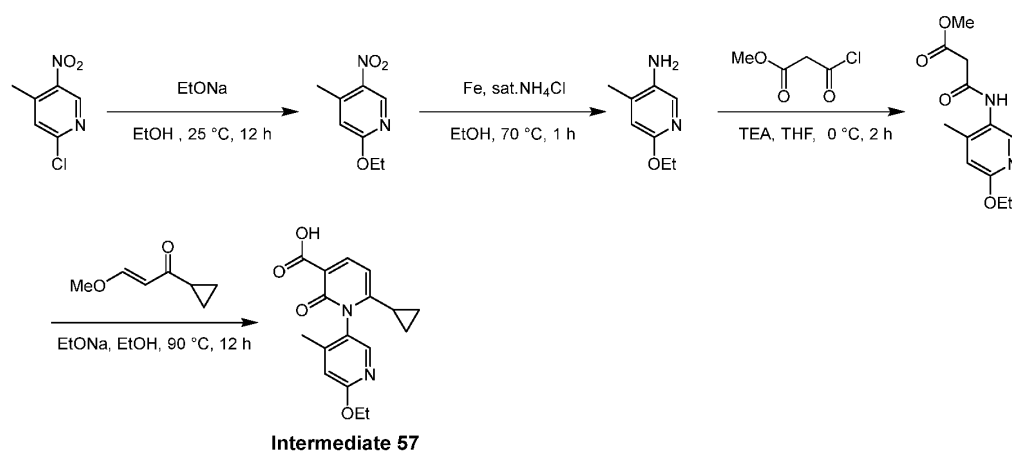
250 mm, diameter: 100 mm, 100-200 mesh silica gel, pet. ether/ethyl acetate=1/0, 1/1) to afford methyl 3-[(2-methoxy-4-methyl-pyrimidin-5-yl)amino]-3-oxo-propanoate (0.8 g, 77.85% yield) as light brown solid. ¹H NMR (400 MHz, DMSO-d₆): δ 9.83 (br s, 1 H) 8.42 (s, 1 H) 3.80 - 3.91 (m, 3 H) 3.59 - 3.70 (m, 3 H) 3.52 (s, 2 H) 2.33 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₀H₁₃N₃O₄+H]⁺: 240.09, found: 240.1, *t_R* = 0.574 min.

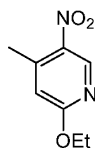
[0923] Synthesis of 1-(2-methoxy-4-methyl-pyrimidin-5-yl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 56]



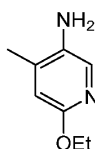
[0924] To a mixture of methyl 3-[(2-methoxy-4-methyl-pyrimidin-5-yl)amino]-3-oxo-propanoate (250.00 mg, 1.05 mmol, 1.00 *eq*), (E)-4-ethoxy-1,1,1-trifluoro-but-3-en-2-one (210.82 mg, 1.25 mmol, 178.66 μL, 1.20 *eq*) in EtOH (10 mL) was added EtONa (355.57 mg, 5.23 mmol, 5.00 *eq*) and the mixture was stirred at 90 °C for 15 h. LCMS showed the reaction was completed. The residue was poured into H₂O (50 mL). The aqueous phase was extracted with ethyl acetate (3x30 mL). The combined organic phase was washed with brine (3x30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by prep-HPLC(column: Phenomenex Luna C18 100*30mm*5um; mobile phase: [H₂O(0.2% Formic acid)-MeCN];gradient:20%-55% B over 8.0 min) to afford 1-(2-methoxy-4-methyl-pyrimidin-5-yl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (0.2 g, 58.13% yield) as yellow solid. ¹H NMR (400 MHz, DMSO-d₆): δ 8.64 (s, 1 H) 8.36 (d, J=7.38 Hz, 1 H) 7.26 (d, J=7.50 Hz, 1 H) 3.98 (s, 3 H) 2.20 (s, 3 H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₁₀F₃N₃O₄+H]⁺: 330.06, found: 330.1, *t_R* = 1.371 min.

[0925] Synthesis of 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 57]:



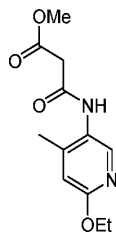
[0926] Synthesis of 2-ethoxy-4-methyl-5-nitro-pyridine

To a solution of 2-chloro-4-methyl-5-nitro-pyridine (10.00 g, 57.95 mmol, 1.00 eq) in EtOH (100 mL) was added EtONa (39.43 g, 579.48 mmol, 10.00 eq). The mixture was stirred at 25 °C for 12 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O (200 mL) and then extracted with EtOAc (3×200 mL). The combined organic layer was washed successively with brine (300 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 2-ethoxy-4-methyl-5-nitro-pyridine (9.00 g, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.72 (s, 1 H) 8.11 (s, 1 H) 7.77 (s, 1 H) 7.08 (d, J=7.25 Hz, 1 H) 2.18 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₈H₁₀N₂O₃+H]⁺: 183.06, found: 183.2, *t*_R= 0.494 min.

[0927] Synthesis of 6-ethoxy-4-methyl-pyridin-3-amine

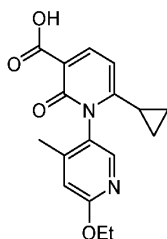
[0928] To a solution of 2-ethoxy-4-methyl-5-nitro-pyridine (9.00 g, 49.40 mmol, 1.00 eq) in EtOH (100 mL) was added saturated NH₄Cl (25 mL) and Fe (13.79 g, 247.01 mmol, 5.00 eq) at 70 °C. The mixture was stirred at 70 °C for 1 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc (2×100 mL). The resulting filtrate was extracted with EtOAc (2×100 mL). The combined organic layer was washed successively with water (2×100 mL) and brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=1/0 to 85/15) to afford 6-ethoxy-4-methyl-pyridin-3-amine (9.00 g, crude) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.45 (s, 1 H) 6.42 (s, 1 H) 4.50 (s, 2 H) 4.11 (q, J=7.09 Hz, 2 H) 2.05 (s, 3 H) 1.23 (t, J=7.00 Hz, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₈H₁₀N₂O₃+H]⁺: 153.09, found: 153.3, *t*_R= 0.163 min.

[0929] Synthesis of methyl 3-[(6-ethoxy-4-methyl-3-pyridyl)amino]-3-oxo-propanoate



[0930] To a solution of 6-ethoxy-4-methyl-pyridin-3-amine (5.00 g, 32.85 mmol, 1.00 eq) in THF (50 mL) was added TEA (9.97 g, 98.56 mmol, 13.72 mL, 3.00 eq) and methyl 3-chloro-3-oxo-propanoate (6.73 g, 49.28 mmol, 5.26 mL, 1.50 eq) at 0 °C. The mixture was stirred at 0 °C for 2 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O 50 mL, and then extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine 50 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with pet. ether: EtOAc (1:1) at 25 °C for 60 min to afford methyl 3-[(6-ethoxy-4-methyl-3-pyridyl)amino]-3-oxo-propanoate (5.50 g, 66.36% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 9.62 (s, 1 H) 7.98 (s, 1 H) 6.68 (s, 1 H) 4.25 (q, J=7.00 Hz, 2 H) 3.66 (s, 3 H) 3.48 (s, 2 H) 2.15 (s, 3 H) 1.29 (t, J=7.00 Hz, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₆O₄N₂+H]⁺: 253.11, found: 253.2, *t*_R = 0.307 min.

[0931] Synthesis of 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 57]

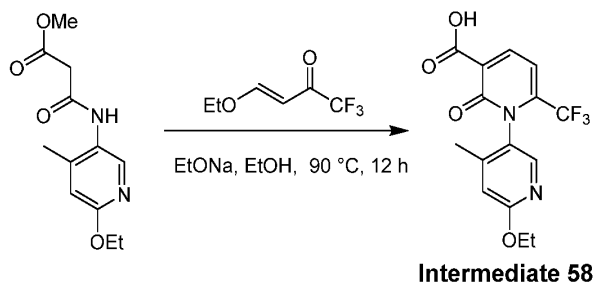


[0932] To a solution of methyl 3-[(6-ethoxy-4-methyl-3-pyridyl)amino]-3-oxo-propanoate (200.00 mg, 792.81 μmol, 1.00 eq) and (E)-1-cyclopropyl-3-methoxy-prop-2-en-1-one (150.02 mg, 1.19 mmol, 1.50 eq) in EtOH (3 mL) was added EtONa (269.76 mg, 3.96 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3×20 mL), then the aqueous phase adjusting the pH to 2 with 2N HCl. Then the resulting solution was extracted with EtOAc (2×20 mL). The combined organic layer was washed successively with water (2×20 mL) and brine (20 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue to afford 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-

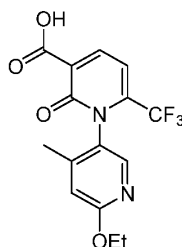
carboxylic acid (150.00 mg, crude) as a yellow oil. MS(ES+) m/z calc'd for

$[M+H]^+$ $[C_{17}H_{18}O_4N_2+H]^+$: 315.12, found: 315.0, t_R = 0.801 min.

[0933] Synthesis of 1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 58]:

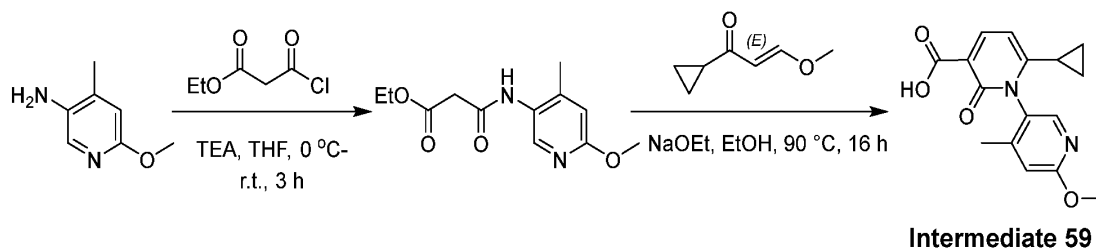


[0934] Synthesis of 1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid [Intermediate 58]

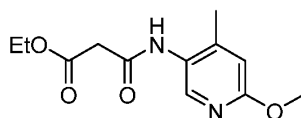


[0935] To a solution of methyl 3-[(6-ethoxy-4-methyl-3-pyridyl)amino]-3-oxopropanoate (300.00 mg, 1.19 mmol, 1.00 eq) and (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (299.89 mg, 1.78 mmol, 254.14 μ L, 1.50 eq) in EtOH (6 mL) was added EtONa (404.63 mg, 5.95 mmol, 5.00 eq). The mixture was stirred at 90 °C for 12 h. LCMS showed the reaction was completed. The reaction mixture was quenched by addition of H₂O (20 mL) and then extracted with EtOAc (3 $\times$ 20 mL), then the aqueous phase adjusting the pH to 2 with 2N HCl. Then the resulting solution was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give 1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (400.00 mg, crude) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 13.42 (br s, 1 H) 8.40 (d, J =7.38 Hz, 1 H) 8.12 (s, 1 H) 7.27 (d, J =7.50 Hz, 1 H) 6.89 (s, 1 H) 4.34 (br dd, J =7.07, 2.69 Hz, 2 H) 2.00 (s, 3 H) 1.33 (t, J =7.00 Hz, 3 H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{15}H_{13}O_4N_2F_3+H]^+$: 343.08, found: 343.2, t_R = 0.479 min.

[0936] Synthesis of 6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid [Intermediate 59]:

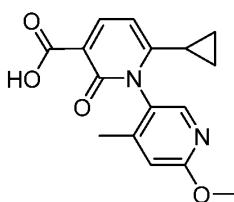


[0937] Synthesis of ethyl 3-((6-methoxy-4-methylpyridine-3-yl)amino)-3-oxopropanoate



[0938] To a stirred solution of 6-methoxy-4-methylpyridin-3-amine (10 g, 72.375 mmol, 1.00 eq) in THF (100 mL), triethylamine (30.4 mL, 346 mmol, 3.00 eq) was added and stirred at 0 °C for 10 min. Then ethyl 3-chloro-3-oxopropanoate (11 mL, 173 mmol, 1.50 eq) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 1 hour. After completion of reaction, the reaction mixture was diluted by Na₂CO₃ solution (100 mL) and extracted by ethyl acetate (2x100 mL). Combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to obtain crude product. The crude product was purified by silica gel column chromatography, using 40-50% ethyl acetate-hexane as a gradient to afford ethyl 3-((6-methoxy-4-methylpyridine-3-yl)amino)-3-oxopropanoate (7.90 g, 43% yield) as pale brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₆N₂O₄+H]⁺: 253.27, found: 253.0, *t_R* = 1.54 min.

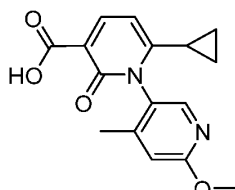
[0939] Synthesis of 6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid [Intermediate 59]



[0940] To a stirred solution of ethyl 3-((6-methoxy-4-methylpyridin-3-yl)amino)-3-oxopropanoate (10.35 g, 41.03 mmol, 1.0 eq) in ethanol (100 mL) was added (*E*)-1-cyclopropyl-3-methoxyprop-2-en-1-one (5.0 g, 61.54 mmol, 1.5 eq) and sodium ethoxide 20% in ethanol (19.3 g, 123.1 mmol, 3 eq) at 0 °C. The reaction mixture was stirred for 16 h at 80 °C. After completion of the reaction, reaction mixture was concentrated under vacuum get crude residue. The residue was dissolved in water (100 mL) and extracted with ethyl acetate (150 mL). Aqueous layer was acidified with 1N HCl to adjust pH 1-2 at 0 °C, resulting precipitate was filtered and washed with water (50 mL) and dried under vacuum to afford 6-cyclopropyl-6'-

methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (4.9 g, 40% yield) as pale-yellow solid. ^1H NMR (401 MHz, $\text{DMSO-}d_6$) δ (ppm) = 14.05 (s, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 8.20 (s, 1H), 6.98 (s, 1H), 6.56 (d, $J = 7.8$ Hz, 1H), 3.91 (s, 3H), 2.03 (s, 3H), 1.48 - 1.33 (m, 1H), 1.06 - 0.84 (m, 4H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4+\text{H}]^+$: 301.3, found: 253.0, $t_R = 1.54$ min.

[0941] Purification of 6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid: Atropisomer-1 (P1) of Intermediate 59]:



Atropisomer 1

[0942] 4.9g of racemic compound was submitted for chiral separation and isolated Atropisomer-1 (P1) = 2.1 g and Atropisomer-1 (P2) = 1.6 g.

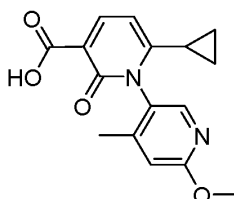
[0943] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 2.1 g (Atrop-1) of the titled compound as a pale-yellow solid.

[0944] SFC Purification method: No Of Injections 60 (81.0mg/inj/11.0min), Column Chiral Pak-IG (30 X 250mm, 5 μm), MP(A)C02 70.0 g/min, MP(B)Co-Solvent 30.0ml/min (MeOH:MeCN), Total Flow rate (mL/min) 100g-30%-100bar, Diluent MP+THF, Detection 340 nm.

[0945] ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm) = 14.03 (s, 1H), 8.40 (d, $J = 7.8$ Hz, 1H), 8.19 (s, 1H), 6.98 (s, 1H), 6.56 (d, $J = 8.0$ Hz, 1H), 3.91 (s, 3H), 2.03 (s, 3H), 1.48 - 1.27 (m, 1H), 1.04 - 0.82 (m, 4H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4+\text{H}]^+$: 301.3, found: 301.46, $t_R = 4.1$ min. Chiral HPLC purity: 98.38 %, $t_R = 2.283$ min, ee = 96.76 %.

[0946] Specific optical rotation (SOR): 46.4, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.05 w/v%.

[0947] Purification of 6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid: Atropisomer-2 (P2) of Intermediate 59]:

**Atropisomer 2**

[0948] 4.9 g of racemic compound was submitted for chiral separation and isolated

Atropisomer-1 (P1) = 2.1 g and Atropisomer-1 (P2) = 1.6 g.

[0949] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 1.6 g (Atrop-2) of the titled compound as a pale-yellow solid.

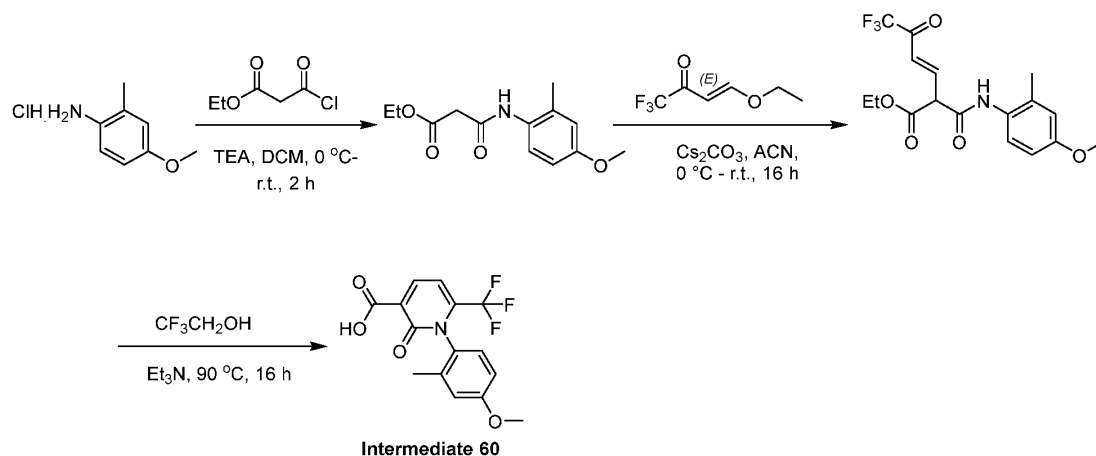
[0950] SFC Purification method: No Of Injections 60 (81.0 mg/inj/11.0min), Column ChiralPak-IG (30X250mm,5 μ m), MP(A)C02 70.0 g/min, MP(B)Co-Solvent 30.0ml/min (MeOH:MeCN), Total Flow rate (mL/min) 100g-30%-100bar, Diluent MP+THF, Detection 340 nm.

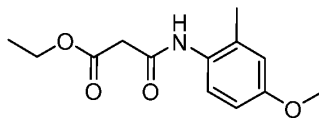
[0951] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) = 14.04 (s, 1H), 8.40 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 6.98 (s, 1H), 6.56 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 2.03 (s, 3H), 1.45 - 1.33 (m, 1H), 1.01 - 0.86 (m, 4H). MS(ES)+ m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2+\text{H}]^+$: 301.3, found: 301.46, t_R = 4.12 min.

[0952] Chiral HPLC purity: 96.58%, t_R = 3.831 min, ee = 93.16 %.

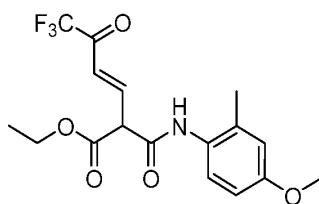
[0953] Specific optical rotation (SOR): -22.8, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.05 w/v%

[0954] **Synthesis of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 60]:**



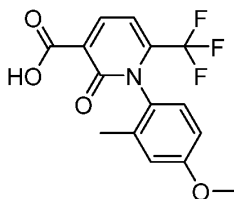
[0955] Synthesis of ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxo-propanoate

[0956] To a stirred solution of 4-methoxy-2-methyl-aniline hydrochloride (19.0 g, 138.5 mmol, 1.0 eq) in THF (160 mL), TEA (58.2 mL, 415.5 mmol 3.0 eq) was added and stirred at 0 °C for 10 min. Then ethyl 3-chloro-3-oxo-propanoate (31.28 g, 207.8 mmol, 1.50 eq) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 1 hour. After completion of reaction, the reaction mixture was diluted by Na₂CO₃ solution (100 mL) and extracted with ethyl acetate (2x100 mL). Combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to obtain crude product. The crude product was purified by silica gel column chromatography, using 10-15% ethyl acetate-hexane as a gradient to afford ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxo-propanoate (18.00 g, 88% yield) as pale brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₃H₁₇NO₄+H]⁺: 251.1, found: 251.9, *t_R* = 1.66 min.

[0957] Synthesis of ethyl (*E*)-6,6,6-trifluoro-2-[(4-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate

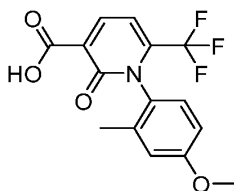
[0958] To a stirred solution of ethyl 3-(4-methoxy-2-methyl-anilino)-3-oxo-propanoate (16.0 g, 63.67 mmol, 1.0 eq) and cesium carbonate (29.1 g, 89.2 mmol, 1.40 eq) in MeCN (180.0 mL) at 25 °C, (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (12.84 g, 76.38 mmol, 1.20 eq) was added dropwise, and the reaction mixture was stirred at 25 °C for 16 hours. After consumption of starting material, reaction mixture was concentrated under reduced pressure to afford ethyl (*E*)-6,6,6-trifluoro-2-[(4-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate (17.00 g, 25.03% yield) as brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₇H₁₈F₃NO₅+H]⁺: 373.2 found: 374.0, *t_R* = 2.16 min.

[0959] Synthesis of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 60]



[0960] To a stirred solution of ethyl (*E*)-6,6,6-trifluoro-2-[(4-methoxy-2-methyl-phenyl)carbamoyl]-5-oxo-hex-3-enoate (20.0 g, 53.58 mmol, 1.0 eq) in trifluoroethanol (200 mL), triethylamine (23 mL, 160.7 mmol, 3.00 eq) was added and heated at 90 °C for 16 hours. After consumption of starting material, reaction mixture was concentrated under reduced pressure to obtain crude residue. The crude was dissolved in water (100 mL) and washed with ethyl acetate (2x100 mL). The aqueous layer was acidified with 2 N HCl to pH ~2-3 and extracted with ethyl acetate (2x500 mL). Combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to afford 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (10 g, 57% yield) as pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.65 (s, 1H), 8.44 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.7 Hz, 1H), 3.81 (s, 3H), 2.01 - 1.95 (m, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄+H]⁺: 328.01, found: 327.8, *t*_R = 1.919 min.

[0961] Purification of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid: Atropisomer-1 (P1) of Intermediate 60:



Atropisomer 1

[0962] 10 g of racemic compound was submitted for chiral separation and isolated Atropisomer-1 (P1) = 3.6 g and Atropisomer-2 (P2) = 2.1 g.

[0963] Atropisomer was separated by chiral SFC (Instrument name: Waters-2767, prep-SFC 100) method to afford 3.6 g (Atrope-1) of the titled compound as a brown solid.

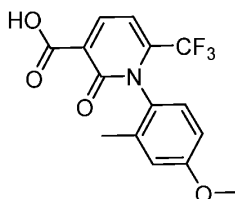
[0964] Chiral Prep SFC Method: No Of Injections 170 (60.0 mg / inj / 15 min), Column CHIARALPAK IC(30X250mm,5μm), MP(A)C02 70.0 g/min, MP(B)Co-Solvent 30.0 ml/min (0.1% Methanolic Ammonia in MEOH), Total Flow rate (mL/min), 100g-30%- 100 bar, Diluent Methanol, Detection 220 nm, Nature HALF WHITE, Instrument ID: SFC-05.

[0965] ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.44 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.91 (dd, *J* = 2.8, 8.8 Hz, 1H), 3.81 (s, 3H), 1.98 (s, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₂F₃NO₄+H]⁺: 328.1, found: 328.2, *t*_R = 3.832 min.

[0966] Chiral HPLC purity: 100 %, t_R = 3.634 min, ee = 100 %.

[0967] Specific optical rotation (SOR): 192.02, Method: Light Source Na, Monitor wavelength 589 nm, D.I.T. 5 sec, No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture(L) Auto, Mode Specific O.R., Path Length 10 mm, Concentration 0.1078 w/v%, Water content of sample 0 %, Factor 1.

[0968] **Purification of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid: Atropisomer-2 (P2) of Intermediate 60:**



Atropisomer 2

[0969] 10 g of racemic compound was submitted for chiral separation and isolated Atropisomer-1 (P1) = 3.6 g and Atropisomer-2 (P2) = 2.1 g.

[0970] Atropisomer was separated by chiral SFC (Instrument name: Waters-2767, prep-SFC 100), method to afford 2.1 g yield of the titled compound as brown gummy substance.

[0971] Chiral Prep SFC Method: No Of Injections 170 (60.0 mg / inj / 15 min), Column CHIARALPAK IC(30X250mm,5 μ m) , MP(A)C02 70.0 g/min, MP(B)Co-Solvent 30.0 ml/min (0.1% Methanolic Ammonia in MEOH), Total Flow rate (mL/min),

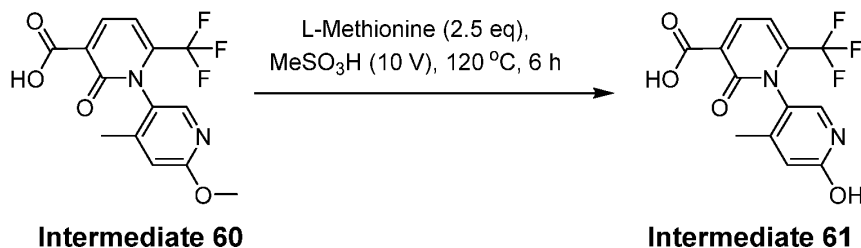
[0972] 100g-30%- 100 bar, Diluent Methanol, Detection 220 nm, Nature HALF WHITE, Instrument ID: SFC-05.

[0973] ^1H NMR (400 MHz, DMSO- d_6): δ (ppm) = 13.82 - 13.36 (m, 1H), 8.43 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 6.98 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 2.8, 8.8 Hz, 1H), 3.81 (s, 3H), 1.98 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{15}\text{H}_{12}\text{F}_3\text{NO}_4+\text{H}]^+$: 328.1, found: 328.2, t_R = 3.50 min.

[0974] Chiral HPLC purity: 99.27 %, t_R = 3.882, ee = 98.54 %.

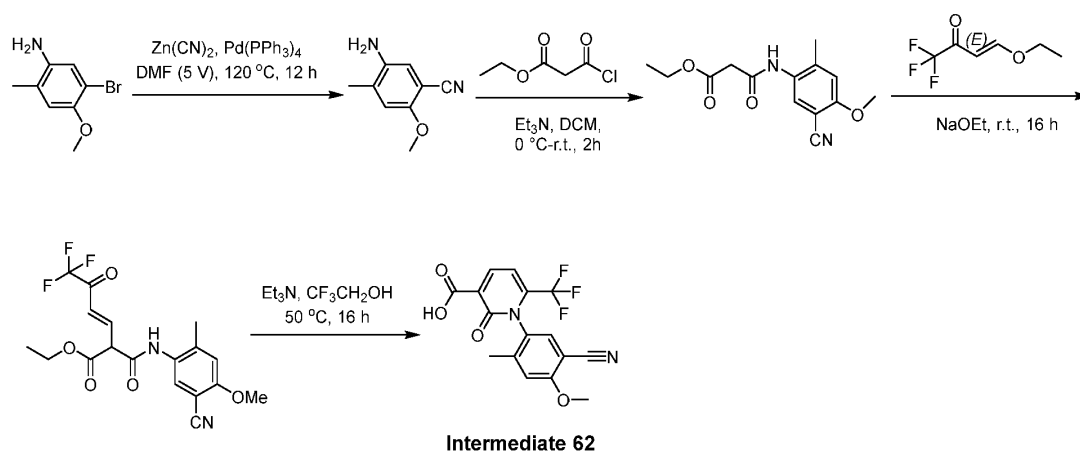
[0975] Specific optical rotation (SOR): -119.00, Method: Light Source Na, Monitor wavelength: 589 nm, D.I.T. - 5 sec, No. of cycle-5, Cycle interval 5-sec, Temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture(L) Auto, Mode Specific O.R. Path Length: 10 mm, Concentration: 0.1 w/v%, Water content of sample 0 %, Factor- 1.

[0976] **Synthesis of 1-(6-hydroxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 61]:**

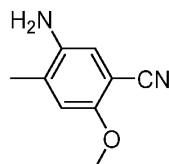


[0977] To a stirred solution of 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (5 g, 15.23 mmol, 1.0 eq) in methanesulfonic acid (50 mL) was added L-Methionine (6.888 g, 45.70 mmol, 3 eq) at room temperature. After completion of reaction, the reaction mixture was poured into chilled water (100 mL) and extracted with ethyl acetate (2x100 mL). Combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to afford 1-(6-hydroxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (2.8 g, 56% yield) as pale-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.37 (d, J = 7.5 Hz, 1H), 7.67 (s, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.34 (s, 1H), 1.84 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{13}\text{H}_9\text{F}_3\text{N}_2\text{O}_4+\text{H}]^+$: 315.2, found: 314.9, t_R = 1.43 min.

[0978] Synthesis of 1-(5-cyano-4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid (Intermediate 62):



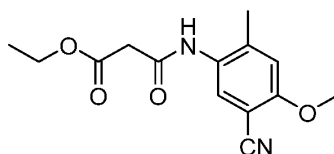
[0979] Synthesis of 5-amino-2-methoxy-4-methylbenzonitrile



[0980] To a stirred solution of 5-bromo-4-methoxy-2-methylaniline (7g, 32.395 mmol, 1.00 eq) in DMF (70 mL), was added zinc cyanide (7.685 g, 64.791 mmol, 2.0 eq) at room

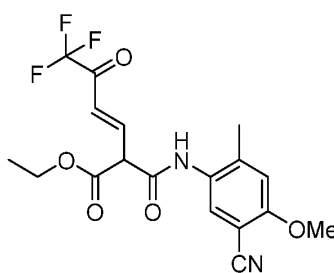
temperature, and reaction mixture was purged with nitrogen for 5 minutes, then added tetrakis(triphenylphosphine)palladium(0) (3.7814 g, 3.2396 mmol, 0.1 eq) at room temperature. Reaction mixture was stirred at 120°C for 16 hours. After completion of the reaction, reaction mass was poured in chilled water (100 mL) and extracted with Ethyl acetate (2x50 mL). The organic layer was dried over Na₂SO₄ and concentrated under vacuum. The crude compound was purified by combi flash using YMC 80 g cartridge, eluting with 0-40% ethyl acetate/heptane to afford 5-amino-2-methoxy-4-methylbenzonitrile (2.1 g, 38 % yield) as pale-yellow solid. MS (ES+) m/z calc'd for [M+H]⁺ [C₉H₁₀N₂O+H]⁺: 162.19, found: 162.9, t_R= 1.43 min.

[0981] Synthesis of ethyl 3-(5-cyano-4-methoxy-2-methyl-anilino)-3-oxo-propanoate



[0982] To a stirred solution of 5-amino-2-methoxy-4-methyl-benzonitrile (2 g, 12.331 mmol, 1.0 eq) in tetrahydrofuran (20 mL), was added triethylamine (2.51 g, 24.662 mmol, 2.0 eq) at 0 °C stirred for 5 min., then added ethyl 3-chloro-3-oxo-propanoate (2.0422 g, 13.564 mmol, 1.1 eq) at 0 °C drop wise. Reaction mass stirred at room temperature for 16 hours. After completion of the reaction, reaction mass diluted with water (50 mL) and extracted with ethyl acetate (3x30mL). Organic layer was dried over Na₂SO₄ and concentrated under vacuum get crude product. The crude product was washed with diethyl ether (2x10 mL) and dried to afford ethyl 3-(5-cyano-4-methoxy-2-methyl-anilino)-3-oxo-propanoate (2.00 g, 55.05 % yield) as pale-yellow solid. MS(ES+) m/z calc'd for [M+H]⁺ [C₁₄H₁₆N₂O₄+H]⁺: 276.3, found: 276.9, t_R= 1.66 min.

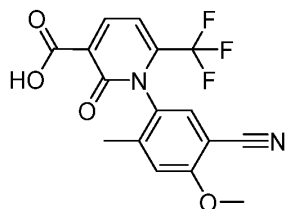
[0983] Synthesis of ethyl (E)-2-((5-cyano-4-methoxy-2-methylphenyl)carbamoyl)-6,6,6-trifluoro-5-oxohex-3-enoate



[0984] To a stirred solution of ethyl 3-((5-cyano-4-methoxy-2-methylphenyl)amino)-3-oxopropanoate (2 g, 6.788 mmol, 1.0 eq) in Acetonitrile (20 mL) to that added Caesium carbonate (6.64 g, 20.4 mmol, 3.0 eq) then added (E)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (1.369 g, 8.143 mmol, 1.2 eq) at room temperature. Reaction mass stirred at room temperature for 16 hours. After completion of the reaction, reaction mass was concentrated under vacuum to get crude product. The crude product was washed with diethyl ether (2x10 mL) and dried to

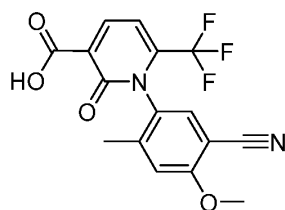
afford ethyl (*E*)-2-((5-cyano-4-methoxy-2-methylphenyl)carbamoyl)-6,6,6-trifluoro-5-oxohex-3-enoate (4.9 g, 63% yield of the titled compound as yellow solid. MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₈H₁₇F₃N₂O₅+H]⁺: 398.1, found: 398.8, *t_R* = 1.83 min.

[0985] Synthesis of 1-(5-cyano-4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid [Intermediate 62]



[0986] To a stirred solution of ethyl (*E*)-2-((5-cyano-4-methoxy-2-methylphenyl)carbamoyl)-6,6,6-trifluoro-5-oxohex-3-enoate (4.9 g, 12 mmol, 1.0 eq) in 2,2,2-trifluoroethanol (30 mL) was added Triethylamine (5.2 mL, 37 mmol, 3 eq) at 0 °C. The reaction mixture was stirred at 90 °C for 16 h. After completion of the reaction, reaction mixture was concentrated under reduced pressure to obtain crude residue. The crude was dissolved in water (100 mL) and extracted with ethyl acetate (2x50 mL). Aqueous layer was acidified with 1N HCl to adjust pH-2-3 at 0 °C, extracted with ethyl acetate (3x30 mL). Combined organic layer were dried over anhydrous Na₂SO₄, then concentrated under vacuum to afford 1-(5-cyano-4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxylic acid (3.0 g, 59% yield) as pale-yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 13.45 (s, 1H), 8.39 (d, *J* = 7.4 Hz, 1H), 7.91 (s, 1H), 7.36 (s, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 3.99 (s, 3H), 2.10 (s, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₁F₃N₂O₅+H]⁺: 352.3, found: 353.25, *t_R* = 3.56 min.

[0987] Purification of 1-(5-cyano-4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid: Atropisomer-1 (P1) of Intermediate 62:



Atropisomer 1

[0988] 3.0 g of racemic compound was submitted for chiral separation and isolated atropisomer-1 (P1) = 1.0 g and atropisomer-2 (P2) = 750 mg.

[0989] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 1.0 g (Atrope-1) of the titled compound as a pale-yellow solid.

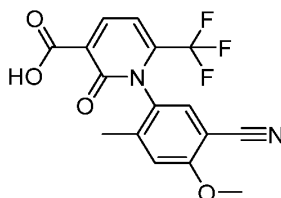
[0990] SFC Purification method: No of Injections: 160 (20.0 mg / inj /7 min), Column: CHIRALPAK IK (30X250mm,5 μ m), MP(A)C02: 72.0 g/min, MP(B)Co-Solvent: 18.0 ml/ min (Methanol), Total Flow rate: (mL/min)-90g-20%-100 ba. Diluent: Methanol. Detection: 240 nm.

[0991] ^1H NMR (400 MHz, DMSO- d_6) δ = 13.53 - 13.33 (s, 1H), 8.37 (d, J = 7.3 Hz, 1H), 7.91 (s, 1H), 7.36 (s, 1H), 7.25 (d, J = 7.5 Hz, 1H), 3.99 (s, 3H), 2.10 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_5+\text{H}]^+$: 352.3, found: 353.25, t_R = 3.56 min.

[0992] Chiral HPLC purity: 98.12%, t_R = 3.021 min, ee = 96.24 %.

[0993] Specific optical rotation (SOR): 28.4, Light Source Na, Monitor wavelength 589 nm, D.I.T. 5 sec, No. of cycle 5, Cycle interval 5 sec, temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture (L) Auto, Mode Specific O.R., Path Length 10 mm, Concentration 0.1 w/v%.

[0994] Purification of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid: Atropisomer-2 (P2) of Intermediate 62:



Atropisomer 2

[0995] 3.0 g of racemic compound was submitted for chiral separation and isolated atropisomer-1 (P1) = 1.0 g and atropisomer-2 (P2) = 750 mg.

[0996] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 570mg (Atrope-2) of the titled compound as a pale yellow solid.

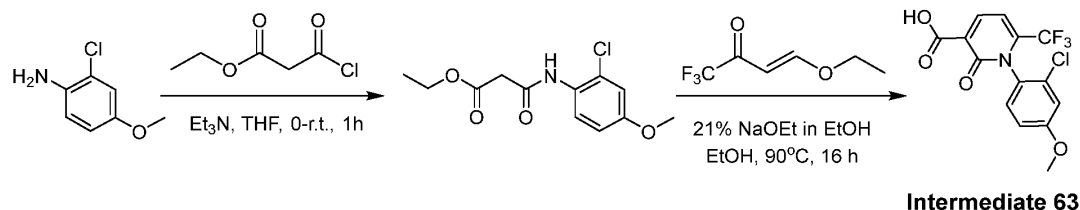
[0997] SFC Purification method: No Of Injections- 160 (20.0 mg/inj /7 min), Column- CHIRALPAK IK (30X250mm,5 μ m) ,MP(A)C02- 72.0 g/min, MP(B)Co-Solvent- 18.0 ml/ min (Methanol), Total Flow rate (mL/min)-90g-20%-100 ba ,Diluent- Methanol Detection -240 nm.

[0998] ^1H NMR (400 MHz, DMSO- d_6) δ = 13.65 - 13.27 (s, 1H), 8.37 (d, J = 7.5 Hz, 1H), 7.91 (s, 1H), 7.37 (s, 1H), 7.25 (d, J = 7.5 Hz, 1H), 4.00 (s, 3H), 2.10 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_2\text{O}_5+\text{H}]$: 352.3, found: 353.25, t_R = 3.56 min.

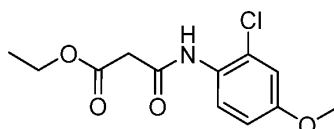
[0999] Chiral HPLC purity: 88.24%, t_R = 2.537 min, ee = 76.48 %.

[1000] Specific optical rotation (SOR): 26.8, Light Source Na, Monitor wavelength 589 nm, D.I.T. 5 sec, No. of cycle 5, Cycle interval 5 sec, temp. Monitor Holder, Temp. Corr. Factor None, Aperture(S) 8.0mm, Aperture (L) Auto, Mode Specific O.R., Path Length 10 mm, Concentration 0.1 w/v%.

[1001] Synthesis of 1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid [Intermediate 63]:

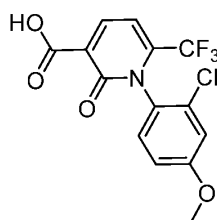


[1002] Synthesis of ethyl 3-((2-chloro-4-methoxyphenyl)amino)-3-oxopropanoate



[1003] To a stirred solution of 2-chloro-4-methoxyaniline (10 g, 63.45 mmol, 1.00 eq) in THF (100.00 mL), triethylamine (27 mL, 190.4 mmol, 3.00 eq) was added and stirred at 0 °C for 10 min. Then, ethyl 3-chloro-3-oxopropanoate (9.7 mL, 76.14 mmol, 1.20 eq) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 1 hour. After completion of reaction, reaction mixture was diluted by Na₂CO₃ solution (100 mL) and extracted by EtOAc (2x100 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuum to obtain crude product. The crude compound was purified by combi flash using YMC 80 g cartridge, eluting with 0-40 % EtOAc/heptane to afford ethyl 3-((2-chloro-4-methoxyphenyl)amino)-3-oxopropanoate (12 g, 44.83 % yield) as pale brown solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₂H₁₄ClNO₄]⁺: 271.1, found: 272.7, *t*_R= 1.79 min.

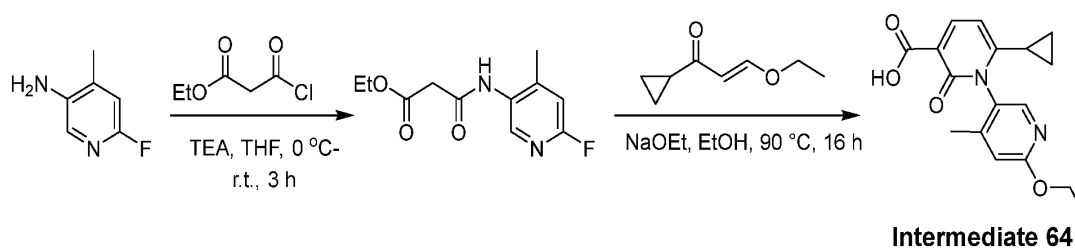
[1004] Synthesis of 1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid [Intermediate 63]



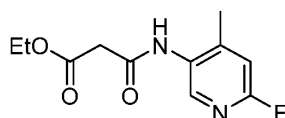
[1005] To a stirred solution of ethyl 3-((2-chloro-4-methoxyphenyl)amino)-3-oxopropanoate (3 g, 11.0 mmol, 1.00 eq) in ethanol (30 mL) was added (*E*)-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (2.23 g, 13.2 mmol, 1.50 eq) and 21% sodium ethoxide in ethanol (13 mL, 33.1 mmol, 3 eq) was added at 25 °C and the reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction, the reaction mass was concentrated under vacuum to get residue. The obtained residue was acidified with 1N HCl up to pH~1-2 at 0 °C. The resulting precipitate was filtered,

washed with water (30 mL), and then dried under reduced pressure to obtain crude. The crude compound was triturated with diethyl ether (40 mL) to afford 1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxylic acid (1 g, 25.3 % yield) as a pale-yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ = 13.53 - 13.31 (m, 1H), 8.46 - 8.30 (m, 1H), 7.69 - 7.51 (m, 1H), 7.43 - 7.19 (m, 2H), 7.16 - 7.01 (m, 1H), 3.94 - 3.80 (m, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{14}\text{H}_9\text{ClF}_3\text{NO}_4]^+$: 347.02, found: 347.9, t_R = 1.96 min.

[1006] Synthesis of 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 64]:

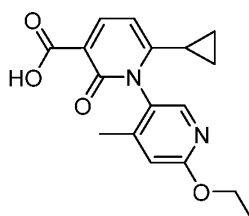


[1007] Synthesis of ethyl 3-((6-fluoro-4-methylpyridin-3-yl)amino)-3-oxopropanoate



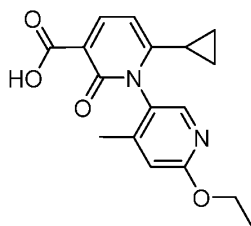
[1008] To a stirred solution of 6-fluoro-4-methyl-pyridin-3-amine (25 g, 198.21 mmol) in THF (250 mL), triethylamine (3.0 equiv., 594.62 mmol) was added and stirred at 0 °C for 10 min. Then, ethyl 3-chloro-3-oxopropanoate (1.1 equiv., 218.03 mmol) was added at 0 °C and the resulting reaction mixture was stirred at room temperature for 3 h. After completion of reaction, the reaction mixture was diluted by Na_2CO_3 solution (100 mL) and extracted by EtOAc (2x250 mL). Combined organic extracts were washed with brine (250 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum to obtain crude product. The crude product was purified by silica gel column chromatography, using 40-50% EtOAc-hexane as a gradient to afford ethyl 3-((6-fluoro-4-methylpyridin-3-yl)amino)-3-oxopropanoate (23.0 g, 48.3% yield) as pale brown solid. MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_4+\text{H}]^+$: 240.09, found: 241.0, t_R = 1.53 min.

[1009] Synthesis of 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid [Intermediate 64]



[1010] To a stirred solution of ethyl 3-[(6-fluoro-4-methyl-3-pyridyl)amino]-3-oxo-propanoate (9.00 g, 37.5 mmol) in ethanol (90.00 mL) was added (~{E})-1-cyclopropyl-3-ethoxy-prop-2-en-1-one (56.2 mmol, 1.5 eq) at 0 °C, followed by Sodium ethoxide 20% in ethanol (112 mmol, 3 eq). The reaction mixture was stirred at 80 °C for 16 hours. After completion of the reaction, reaction mixture was concentrated under vacuum get crude residue. The residue was dissolved in water (100 mL) and extracted with EtOAc (150 mL). Aqueous layer was acidified with 1N HCl to adjust pH~1-2 at 0 °C and resulting precipitate was filtered, washed with water (50 mL) and dried under vacuum to afford 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid (7.2 g, 61% yield) as pale-yellow solid. ¹H NMR (400 MHz, DMSO-d₆) δ = 14.04 (s, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 6.93 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 4.40 - 4.30 (m, 2H), 2.01 (s, 3H), 1.39 - 1.31 (m, 4H), 0.98 - 0.89 (m, 4H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₆N₂O₄+H]⁺ : 314.13, found: 315.3, *t_R* = 4.486 min.

[1011] **Purification 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid: Atropisomer-1 (Peak 2) of Intermediate 64:**



Atropisomer 1

[1012] 4.0 g of racemic compound was submitted for chiral separation and isolated Atropisomer-2 (Peak-1) = 1.5 g and Atropisomer-1 (Peak-2) = 1.0 g.

[1013] Atropisomer was separated by chiral SFC method to afford 1.5 g (Atrop-1) of the titled compound as a pale-yellow solid.

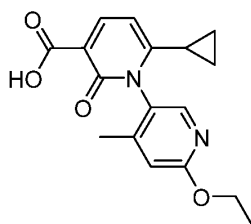
[1014] SFC Purification method: No Of Injections 135 (30 mg/ inj /5.0 min), Column Chiralpak AD-H (20*250mm,5μm), MP(A)C02 42.0 g/min, MP(B)Co-Solvent 18 ml/min (0.1% Formic acid in MeOH:MeCN), Total Flow rate (mL/min) 60g-30% ,100 bar, Diluent MP, Detection 330 nm.

[1015] ¹H NMR (400 MHz, DMSO-d₆) δ = 14.04 (s, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 6.93 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 4.40 - 4.30 (m, 2H), 2.01 (s, 3H), 1.39 - 1.31 (m, 4H), 0.98 - 0.89 (m, 4H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₆N₂O₄+H]⁺ : 314.13, found: 315.36, *t_R* = 3.566 min.

[1016] Chiral HPLC purity: 100 %, *t_R* = 1.254 min, ee = 100 %.

[1017] Specific optical rotation (SOR): -73.2000, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

[1018] Purification 6-cyclopropyl-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid: Atropisomer-2 (Peak-1) of Intermediate 64:



Atropisomer 2

[1019] 4.0 g of racemic compound was submitted for chiral separation and isolated Atropisomer-1 (P1) = 1.5 g and Atropisomer-2 (P2) = 1.0 g.

[1020] Atropisomer was separated by chiral SFC method to afford 1.0 g (Atrop-2) of the titled compound as a pale-yellow solid.

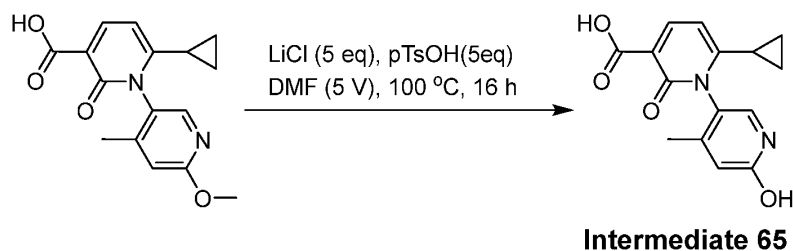
[1021] SFC Purification method: No Of Injections 135 (30 mg/ inj /5.0 min), Column Chiralpak AD-H (20*250mm,5μm), MP(A)C02 42.0 g/min, MP(B)Co-Solvent 18 ml/min (0.1% Formic acid in MeOH:MeCN), Total Flow rate (mL/min) 60g-30% ,100 bar, Diluent MP, Detection 330 nm.

[1022] ¹H NMR (400 MHz, DMSO-d₆) δ = 14.04 (s, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 8.16 (s, 1H), 6.93 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 4.40 - 4.30 (m, 2H), 2.01 (s, 3H), 1.39 - 1.31 (m, 4H), 0.98 - 0.89 (m, 4H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₆H₁₆N₂O₄+H]⁺ : 314.13, found: 315.36, *t_R* = 3.549 min.

[1023] Chiral HPLC purity: 99.76%, *t_R* = 3.325 min, ee = 99.52 %.

[1024] Specific optical rotation (SOR): 48.960, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

Synthesis of 6-cyclopropyl-6'-hydroxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid [Atropisomer 1, Intermediate 65]:



[1025] To a stirred solution of 6-cyclopropyl-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid (atropisomer 1, 2 g, 6.660 mmol, 1 eq) in N,N-dimethylformamide (20 mL) was added p-toluenesulfonic acid (5.792g, 33.30 mmol, 5 eq) and lithium chloride (1.426g, 33.30 mmol, 5 eq) at room temperature. The resulting mixture was stirred at 80°C for 16 h and progress was monitored by LCMS and TLC. After completion, the reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3x50 mL). Combined the organic layers was dried over sodium sulphate and concentrated under vacuum get crude product which was purified by combi flash by using 40g YMC cartridge and 5-10% MeOH in DCM as an eluent to afford 6-cyclopropyl-6'-hydroxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (1.8 g, 76% yield) as off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 14.08 (s, 1 H) 11.86 (s, 1 H) 8.36 (d, *J*=7.75 Hz, 1 H) 7.69 (s, 1 H) 6.50 (d, *J*=7.75 Hz, 1 H) 6.40 (s, 1 H) 1.84 (s, 3 H) 1.56 - 1.66 (m, 1 H) 0.91 - 1.02 (m, 4 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₅H₁₄N₂O₄+H]⁺ : 286.3 found: 287.21, *t*_R= 3.07 min.

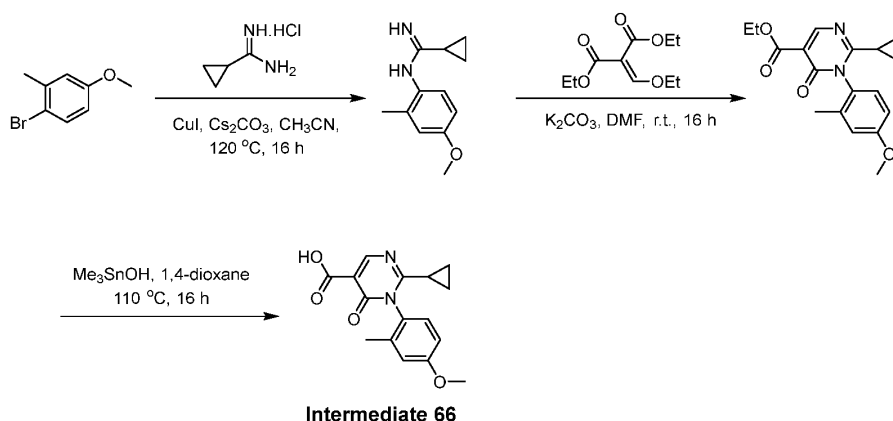
[1026] Method Details: TFA 10 MINS

[1027] Column : XBridge BEH C18 (2.1*30)mm, 2.5um Flow rate: 0.5 mL/min. Mobile Phase A: 0.05%TFA in Water Mobile Phase B: 0.05%TFA in Acetonitrile Column Temp.: 40°C Gradient Program Time/B: 0.0/2, 1.5/2, 6/98, 8/98, 9.0/2,10/2.

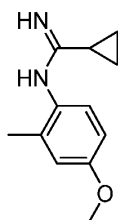
[1028] Chiral HPLC purity :100%, *t*_R= 2.749 min, ee= 100 %. Column Name : CHIRALPAK AD-H (150*4.6mm,5μm), Mobile Phase A : CO₂ MobilePhase B : 0.1% MEONH₂ in MEOH, A B : 70:30 Column ID : M-ARD-CAL-049 Flow rate : 3g-30% System Name : AMC_SFC_07.

[1029] Specific optical rotation (SOR): +17.43, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.100943 w/v% Water content of sample 0 % Factor 1; solvent -methanol.

[1030] Synthesis of 2-cyclopropyl-1-(4-methoxy-2-methylphenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid [Intermediate 66]:

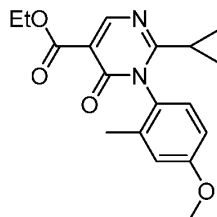


[1031] Synthesis of N-(4-methoxy-2-methylphenyl)cyclopropanecarboximidamide



[1032] To a stirred solution of 1-bromo-4-methoxy-2-methyl-benzene (8.3337 g, 41.449 mmol, 1 eq) in MeCN (50 mL), cesium carbonate (27 g, 82.8 mmol, 3 eq) was added at room temperature. Then, cyclopropanecarboximidine;hydrochloride (5 g, 41.466 mmol, 1.0 eq) followed by copper(I) iodide (789.7 mg, 4.147 mmol, 0.1 eq) were added at room temperature and the resulting reaction mixture was stirred at 120 °C for 16 hours. After consumption of starting material, reaction mixture was filtered through celite bed, washed with DCM and then filtrate was concentrated to get crude product. The obtained residue was diluted with ethyl acetate (50 mL) and washed with water (40 mL). The organic layer dried over sodium sulfate and concentrated under vacuum to get crude product which was triturated with n-pentane (10 mL), decant the layer and dried under vacuum to afford N-(4-methoxy-2-methylphenyl)cyclopropanecarboximidamide (1.5 g, 13% yield) as pale green gummy liquid. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{12}H_{16}N_2O+H]^+$: 205.27, found: 205.1, t_R = 1.09 min, Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5 μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

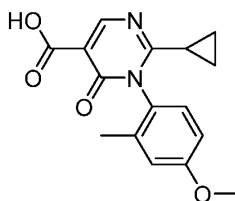
[1033] Synthesis of ethyl 2-cyclopropyl-1-(4-methoxy-2-methylphenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate



[1034] To a stirred solution of N-(4-methoxy-2-methylphenyl)cyclopropanecarboximidamide (1.5 g, 5.5 mmol, 1 eq) in N,N-dimethylformamide (15 mL), cesium carbonate (2.7 g, 8.3 mmol, 1.5 eq) and diethyl 2-(ethoxymethylene)propanedioate (1.3 mL, 6.5 mmol, 1.2 eq) were added at 0 °C. The resulting mixture was stirred at room temperature for 16 h. After completion, reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (2x30 mL). The combined organic layer was washed with saturated brine solution (2x30 mL), dried (Na₂SO₄), filtered and concentrated to get crude product which was then purified by flash column chromatography eluting 30-35% EtOAc in heptane to afford ethyl 2-cyclopropyl-1-(4-methoxy-2-methylphenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (650 mg, 26% yield) as pale-yellow semi solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.51 (s, 1 H) 7.27 (d, *J*=8.63 Hz, 1 H) 7.04 (d, *J*=2.50 Hz, 1 H) 6.96 (dd, *J*=8.57, 2.69 Hz, 1 H) 4.18 - 4.25 (m, 3 H) 3.82 (s, 3 H) 2.02 (s, 3 H) 1.32 - 1.39 (m, 1 H) 1.25 (t, *J*=7.07 Hz, 3 H) 1.13 - 1.19 (m, 2 H) 0.95 - 1.02 (m, 2 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₁₈H₂₀N₂O₄+H]⁺: 329.4, found: 329.0, *t*_R: 1.89 min.

[1035] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

[1036] **Synthesis of 2-cyclopropyl-1-(4-methoxy-2-methylphenyl)-6-oxo-1,6-dihydropyrimidine-5-carboxylic acid [Intermediate 66]**



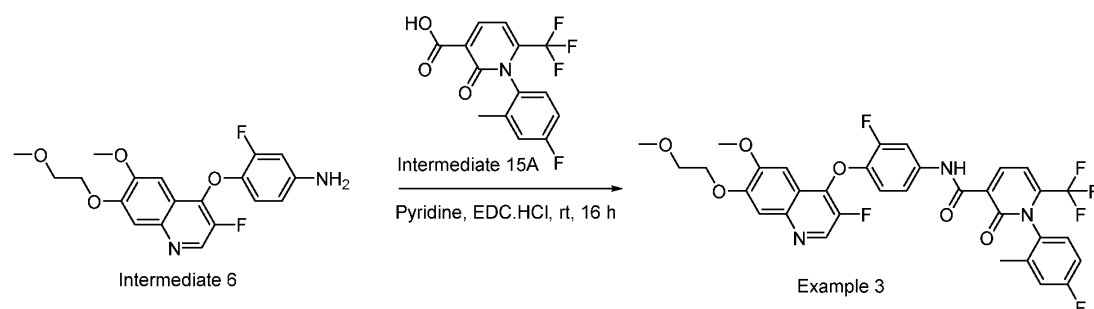
[1037] To a stirred solution of ethyl 2-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxylate (550.00 mg, 1.209 mmol, 1 eq) in 1,4-dioxane (12 mL) was added Trimethyltinhydroxide (927 mg, 5.024 mmol, 3 eq) at 0 °C and stirred at 110 °C for 16 h. After completion of reaction, solids were filtered and collected filtrate was concentrated under vacuum to get crude product, which was purified by combi flash by using 12 g YMC cartridge 35-40% ethyl acetate in heptane as an eluent to afford 2-cyclopropyl-1-(4-methoxy-2-methylphenyl)-6-

oxo-1,6-dihydropyrimidine-5-carboxylic acid (300 mg, 76.8% yield) as pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ ppm: 12.87 (s, 1 H) 8.65 (s, 1 H) 7.34 (d, $J=8.76$ Hz, 1 H) 7.06 (d, $J=2.50$ Hz, 1 H) 6.98 (dd, $J=8.63$, 2.63 Hz, 1 H) 3.82 (s, 3 H) 2.04 (s, 3 H) 1.41 (dq, $J=8.02$, 4.00 Hz, 1 H) 1.16 - 1.25 (m, 2 H) 1.00 - 1.09 (m, 2 H). MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4+\text{H}]^+$: 301.3, found: 301.4 t_R : 3.363 min.

[1038] Method Details: Column: X-Select CSH C18, (50mm*3.0mm,2.5 μ), Mobile Phase A: 0.05% Formic Acid in Water, Mobile Phase B: 0.05% Formic Acid in Acetonitrile, Flow rate: 1.0mL/min. Column temperature: 40°C, Gradient Program (B%) :0.01/2, 0.3/2, 2.0/98, 2.8/98, 3.0/2,3.7/2.

Final Product Synthesis.

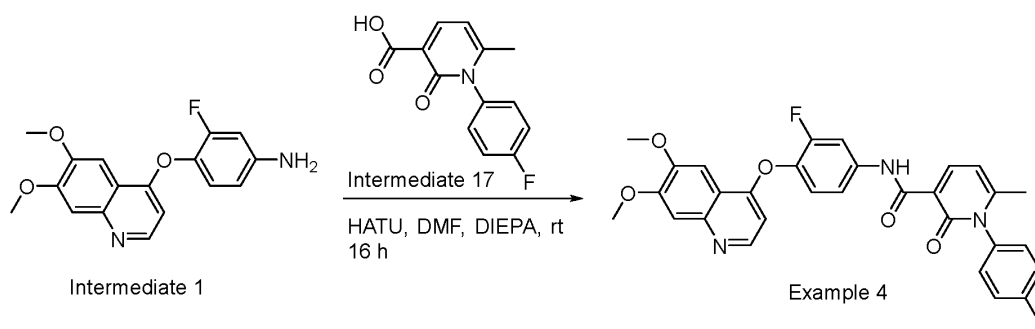
[1039] Synthesis of *N*-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 3]:



[1040] A stirred solution of 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 15A (59 mg, 0.186 mmol, 1.00 eq) in pyridine (1 mL, 0.186 M) was charged with EDC.HCl (107 mg, 0.558 mmol, 3.00 eq), followed by 3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline (70 mg, 0.186 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate (100 mL) and the organic layer was washed with water (2 $\times$ 10 mL), then with saturated brine solution. The organic layer was separated and dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to get the crude product. The crude product was purified by prep-HPLC, [Method F]. After purification, fractions were lyophilized to afford 17 mg, 13.54% yield of Example 3 as a pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.63 (s, 1H), 8.77 (d, $J=2.9$ Hz, 1H), 8.67 (d, $J=7.6$ Hz, 1H), 8.01 (dd, $J=2.6$, 13.1 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.43 - 7.34 (m, 4H), 7.28 - 7.24 (m, 1H), 7.14 - 7.09 (m, 1H), 4.32 - 4.28 (m, 2H), 3.91 (s, 3H), 3.78 - 3.75 (m, 2H), 3.36 (s, 3H), 2.06 (s, 3H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{33}\text{H}_{25}\text{F}_6\text{N}_3\text{O}_6+\text{H}]^+$: 674.16, found: 673.9, $t_R=5.351$ min, [Method W]. Chiral HPLC purity: 99.630%, $t_R=7.034$, ee=

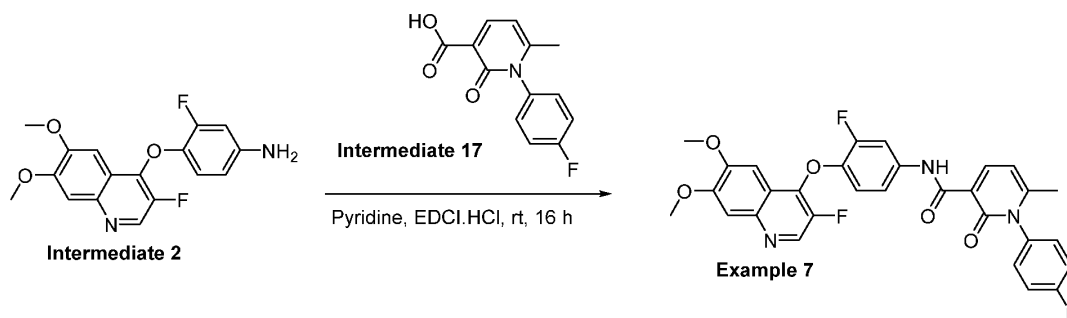
99.26%, Method: Column: CHIRALPAK-IK (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A/B: 80/20 Flow: 1.0 mL/min, COLUMN ID: M-ARD-CAL-038. Specific Optical Rotation (SOR): 89.120, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v% Water content of sample 0 % Factor 1.

[1041] Synthesis of *N*-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide [Example 4]:



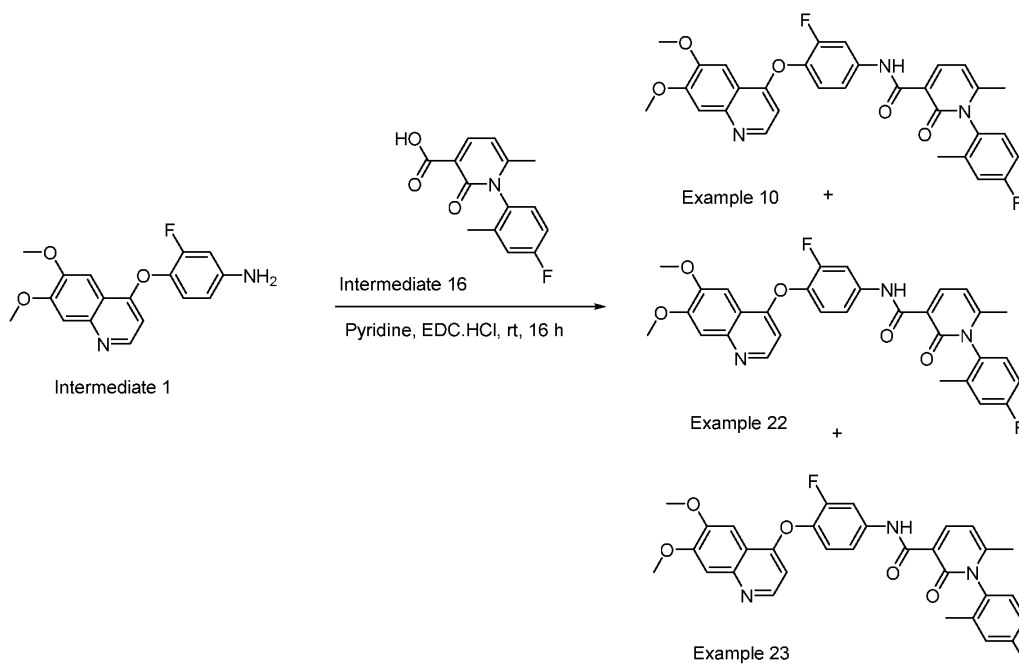
[1042] A solution of 1-(4-fluorophenyl)-1,2-dihydro-6-methyl-2-oxo-3-pyridine carboxylic acid (2.05 g, 8.27 mmol, 1.30 eq) in DMF (5 mL, 1.2726 M), DIPEA (5.5 mL, 31.8 mmol, 5.00 eq) and HATU (6.04 g, 15.9 mmol, 2.50 eq) was charged with 4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (2.00 g, 6.36 mmol, 1.00 eq) at room temperature and reaction mixture was stirred at this temperature for an additional 16 h. (Note: 4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline, Intermediate 17 is from commercial sources). The crude product was purified by Combiflash, Column: Hi-purit Flash Column Silica 40 g, Mobile phase: EtOAc:Heptane (78:22), Flow rate: 30 mL/min. Pure fractions concentrated under reduced pressure to afford 1.02 g, 29.51% yield of Intermediate 4 as a pale orange solid. ¹H NMR (400 MHz, DMSO-d₆): δ 12.09 (s, 1H), 8.53 - 8.44 (m, 2H), 8.05 (dd, *J* = 2.4, 13.0 Hz, 1H), 7.52 - 7.42 (m, 8H), 6.72 (d, *J* = 8.1 Hz, 1H), 6.50 - 6.44 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.08 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₀H₂₃F₂N₃O₅+H]⁺: 544.16, Found: 544.1, *t_R* = 3.744 min, [Method Q]; HPLC purity: 99.74%, *t_R* = 6.284 min, [Method B].

[1043] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide [Example 7]:



[1044] A solution of 1-(4-fluorophenyl)-1,2-dihydro-6-methyl-2-oxo-3-pyridine carboxylic acid (36 mg, 0.144 mmol, 1.20 eq) in pyridine (2 mL, 0.0602 M) was charged with EDCI.HCl (46 mg, 0.241 mmol, 2.00 eq) followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (40 mg, 0.120 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h (Note: 1-(4-fluorophenyl)-1,2-dihydro-6-methyl-2-oxo-3-pyridine carboxylic acid, Intermediate 17 was from commercial sources). The crude reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude. The crude was further purified by prep-HPLC, [Method C]. The pure fractions were lyophilized to afford 29 mg, 41.01% yield of example 7 as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.98 (s, 1H), 8.75 (d, *J* = 2.9 Hz, 1H), 8.47 (d, *J* = 7.3 Hz, 1H), 7.98 (dd, *J* = 2.4, 13.2 Hz, 1H), 7.51 - 7.40 (m, 5H), 7.32 (s, 2H), 7.06 (t, *J* = 9.3 Hz, 1H), 6.71 (d, *J* = 8.3 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.07 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562.52, found: 562.1, *t*_R = 4.851 min, [Method Q].

[1045] Synthesis of *N*-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide [Example 10; Example 22; Example 23]:



[1046] A stirred solution of 1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 16 (416 mg, 1.59 mmol, 1.00 eq) in pyridine (5 mL, 0.3181 M) was charged with EDC.HCl (915 mg, 4.77 mmol, 3.00 eq) and 4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline (500 mg, 1.59 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The crude reaction mixture was treated with water (50 mL) and extracted with DCM (3 × 30 mL). The combined organic layers were washed with brine solution (30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude was purified by flash column chromatography eluting 5% MeOH in DCM. to afford 500 mg, 56.08% yield of Example 10 as a pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.07 (s, 1H), 8.54 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 5.5 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.55 - 7.52 (m, 2H), 7.45 - 7.36 (m, 4H), 7.30 - 7.24 (m, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.47 (d, *J* = 5.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.2, *t*_R = 4.39 min, [Method O].

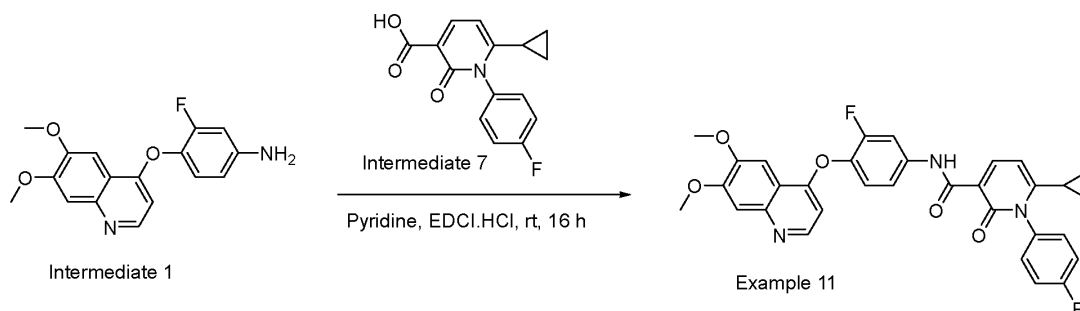
[1047] [Example 10 atropisomer mixture] (500mg) was submitted for chiral separation using chiral SFC (instrument name: waters-2767, prep-SFC 100) method to afford 75 mg of Example 22 and 65 mg of Example 23 as an off white solid. Chiral SFC (instrument name: waters-2767, prep-SFC 100), Column: CHIRALPAK- IG (250 X 4.6mm, 5μm), Mobile phase A: ACN, Mobile phase B: IPA, Eluent A: B (50:50), Flow rate: 60 ml/min.

[1048] *N*-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide [Example 22]:

[1049] ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.07 (s, 1H), 8.54 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 8.05 (dd, *J* = 2.0, 13.0 Hz, 1H), 7.55 - 7.52 (m, 2H), 7.45 - 7.41 (m, 2H), 7.41 (s, 1H), 7.40 - 7.36 (m, 1H), 7.30 - 7.24 (m, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.48 - 6.45 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.2, *t*_R = 3.04 min, [Method J]; Chiral HPLC: ee: 99.70%, *t*_R = 6.21 min [method file: COLUMN : CHIRALPAK-IG (250 × 4.6 mm, 5 μm), Mobile Phase: ACN/IPA(50/50) Flow:: 1.0 ML/min, COLUMN ID: M-ARD-CAL/OLD-011]. Specific Optical Rotation (SOR): -36.12, method: Instrument Name E-AMC-Polarimeter-01 Model Name P-2000 Serial No. B166161232 Polarizer Dichrom Faraday Cell Flint Glass, Temperature 25 °C, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%, Water content of sample 0%.

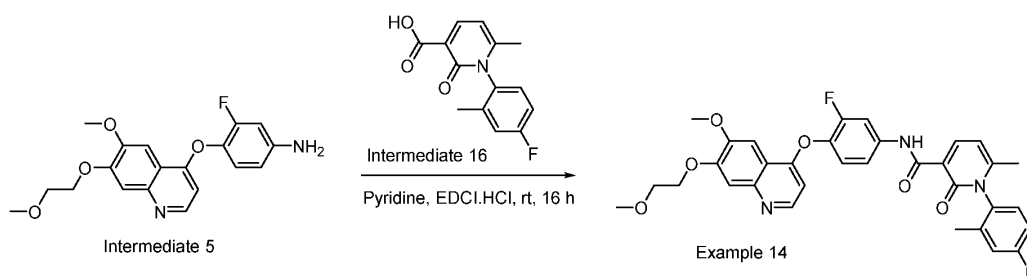
[1050] *N*-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide **[Example 23]**: ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.07 (s, 1H), 8.54 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 8.05 (dd, *J* = 2.0, 13.0 Hz, 1H), 7.56 - 7.50 (m, 2H), 7.50 - 7.41 (m, 2H), 7.41 (s, 1H), 7.38 (dd, *J* = 2.8, 9.8 Hz, 1H), 7.31 - 7.23 (m, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.49 - 6.44 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.02, *t*_R = 3.05 min, [Method J]; Chiral HPLC: ee: 99.98%, *t*_R = 8.09 min [method file: COLUMN : CHIRALPAK-IG (250 × 4.6 mm, 5 μm) Mobile Phase: ACN/IPA(50/50) Flow:: 1.0 ML/min, COLUMN ID: M-ARD-CAL/OLD-011]. Specific Optical Rotation (SOR): 29.08, method: Instrument Name E-AMC-Polarimeter-01 Model Name P-2000 Serial No. B166161232 Polarizer Dichrom Faraday Cell Flint Glass, Temperature 25 °C, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v%, Water content of sample 0%.

[1051] **Synthesis of 6-cyclopropyl-*N*-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide [Example 11]:**



[1052] A solution 6-cyclopropyl-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 7 (70 mg, 0.255 mmol, 1.00 eq) in pyridine (1 mL, 0.2545 M) was charged with EDCI.HCl (146 mg, 0.764 mmol, 3.00 eq) followed by the addition of 4-((6,7-dimethoxyquinolin-4-yl)oxy)-3-fluoroaniline, Intermediate 1 (80 mg, 0.255 mmol, 1.00 eq) at rt. The reaction was stirred at this temperature for an additional 16 h. The crude reaction mixture was diluted with crushed ice water (50 mL) upon which a solid precipitated. The precipitate was filtered and washed with ice water and diethyl ether (30 mL) to afford 46 mg, 30.94% yield of Example 11, as a pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 12.09 (s, 1H), 8.51 - 8.45 (m, 2H), 8.07 - 8.01 (m, 1H), 7.57 - 7.49 (m, 4H), 7.49 - 7.39 (m, 4H), 6.49 - 6.45 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 1.39 - 1.31 (m, 1H), 0.95 - 0.89 (m, 2H), 0.87 - 0.80 (m, 2H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₂H₂₅F₂N₃O₅+H]⁺: 570.56, found: 570.1, at *t*_R= 4.429 min, [Method V].

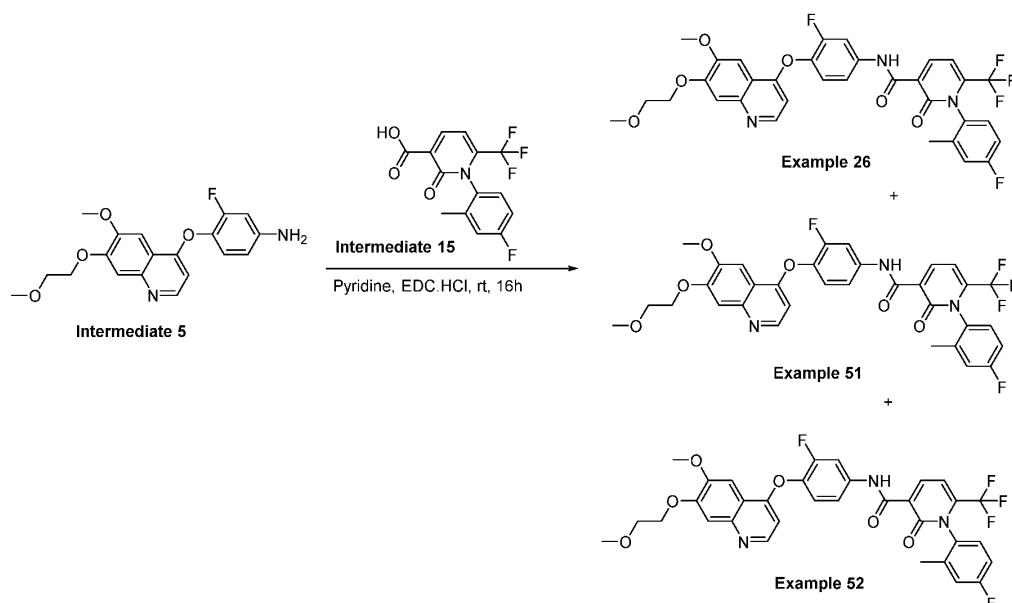
[1053] Synthesis of *N*-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide [Example 14]:



[1054] A stirred solution of 1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 16 (61 mg, 0.234 mmol, 1.20 eq) in pyridine (1 mL, 0.1953 M) was charged with EDCI.HCl (112 mg, 0.586 mmol, 3.00 eq) followed by the addition of 3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline, Intermediate 5 (70 mg, 0.195 mmol, 1.00 eq) at rt, and stirring was continued for 16 h. The crude reaction mixture was diluted with water (15 mL), extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get the crude product. This crude was purified by prep-HPLC, [Method M]. The pure fractions

were lyophilized to afford 34 mg, 28.87% yield of Example 14 (atropisomer mixture) as a pale yellow solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.49 - 8.46 (m, 1H), 8.05 (dd, J = 2.4, 13.1 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.45 - 7.36 (m, 4H), 7.30 - 7.24 (m, 1H), 6.78 - 6.75 (m, 1H), 6.48 - 6.46 (m, 1H), 4.30 - 4.26 (m, 2H), 3.95 (s, 3H), 3.77 - 3.75 (m, 2H), 3.35 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{33}\text{H}_{29}\text{F}_2\text{N}_3\text{O}_6+\text{H}]^+$: 602.21, found: 601.9, t_R = 3.96 min, [Method Q].

[1055] Synthesis of *N*-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 26; Example 51; Example 52]:



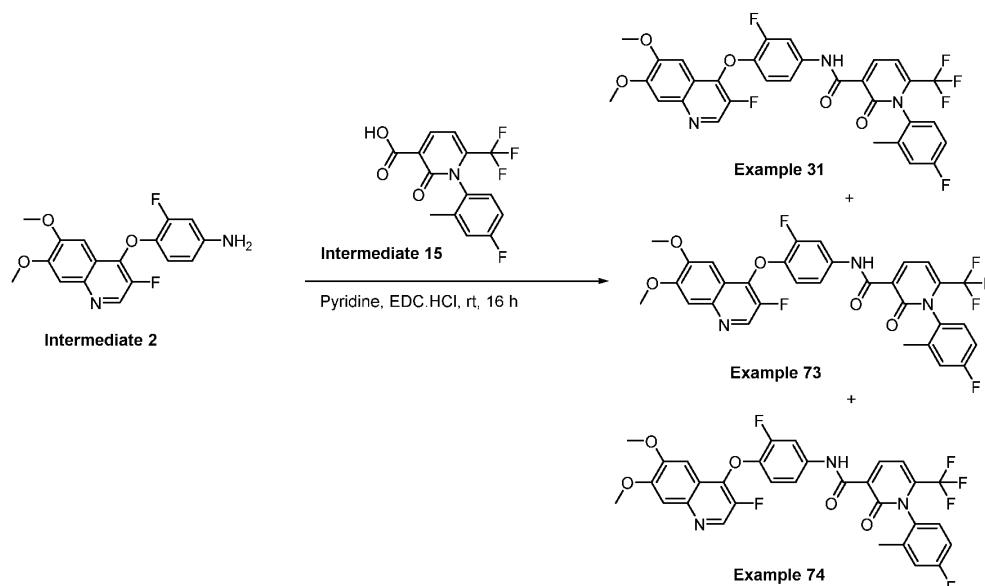
[1056] A stirred solution of 1-(4-methoxyphenyl)-6-methyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 15 (87 mg, 0.335 mmol, 1.20 eq) in pyridine (1.5 mL, 0.186 m) was charged with EDC.HCl (160 mg, 0.837 mmol, 3.00 eq) followed by the addition of 3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline, Intermediate 5 (100 mg, 0.279 mmol, 1.00 eq) at rt and the reaction mixture was stirred at rt for an additional 16 h. The reaction mixture was diluted with water (10 mL) upon which a solid precipitated. The precipitate was filtered and washed with diethyl ether (3mL) and acetonitrile (3mL) and dried to afford 44 mg, 29.43% yield of Example 26, as a pale brown solid. ^1H NMR (400 MHz, DMSO- d_6): δ 11.72 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.62 (td, J = 1.2, 8.8 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.48 - 7.44 (m, 1H), 7.42 - 7.34 (m, 3H), 7.26 (dt, J = 2.8, 8.6 Hz, 1H), 6.47 (dd, J = 0.9, 5.3 Hz, 1H), 4.28 (dd, J = 3.5, 5.4 Hz, 2H), 3.95 (s, 3H), 3.79 - 3.72 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{33}\text{H}_{26}\text{F}_5\text{N}_3\text{O}_6+\text{H}]^+$: 656.18, found: 655.9, t_R = 4.281 min, [Method W].

[1057] [Example 26 atropisomer mixture] (40 mg) was submitted for chiral separation using chiral SFC (instrument name: waters-2767, prep-SFC 100); Pak IA (30 × 250 × 4.6 mm, 5 u), Mobile Phase A: HEX, Mobile Phase B: EtOH-MeOH, Eluent A:B:-20-80, Total Flow rate (mL/min) 26 Diluent MP Detection 240 nm. which afforded 11 mg of Example 51 and 12 mg of Example 52 as an off white solid.

[1058] *N*-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 51]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.71 (s, 1H), 8.68 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 5.5 Hz, 1H), 8.05 (dd, *J* = 2.3, 12.8 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.35 (d, *J* = 9.5 Hz, 1H), 7.30 - 7.22 (m, 1H), 6.47 (d, *J* = 5.0 Hz, 1H), 4.32 - 4.24 (m, 2H), 3.95 (s, 3H), 3.80 - 3.74 (m, 2H), 3.35 (s, 3H), 2.07 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₃H₂₆F₅N₃O₆+H]⁺: 656.58, found: 655.9, *t*_R = 4.296 min, [Method W]; Chiral HPLC purity: 100%, *t*_R = 6.856 min, ee = 100%; Specific Optical Rotation (SOR): -23.76, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%

[1059] *N*-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 52]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.71 (s, 1H), 8.68 (d, *J* = 7.0 Hz, 1H), 8.48 (d, *J* = 5.0 Hz, 1H), 8.05 (dd, *J* = 2.0, 13.0 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.55 - 7.49 (m, 2H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.38 - 7.32 (m, 1H), 7.29 - 7.21 (m, 1H), 6.47 (d, *J* = 5.0 Hz, 1H), 4.31 - 4.25 (m, 2H), 3.95 (s, 3H), 3.79 - 3.66 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₃H₂₆F₅N₃O₆+H]⁺: 656.58, found: 656.0, *t*_R = 4.650 min, [Method O]; Chiral HPLC purity: 97.42%, *t*_R = 9.524, ee = 94.84%; Specific Optical Rotation (SOR): 27.04, method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

[1060] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 31; Example 73; Example 74]:



[1061] A stirred solution of 1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 15 (76 mg, 0.241 mmol, 1.00 eq) in pyridine (1 mL, 0.2407 M) was charged with EDC.HCl (138 mg, 0.722 mmol, 3.00 eq) followed by the addition of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline, Intermediate 2 (80 mg, 0.241 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The reaction mixture was diluted with crushed ice water (100 mL) upon which a solid precipitated. The precipitate was filtered and washed with ice water and diethyl ether (30 mL) to get crude. Crude was purified by prep-HPLC and after purification pure fractions were lyophilized to afford 23 mg, 15.15% yield of Example 31 as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6): δ 11.61 (s, 1H), 8.75 (d, $J = 2.9$ Hz, 1H), 8.65 (d, $J = 7.8$ Hz, 1H), 8.01 - 7.96 (m, 1H), 7.52 - 7.47 (m, 1H), 7.47 - 7.45 (m, 1H), 7.42 - 7.35 (m, 3H), 7.34 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (t, $J = 9.2$ Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{31}\text{H}_{21}\text{F}_6\text{N}_3\text{O}_5+\text{H}]^+$: 629.52, found: 629.9, $t_R = 5.397$ min, [Method W].

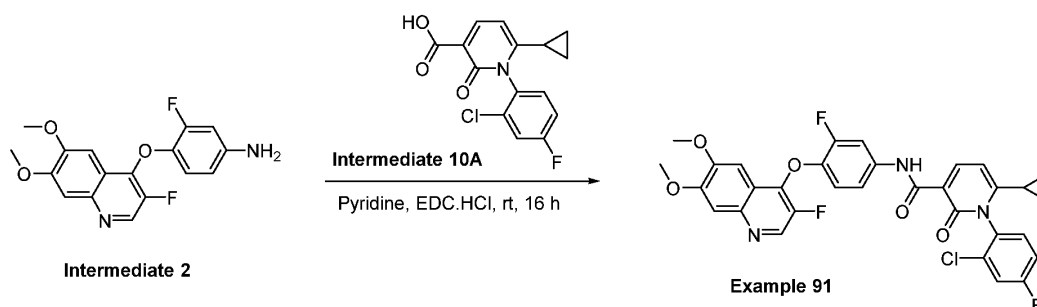
[1062] [Example 31 atropisomer mixture] (70 mg) was submitted for chiral separation using chiral SFC (instrument name: waters-2767, prep-SFC 100); SFC purification method: Column Name: IK (30 $\times$ 250 $\times$ 4.6 mm, 5 μ), Mobile Phase A: n-hexane, Mobile Phase B: EtOH:MeOH(1:1) A:B : 20:80, total flow rate : 42 mL/min which afforded 12 mg of Example 73 and 15.5 mg of Example 74 as an off white solid.

[1063] *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 73]: ^1H NMR (400 MHz, DMSO- d_6): δ 11.61 (s, 1H), 8.75 (d, $J = 2.7$ Hz, 1H), 8.65 (d, $J = 7.6$ Hz, 1H), 7.99 (dd, $J = 2.4, 13.4$ Hz, 1H), 7.52 - 7.47 (m, 1H), 7.46 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 3H), 7.33 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (t, $J = 8.9$ Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H);

MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁F₆N₃O₅]⁺: 630.52, found: 629.9, *t*_R = 5.028 min, [Method O]. Chiral HPLC purity: 100%, *t*_R = 10.298, ee = 100%. Specific Optical Rotation (SOR): 122.24, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%.

[1064] N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 74]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.62 (s, 1H), 8.76 (d, *J* = 2.5 Hz, 1H), 8.66 (d, *J* = 7.5 Hz, 1H), 7.99 (dd, *J* = 2.5, 13.5 Hz, 1H), 7.50 (dd, *J* = 5.8, 8.8 Hz, 1H), 7.46 (s, 1H), 7.37 (d, *J* = 7.5 Hz, 3H), 7.34 - 7.28 (m, 2H), 7.27 - 7.21 (m, 1H), 7.09 (t, *J* = 9.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.05 (s, 3H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁F₆N₃O₅+H]⁺: 630.52, found: 629.9, *t*_R = 5.025 min, [Method O]. Chiral HPLC purity: 99.06%, *t*_R = 13.106, ee = 98.12%. Specific Optical Rotation (SOR): -95.28, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture (S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v%

[1065] Synthesis of 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 91]:



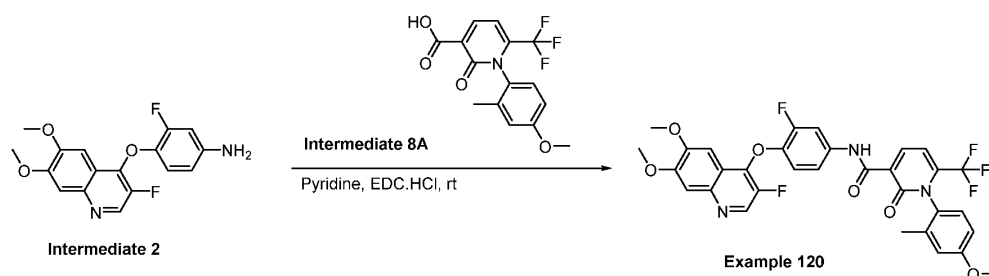
[1066] A stirred solution of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline, Intermediate 2 (80 mg, 0.241 mmol, 1.00 eq) in pyridine (0.5 mL, 0.4815 M) was charged with EDC.HCl (138 mg, 0.722 mmol, 3.00 eq), followed by 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10A (74 mg, 0.241 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. Then the reaction mixture was diluted with crushed ice water (50 mL) upon which a solid was precipitated. The precipitate was filtered and washed with ice water and diethyl ether (10 mL) to afford 90 mg, 57.62% yield of Example 91 as a pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.81 (s, 1H), 8.75 (d, *J* = 2.8 Hz, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.81 (dd, *J* = 2.8, 8.5 Hz, 1H), 7.77 (dd, *J* = 5.6, 8.9 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.47 - 7.44 (m, 1H), 7.36 - 7.31 (m, 2H), 7.06 (t, *J* = 9.1 Hz, 1H), 6.51 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.35 - 1.29 (m, 1H), 0.93 - 0.81 (m, 4H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₃ClF₃N₃O₅+H]⁺: 622.0, found: 622.2, *t*_R =

5.139 min, [Method O]; Chiral HPLC purity: 100%, t_R = 6.122 min, ee = 100%. Method: Column: CHIRALPAK- IK (250 × 4.6 mm, 5 μ m), Mobile Phase A: MeOH:EtOH (1:1) Mobile Phase B: ACN, A/B: 80:20, Flow: 1.5 mL/min; Specific Optical Rotation (SOR): 93.36, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1

[1067] Synthesis of 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 92]:

[1068] Synthesis of Example 92 followed the same procedure used for Example 91 except used 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10B in place of Intermediate 10A resulting in 48 mg, 30.48% yield of Example 92 as a pale brown solid. ^1H NMR (400 MHz, DMSO- d_6): δ 11.81 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.81 (dd, J = 2.5, 8.5 Hz, 1H), 7.77 (dd, J = 5.8, 8.8 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.46 (s, 1H), 7.35 - 7.29 (m, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.35 - 1.29 (m, 1H), 0.94 - 0.81 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{32}\text{H}_{23}\text{ClF}_3\text{N}_3\text{O}_5+\text{H}]^+$: 622.5, found: 622.2, t_R = 5.484 min, [Method L']; Chiral HPLC purity: 99.799%, t_R = 7.496 min, ee = 99.589% Column: CHIRALPAK- IK (250 × 4.6 mm, 5 μ m), Mobile Phase A: MeOH:EtOH (1:1), Mobile Phase B: ACN, A/B: 80:20, Flow: 1.5 mL/min; Specific Optical Rotation (SOR): -99.04, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 %.

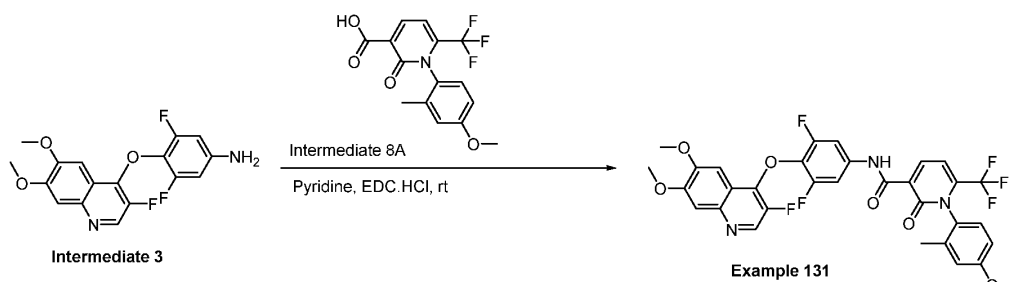
[1069] Synthesis of N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 120]:



[1070] A stirred solution of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 8A (59 mg, 0.181 mmol, 1.00 eq) in pyridine (1 mL, 0.1806 M) was charged with EDC.HCl (79 mg, 0.410 mmol, 2.27 eq), followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline, Intermediate 2 (60 mg, 0.181

mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The reaction mixture was concentrated to dryness and the residue was dissolved in ethyl acetate (100 mL) and the combined organic layers were washed with water (2×10 mL), then saturated brine solution. The organic layer was separated and dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by prep-HPLC, [Method F]. After purification, combined fractions were lyophilized to afford 40 mg, 34.50% yield of Example 120 as a pale yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.70 (s, 1H), 8.75 (d, $J = 3.0$ Hz, 1H), 8.64 (d, $J = 7.8$ Hz, 1H), 7.99 (dd, $J = 2.6, 13.1$ Hz, 1H), 7.46 (s, 1H), 7.40 - 7.37 (m, 1H), 7.36 - 7.27 (m, 3H), 7.09 (t, $J = 9.1$ Hz, 1H), 6.99 (d, $J = 2.8$ Hz, 1H), 6.91 (dd, $J = 2.8, 8.8$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{32}\text{H}_{24}\text{F}_5\text{N}_3\text{O}_6+\text{H}]^+$: 642.55, found: 641.8, $t_R = 5.355$ min, [Method W]; Chiral HPLC purity: 100%, $t_R = 4.181$ min, ee = 100%, Method: Column: CHIRALPAK IK (250×4.6 mm, 5 μm), Mobile Phase A: EtOH:MeOH (1:1), Mobile Phase B: ACN, A/B: 80/20, Flow: 1.0 mL/min, COLUMN ID:M-ARD-CAL/OLD-028 PUR REF:305140; Specific Optical Rotation (SOR): +98.32, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.1 w/v% Water content of sample 0% Factor 1.

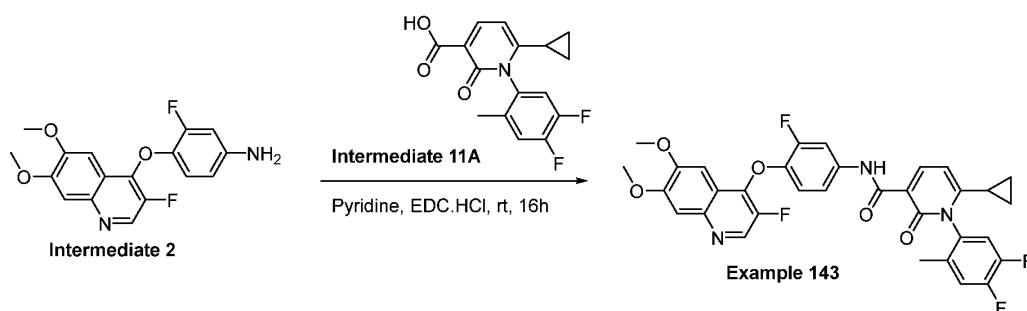
[1071] Synthesis of *N*-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 131]:



[1072] A stirred solution of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 8A (47 mg, 0.143 mmol, 1.00 eq) in pyridine (2 mL, 0.0714 M), was charged with EDC.HCl (137 mg, 0.714 mmol, 5.00 eq), followed by 3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline, Intermediate 3 (50 mg, 0.143 mmol, 1.00 eq) at rt and reaction mixture was stirred for an additional 16 h. The reaction mixture was poured into a saturated solution of sodium bicarbonate (15 mL) upon which a brown thick sticky mass was separated out. The crude product was extracted with ethyl acetate ($20 \text{ mL} \times 3$) and the combined organic layers were dried over anhydrous sodium sulfate,

filtered, and concentrated at reduced pressure to give crude product. The crude product was purified by prep-HPLC, [Method F], to afford 34 mg, 36.05% yield of Example 131 as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.83 (s, 1H), 8.68 (d, $J = 3.4$ Hz, 1H), 8.65 (d, $J = 7.8$ Hz, 1H), 7.78 (d, $J = 10.3$ Hz, 2H), 7.50 (s, 1H), 7.44 (s, 1H), 7.35 (d, $J = 7.3$ Hz, 1H), 7.30 (d, $J = 8.8$ Hz, 1H), 7.00 (d, $J = 2.4$ Hz, 1H), 6.92 (dd, $J = 2.7, 8.6$ Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{32}\text{H}_{23}\text{F}_6\text{N}_3\text{O}_6+\text{H}]^+$: 660.18, found: 659.9, $t_R = 5.48$ min, [Method W]; Chiral HPLC: Purity: 99.34% ee= 98.68%, $t_R = 3.917$ min, Chiral HPLC method: Method File Name: CHIRAL-MET-B20-1.5mL.lcm, Column: CHIRALPAK- IK (250 $\times$ 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN A/B: 80/20, Flow: 1.5 mL/min, COLUMN ID: PDA: IK_028; HPLC Purity: 99.34%, $t_R = 3.917$ min, ee= 98.68%, Method: Column: CHIRALPAK- IK (250 $\times$ 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN A/B: 80/20 Flow: 1.5 mL/min, COLUMN ID: PDA: IK_028; SOR: 73.72, SOR method: Instrument Name E-AMC-Polarimeter-01, Temperature: 25.00 C, Light Source: WI Monitor wavelength 589 nm, D.I.T. 5 sec No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C, Aperture(S) 8.0mm, Specific O.R. Path Length: 50 mm, Concentration: 0.1 w/v%, Water content of sample 0 %.

[1073] Synthesis of 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 143]:



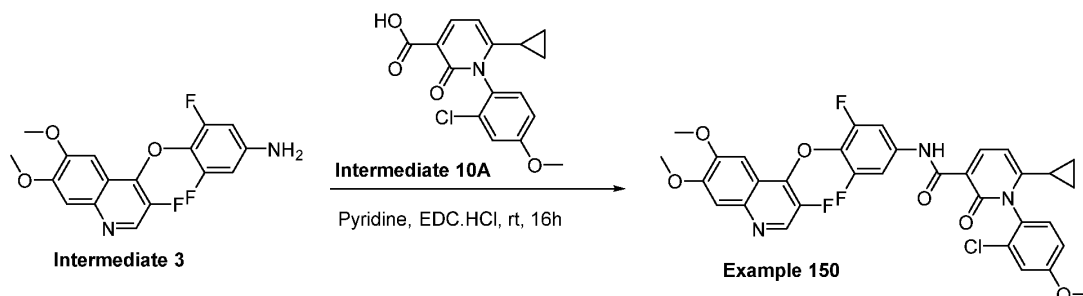
[1074] A stirred solution of 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 11A (77 mg, 0.253 mmol, 1.20 eq) in pyridine (2 mL, 0.1053 M), was charged with EDC.HCl (202 mg, 1.05 mmol, 5.00 eq), followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (70 mg, 0.211 mmol, 1.00 eq) at rt and kept at this temperature for 16 h. The reaction mixture was poured into saturated solution of sodium bicarbonate (15 mL) and the resultant solid was filtered and washed with water (10 mL) and heptane (20 mL) and dried under vacuum to get crude product. The crude was purified by prep-HPLC, [Method P] to afford 39 mg, 29.83% yield of Example 143 as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.89 (s, 1H), 8.75 (d, $J = 2.9$ Hz, 1H), 8.48 (d, $J = 7.8$ Hz, 1H),

7.99 (dd, $J = 2.4, 13.7$ Hz, 1H), 7.72 (dd, $J = 7.8, 10.8$ Hz, 1H), 7.62 (dd, $J = 9.0, 11.0$ Hz, 1H), 7.46 (s, 1H), 7.34 - 7.29 (m, 2H), 7.07 (t, $J = 9.0$ Hz, 1H), 6.48 (d, $J = 7.8$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.00 (s, 3H), 1.37 - 1.31 (m, 1H), 0.95 - 0.90 (m, 2H), 0.89 - 0.85 (m, 2H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.17, found: 619.9, $t_R = 5.273$ min, [Method W]; Chiral HPLC: Purity: 99.971%, ee: 99.94%, t_R : 7.301 min, Chiral HPLC method: Method File Name: CHIRAL-MET-B20-1.5mL.lcm, Column: CHIRALPAK- IK (250 × 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN A/B: 80/20, Flow: 1.5 mL/min, COLUMN ID: PDA: IK_028; SOR: 43.84, SOR method: Instrument Name E-AMC-Polarimeter-01, Temperature: 25.00 C, Light Source: WI Monitor wavelength 589 nm, D.I.T. 5 sec No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C, Aperture(S) 8.0mm, Specific O.R. Path Length: 50 mm, Concentration: 0.1 w/v%, Water content of sample 0 %.

[1075] Synthesis of 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 144]:

[1076] Synthesis of Example 144 followed the same procedure used in the synthesis of Example 143 except used 6-cyclopropyl-1-(4,5-difluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 11B in place of Intermediate 11A to afford 23 mg, 17.74% yield of the title compound as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.89 (s, 1H), 8.75 (d, $J = 3.0$ Hz, 1H), 8.48 (d, $J = 7.8$ Hz, 1H), 7.99 (dd, $J = 2.5, 13.3$ Hz, 1H), 7.72 (dd, $J = 7.9, 10.9$ Hz, 1H), 7.62 (dd, $J = 8.6, 11.4$ Hz, 1H), 7.46 (s, 1H), 7.36 - 7.25 (m, 2H), 7.06 (t, $J = 9.3$ Hz, 1H), 6.47 (d, $J = 7.8$ Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.00 (s, 3H), 1.37 - 1.29 (m, 1H), 0.97 - 0.90 (m, 2H), 0.90 - 0.85 (m, 2H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.18, found: 619.9, $t_R = 5.28$ min, [Method W]; Chiral HPLC: Purity: 98.944%, ee 98.31%, t_R : 9.353 min, Chiral HPLC method: Method File Name: CHIRAL-MET-B20-1.5mL.lcm, Column: CHIRALPAK- IK (250 × 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN A/B : 80/20, Flow: 1.5 mL/min, COLUMN ID: PDA: IK_028; SOR: -40.28, SOR method: Instrument Name E-AMC-Polarimeter-01, Temperature: 25.00 C, Light Source: WI Monitor wavelength 589 nm, D.I.T. 5 sec No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C, Aperture(S) 8.0mm, Specific O.R. Path Length: 50 mm, Concentration: 0.1 w/v%, Water content of sample 0 %.

[1077] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 150]:



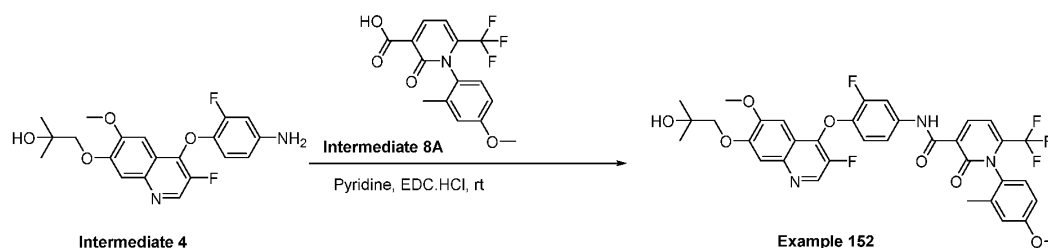
[1078] A stirred solution of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10A (55 mg, 0.171 mmol, 1.00 eq) in pyridine (1 mL, 0.1713 M) was charged with EDC.HCl (98 mg, 0.514 mmol, 3.00 eq), followed by 3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (60 mg, 0.171 mmol, 1.00 eq) at rt and was stirred at this temperature for an additional 16 h. The reaction mixture was diluted with crushed ice water (50 mL) upon which a solid was precipitated. The precipitate was filtered and washed with ice-water and ethyl acetate (10 mL) to afford 38 mg, 33.99% yield of Example 150 as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.03 (s, 1H), 8.68 (d, J = 3.5 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 10.3 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.34 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 2.9, 8.9 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 1.38 - 1.30 (m, 1H), 0.95 - 0.81 (m, 4H); MS(ES $^+$) m/z calc'd for $[\text{m}+\text{H}]^+$ $[\text{C}_{33}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}_6+\text{H}]^+$: 653.02, found: 652.2, t_R = 5.702 min, [Method W]; SFC purification Method File Name: Chiral_met -B.lcm Report File Name: Default.lcr Data Acquired: 09/13/2023 12:55:20 Description: Column: CHIRALPAK-IK (250 $\times$ 4.6 mm, 5 μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 mL/min, COLUMN ID: M-ARD-CAL-038; Chiral HPLC purity: 100%, t_R = 6.572 min, ee = 100 %; Specific optical rotation (SOR): 86.880, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[1079] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 151]:

[1080] Synthesis of Example 151 followed the same procedure used in for the synthesis of Example 150 except used 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10B in place of Intermediate to afford 100 mg, 89.22% yield of Example 151 as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.04 (s, 1H), 8.68 (d, J = 3.7 Hz, 1H), 8.48 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 10.3 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 2.9, 8.8 Hz, 1H), 6.48 (d, J = 7.8 Hz,

1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 1.38 - 1.31 (m, 1H), 0.95 - 0.84 (m, 4H). LCMS: ms (es⁺) m/z calc'd for [m+H]⁺ [C₃₃H₂₅ClF₃N₃O₆+H]⁺: 653.02, found: 652.2, t_R = 5.701 min, [Method W]; SFC purification method: Method File Name: Chiral_met-B.lcm Report File Name: Default.lcr Data Acquired: 09/13/2023 12:34:48 Description: Column: CHIRALPAK-
IK (250 x 4.6mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 mL/min, COLUMN ID:M-ARD-CAL-03; Chiral HPLC purity: 94.885%, t_R = 7.220 min, ee = 94.8764%; Specific optical rotation (SOR): -22.80, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

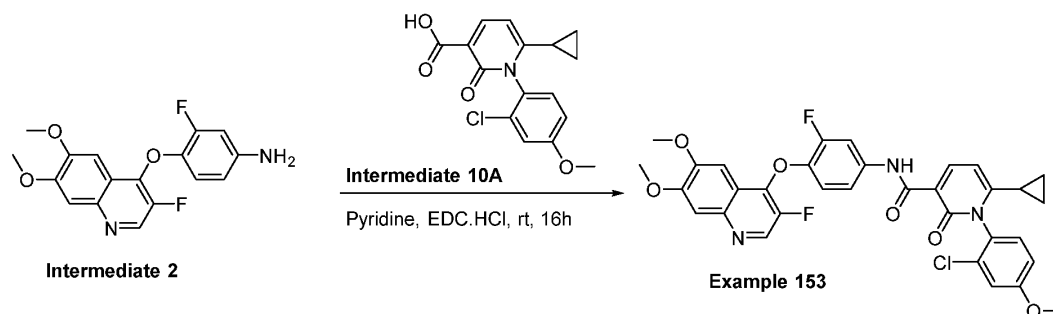
[1081] Synthesis of *N*-[3-fluoro-4-[[3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 152]:



[1082] A stirred solution of 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 8A (50 mg, 0.154 mmol, 1.00 eq) in pyridine (1 mL, 0.1537 M) was charged with EDC.HCl (0.088 g, 0.461 mmol, 3.00 eq) followed by 1-[[4-(4-amino-2-fluoro-phenoxy)-3-fluoro-6-methoxy-7-quinolyl]oxy]-2-methyl-propan-2-ol, Intermediate 4 (60 mg, 0.154 mmol, 1.00 eq) at rt and the reaction mixture was stirred at the same temperature for an additional 16 h. The reaction mixture was diluted with crushed ice water (50mL) upon which a solid was precipitated. The precipitate was filtered and washed with ice water and ethyl acetate (10mL) to afford 72 mg, 63.69% yield of the Example 152 as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.71 (s, 1H), 8.75 (d, *J* = 2.4 Hz, 1H), 8.64 (d, *J* = 7.8 Hz, 1H), 7.99 (dd, *J* = 2.3, 13.6 Hz, 1H), 7.45 - 7.30 (m, 5H), 7.09 (t, *J* = 8.9 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.91 (dd, *J* = 2.7, 8.3 Hz, 1H), 4.68 (s, 1H), 3.90 (s, 5H), 3.81 (s, 3H), 1.99 (s, 3H), 1.25 (s, 6H); MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₅N₃O₇+H]⁺: 700.63, found: 700.62, t_R = 4.71 min, [Method AD]; Chiral HPLC purity: 99.704%, ee: 99.408%, t_R: 4.747 min, Column: CHIRALPAK-
IK (250 x 4.6mm, 5μm) Mobile Phase A: EtOH/MeOH(50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 mL/MIN COLUMN ID:M-ARD-CAL-038; Specific optical rotation (SOR): 30.72, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr.

Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm
Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[1083] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 153]:

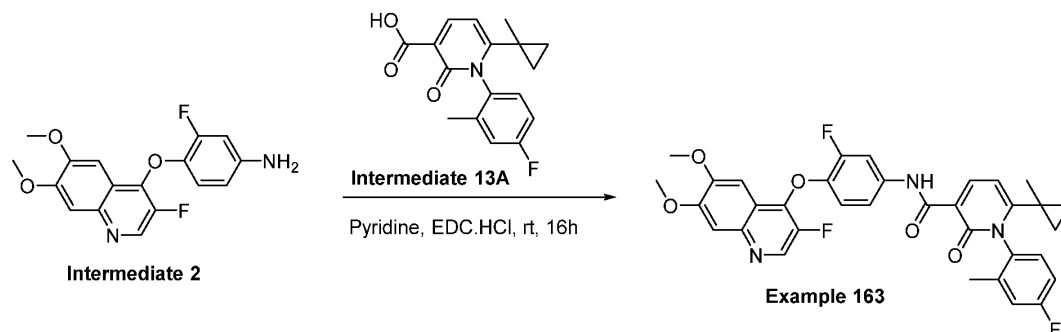


[1084] A stirred solution of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10A (115 mg, 0.361 mmol, 1.20 eq) in pyridine (1.5 mL, 0.2006 m) was added EDC.HCl (173 mg, 0.903 mmol, 3.00 eq), followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg, 0.301 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2 × 10 mL) and the combined organic layers were washed with brine (10 mL), then dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to get crude product. The crude was purified by prep-HPLC, [Method C]. The pure fractions were evaporated under reduced pressure to afford 20 mg, 10.46% yield of the title compound as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.91 (s, 1H), 8.75 (d, *J* = 2.9 Hz, 1H), 8.48 (d, *J* = 7.8 Hz, 1H), 7.99 (dd, *J* = 2.6, 13.6 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.31 (m, 3H), 7.14 (dd, *J* = 2.7, 8.8 Hz, 1H), 7.07 (t, *J* = 8.9 Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 1.35 - 1.30 (m, 1H), 0.93 - 0.85 (m, 4H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₃H₂₆ClF₂N₃O₆+H]⁺: 634.09, found: 634.2, *t*_R = 5.586 min, [Method AC]; SFC Purification Method: Method file name: Chiral_met -b 1.5mL.lcm report file NAME: Default.lcr data acquired: 10:43:42 description: Column: chiralpak-ik (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A/B: 80/20 flow: 1.5 mL/min. Chiral HPLC purity: 100.00%, *t*_R = 5.495 min, ee = 100%; Specific Optical Rotation (SOR): 129.200, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.1 w/v%.

[1085] Synthesis of 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide [Example 154]:

[1086] Synthesis of Example 154 followed the same procedure used in the synthesis of Example 153 except used 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid, Intermediate 10B in place of Intermediate 10A to afford 50 mg, 26.17% yield of Example 154 as an off white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 11.91 (s, 1H), 8.75 (d, J = 2.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.31 (m, 3H), 7.14 (dd, J = 2.6, 8.9 Hz, 1H), 7.09 - 7.04 (m, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.87 (d, J = 8.5 Hz, 6H), 1.36 - 1.32 (m, 1H), 0.93 - 0.87 (m, 4H); MS(ES^+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{33}\text{H}_{26}\text{ClF}_2\text{N}_3\text{O}_6+\text{H}]^+$: 634.09, found: 633.9, t_R = 5.308 min, [Method W]; SFC Purification Method: Method File Name: Chiral_met -B 1.5ML.1cm Report File Name: Default.lcr Data Acquired: 09/13/2023 10:43:42 Description: Column: CHIRALPAK-IK (250×4.6 mm, 5 μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A/B: 80/20 Flow: 1.5 mL/min; Chiral HPLC purity: 99.934 %, t_R = 7.359 min, ee = 99.868%. Specific Optical Rotation (SOR): -27.4000, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.1 w/v%.

[1087] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxamide [Example 163]:



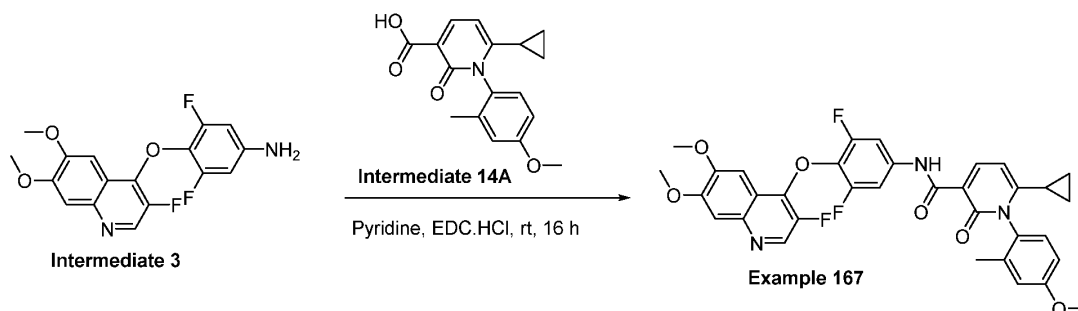
[1088] A stirred solution of 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid (54 mg, 0.181 mmol, 1.00 eq) in pyridine (1 mL, 0.1806 M) was charged with EDC.HCl (104 mg, 0.542 mmol, 3.00 eq), followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (60 mg, 0.181 mmol, 1.00 eq) at rt and stirred at this temperature for an additional 16 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL) and the combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulphate, filtered, and concentrated under reduced pressure to get crude. This crude was purified by prep-HPLC, [Method F]. The pure fractions were lyophilized to afford 48 mg, 43.05% yield of the titled compound as a pale brown solid. ^1H

NMR (400 MHz, DMSO-*d*₆): δ 11.96 (s, 1H), 8.74 (d, *J* = 3.0 Hz, 1H), 8.52 (d, *J* = 7.5 Hz, 1H), 7.98 (dd, *J* = 2.5, 13.5 Hz, 1H), 7.55 (dd, *J* = 5.4, 8.6 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.30 (m, 3H), 7.27 - 7.21 (m, 1H), 7.06 (t, *J* = 9.1 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.00 (s, 3H), 1.07 - 1.02 (m, 1H), 0.97 (s, 3H), 0.94 - 0.90 (m, 1H), 0.56 - 0.48 (m, 2H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₅+H]⁺: 616.6, found: 615.9, *t*_R = 5.430 min, [Method W]; Chiral HPLC purity: 99.94%, *t*_R = 7.397 min, ee = 99.88%. Method: Column: CHIRALPAK-IK (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH:MeOH (1:1), Mobile Phase B: ACN, A:B: 80:20 Flow rate: 1.000 mL/min; Specific optical rotation (SOR): 77.96, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor HolderTemp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) AutoMode Specific O.R.Path Length 50 mm Concentration 0.1 w/v% Water content of sample 0 % Factor 1.

[1089] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxamide [Example 164]:

[1090] Synthesis of Example 164 followed the same procedure used for the synthesis of Example 163 except used 1-(4-fluoro-2-methyl-phenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 13B in place of Intermediate 13A. Resulted in 46 mg, 40.40% yield of Example 164 as a pale brown solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.96 (s, 1H), 8.74 (d, *J* = 3.0 Hz, 1H), 8.52 (d, *J* = 7.8 Hz, 1H), 7.98 (dd, *J* = 2.5, 13.3 Hz, 1H), 7.55 (dd, *J* = 5.5, 8.8 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.30 (m, 3H), 7.27 - 7.21 (m, 1H), 7.06 (t, *J* = 9.3 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.00 (s, 3H), 1.07 - 1.02 (m, 1H), 0.97 (s, 3H), 0.95 - 0.90 (m, 1H), 0.53 - 0.48 (m, 2H); MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₅+H]⁺: 616.6, found: 615.9, *t*_R = 5.433 min, [Method W]; Chiral HPLC purity: 99.77%, *t*_R = 8.827 min, ee = 99.54%. Method: Column: CHIRALPAK-IK (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH:MeOH (1:1), Mobile Phase B: ACN, A:B: 80:20 Flow rate: 1.000 mL/min; Specific optical rotation (SOR): -96.12, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor HolderTemp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) AutoMode Specific O.R.Path Length 50 mm Concentration 0.1 w/v% Water content of sample 0 % Factor 1.

[1091] Synthesis of 6-cyclopropyl-*N*-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide [Example 167]:



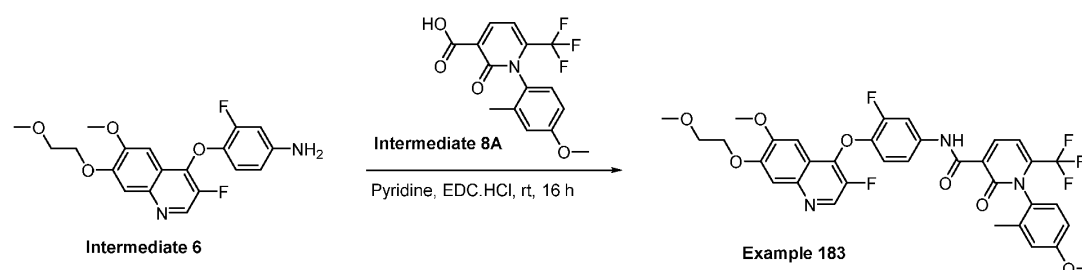
[1092] A stirred solution of 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 14A (51 mg, 0.171 mmol, 1.20 eq) in pyridine (2 mL, 0.0714 M), was charged with EDC.HCl (137 mg, 0.714 mmol, 5.00 eq), followed by 3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (50 mg, 0.143 mmol, 1.00 eq) at rt and was stirred at this temperature for an additional 16 h. The reaction mixture was poured in saturated solution of sodium bicarbonate (15 mL) forming a brown thick sticky mass that was separated out and aqueous layer was decanted and gummy was washed with water (10 mL) and dried well to give crude product. Crude product was purified by prep-HPLC, [Method F]. The pure fractions were lyophilized to afford 36 mg, 39.24% yield of the titled compound as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.20 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.46 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 10.3 Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 2.7, 8.6 Hz, 1H), 6.42 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H), 1.36 - 1.28 (m, 1H), 0.98 - 0.86 (m, 4H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{34}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_6+\text{H}]^+$: 632.20, found: 631.9, t_R = 5.42 min, [Method W]; Chiral HPLC: Purity: 99.95% ee: 99.90%, t_R = 6.57 min, Chiral HPLC method: Method File Name : CHIRAL-MET-B20-1.5mL.lcm, : Column: CHIRALPAK- IK (250 $\times$ 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN, A/B : 80/20, Flow : 1.5 mL/min, COLUMN ID: PDA : IK_028; SOR: 75.80, SOR method: Instrument Name E-AMC-Polarimeter-01, Temperature: 25.00 C, Light Source: WI Monitor wavelength 589 nm, D.I.T. 5 sec No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C, Aperture(S) 8.0mm, Specific O.R. Path Length: 50 mm, Concentration: 0.1 w/v%, Water content of sample 0 %.

[1093] Synthesis of 6-cyclopropyl-*N*-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide [Example 168]:

[1094] Synthesis of Example 168 followed the same procedure used for the synthesis of Example 167 except 6-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxylic acid, Intermediate 14B was used in place of Intermediate 14A resulting in 32 mg, 34.97% yield of Example 168 as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 12.19 (s,

1H), 8.67 (d, $J = 3.5$ Hz, 1H), 8.46 (d, $J = 8.0$ Hz, 1H), 7.72 (d, $J = 10.5$ Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.25 (d, $J = 8.5$ Hz, 1H), 7.04 (d, $J = 2.5$ Hz, 1H), 6.96 (dd, $J = 3.0, 8.5$ Hz, 1H), 6.42 (d, $J = 8.0$ Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H), 1.35 - 1.28 (m, 1H), 0.99 - 0.86 (m, 4H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₆+H]⁺: 632.20, found: 631.9, $t_R = 5.43$ min, [Method W]; Chiral HPLC: Purity: 99.67% ee: 99.35%, $t_R = 7.66$ min, Chiral HPLC method: Method File Name : CHIRAL-MET-B20-1.5mL.lcm, : Column:: CHIRALPAK-IK(250 × 4.6 mm, 5 μm), Mobile Phase A: MeOH/EtOH (50/50), Mobile Phase B: ACN, A/B : 80/20, Flow : 1.5 mL/min, COLUMN ID: PDA : IK_028; SOR: -8.60, SOR method: Instrument Name E-AMC-Polarimeter-01, Temperature: 25.00 C, Light Source: WI Monitor wavelength 589 nm, D.I.T. 5 sec No. of cycle 5, Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C, Aperture(S) 8.0mm, Specific O.R. Path Length: 50 mm, Concentration: 0.1 w/v%, Water content of sample 0 %.

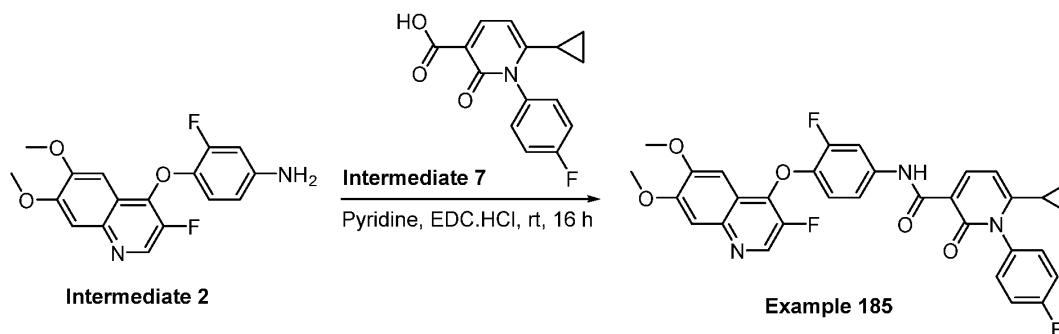
[1095] Synthesis of *N*-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example 183]:



[1096] A stirred solution of (Atropisomer 1) 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid, Intermediate 8A (70 mg, 0.213 mmol, 1.00 eq) in pyridine (1 mL, 0.2126 M) was charged with EDC-HCl (0.12 g, 0.638 mmol, 3.00 eq) followed by 3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]aniline (80 mg, 0.213 mmol, 1.00 eq) at rt and was stirred at this temperature for an additional 16 h. The crude product was purified by prep-HPLC, [Method F]. After purification, fractions were lyophilized to afford 56 mg, 37.97% yield of Example 183 as a pale yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.7 (s, 1H), 8.74 (d, $J = 2.8$ Hz, 1H), 8.64 (d, $J = 7.8$ Hz, 1H), 7.98 (dd, $J = 2.4, 13.2$ Hz, 1H), 7.47 (s, 1H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.35 - 7.27 (m, 3H), 7.09 (t, $J = 9.2$ Hz, 1H), 7.00 - 6.98 (m, 1H), 6.91 (dd, $J = 3.2, 8.8$ Hz, 1H), 4.30 - 4.27 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.78 - 3.73 (m, 2H), 3.33 (s, 3H), 1.99 (s, 3H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₅N₃O₇+H]⁺: 686.6, found: 685.9, $t_R = 5.365$ min, [Method W]; SFC purification method file name : Injection Volume : 4 uL Data File Name : 10102023 B01.lcd Method File Name: Chiral_met-B.lcm Report File Name: Default.lcr Data Acquired: 10/09/2023 17:25:46 Description : Column : CHIRALPAK-IK (250 × 4.6 mm, 5 μm), Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase

B: ACN, A/B: 80/20 Flow: 1.0 mL/min, COLUMN ID:M-ARD-CAL-026; Chiral HPLC purity: 96.967%, t_R = 8.484 min, ee = 93.934%; Specific optical rotation (SOR): 5.600 Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

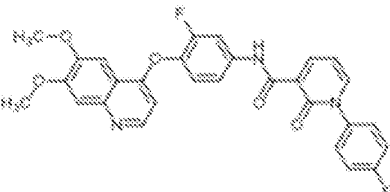
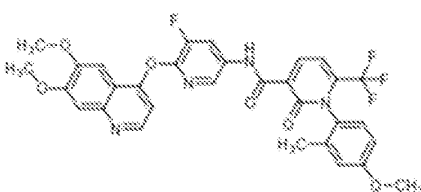
[1097] Synthesis of 6-cyclopropyl-*N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide [Example 185]:

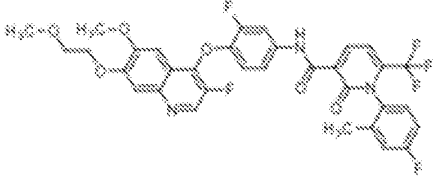
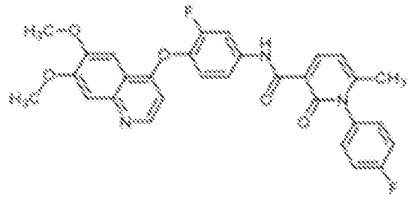


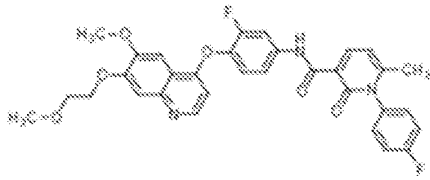
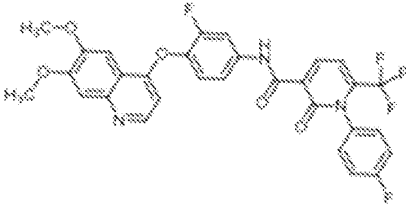
[1098] A stirred solution of 6-cyclopropyl-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxylic acid (123 mg, 0.451 mmol, 1.50 eq) in pyridine (1 mL, 0.3009 M) was charged with EDC.HCl (288 mg, 1.50 mmol, 5.00 eq) was added, followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg, 0.301 mmol, 1.00 eq) at rt and reaction mixture was stirred for 16 h. Then the reaction mixture was treated with water (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated solution of sodium bicarbonate (2 × 20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give crude product. The crude was purified by prep-HPLC, [Method F] to afford 21 mg, 11.92% yield of Example 185 as an off white solid. ^1H NMR (400 MHz, DMSO- d_6): δ 11.98 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 13.3, 2.4 Hz, 1H), 7.55-7.49 (m, 2H), 7.47-7.39 (m, 3H), 7.34-7.28 (m, 2H), 7.06 (t, J = 9.2 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 1.41-1.27 (m, 1H), 0.90 (dd, J = 5.3, 2.0 Hz, 2H), 0.85-0.79 (m, 2H); MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{32}\text{H}_{24}\text{F}_3\text{N}_3\text{O}_5+\text{H}]^+$: 588.17, found: 587.9, t_R = 5.12 min, [Method W].

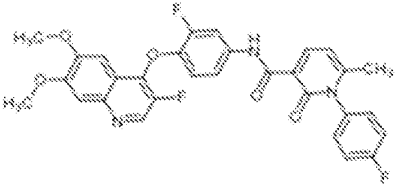
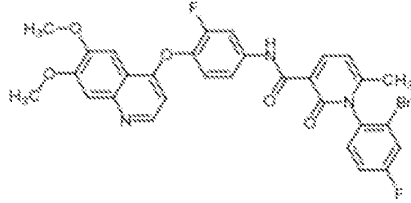
[1099] The following compounds in **TABLE 1** were referenced above or made following similar procedures as described above.

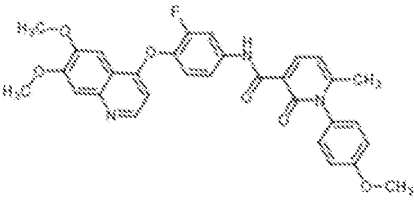
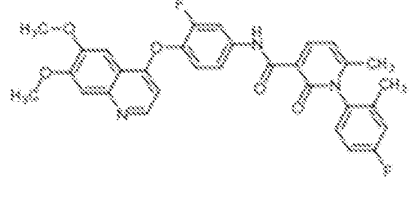
TABLE 1

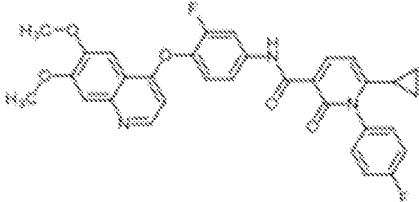
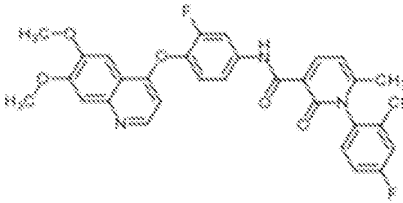
Ex	STRUCTURE	H-NMR / LCMS	Stereo Note	SOR ^a
1	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR δ 12.13 (s, 1H), 8.62 - 8.58 (m, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.16 - 8.13 (m, 1H), 8.08 - 8.03 (m, 1H), 7.64 - 7.59 (m, 2H), 7.55 - 7.51 (m, 2H), 7.47 - 7.41 (m, 4H), 6.74 (t, J = 7.0 Hz, 1H), 6.48 (d, J = 4.6 Hz, 1H), 3.95 (d, J = 1.5 Hz, 6H) MS (ES+) m/z calc'd for [M+H]⁺ [C₂₉H₂₁F₂N₃O₅+H]⁺: 530.5, found: 530.6, tR = 2.757 min. [Method W]		NA
2	 N-[6-[(6,7-dimethoxy-4-quinolyl)oxy]-5-fluoro-3-pyridyl]-1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.85 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.53 (dd, J = 2.4, 13.2 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 7.43 - 7.30 (m, 4H), 7.05 - 6.95 (m, 1H), 6.95 - 6.89 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 2.00 (s, 3H) MS (es+) m/z calc'd for [m+H]⁺ [C₃₁H₂₄F₄N₄O₆+H]⁺: 625.55, found: 629.9 tR = 4.283min [Method W]	Atrop 1	5.12

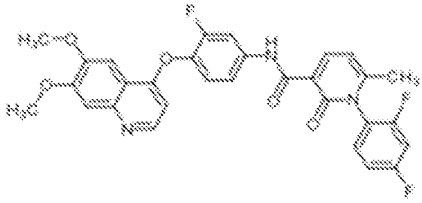
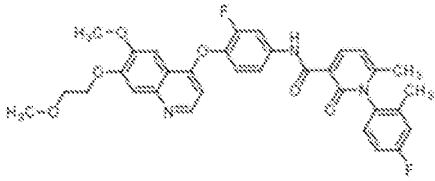
3	 N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.63 (s, 1H), 8.77 (d, J = 2.9 Hz, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.01 (dd, J = 2.6, 13.1 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.43 - 7.34 (m, 4H), 7.28 - 7.24 (m, 1H), 7.14 - 7.09 (m, 1H), 4.32 - 4.28 (m, 2H), 3.91 (s, 3H), 3.78 - 3.75 (m, 2H), 3.36 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₆N₃O₆+H]⁺: 674.16, found: 673.9, tR = 5.351 min, [Method W]	Atrop 1	89.12
4	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.09 (s, 1H), 8.52 - 8.46 (m, 2H), 8.07 - 8.01 (m, 1H), 7.55 - 7.48 (m, 4H), 7.47 - 7.39 (m, 4H), 6.72 (d, J = 8.1 Hz, 1H), 6.49 - 6.46 (m, 1H), 3.95 (d, J = 2.1 Hz, 6H), 2.09 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₃F₂N₃O₅+H]⁺: 543.52, found 544.5, tR = 2.983 min. [Method W]		NA

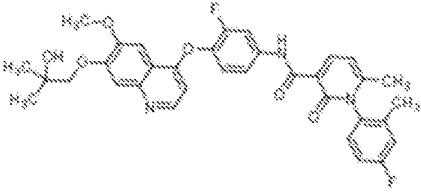
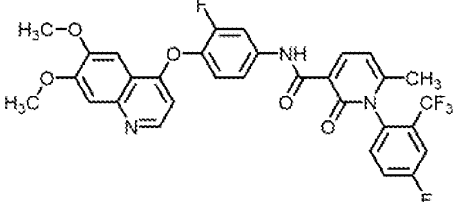
5	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 9.95 (d, J = 8.0 Hz, 2H), 8.88 (s, 1H), 8.43 (s, 1H), 8.28 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 2.4, 12.9 Hz, 1H), 7.80 (br s, 1H), 7.70 (br d, J = 0.8 Hz, 1H), 7.55 (ddd, J = 1.6, 8.3, 9.3 Hz, 2H), 7.43 (t, J = 9.3 Hz, 1H), 7.30 - 7.23 (m, 3H), 4.01 (s, 3H), 3.91 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₂₆H₂₁FN₆O₃+H]⁺: 485.49, found: 485.1, tR = 3.530 min, [Method N]		NA
6	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), 8.65 (d, J = 7.3 Hz, 1H), 8.48 (d, J = 4.9 Hz, 1H), 8.05 (dd, J = 2.4, 12.7 Hz, 1H), 7.60 (br s, 3H), 7.52 (s, 1H), 7.47 - 7.40 (m, 4H), 7.33 (d, J = 7.8 Hz, 1H), 6.48 (dd, J = 1.2, 5.1 Hz, 1H), 3.94 (s, 3H), 3.94 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₀F₅N₃O₅+H]⁺: 598.13, found: 598.1, tR = 4.076 min, [Method W]		NA

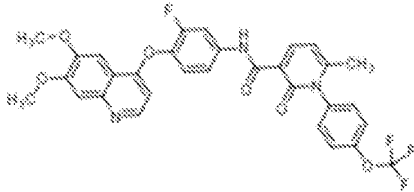
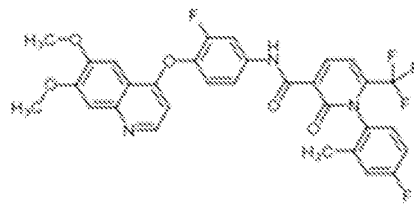
7	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.98 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.47 (d, J = 7.3 Hz, 1H), 7.98 (dd, J = 2.4, 13.2 Hz, 1H), 7.51 - 7.40 (m, 5H), 7.32 (s, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562.52, found: 562.1, tR= 4.851 min, [Method Q]		NA
8	 1-(2-bromo-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.93 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.94 (dd, J = 2.9, 8.4 Hz, 1H), 7.74 (dd, J = 5.5, 9.0 Hz, 1H), 7.59 - 7.51 (m, 3H), 7.46 - 7.42 (m, 1H), 7.41 (s, 1H), 6.81 - 6.77 (m, 1H), 6.47 (dd, J = 1.0, 5.3 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂BrF₂N₃O₅+H]⁺: 623.42, found: 623.9, tR= 3.920 min, [Method Q]	racemic	NA

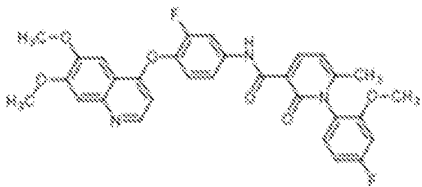
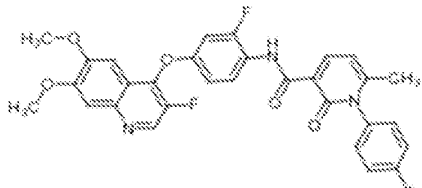
9	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxyphenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.18 (s, 1H), 8.51 - 8.46 (m, 2H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.45 - 7.39 (m, 2H), 7.35 - 7.28 (m, 2H), 7.15 - 7.11 (m, 2H), 6.72 - 6.68 (m, 1H), 6.47 (dd, J = 1.0, 5.3 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.84 (s, 3H), 2.09 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₆FN₃O₆+H]⁺: 556.6, found: 556.2, tR= 3.574 min, [Method Q]		NA
10	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆) δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.55 - 7.52 (m, 2H), 7.45 - 7.36 (m, 4H), 7.30 - 7.24 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 5.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.2, tR= 4.39 min, [Method O]	racemic	NA

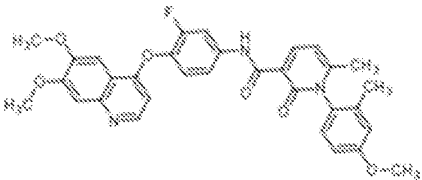
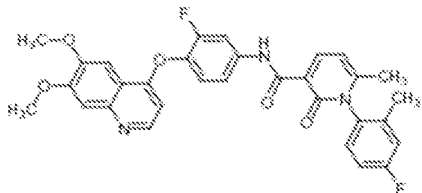
11	 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.09 (s, 1H), 8.51 - 8.45 (m, 2H), 8.07 - 8.01 (m, 1H), 7.57 - 7.49 (m, 4H), 7.49 - 7.39 (m, 4H), 6.49 - 6.45 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 1.39 - 1.31 (m, 1H), 0.95 - 0.89 (m, 2H), 0.87 - 0.80 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₂N₃O₅H]⁺: 570.56, found: 570.1, at t_R = 4.429 min, [Method V]		NA
12	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.92 (s, 1H), 8.57 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.84 (dd, J = 2.8, 8.5 Hz, 1H), 7.76 (dd, J = 5.6, 8.9 Hz, 1H), 7.57 - 7.50 (m, 3H), 7.46 - 7.41 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 5.0 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 2.09 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂ClF₂N₃O₅S+H]⁺: 577.97, found: 577.9, t_R = 3.963, [Method N]	racemic	NA

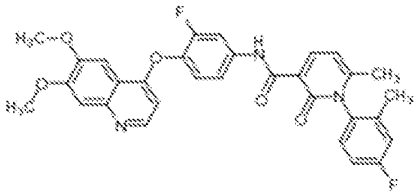
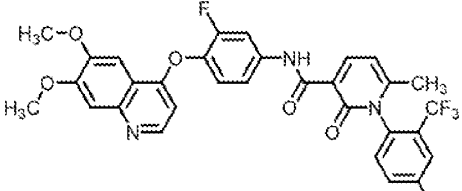
13	 1-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluorophenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.87 (s, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.04 (dd, J = 2.5, 13.3 Hz, 1H), 7.77 - 7.69 (m, 1H), 7.68 - 7.61 (m, 1H), 7.57 - 7.51 (m, 2H), 7.47 - 7.34 (m, 3H), 6.78 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 5.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.14 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562.52, found: 561.9, tR= 3.881 min, [Method Q]	racemic	NA
14	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.49 - 8.46 (m, 1H), 8.05 (dd, J = 2.4, 13.1 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.45 - 7.36 (m, 4H), 7.30 - 7.24 (m, 1H), 6.78 - 6.75 (m, 1H), 6.48 - 6.46 (m, 1H), 4.30 - 4.26 (m, 2H), 3.95 (s, 3H), 3.77 - 3.75 (m, 2H), 3.35 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₉F₂N₃O₆+H]⁺: 602.21, found: 601.9, tR= 3.96 min, [Method Q]	racemic	NA

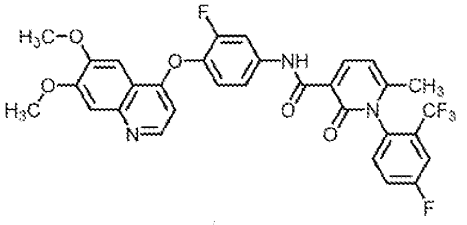
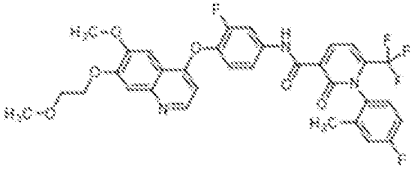
15	 N-[3-fluoro-4-[[7-(2-hydroxy-2-methylpropoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (s, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.56 - 7.51 (m, 2H), 7.47 - 7.35 (m, 4H), 7.31 - 7.25 (m, 1H), 6.79 - 6.76 (m, 1H), 6.48 - 6.46 (m, 1H), 4.67 (s, 1H), 3.96 (s, 3H), 3.90 (s, 2H), 2.05 (s, 3H), 2.03 (s, 3H), 1.27 (s, 6H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₃₁F₂N₃O₆+H]⁺: 616.23, found: 615.9, tR= 3.92 min, [Method Q]	racemic	NA
16	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[4-fluoro-2-(trifluoromethyl)phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.86 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.48 - 8.46 (m, 1H), 8.06 - 8.02 (m, 1H), 8.01 - 7.98 (m, 1H), 7.89 - 7.84 (m, 2H), 7.55 - 7.51 (m, 2H), 7.44 - 7.39 (m, 2H), 6.79 - 6.76 (m, 1H), 6.48 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.08 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₂₆H₂₅FN₆O₄S+H]⁺: 612.53, found: 611.8, tR= 4.026 min, [Method Q]	racemic	NA

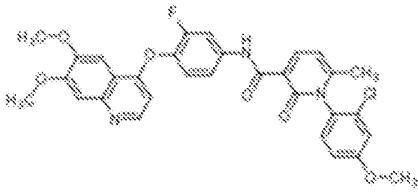
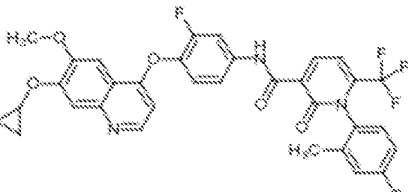
17	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-1-[4-(trifluoromethoxy)phenyl]pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.03 (s, 1H), 8.53 - 8.50 (m, 1H), 8.49 - 8.47 (m, 1H), 8.07 - 8.02 (m, 1H), 7.62 (s, 4H), 7.56 - 7.52 (m, 2H), 7.45 - 7.40 (m, 2H), 6.76 - 6.73 (m, 1H), 6.49 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.09 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₃F₄N₃O₆+H]⁺: 610.16, found: 609.9, tR= 4.128 min, [Method W]		NA
18	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.07 - 8.03 (m, 1H), 7.63 - 7.59 (m, 1H), 7.54 - 7.50 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.41 - 7.34 (m, 3H), 7.28 - 7.23 (m, 1H), 6.49 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₅+H]⁺: 612.53, found: 611.8, tR= 4.258 min, [Method W]	racemic	NA

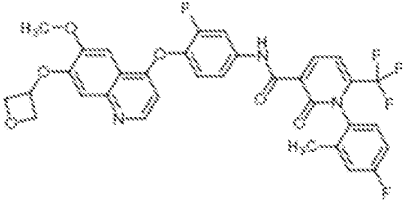
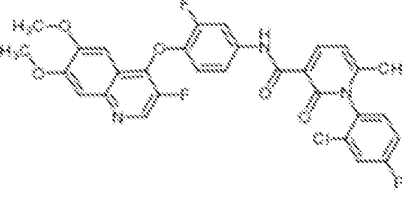
19	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methoxy-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.06 (s, 1H), 8.55 - 8.44 (m, 2H), 8.07 - 8.01 (m, 1H), 7.58 - 7.50 (m, 2H), 7.49 - 7.34 (m, 3H), 7.27 - 7.21 (m, 1H), 7.03 - 6.96 (m, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 5.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.80 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₆+H]⁺: 574.55, found: 573.9, tR= 3.861, [Method W]	racemic	NA
20	 N-[2-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.05 (d, J = 1.8 Hz, 1H), 8.80 (d, J = 2.5 Hz, 1H), 8.47 (d, J = 7.5 Hz, 1H), 8.42 - 8.36 (m, 1H), 7.51 - 7.39 (m, 5H), 7.23 - 7.17 (m, 2H), 6.93 - 6.86 (m, 1H), 6.72 - 6.67 (m, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562., found: 561.9, tR= 4.905 min, [Method W]		NA

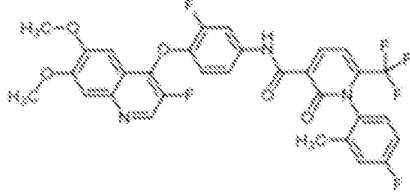
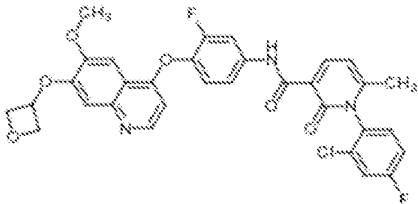
21	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.18 (s, 1H), 8.55 - 8.46 (m, 2H), 8.08 - 8.02 (m, 1H), 7.55 - 7.50 (m, 2H), 7.46 - 7.39 (m, 2H), 7.25 - 7.21 (m, 1H), 7.07 - 7.03 (m, 1H), 6.98 - 6.93 (m, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.49 - 6.45 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.83 (s, 3H), 2.04 (s, 3H), 1.98 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₈FN₃O₆+H]⁺: 570.1, found: 570.2, tR= 4.40 min, [Method O]	racemic	NA
22	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.0, 13.0 Hz, 1H), 7.55 - 7.52 (m, 2H), 7.45 - 7.41 (m, 2H), 7.41 (s, 1H), 7.40 - 7.36 (m, 1H), 7.30 - 7.24 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.48 - 6.45 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.2, tR= 3.04 min, [Method W]	Atrop 1	-36.12

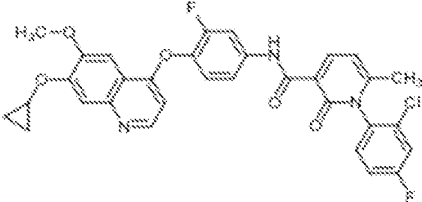
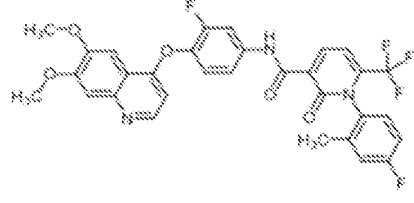
23	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.0, 13.0 Hz, 1H), 7.56 - 7.50 (m, 2H), 7.50 - 7.41 (m, 2H), 7.41 (s, 1H), 7.38 (dd, J = 2.8, 9.8 Hz, 1H), 7.31 - 7.23 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.49 - 6.44 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅+H]⁺: 558.18, found: 558.02, t_R = 3.05 min, [Method W]	Atrop 2	29.08
24	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[4-fluoro-2-(trifluoromethyl)phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.86 (s, 1H), 8.56 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 5.1 Hz, 1H), 8.06 - 7.97 (m, 2H), 7.89 - 7.84 (m, 2H), 7.55 - 7.51 (m, 2H), 7.45 - 7.39 (m, 2H), 6.78 (dd, J = 0.8, 7.6 Hz, 1H), 6.47 (dd, J = 0.9, 5.1 Hz, 1H), 3.95 (d, J = 2.1 Hz, 6H), 2.08 (s, 3H). MS (ES+) m/z: calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₅] : 612.53, found : 611.9, t_R = 4.026 min, [Method W]	Atrop 1	ND

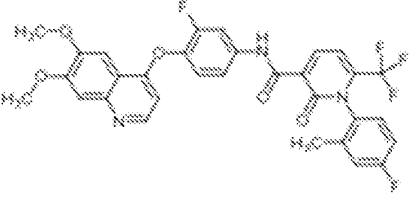
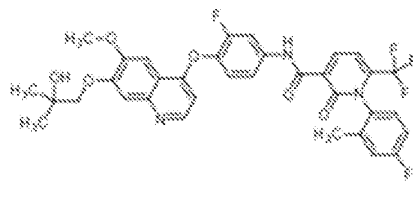
25	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-[4-fluoro-2-(trifluoromethyl)phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.85 (s, 1H), 8.56 (d, J = 7.6 Hz, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.06 - 7.97 (m, 2H), 7.89 - 7.83 (m, 2H), 7.55 - 7.51 (m, 2H), 7.45 - 7.38 (m, 2H), 6.78 (d, J = 7.8 Hz, 1H), 6.49 - 6.44 (m, 1H), 3.95 (d, J = 2.0 Hz, 6H), 2.08 (s, 3H). MS (ES+) m/z: calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₅]: 612.53, found: 611.9, tR = 4.032 min, [Method W]	Atrop 2	ND
26	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.62 (td, J = 1.2, 8.8 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.48 - 7.44 (m, 1H), 7.42 - 7.34 (m, 3H), 7.26 (dt, J = 2.8, 8.6 Hz, 1H), 6.47 (dd, J = 0.9, 5.3 Hz, 1H), 4.28 (dd, J = 3.5, 5.4 Hz, 2H), 3.95 (s, 3H), 3.79 - 3.72 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₅N₃O₆+H]⁺: 656.18, found: 655.9, tR = 4.281 min, [Method W]	racemic	NA

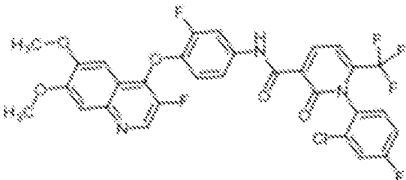
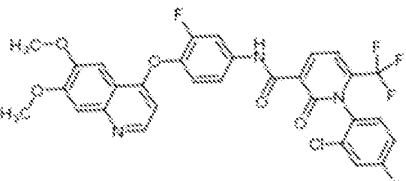
27	 1-(2-chloro-4-methoxy-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.01 (s, 1H), 8.54 (d, J = 7.8 Hz, 1H), 8.50 - 8.45 (m, 1H), 8.07 - 8.02 (m, 1H), 7.61 - 7.49 (m, 3H), 7.46 - 7.39 (m, 2H), 7.36 (d, J = 2.4 Hz, 1H), 7.18 - 7.13 (m, 1H), 6.76 (d, J = 7.3 Hz, 1H), 6.49 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.08 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₅ClFN₃O₆+H]⁺: 590, found: 589.9, tR= 4.011 min, [Method W]	racemic	NA
28	 N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.07 - 8.03 (m, 1H), 7.71 (s, 1H), 7.63 - 7.60 (m, 1H), 7.54 - 7.50 (m, 2H), 7.45 (t, J = 8.9 Hz, 1H), 7.41 - 7.35 (m, 2H), 7.28 - 7.23 (m, 1H), 6.49 (d, J = 5.3 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 2.07 (s, 3H), 0.94 - 0.89 (m, 2H), 0.79 - 0.76 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₄F₅N₃O₅+H]⁺: 638.56, found: 570.1, tR= 4.429 min, [Method W]	racemic	NA

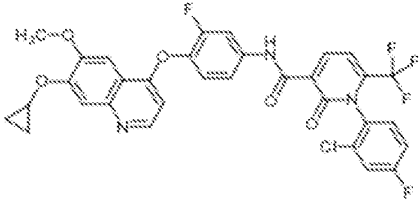
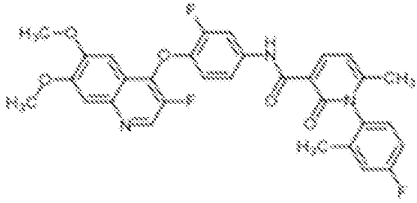
29	 N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.49 - 8.46 (m, 1H), 8.12 - 8.01 (m, 1H), 7.65 - 7.57 (m, 2H), 7.55 - 7.49 (m, 1H), 7.45 (t, J = 9.0 Hz, 1H), 7.41 - 7.33 (m, 2H), 7.30 - 7.20 (m, 1H), 7.04 (s, 1H), 6.49 (d, J = 4.5 Hz, 1H), 5.50 (t, J = 5.0 Hz, 1H), 5.04 (t, J = 6.8 Hz, 2H), 4.80 - 4.58 (m, 2H), 3.98 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₄F₅N₃O₆+H]⁺: 655.56, found: 653.9, tR= 4.313 min, [Method W]	racemic	NA
30	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 7.5 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.84 - 7.80 (m, 1H), 7.75 - 7.71 (m, 1H), 7.53 - 7.48 (m, 1H), 7.46 (s, 1H), 7.36 - 7.29 (m, 2H), 7.07 (t, J = 9.1 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₁ClF₃N₃O₅+H]⁺: 596.96, found: 595.8, tR= 5.116 min, [Method W]	racemic	NA

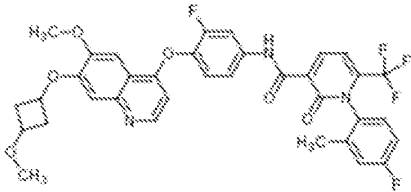
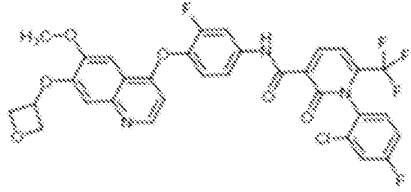
31	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.65 (d, J = 7.8 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.52 - 7.47 (m, 1H), 7.47 - 7.45 (m, 1H), 7.42 - 7.35 (m, 3H), 7.34 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (t, J = 9.2 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁F₆N₃O₅+H]⁺: 629.52, found: 629.9, tR= 5.397 min, [Method W]	racemic	NA
32	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.04 (dd, J = 13.0, 2.4 Hz, 1H), 7.84 (dd, J = 8.6, 2.8 Hz, 1H), 7.75 (dd, J = 8.9, 5.6 Hz, 1H), 7.58 (s, 1H), 7.56 - 7.49 (m, 2H), 7.46 - 7.40 (m, 1H), 7.04 (s, 1H), 6.80 - 6.76 (m, 1H), 6.49 (dd, J = 5.3, 0.9 Hz, 1H), 5.49 (t, J = 5.4 Hz, 1H), 5.04 (t, J = 6.9 Hz, 2H), 4.64 (dd, J = 7.6, 4.8 Hz, 2H), 3.98 (s, 3H), 2.08 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₆+H]⁺: 620.13, found: 619.9, tR= 4.06 min, [Method W].	racemic	NA

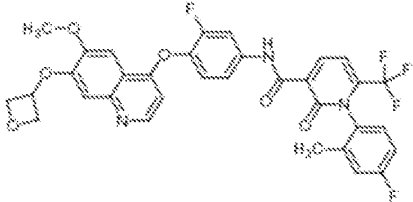
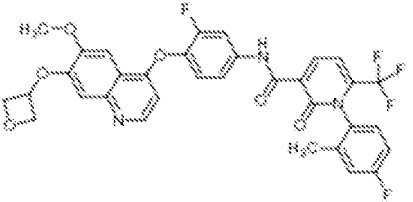
33	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.06 - 8.02 (m, 1H), 7.85 - 7.82 (m, 1H), 7.75 (dd, J = 5.5, 9.0 Hz, 1H), 7.71 (s, 1H), 7.56 - 7.51 (m, 3H), 7.42 (t, J = 9.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.49 - 6.47 (m, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 2.08 (s, 3H), 0.93 - 0.88 (m, 2H), 0.79 - 0.74 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₅+H]⁺: 605.01, found: 603.9, tR= 4.158 min, [Method W]	racemic	NA
34	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.08 - 8.02 (m, 1H), 7.64 - 7.58 (m, 1H), 7.54 - 7.49 (m, 2H), 7.46 (t, J = 8.9 Hz, 1H), 7.42 - 7.34 (m, 3H), 7.29 - 7.23 (m, 1H), 6.48 (d, J = 5.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₅+H]⁺: 612.53, found: 611.9, tR= 4.265 min, [Method N]	Atrop 1	-92.8

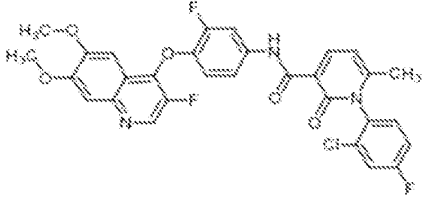
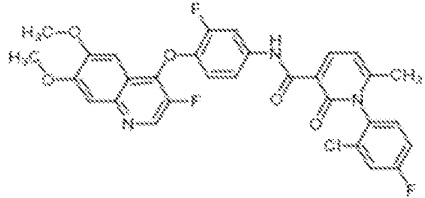
35	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.67 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.08 - 8.02 (m, 1H), 7.63 - 7.58 (m, 1H), 7.56 - 7.49 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.42 - 7.32 (m, 3H), 7.30 - 7.22 (m, 1H), 6.49 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₅+H]⁺: 612.53, found: 611.9, tR= 4.269 min, [Method N].	Atrop 2	79.6
36	 N-[3-fluoro-4-[[7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.07 - 8.03 (m, 1H), 7.63 - 7.60 (m, 1H), 7.54 - 7.46 (m, 3H), 7.40 - 7.35 (m, 3H), 7.28 - 7.24 (m, 1H), 6.48 - 6.46 (m, 1H), 4.67 (s, 1H), 3.96 (s, 3H), 3.90 (s, 2H), 2.07 (s, 3H), 1.27 (s, 6H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₅N₃O₆+H]⁺: 670.6, found: 669.9, tR= 4.362 min, [Method W]	racemic	NA

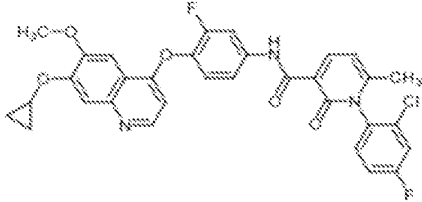
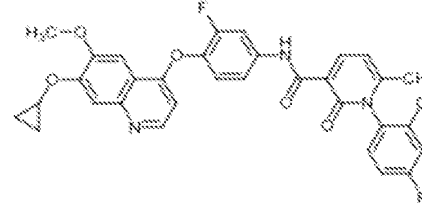
37	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (s, 1H), 8.76 (d, J = 2.8 Hz, 1H), 8.67 (d, J = 7.3 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.86 - 7.78 (m, 2H), 7.53 - 7.48 (m, 1H), 7.46 (s, 1H), 7.44 - 7.38 (m, 2H), 7.32 (s, 1H), 7.09 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H) MS (ES+) m/z calc'd for [M]⁺ [C₃₀H₁₈ClF₆N₃O₅+H]⁺: 649.93, found: 649.7, tR= 5.472, [Method W]	racemic	NA
38	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, CHLOROFORM-d): δ 11.60 (s, 1H), 8.83 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 7.95 (dd, J = 2.5, 12.0 Hz, 1H), 7.58 (s, 1H), 7.43 (s, 1H), 7.42 - 7.38 (m, 2H), 7.38 - 7.36 (m, 1H), 7.27 - 7.19 (m, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.44 - 6.39 (m, 1H), 4.06 (s, 3H), 4.05 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₁₉ClF₅N₃O₅+H]⁺: 632.94, found: 632.0, tR= 4.675 min, [Method O]	racemic	NA

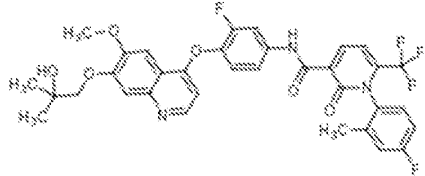
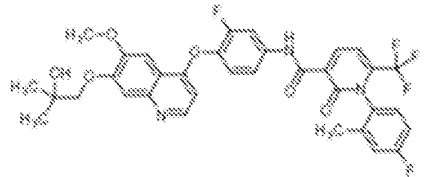
39	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.0 Hz, 1H), 8.49 (d, J = 5.5 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.88 - 7.82 (m, 2H), 7.71 (s, 1H), 7.65 - 7.61 (m, 1H), 7.55 - 7.49 (m, 2H), 7.48 - 7.40 (m, 2H), 6.49 (d, J = 5.0 Hz, 1H), 4.08 - 4.01 (m, 1H), 3.92 (s, 3H), 0.93 - 0.88 (m, 2H), 0.79 - 0.75 (m, 2H) MS (ES⁺) m/z calc'd for [M]⁺ [C₃₂H₂₁ClF₅N₃O₅+H]⁺: 657.98, found: 657.8, tR= 4.615, [Method W]	racemic	NA
40	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.01 - 7.97 (m, 1H), 7.46 (s, 1H), 7.44 - 7.29 (m, 4H), 7.28 - 7.24 (m, 1H), 7.07 (t, J = 9.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄F₃N₃O₅+H]⁺: 576.54, found: 576.2, tR= 4.958 min, [Method O]	racemic	NA

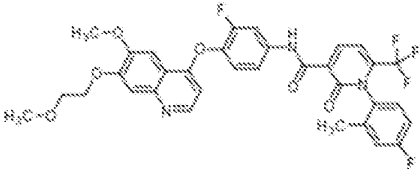
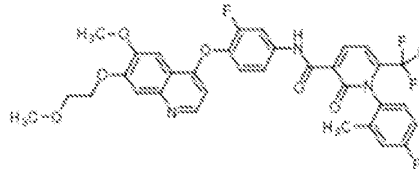
41	 N-[3-fluoro-4-[[6-methoxy-7-(3-methoxycyclobutoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.08 - 8.02 (m, 1H), 7.65 - 7.58 (m, 1H), 7.55 - 7.48 (m, 2H), 7.48 - 7.42 (m, 1H), 7.40 - 7.33 (m, 2H), 7.30 - 7.22 (m, 1H), 7.14 (s, 1H), 6.49 - 6.45 (m, 1H), 5.05 - 4.98 (m, 1H), 4.16 - 4.09 (m, 1H), 3.95 (s, 3H), 3.20 (s, 3H), 2.58 - 2.51 (m, 2H), 2.45 - 2.37 (m, 2H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₂₈F₅N₃O₆+H]⁺: 682.19, found: 681.9, tR= 4.564 min, [Method W]	racemic	NA
42	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.87 - 7.81 (m, 2H), 7.66 - 7.60 (m, 1H), 7.58 (s, 1H), 7.55 - 7.49 (m, 1H), 7.48 - 7.41 (m, 2H), 7.04 (s, 1H), 6.51 - 6.48 (m, 1H), 5.52 - 5.46 (m, 1H), 5.06 - 5.01 (m, 2H), 4.66 - 4.62 (m, 2H), 3.98 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₁ClF₄N₃O₆+H]⁺: 674.10, found: 673.9, tR= 4.432 min, [Method W].	racemic	NA

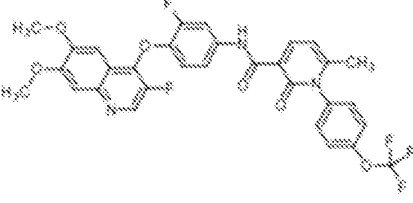
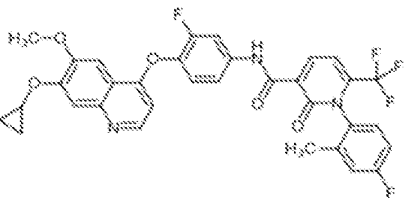
43	 N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.63 - 7.57 (m, 2H), 7.54 - 7.49 (m, 1H), 7.48 - 7.43 (m, 1H), 7.40 - 7.34 (m, 2H), 7.28 - 7.23 (m, 1H), 7.06 - 7.02 (m, 1H), 6.49 (d, J = 5.0 Hz, 1H), 5.52 - 5.47 (m, 1H), 5.06 - 5.01 (m, 2H), 4.67 - 4.61 (m, 2H), 3.98 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z cal'd for [M+H]⁺ [C₃₃H₂₄F₅N₆O₃+H]⁺: 654.56, found: 654.2, tR= 4.578 min, [Method O]	Atrop 1	-19.66
44	 N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.64 - 7.57 (m, 2H), 7.51 (dd, J = 5.5, 8.5 Hz, 1H), 7.45 (t, J = 9.0 Hz, 1H), 7.40 - 7.33 (m, 2H), 7.29 - 7.22 (m, 1H), 7.04 (s, 1H), 6.49 (d, J = 4.5 Hz, 1H), 5.52 - 5.46 (m, 1H), 5.07 - 5.01 (m, 2H), 4.67 - 4.62 (m, 2H), 3.98 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₄F₅N₆O₃+H]⁺: 654.56, found: 654.29, tR= 4.578 min, [Method O]	Atrop 2	38.56

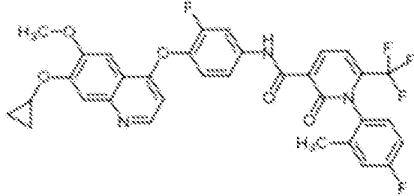
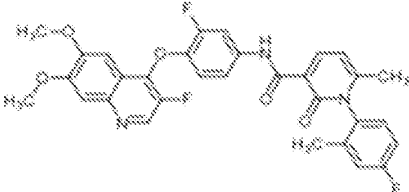
45	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.79 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.82 (dd, J = 2.5, 8.5 Hz, 1H), 7.73 (dd, J = 5.8, 8.8 Hz, 1H), 7.54 - 7.48 (m, 1H), 7.46 (s, 1H), 7.35 - 7.31 (m, 2H), 7.07 (t, J = 9.3 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M]⁺ [C₃₀H₂₁ClF₃N₃O₅] +: 595.96, found: 595.8, tR= 5.082 min, [Method W]	Atrop 1	44.64
46	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.82 (dd, J = 2.5, 8.5 Hz, 1H), 7.73 (dd, J = 5.5, 8.5 Hz, 1H), 7.53 - 7.48 (m, 1H), 7.46 (s, 1H), 7.35 - 7.31 (m, 2H), 7.07 (t, J = 8.8 Hz, 1H), 6.77 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M]⁺ [C₃₀H₂₁ClF₃N₃O₅] +: 595.96, found: 595.8, tR= 5.080 min, [Method W]	Atrop 2	-21.52

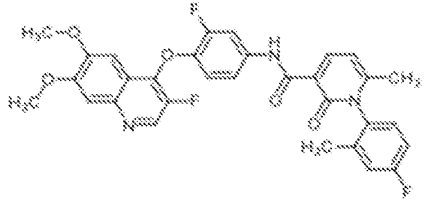
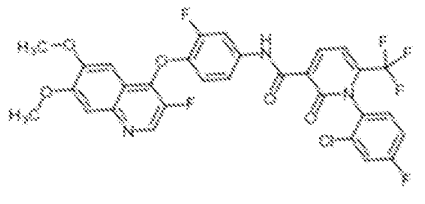
47	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.84 (dd, J = 3.0, 8.5 Hz, 1H), 7.75 (dd, J = 5.8, 8.8 Hz, 1H), 7.71 (s, 1H), 7.61 - 7.48 (m, 3H), 7.42 (t, J = 9.0 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 4.07 - 4.02 (m, 1H), 3.92 (s, 3H), 2.08 (s, 3H), 0.93 - 0.87 (m, 2H), 0.80 - 0.72 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₅+H]⁺: 605.01, found: 603.9, tR = 4.171, [Method W]	Atrop 1	-65.68
48	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.56 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.84 (dd, J = 3.0, 8.5 Hz, 1H), 7.75 (dd, J = 5.5, 9.0 Hz, 1H), 7.71 (s, 1H), 7.57 - 7.50 (m, 3H), 7.42 (t, J = 9.0 Hz, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.48 (d, J = 5.5 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 2.08 (s, 3H), 0.93 - 0.88 (m, 2H), 0.79 - 0.75 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₅+H]⁺: 605.01, found: 603.9, tR = 4.174 min, [Method W]	Atrop 2	35.2

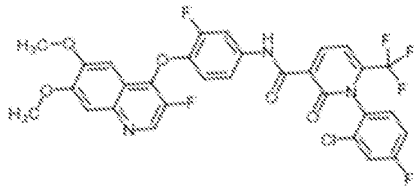
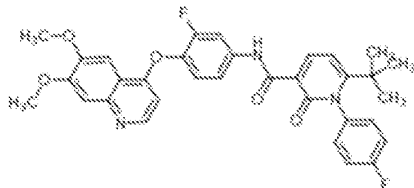
49	 N-[3-fluoro-4-[[7-(2-hydroxy-2-methylpropoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.54 - 7.49 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.40 - 7.34 (m, 3H), 7.28 - 7.23 (m, 1H), 6.48 - 6.46 (m, 1H), 4.67 (s, 1H), 3.96 (s, 3H), 3.90 (s, 2H), 2.07 (s, 3H), 1.27 (s, 6H) MS (ES⁺) m/z: calc'd for [M]⁺ [C₃₄H₂₈F₅N₃O₆+H]⁺: 670.6, found: 669.9, tR= 4.226 min, [Method W]	Atrop 1	33.84
50	 N-[3-fluoro-4-[[7-(2-hydroxy-2-methylpropoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.57 - 7.49 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.42 - 7.35 (m, 3H), 7.29 - 7.22 (m, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.67 (s, 1H), 3.96 (s, 3H), 3.90 (s, 2H), 2.06 (s, 3H), 1.26 (s, 6H) MS (ES⁺) m/z: calc'd for [M+H]⁺ [C₃₄H₂₈F₅N₃O₆+H]⁺: 670.6, found: 669.9, tR= 4.219 min, [Method W]	Atrop 2	-67.68

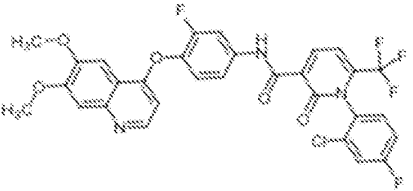
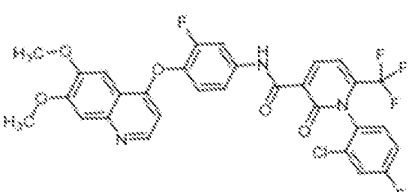
51	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.43 - 7.37 (m, 2H), 7.35 (d, J = 9.5 Hz, 1H), 7.30 - 7.22 (m, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.32 - 4.24 (m, 2H), 3.95 (s, 3H), 3.80 - 3.74 (m, 2H), 3.35 (s, 3H), 2.07 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₅N₃O₆+H]⁺: 656.58, found: 655.9, tR= 4.296 min, [Method W].	Atrop 1	-23.76
52	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.0, 13.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.55 - 7.49 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.43 - 7.38 (m, 2H), 7.38 - 7.32 (m, 1H), 7.29 - 7.21 (m, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.31 - 4.25 (m, 2H), 3.95 (s, 3H), 3.79 - 3.66 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₅N₃O₆+H]⁺: 656.58, found: 656.0, tR= 4.650 min, [Method O]	Atrop 2	27.04

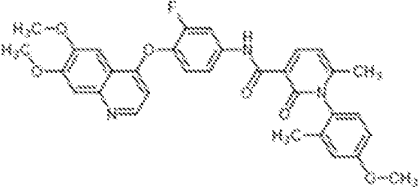
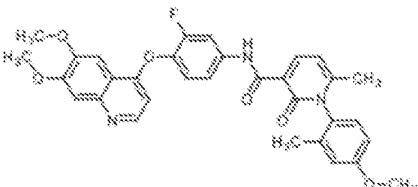
53	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-1-[4-(trifluoromethoxy)phenyl]pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.93 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.49 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.5 Hz, 1H), 7.61 (s, 4H), 7.46 (s, 1H), 7.36 - 7.31 (m, 2H), 7.07 (t, J = 9.3 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.09 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₂F₅N₃O₆+H]⁺: 628.52, found: 628.2, tR= 5.081 min, [Method O].		NA
54	 N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.3 Hz, 1H), 8.49 (d, J = 5.1 Hz, 1H), 8.07 - 8.03 (m, 1H), 7.71 (s, 1H), 7.64 - 7.59 (m, 1H), 7.54 - 7.50 (m, 2H), 7.46 (t, J = 8.9 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.28 - 7.23 (m, 1H), 6.50 - 6.47 (m, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 2.06 (s, 3H), 0.93 - 0.88 (m, 2H), 0.80 - 0.74 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₄F₅N₃O₅+H]⁺: 638.56, found : 638.2, tR= 4.785 min, [Method O]	Atrop 1	14

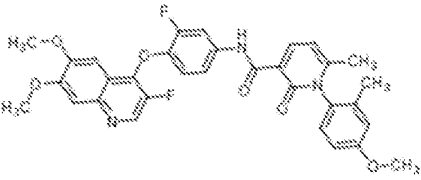
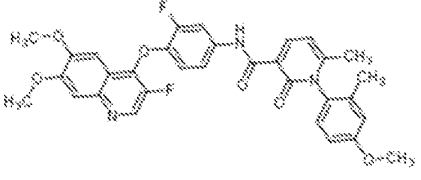
55	 N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.1 Hz, 1H), 8.49 (d, J = 5.1 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.71 (s, 1H), 7.64 - 7.59 (m, 1H), 7.54 - 7.50 (m, 2H), 7.46 (t, J = 9.0 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.29 - 7.23 (m, 1H), 6.49 (d, J = 5.1 Hz, 1H), 4.05 (dd, J = 3.2, 5.9 Hz, 1H), 3.92 (s, 3H), 2.06 (s, 3H), 0.94 - 0.88 (m, 2H), 0.79 - 0.76 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₄F₅N₃O₅+H]⁺: 638.56, found: 638.2, tR= 4.776 min, [Method O]	Atrop 2	-6.88
56	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.5 Hz, 1H), 7.46 (s, 1H), 7.42 - 7.36 (m, 2H), 7.35 - 7.30 (m, 2H), 7.28 - 7.22 (m, 1H), 7.07 (t, J = 9.0 Hz, 1H), 6.76 - 6.73 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄F₃N₃O₅+H]⁺: 576.54, found: 576.0, tR= 5.043 min, [Method W]	Atrop 1	54.64

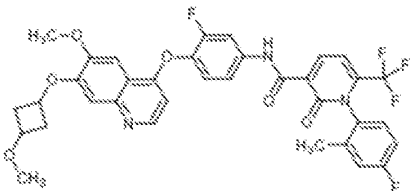
57	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.5 Hz, 1H), 7.46 (s, 1H), 7.42 - 7.36 (m, 2H), 7.35 - 7.30 (m, 2H), 7.28 - 7.22 (m, 1H), 7.07 (t, J = 9.0 Hz, 1H), 6.76 - 6.73 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄F₃N₃O₅+H]⁺: 576.54, found: 576.0, tR= 5.043min, [Method O]	Atrop 2	-70.16
58	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (s, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.82 (dd, J = 3.0, 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 (s, 1H), 7.44 - 7.38 (m, 2H), 7.32 (s, 1H), 7.09 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₀H₁₈ClF₆N₃O₅+H]⁺: 650.93, found: 649.8, tR= 5.410 min, [Method W]	Atrop 1	39.12

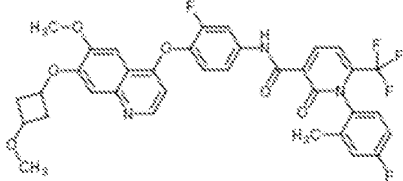
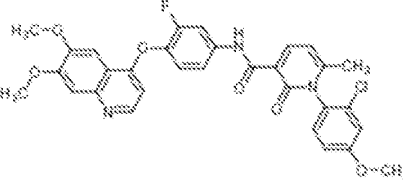
59	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (s, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.82 (dd, J = 3.0, 8.5 Hz, 2H), 7.54 - 7.48 (m, 1H), 7.46 (s, 1H), 7.44 - 7.38 (m, 2H), 7.32 (s, 1H), 7.09 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₁₈ClF₆N₃O₅+H]⁺: 650.93, found: 649.8, tR= 5.414 min, [Method W]	Atrop 2	-34.32
60	 6-tert-butyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.99 (s, 1H), 8.52 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.06 - 8.00 (m, 1H), 7.56 - 7.48 (m, 4H), 7.44 - 7.37 (m, 4H), 6.91 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 5.3 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.14 (s, 9H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₉F₂N₃O₅+H]⁺: 586.61, found: 585.9, tR= 4.212 min, [Method W]		NA

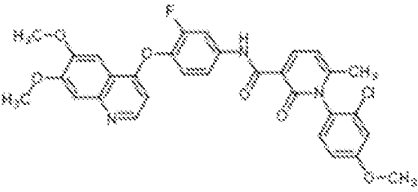
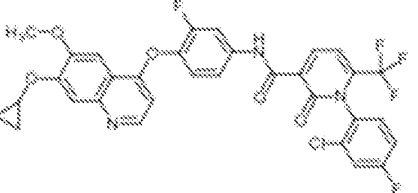
61	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.88 - 7.81 (m, 2H), 7.65 - 7.61 (m, 1H), 7.56 - 7.40 (m, 5H), 6.48 (d, J = 5.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₀H₁₉ClF₅N₃O₅] +: 632.94, found: 632.2, tR= 4.652 min, [Method O]	Atrop 1	75.2
62	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.87 - 7.81 (m, 2H), 7.65 - 7.60 (m, 1H), 7.55 - 7.49 (m, 2H), 7.48 - 7.41 (m, 3H), 6.48 (d, J = 4.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H) LCMS (ES⁺) m/z calc,d for [M+H]⁺ [C₃₀H₁₉ClF₅N₃O₅+H]⁺: 632.94, found: 632.2, tR= 4.690 min, [Method O]	Atrop 2	-69.28

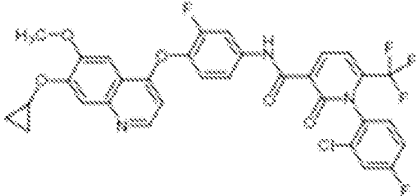
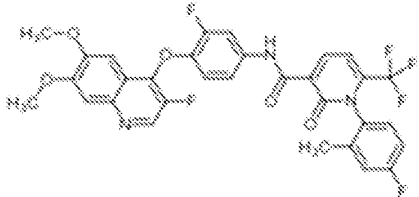
63	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.17 (s, 1H), 8.52 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.04 (dd, J = 2.3, 12.8 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.45 - 7.40 (m, 2H), 7.23 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 3.0 Hz, 1H), 6.96 (dd, J = 2.5, 8.5 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.48 - 6.46 (m, 1H), 3.95 (d, J = 2.0 Hz, 6H), 3.83 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₈FN₃O₆+H]⁺: 570.1, found: 570.0, tR = 3.97 min, [Method L']	Atrop 1	63.52
64	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.17 (s, 1H), 8.52 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.04 (dd, J = 2.0, 13.0 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.45 - 7.40 (m, 2H), 7.23 (d, J = 9.0 Hz, 1H), 7.04 (d, J = 3.0 Hz, 1H), 6.96 (dd, J = 2.8, 8.8 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 6.47 (d, J = 4.5 Hz, 1H), 3.95 (d, J = 2.0 Hz, 6H), 3.82 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₈FN₃O₈+H]⁺: 570.1, found: 570.0, tR = 4.11 min, [Method O]	Atrop 2	-89.12

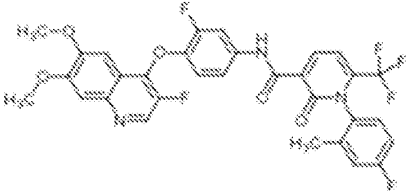
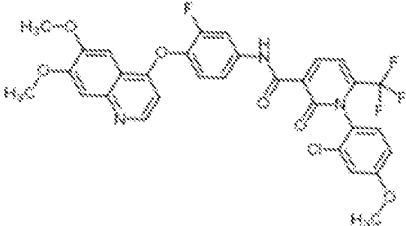
65	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.06 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.49 (d, J = 7.3 Hz, 1H), 7.98 (dd, J = 2.4, 13.2 Hz, 1H), 7.46 (s, 1H), 7.33 - 7.29 (m, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.07 (t, J = 8.8 Hz, 1H), 7.03 (d, J = 2.9 Hz, 1H), 6.94 (dd, J = 2.9, 8.3 Hz, 1H), 6.72 (d, J = 7.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₇F₂N₃O₆+H]⁺: 588.58, found: 588.0, tR= 4.667 min, [Method O]	Atrop 1	62.88
66	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.06 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.49 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.3, 13.3 Hz, 1H), 7.46 (s, 1H), 7.33 - 7.29 (m, 2H), 7.21 (d, J = 8.5 Hz, 1H), 7.07 (t, J = 9.3 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.94 (dd, J = 2.8, 8.8 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₇F₂N₃O₆+H]⁺: 588.58, found: 588.0, tR= 5.095 min, [Method L²].	Atrop 2	-60.88

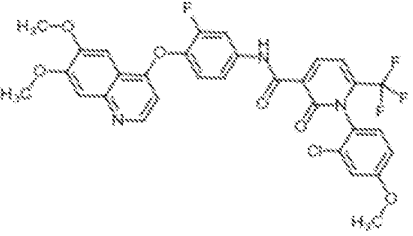
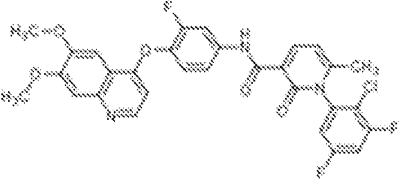
67	 N-[3-fluoro-4-[[6-methoxy-7-(3-methoxycyclobutoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.63 - 7.59 (m, 1H), 7.54 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.26 (m, J = 3.0, 8.5 Hz, 1H), 7.14 (s, 1H), 6.47 (dd, J = 1.0, 5.0 Hz, 1H), 5.05 - 4.99 (m, 1H), 4.16 - 4.09 (m, J = 7.0, 7.0 Hz, 1H), 3.95 (s, 3H), 3.20 (s, 3H), 2.57 - 2.52 (m, 2H), 2.44 - 2.37 (m, 2H), 2.06 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₂₈F₅N₃O₆+H]⁺: 682.19, found: 681.9, tR= 4.401 min, [Method W]	Atrop 1	-34.24
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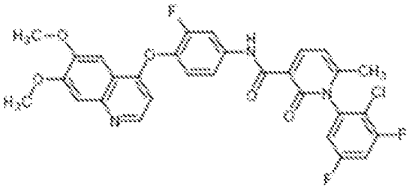
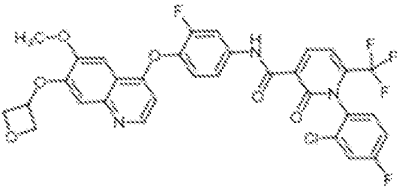
68	 N-[3-fluoro-4-[[6-methoxy-7-(3-methoxycyclobutoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.63 - 7.59 (m, J = 8.8 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.28 - 7.23 (m, J = 8.5, 8.5 Hz, 1H), 7.14 (s, 1H), 6.49 - 6.46 (m, 1H), 5.05 - 4.99 (m, 1H), 4.16 - 4.09 (m, 1H), 3.95 (s, 3H), 3.20 (s, 3H), 2.52 - 2.51 (m, 2H), 2.45 - 2.38 (m, 2H), 2.06 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₂₈F₅N₃O₆+H]⁺: 682.19, found: 681.9, t_R = 4.403 min, [Method W]	Atrop 2	39.16
69	 1-(2-chloro-4-methoxy-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluorophenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.01 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.57 - 7.52 (m, 3H), 7.45 - 7.40 (m, 2H), 7.35 (d, J = 2.5 Hz, 1H), 7.17 - 7.14 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 5.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H), 2.08 (s, 3H) MS (ES⁺) m/z calc'd for [M]⁺ [C₃₁H₂₅ClFN₃O₆]⁺: 590, found: 589.9, t_R = 4.192 min, [Method O]	Atrop 1	78.96

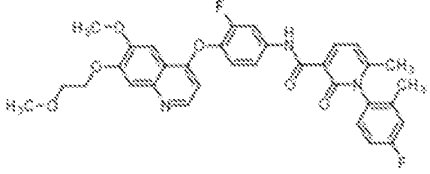
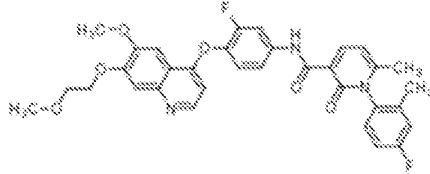
70	 1-(2-chloro-4-methoxy-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.01 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.56 - 7.52 (m, 3H), 7.45 - 7.40 (m, 2H), 7.35 (d, J = 2.5 Hz, 1H), 7.17 - 7.14 (m, 1H), 6.76 (d, J = 7.5 Hz, 1H), 6.48 (d, J = 4.5 Hz, 1H), 3.95 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H), 2.08 (s, 3H). MS (ES⁺) m/z calc'd for [M]⁺ [C₃₁H₂₅ClF₃N₃O₆]⁺: 590, found: 589.9, t_R = 4.203 min, [Method O].	Atrop 2	-113.6
71	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.87 - 7.82 (m, 2H), 7.71 (s, 1H), 7.65 - 7.60 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 - 7.40 (m, 2H), 6.51 - 6.47 (m, 1H), 4.08 - 4.02 (m, 1H), 3.92 (s, 3H), 0.94 - 0.87 (m, 2H), 0.79 - 0.74 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₁ClF₅N₃O₅+H]⁺: 658.98, found: 657.8, t_R = 4.581 min, [Method O].	Atrop 1	135.2

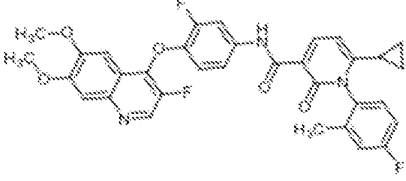
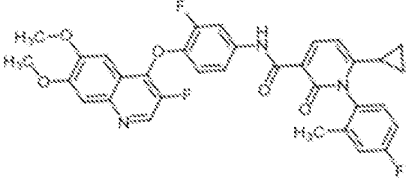
72	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.6 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.08 - 8.02 (m, 1H), 7.87 - 7.81 (m, 2H), 7.71 (s, 1H), 7.65 - 7.61 (m, 1H), 7.55 - 7.49 (m, 2H), 7.46 - 7.41 (m, 2H), 6.52 - 6.47 (m, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 0.93 - 0.88 (m, 2H), 0.80 - 0.74 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₁ClF₅N₃O₅+H]⁺: 658.98, found: 657.8, tR= 4.580 min, [Method O]	Atrop 2	-160.3
73	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.75 (d, J = 2.7 Hz, 1H), 8.65 (d, J = 7.6 Hz, 1H), 7.99 (dd, J = 2.4, 13.4 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.46 (s, 1H), 7.37 (d, J = 8.1 Hz, 3H), 7.33 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (t, J = 8.9 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁F₆N₃O₅+]⁺: 630.52, found: 629.9, tR= 5.028 min, [Method O]	Atrop 1	122.24

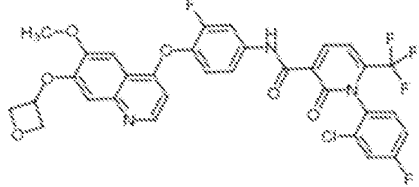
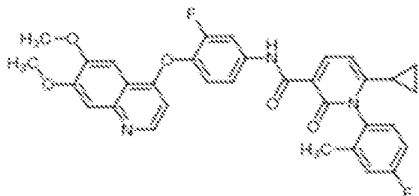
74	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (s, 1H), 8.76 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.5 Hz, 1H), 7.50 (dd, J = 5.8, 8.8 Hz, 1H), 7.46 (s, 1H), 7.37 (d, J = 7.5 Hz, 3H), 7.34 - 7.28 (m, 2H), 7.27 - 7.21 (m, 1H), 7.09 (t, J = 9.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.05 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁F₆N₃O₅+H]⁺: 630.52, found: 629.9, tR= 5.025 min, [Method O]	Atrop 2	-95.28
75	 1-(2-chloro-4-methoxy-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluorophenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (s, 1H), 8.69 (d, J = 7.3 Hz, 1H), 8.49 (d, J = 5.1 Hz, 1H), 8.07 - 8.03 (m, 1H), 7.62 (d, J = 9.0 Hz, 2H), 7.53 (s, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 2.7, 8.8 Hz, 1H), 6.48 (d, J = 4.9 Hz, 1H), 3.95 (s, 3H), 3.95 (s, 3H), 3.88 (s, 3H) MS (ES⁺) m/z calc'd for [M]⁺ [C₃₁H₂₂ClF₄N₃O₆]⁺: 643.98, found: 643.8, tR= 4.452 min, [Method O]	Atrop 1	200.96

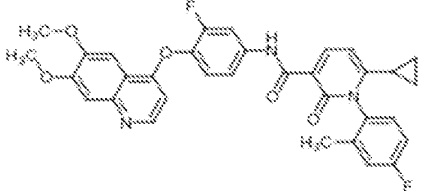
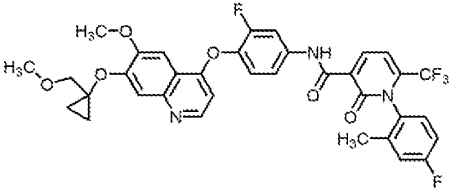
76	 1-(2-chloro-4-methoxy-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.66 (s, 1H), 8.69 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H), 8.07 - 8.02 (m, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 7.46 (t, J = 9.0 Hz, 1H), 7.41 - 7.38 (m, 2H), 7.34 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 2.8, 8.9 Hz, 1H), 6.48 (d, J = 5.4 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.88 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₂ClF₄N₃O₆] +: 643.98, found: 643.8, tR= 4.445 min, [Method O]	Atrop 2	-199.8
77	 1-(2-chloro-3,5-difluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.79 (s, 1H), 8.58 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.89 - 7.84 (m, 1H), 7.74 - 7.70 (m, 1H), 7.57 - 7.53 (m, 2H), 7.46 - 7.41 (m, 2H), 6.81 (d, J = 8.0 Hz, 1H), 6.48 - 6.46 (m, 1H), 3.95 (s, 6H), 2.14 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₁ClF₃N₃O₅+H]⁺: 596.11, found: 595.9, tR: 4.078 min, [Method W]	Atrop 1	ND

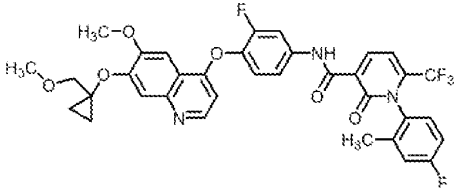
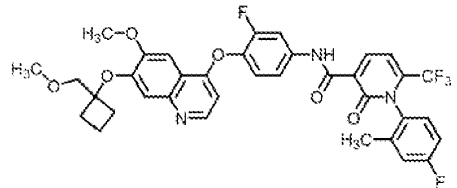
78	 1-(2-chloro-3,5-difluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.79 (s, 1H), 8.58 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.89 - 7.84 (m, 1H), 7.73 - 7.70 (m, 1H), 7.57 - 7.52 (m, 2H), 7.45 - 7.41 (m, 2H), 6.81 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 5.0 Hz, 1H), 3.95 (s, 6H), 2.14 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₁ClF₃N₃O₅+H]⁺: 596.10, found: 595.9, tR= 4.085 min, [Method W]	Atrop 2	ND
79	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.3 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.5, 12.8 Hz, 1H), 7.87 - 7.82 (m, 1H), 7.65 - 7.61 (m, 2H), 7.58 (s, 1H), 7.55 - 7.41 (m, 3H), 7.04 (s, 1H), 6.51 - 6.49 (m, 1H), 5.52 - 5.48 (m, 1H), 5.04 (t, J = 6.5 Hz, 2H), 4.64 (dd, J = 5.3, 7.5 Hz, 2H), 3.98 (s, 3H); MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₁ClF₄N₃O₆+H]⁺: 674.10, found: 673.8, tR= 4.432 min, [Method W]	Atrop 1	-68.88

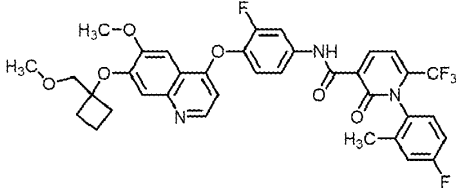
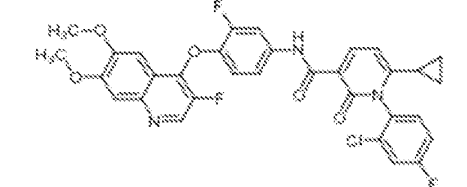
80	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.47 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.55 - 7.52 (m, 2H), 7.45 - 7.37 (m, 4H), 7.30 - 7.24 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.48 - 6.45 (m, 1H), 4.30 - 4.26 (m, 2H), 3.95 (s, 3H), 3.77 - 3.74 (m, 2H), 3.35 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₉F₂N₃O₆+H]⁺: 602.6, found: 602.0, tR= 4.022 min, [Method W]	Atrop 1	62.16
81	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.49 - 8.44 (m, 1H), 8.08 - 8.01 (m, 1H), 7.56 - 7.51 (m, 2H), 7.46 - 7.36 (m, 4H), 7.31 - 7.24 (m, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.52 - 6.41 (m, 1H), 4.31 - 4.25 (m, 2H), 3.95 (s, 3H), 3.79 - 3.72 (m, 2H), 3.35 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₉F₂N₃O₆+H]⁺: 602.6, found: 602.0, tR= 4.026 min, [Method W]	Atrop 2	-76.08

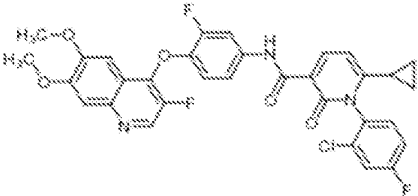
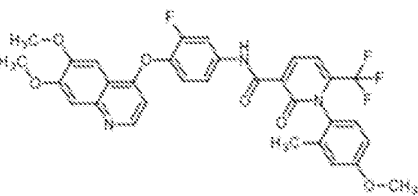
82	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.99 (dd, J = 2.4, 13.4 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.39 - 7.22 (m, 4H), 7.06 (t, J = 8.9 Hz, 1H), 6.46 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.31 - 1.22 (m, 1H), 0.93 - 0.90 (m, 2H), 0.88 - 0.85 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₃N₃O₅+H]⁺: 602.58, found: 601.8, tR= 5.267 min, [Method W]	Atrop 1	53.6
83	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.5, 13.3 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.37 (dd, J = 2.9, 9.6 Hz, 1H), 7.34 - 7.30 (m, 2H), 7.28 - 7.23 (m, 1H), 7.06 (t, J = 9.3 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.03 (s, 3H), 1.31 - 1.25 (m, 1H), 0.93 - 0.83 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₃N₃O₅+H]⁺: 602.58, found: 601.8, tR= 5.260 min, [Method W]	Atrop 2	-50.4

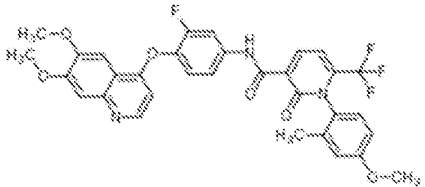
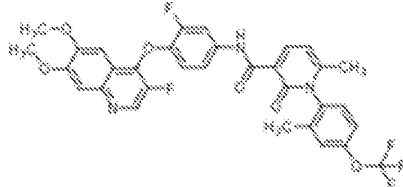
84	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.0 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.5, 12.8 Hz, 1H), 7.87 - 7.82 (m, 2H), 7.65 - 7.61 (m, 1H), 7.58 (s, 1H), 7.55 - 7.41 (m, 3H), 7.04 (s, 1H), 6.50 (d, J = 4.5 Hz, 1H), 5.52 - 5.47 (m, 1H), 5.04 (t, J = 6.9 Hz, 2H), 4.64 (dd, J = 5.1, 7.6 Hz, 2H), 3.97 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₁ClF₄N₃O₆+H]⁺: 674.10, found: 673.8, tR= 4.440 min, [Method W]	Atrop 2	38.92
85	 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (s, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.55 - 7.51 (m, 2H), 7.49 - 7.42 (m, 2H), 7.41 - 7.36 (m, 2H), 7.30 - 7.24 (m, 1H), 6.49 - 6.46 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 1.32 - 1.26 (m, 1H), 0.95 - 0.91 (m, 2H), 0.90 - 0.84 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₇F₂N₃O₅+H]⁺: 584.19, found: 583.9, tR= 4.161 min, [Method W]	Atrop 1	95.28

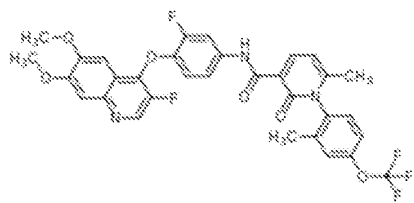
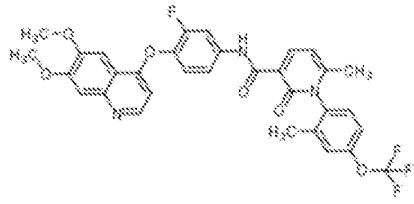
86	 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.08 (s, 1H), 8.51 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.56 - 7.49 (m, 2H), 7.48 - 7.41 (m, 2H), 7.41 - 7.35 (m, 2H), 7.30 - 7.24 (m, 1H), 6.54 - 6.41 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 1.34 - 1.24 (m, 1H), 0.97 - 0.90 (m, 2H), 0.90 - 0.81 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₇F₂N₃O₅+H]⁺: 584.19, found: 583.9, tR = 4.159 min, [Method W]	Atrop 2	-45.52
87	 N-[3-fluoro-4-[[6-methoxy-7-[1-(methoxymethyl)cyclopropoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.0, 13.0 Hz, 1H), 7.64 - 7.59 (m, 2H), 7.55 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.41 - 7.33 (m, 2H), 7.29 - 7.22 (m, 1H), 6.48 (d, J = 5.0 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 2H), 3.27 (s, 3H), 2.06 (s, 3H), 1.10 - 1.05 (m, 2H), 1.05 - 1.01 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₂₈F₅N₃O₆+H]⁺: 682.01, found: 681.9, tR = 4.517 min, [Method W]	Atrop 1	89.52

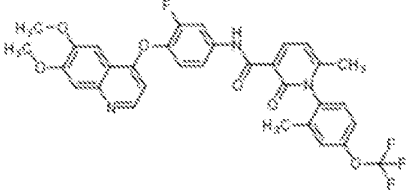
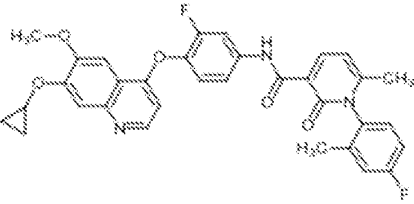
88	 N-[3-fluoro-4-[[6-methoxy-7-[1-(methoxymethyl)cyclopropoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆) δ: 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.5, 12.8 Hz, 1H), 7.64 - 7.59 (m, 2H), 7.54 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.41 - 7.33 (m, 2H), 7.29 - 7.23 (m, 1H), 6.48 (dd, J = 0.8, 5.3 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 2H), 3.27 (s, 3H), 2.06 (s, 3H), 1.09 - 1.05 (m, 2H), 1.05 - 1.00 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₂₈F₅N₃O₆+H]⁺: 682.01, found: 681.9, tR = 4.467 min, [Method W]	Atrop 2	-80.24
89	 N-[3-fluoro-4-[[6-methoxy-7-[1-(methoxymethyl)cyclobutoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.66 - 7.57 (m, 1H), 7.55 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.42 - 7.33 (m, 2H), 7.30 - 7.23 (m, 1H), 7.20 (s, 1H), 6.51 - 6.42 (m, 1H), 3.93 (s, 3H), 3.81 (s, 2H), 3.28 (s, 3H), 2.43 - 2.28 (m, 4H), 2.07 (s, 3H), 1.85 - 1.68 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₆H₃₀F₅N₃O₆+H]⁺: 696.21, found: 695.9, tR= 4.586 min, [Method W]	Atrop 1	76.88

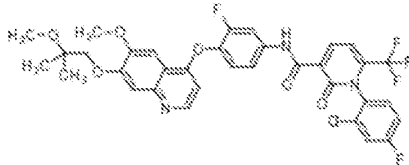
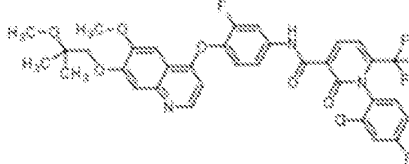
90	 N-[3-fluoro-4-[[6-methoxy-7-[1-(methoxymethyl)cyclobutoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.54 - 7.49 (m, 2H), 7.45 (t, J = 9.0 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.28 - 7.23 (m, 1H), 7.19 (s, 1H), 6.46 (dd, J = 1.0, 5.0 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 2H), 3.28 (s, 3H), 2.40 - 2.32 (m, 4H), 2.06 (s, 3H), 1.79 - 1.71 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₆H₃₀F₅N₃O₆+H]⁺: 696.21, found: 695.9, tR= 4.576 min, [Method W]	Atrop 2	-104.7
91	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.75 (d, J = 2.8 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 8.01 - 7.96 (m, 1H), 7.81 (dd, J = 2.8, 8.5 Hz, 1H), 7.77 (dd, J = 5.6, 8.9 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.47 - 7.44 (m, 1H), 7.36 - 7.31 (m, 2H), 7.06 (t, J = 9.1 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.35 - 1.29 (m, 1H), 0.93 - 0.81 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₃ClF₃N₃O₅+H]⁺: 622.0, found: 622.2, tR= 5.139 min, [Method O]	Atrop 1	93.36

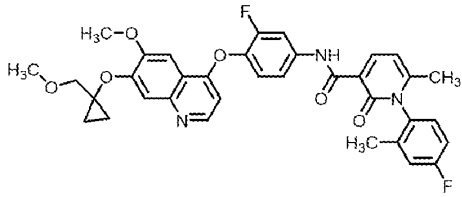
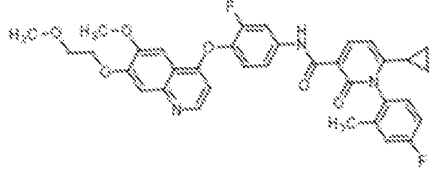
92	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.81 (dd, J = 2.5, 8.5 Hz, 1H), 7.77 (dd, J = 5.8, 8.8 Hz, 1H), 7.54 - 7.47 (m, 1H), 7.46 (s, 1H), 7.35 - 7.29 (m, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.51 (d, J = 7.5 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.35 - 1.29 (m, 1H), 0.94 - 0.81 (m, 4H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₃ClF₃N₃O₅+H]⁺: 622.5, found: 622.2, tR= 5.484 min, [Method L']	Atrop 2	-99.04
93	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (s, 1H), 8.67 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.53 (s, 1H), 7.46 (t, J = 8.8 Hz, 1H), 7.41 (s, 1H), 7.36 (d, J = 7.5 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 2.8, 8.8 Hz, 1H), 6.49 - 6.46 (m, 1H), 3.95 (s, 3H), 3.95 (s, 3H), 3.82 (s, 3H), 2.02 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₄N₃O₆+H]⁺: 623.56, found: 623.9, tR= 4.302 min, [Method W]	Atrop 1	52.32

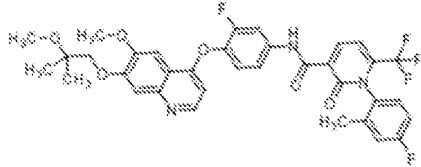
94	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.8 Hz, 1H), 7.62 - 7.59 (m, 1H), 7.53 (s, 1H), 7.46 (t, J = 8.9 Hz, 1H), 7.41 (s, 1H), 7.37 - 7.30 (m, 2H), 7.01 (d, J = 2.8 Hz, 1H), 6.93 (dd, J = 3.0, 8.5 Hz, 1H), 6.47 (d, J = 5.3 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.02 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₄N₃O₆+H]⁺: 623.56, found: 624.2, tR= 5.370 min, [Method C⁺]	Atrop 2	-49.28
95	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.74 (d, J = 2.5 Hz, 1H), 8.52 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.55 - 7.48 (m, 2H), 7.46 (s, 1H), 7.44 - 7.39 (m, 1H), 7.36 - 7.30 (m, 2H), 7.07 (t, J = 9.3 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₅N₃O₆+H]⁺: 642.16, found: 641.9, tR= 5.338 min, [Method W]	Atrop 1	132.4

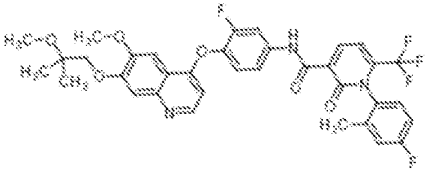
96	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.90 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.52 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.55 - 7.49 (m, 2H), 7.46 (s, 1H), 7.44 - 7.40 (m, 1H), 7.36 - 7.30 (m, 2H), 7.07 (t, J = 9.3 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.04 (s, 3H), 2.04 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₅N₃O₆+H]⁺: 642.16, found: 641.9, tR= 5.338 min, [Method W]	Atrop 2	-88.24
97	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.02 (s, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.58 - 7.49 (m, 4H), 7.46 - 7.35 (m, 3H), 6.78 (d, J = 7.8 Hz, 1H), 6.47 (d, J = 5.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₄N₃O₆+H]⁺: 623.5, found: 623.9, tR= 4.31 min, [Method W]	Atrop 1	73.68

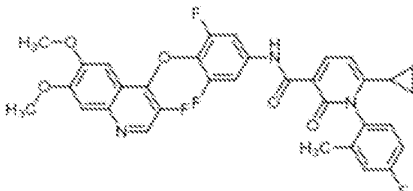
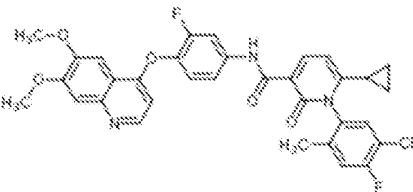
98	 N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-6-methyl-1-[2-methyl-4-(trifluoromethoxy)phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.02 (s, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.59 - 7.49 (m, 4H), 7.49 - 7.35 (m, 3H), 6.78 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 4.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₄N₃O₆]⁺: 623.5, found: 623.9, tR = 4.31 min, [Method W]	Atrop 2	-69.92
99	 N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.49 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.3, 13.0 Hz, 1H), 7.71 (s, 1H), 7.60 - 7.48 (m, 2H), 7.48 - 7.31 (m, 3H), 7.30 - 7.24 (m, 1H), 6.77 (d, J = 8.3 Hz, 1H), 6.48 (dd, J = 0.9, 5.1 Hz, 1H), 4.07 - 4.01 (m, 1H), 3.92 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 0.96 - 0.86 (m, 2H), 0.81 - 0.70 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₇F₂N₃O₅+H]⁺: 584.5, found: 584, tR = 4.18 min, [Method W]	Atrop 1	97.76

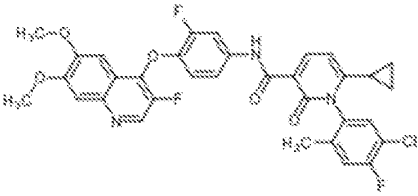
100	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.88 - 7.78 (m, 2H), 7.65 - 7.61 (m, 1H), 7.57 - 7.51 (m, 2H), 7.49 - 7.45 (m, 1H), 7.45 - 7.41 (m, 2H), 6.48 (dd, J = 0.9, 5.1 Hz, 1H), 4.03 (s, 2H), 3.96 (s, 3H), 3.21 (s, 3H), 1.28 (s, 6H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₇ClF₅N₃O₆+H]⁺: 705.05, found: 703.8, tR= 4.647 min, [Method W]	Atrop 1	108.08
101	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.3 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.87 - 7.81 (m, 2H), 7.65 - 7.60 (m, 1H), 7.56 - 7.50 (m, 2H), 7.49 - 7.39 (m, 3H), 6.48 (dd, J = 0.8, 5.3 Hz, 1H), 4.03 (s, 2H), 3.96 (s, 3H), 3.21 (s, 3H), 1.28 (s, 6H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₇ClF₅N₃O₆+H]⁺: 705.05, found: 703.8, tR: 4.598 min, [Method O]	Atrop 2	-94.08

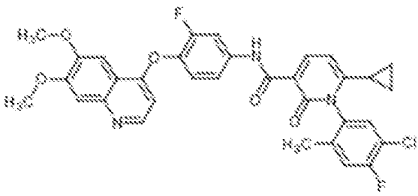
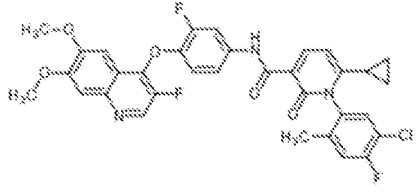
102	 N-[3-fluoro-4-[[6-methoxy-7-[1-(methoxymethyl)cyclopropoxy]-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.54 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.62 (s, 1H), 7.57 - 7.51 (m, 2H), 7.46 - 7.35 (m, 3H), 7.30 - 7.24 (m, 1H), 6.77 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 4.5 Hz, 1H), 3.92 (s, 3H), 3.73 (s, 2H), 3.28 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.11 - 1.00 (m, 4H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₃₁F₂N₃O₆+H]⁺: 628.64, found: 627.9, tR= 4.200 min, [Method O]	Atrop 1	76.88
103	 6-cyclopropyl-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.55 - 7.50 (m, 2H), 7.49 - 7.41 (m, 3H), 7.38 (dd, J = 3.3, 9.8 Hz, 1H), 7.30 - 7.24 (m, 1H), 6.50 - 6.45 (m, 2H), 4.30 - 4.25 (m, 2H), 3.95 (s, 3H), 3.78 - 3.74 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H), 1.32 - 1.27 (m, 1H), 0.98 - 0.91 (m, 2H), 0.90 - 0.84 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₃₁F₂N₃O₆+H]⁺: 628.64, found: 627.9, tR= 4.19 min, [Method W].	Atrop 1	42.72

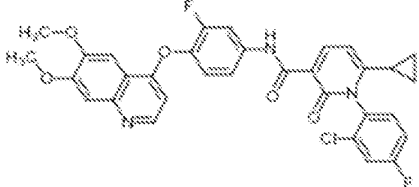
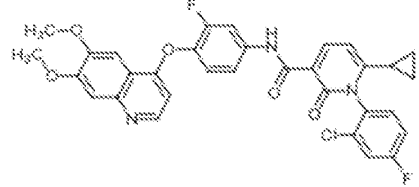
104	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.05 (dd, J = 2.3, 12.8 Hz, 1H), 7.63 - 7.59 (m, 1H), 7.54 - 7.45 (m, 3H), 7.43 (s, 1H), 7.40 - 7.34 (m, 2H), 7.29 - 7.23 (m, 1H), 6.47 (d, J = 5.0 Hz, 1H), 4.03 (s, 2H), 3.96 (s, 3H), 3.21 (s, 3H), 2.07 (s, 3H), 1.28 (s, 6H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₅N₃O₆+H]⁺: 684.63, found: 683.9, tR= 4.547 min, [Method N].	Atrop 1	114.16
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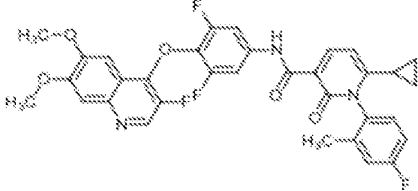
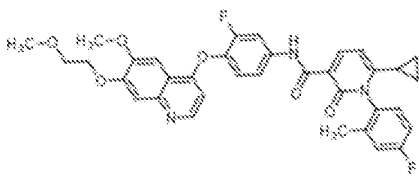
105	 N-[3-fluoro-4-[[6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (s, 1H), 8.69 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.06 (dd, J = 2.2, 12.8 Hz, 1H), 7.64 - 7.60 (m, 1H), 7.54 - 7.35 (m, 6H), 7.29 - 7.23 (m, 1H), 6.48 (d, J = 5.0 Hz, 1H), 4.04 (s, 2H), 3.96 (s, 3H), 3.21 (s, 3H), 2.07 (s, 3H), 1.28 (s, 6H); MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₅N₃O₆+H]⁺: 684.63, found: 683.9, tR= 4.547 min, [Method N]. MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₅N₃O₆+H]⁺: 684.63, found: 683.9, tR= 4.547 min, [Method N].	Atrop 2	-105.5
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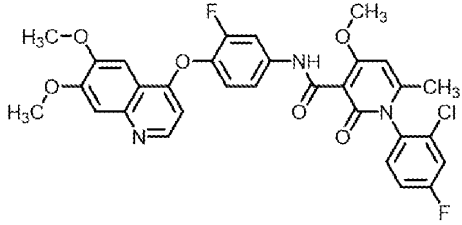
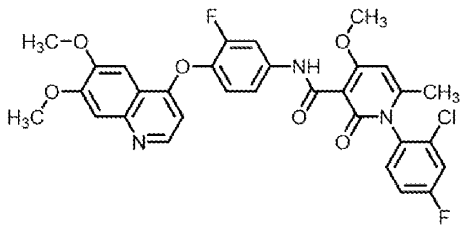
106	 6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (500 MHz, DMSO-d₆): δ 12.09 (s, 1H), 8.68 (d, J = 3.7 Hz, 1H), 8.48 (d, J = 7.6 Hz, 1H), 7.76 - 7.71 (m, 2H), 7.49 (s, 1H), 7.47 - 7.43 (m, 2H), 7.37 (dd, J = 2.7, 9.5 Hz, 1H), 7.29 - 7.24 (m, 1H), 6.47 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.04 (s, 3H), 1.31 - 1.27 (m, 1H), 0.95 - 0.90 (m, 2H), 0.90 - 0.84 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.17, found: 620.0, tR= 5.376 min, [Method W].	Atrop 1	31.2
107	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.99 (s, 1H), 8.51 (d, J = 7.9 Hz, 1H), 8.49 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 13.2 Hz, 1H), 7.85 (d, J = 7.1 Hz, 1H), 7.63 (d, J = 10.0 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.46 - 7.39 (m, 2H), 6.52 - 6.45 (m, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.05 (s, 3H), 1.38 - 1.32 (m, 1H), 0.98 - 0.92 (m, 2H), 0.92 - 0.85 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆ClF₂N₃O₅+H]⁺: 618.15, found: 618.2, tR= 4.625 min, [Method O].	Atrop 1	-110.4

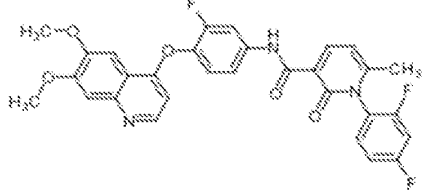
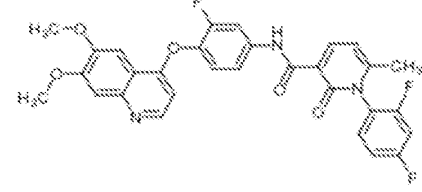
108	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.88 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.99 (dd, J = 2.5, 13.3 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 10.3 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.31 (m, 2H), 7.07 (t, J = 9.1 Hz, 1H), 6.48 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.37 - 1.31 (m, 1H), 0.96 - 0.91 (m, 2H), 0.90 - 0.85 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅ClF₃N₃O₅+H]⁺: 636.14, found: 635.9, tR= 5.412 min, [Method N].	Atrop 1	-75
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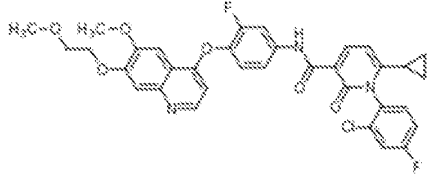
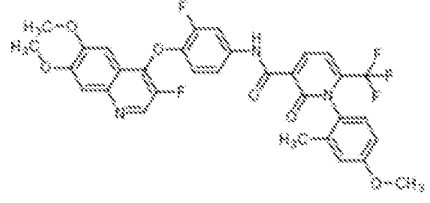
109	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.99 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 5.5 Hz, 1H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.85 (d, J = 7.0 Hz, 1H), 7.62 (d, J = 10.0 Hz, 1H), 7.56 - 7.52 (m, 2H), 7.43 (d, J = 9.0 Hz, 1H), 7.41 (s, 1H), 6.51 - 6.46 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H), 1.38 - 1.31 (m, 1H), 0.96 - 0.92 (m, 2H), 0.92 - 0.86 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₆ClF₂N₃O₅+H]⁺: 618.16, found: 618.20, tR= 4.631 min, [Method O]	Atrop 2	80.4
110	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.88 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.3 Hz, 1H), 7.83 (d, J = 7.1 Hz, 1H), 7.61 (d, J = 10.1 Hz, 1H), 7.46 (s, 1H), 7.32 (s, 2H), 7.07 (t, J = 9.2 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.02 (s, 3H), 1.35 - 1.30 (m, 1H), 0.94 - 0.91 (m, 2H), 0.89 - 0.85 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₅ClF₃N₃O₅+H]⁺: 636.15, found: 635.90, tR= 5.420 min, [Method W].	Atrop 2	82

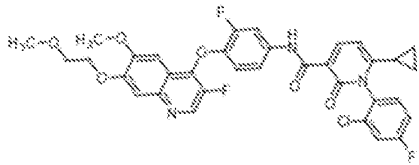
111	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.92 (s, 1H), 8.53 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.0, 13.0 Hz, 1H), 7.84 - 7.77 (m, 2H), 7.56 - 7.52 (m, 3H), 7.50 - 7.41 (m, 2H), 6.53 (d, J = 8.0 Hz, 1H), 6.47 (d, J = 5.0 Hz, 1H), 3.95 (d, J = 2.0 Hz, 6H), 1.38 - 1.33 (m, 1H), 0.94 - 0.86 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₅+H]⁺: 605.01, found: 604.12, tR=4.24 min, [Method AD]	Atrop 1	81.04
112	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.92 (s, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.83 (dd, J = 2.5, 8.5 Hz, 1H), 7.79 (dd, J = 5.8, 8.8 Hz, 1H), 7.56 - 7.50 (m, 3H), 7.45 - 7.40 (m, 2H), 6.53 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 4.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.37 - 1.30 (m, 1H), 0.94 - 0.89 (m, 2H), 0.89 - 0.80 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₄ClF₂N₃O₆+H]⁺: 605.01, found: 604.12, tR= 5.425 min, [Method AC].	Atrop 2	-101

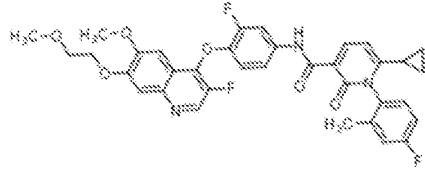
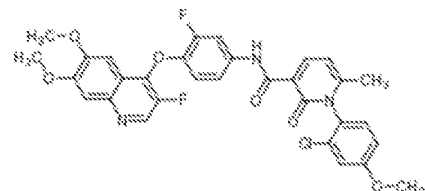
113	 6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (500MHz, DMSO-d₆): δ 12.09 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.48 (d, J = 7.9 Hz, 1H), 7.75 - 7.72 (m, 2H), 7.49 (s, 1H), 7.47 - 7.42 (m, 2H), 7.37 (dd, J = 2.9, 9.3 Hz, 1H), 7.29 - 7.24 (m, 1H), 6.47 (d, J = 7.9 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.04 (s, 3H), 1.31 - 1.27 (m, 1H), 0.94 - 0.90 (m, 2H), 0.90 - 0.85 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.17, found : 619.9, tR= 5.383 min, [Method W].	Atrop 2	-3.44
114	 6-cyclopropyl-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 5.5 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.55 - 7.50 (m, 2H), 7.49 - 7.41 (m, 3H), 7.38 (dd, J = 3.3, 9.8 Hz, 1H), 7.30 - 7.24 (m, 1H), 6.50 - 6.45 (m, 2H), 4.30 - 4.25 (m, 2H), 3.95 (s, 3H), 3.78 - 3.74 (m, 2H), 3.35 (s, 3H), 2.06 (s, 3H), 1.32 - 1.27 (m, 1H), 0.98 - 0.91 (m, 2H), 0.90 - 0.84 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₃₁F₂N₃O₆+H]⁺: 628.64, found: 627.9, tR= 4.19 min, [Method W].	Atrop 2	-34.16

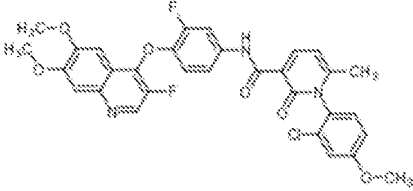
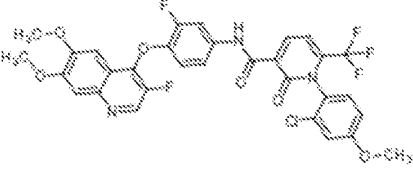
115	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-methoxy-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.46 (d, J = 5.1 Hz, 1H), 7.94 (dd, J = 2.1, 13.3 Hz, 1H), 7.77 (dd, J = 2.7, 8.6 Hz, 1H), 7.58 - 7.48 (m, 3H), 7.48 - 7.38 (m, 3H), 6.62 (s, 1H), 6.50 - 6.43 (m, 1H), 3.95 (s, 6H), 3.94 (s, 3H), 2.00 (s, 3H). MS(ES)⁺ m/z calc'd for [M]⁺ [C₃₁H₂₄ClF₂N₃O₆] +: 607.9, found: 607.9, tR = 3.73 min, [Method N].	Atrop 1	100.16
116	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-4-methoxy-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 10.69 (s, 1H), 8.46 (d, J = 5.3 Hz, 1H), 7.94 (br dd, J = 1.8, 13.3 Hz, 1H), 7.77 (dd, J = 2.8, 8.5 Hz, 1H), 7.55 - 7.45 (m, 6H), 6.62 (s, 1H), 6.46 (d, J = 5.0 Hz, 1H), 3.95 - 3.94 (m, 9H), 2.00 (s, 3H). MS (ES⁺) m/z calc'd for [M]⁺ [C₃₁H₂₄ClF₂N₃O₆] +: 607.99, found: 607.9, tR = 3.718, [Method N].	Atrop 2	-63.12

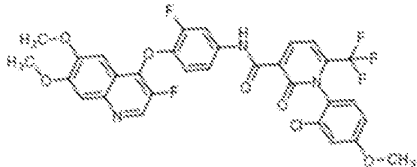
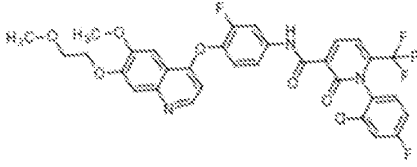
117	 1-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluorophenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.87 (s, 1H), 8.55 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 5.4 Hz, 1H), 8.04 (dd, J = 2.6, 12.8 Hz, 1H), 7.77 - 7.69 (m, 1H), 7.68 - 7.61 (m, 1H), 7.57 - 7.52 (m, 2H), 7.45 - 7.36 (m, 3H), 6.78 (d, J = 7.8 Hz, 1H), 6.48 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.14 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562.52, found: 561.9, tR = 3.945 min, [Method W].	Atrop 1	8.4
118	 1-(2,4-difluorophenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluorophenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.87 (s, 1H), 8.55 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 5.1 Hz, 1H), 8.04 (dd, J = 2.4, 13.0 Hz, 1H), 7.76 - 7.69 (m, 1H), 7.68 - 7.61 (m, 1H), 7.57 - 7.52 (m, 2H), 7.46 - 7.35 (m, 3H), 6.78 (d, J = 8.3 Hz, 1H), 6.48 (d, J = 4.6 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.14 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₃N₃O₅+H]⁺: 562.52, found: 561.9, tR = 3.944 min, [Method W].	Atrop 2	-27.04

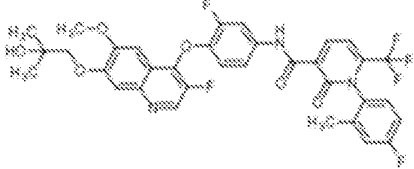
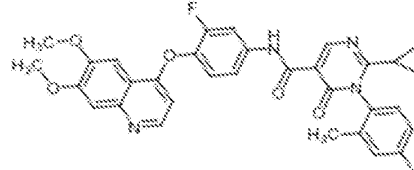
119	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.92 (s, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.47 (d, J = 5.3 Hz, 1H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.85 - 7.75 (m, 2H), 7.59 - 7.48 (m, 3H), 7.46 - 7.36 (m, 2H), 6.53 (d, J = 7.8 Hz, 1H), 6.47 (dd, J = 0.8, 5.3 Hz, 1H), 4.31 - 4.25 (m, 2H), 3.95 (s, 3H), 3.79 - 3.73 (m, 2H), 3.35 (s, 3H), 1.37 - 1.28 (m, 1H), 0.98 - 0.78 (m, 4H). MS (ES+) m/z calc'd for [M]⁺ [C₃₄H₂₈ClF₂N₂O₆] +: 648.06, found: 647.9, tR = 4.225 min, [Method W].	Atrop 1	78.84
120	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.6, 13.1 Hz, 1H), 7.46 (s, 1H), 7.40 - 7.37 (m, 1H), 7.36 - 7.27 (m, 3H), 7.09 (t, J = 9.1 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 2.8, 8.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₅N₃O₆+H]⁺: 642.55, found: 641.8, tR = 5.355 min, [Method W].	Atrop 1	98.3

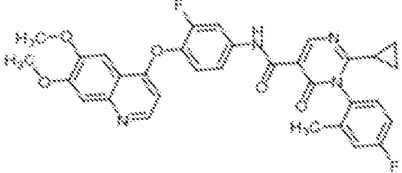
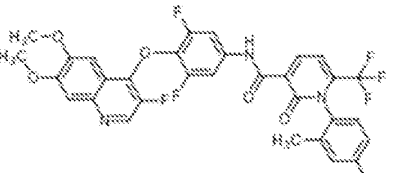
121	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.74 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.3, 13.3 Hz, 1H), 7.81 (dd, J = 2.8, 8.4 Hz, 1H), 7.77 (dd, J = 5.5, 8.9 Hz, 1H), 7.53 - 7.49 (m, 1H), 7.49 - 7.47 (m, 1H), 7.35 - 7.32 (m, 2H), 7.07 (t, J = 9.4 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 4.29 - 4.26 (m, 2H), 3.89 (s, 3H), 3.76 - 3.73 (m, 2H), 3.34 (s, 3H), 1.28 - 1.24 (m, 1H), 0.93 - 0.89 (m, 2H), 0.88 - 0.83 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₇ClF₃N₃O₆+H]⁺: 666.16, found: 666.20, tR= 5.617 min, [Method AC].	Atrop 1	106
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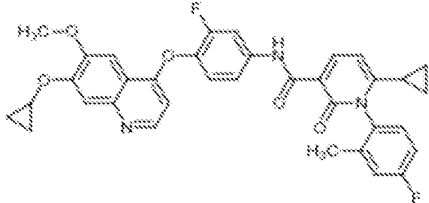
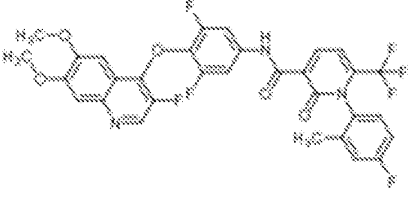
122	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.5 Hz, 1H), 7.49 - 7.41 (m, 2H), 7.39 - 7.29 (m, 3H), 7.29 - 7.22 (m, 1H), 7.07 (t, J = 9.3 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.31 - 4.24 (m, 2H), 3.89 (s, 3H), 3.77 - 3.72 (m, 2H), 3.34 (s, 3H), 2.04 (s, 3H), 1.29 - 1.24 (m, 1H), 0.94 - 0.89 (m, 2H), 0.88 - 0.83 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₃N₃O₆+H]⁺: 646.6, found: 645.9, tR= 5.223 min, [Method N].	Atrop 1	31.04
123	 1-(2-chloro-4-methoxy-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.90 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.51 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.4 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.31 (m, 3H), 7.14 (dd, J = 2.8, 8.8 Hz, 1H), 7.07 (t, J = 9.3 Hz, 1H), 6.76 - 6.73 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.07 (s, 3H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄ClF₂N₃O₆]⁺: 608.99, found: 607.9, tR= 5.121 min, [Method W].	Atrop 1	128.48

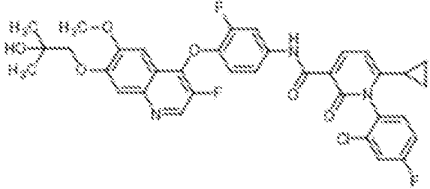
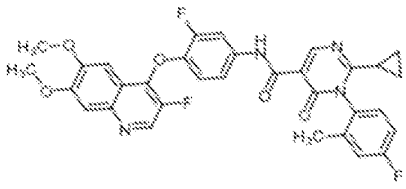
124	 1-(2-chloro-4-methoxy-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-6-methyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.90 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.51 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.30 (m, 3H), 7.14 (dd, J = 2.8, 9.0 Hz, 1H), 7.07 (t, J = 9.4 Hz, 1H), 6.75 - 6.73 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 2.06 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₄ClF₂N₃O₆] +: 608.99, found: 607.9, tR= 5.126 min, [Method W].	Atrop 2	-87.44
125	 1-(2-chloro-4-methoxy-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.55 (s, 1H), 8.76 (d, J = 2.8 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.0 Hz, 1H), 7.60 (d, J = 9.5 Hz, 1H), 7.46 (s, 1H), 7.42 - 7.38 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.33 - 7.31 (m, 2H), 7.15 - 7.10 (m, 1H), 7.10 - 7.05 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₁ClF₅N₃O₆+H]⁺: 662.9, found: 661.8, tR= 5.423 min, [Method W].	Atrop 1	142.6

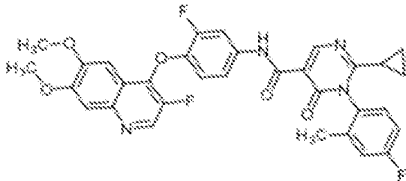
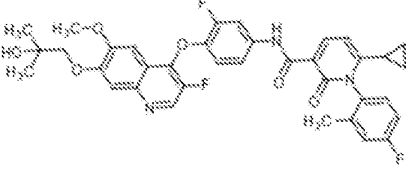
126	 1-(2-chloro-4-methoxy-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.76 (d, J = 3.0 Hz, 1H), 8.67 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.5, 13.3 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.47 (s, 1H), 7.43 - 7.39 (m, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.33 - 7.32 (m, 2H), 7.15 - 7.11 (m, 1H), 7.10 - 7.07 (m, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₁ClF₅N₃O₆] +: 662.9, found: 662.1, tR = 4.87 min, [Method AD].	Atrop 2	-113.1
127	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.70 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 12.9 Hz, 1H), 7.86 - 7.82 (m, 2H), 7.65 - 7.61 (m, 1H), 7.55 - 7.39 (m, 5H), 6.48 (d, J = 5.0 Hz, 1H), 4.30 - 4.27 (m, 2H), 3.95 (s, 3H), 3.78 - 3.74 (m, 2H), 3.35 (s, 3H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₃ClF₅N₃O₆+H]⁺: 676.99, found: 675.8, tR = 4.404 min, [Method W].	Atrop 1	184.6

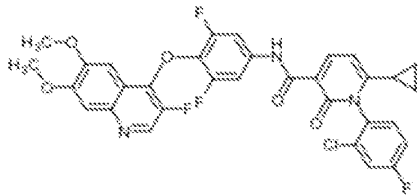
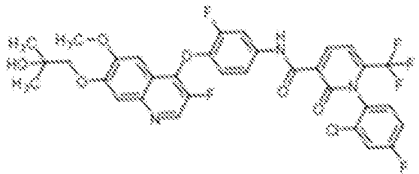
128	 N-[3-fluoro-4-[[3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.65 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.3, 13.0 Hz, 1H), 7.50 (dd, J = 5.5, 8.3 Hz, 1H), 7.44 (s, 1H), 7.42 - 7.31 (m, 4H), 7.27 - 7.21 (m, 1H), 7.09 (t, J = 9.1 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 5H), 2.05 (s, 3H), 1.25 (s, 6H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₇F₆N₃O₆+H]⁺: 688.6 found: 687.9, tR= 5.282 min, [Method U].	Atrop 1	94
129	 2-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.25 (s, 1H), 8.83 (s, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.03 (dd, J = 2.4, 12.9 Hz, 1H), 7.61 - 7.50 (m, 3H), 7.47 - 7.39 (m, 3H), 7.35 - 7.29 (m, 1H), 6.48 - 6.45 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.12 (s, 3H), 1.46 - 1.39 (m, 1H), 1.30 - 1.21 (m, 2H), 1.13 - 1.03 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₆F₂N₄O₅+H]⁺: 585.19, found: 584.9, tR= 4.24 min, [Method W].	Atrop 1	42.08

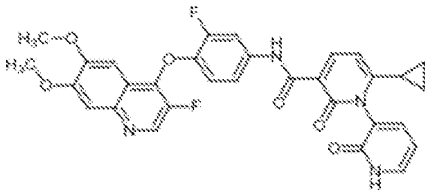
130	 2-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.25 (s, 1H), 8.83 (s, 1H), 8.48 (d, J = 5.0 Hz, 1H), 8.03 (dd, J = 2.4, 12.9 Hz, 1H), 7.61 - 7.52 (m, 3H), 7.47 - 7.40 (m, 3H), 7.35 - 7.30 (m, 1H), 6.48 - 6.46 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.12 (s, 3H), 1.45 - 1.40 (m, 1H), 1.27 - 1.22 (m, 2H), 1.11 - 1.04 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₆F₂N₄O₅+H]⁺: 585.19, found: 584.9, tR= 4.25 min, [Method W].	Atrop 2	-9.2
131	 N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.83 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.65 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 10.3 Hz, 2H), 7.50 (s, 1H), 7.44 (s, 1H), 7.35 (d, J = 7.3 Hz, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 2.7, 8.6 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₃F₆N₃O₆+H]⁺: 660.18, found: 659.9, tR= 5.48 min, [Method W].	Atrop 1	73.72

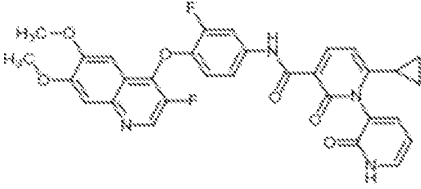
132	 N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-cyclopropyl-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.07 (s, 1H), 8.56 - 8.46 (m, 2H), 8.05 (dd, J = 2.5, 13.0 Hz, 1H), 7.71 (s, 1H), 7.56 - 7.50 (m, 2H), 7.50 - 7.36 (m, 3H), 7.30 - 7.24 (m, 1H), 6.50 - 6.45 (m, 2H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 2.06 (s, 3H), 1.33 - 1.25 (m, 1H), 1.00 - 0.81 (m, 6H), 0.81 - 0.73 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₂₉F₂N₃O₅+H]⁺: 610.63, found: 610.4, tR= 5.437 min, [Method AC]	Atrop 1	78.24
133	 N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.73 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.66 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 10.3 Hz, 2H), 7.51 - 7.49 (m, 2H), 7.44 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.37 - 7.33 (m, 1H), 7.28 - 7.22 (m, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.05 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₀F₇N₃O₅+H]⁺: 648.13, found: 647.9, tR= 5.492 min, [Method W].	Atrop 1	167.88

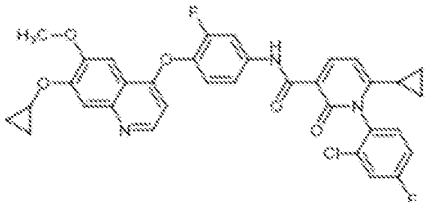
134	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.3, 13.3 Hz, 1H), 7.81 (dd, J = 2.8, 8.3 Hz, 1H), 7.77 (dd, J = 5.8, 8.8 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.44 (s, 1H), 7.37 - 7.30 (m, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 5H), 1.36 - 1.30 (m, 1H), 1.25 (s, 6H), 0.95 - 0.88 (m, 2H), 0.86 - 0.79 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺[C₃₅H₂₉ClF₃N₃O₆+H]⁺: 680.18, found: 680.53, tR= 4.580 min, [Method AD].	Atrop 1	189.6
135	 2-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.14 (s, 1H), 8.80 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 7.96 (dd, J = 2.5, 13.0 Hz, 1H), 7.56 (dd, J = 5.3, 8.8 Hz, 1H), 7.46 (s, 1H), 7.41 (dd, J = 3.0, 9.5 Hz, 1H), 7.36 - 7.29 (m, 3H), 7.08 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.10 (s, 3H), 1.43 - 1.39 (m, 1H), 1.26 - 1.22 (m, 2H), 1.09 - 1.04 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺[C₃₂H₂₅F₃N₄O₅+H]⁺: 602.9, found: 603.2, tR= 5.407 min, [Method AC].	Atrop 1	44.8

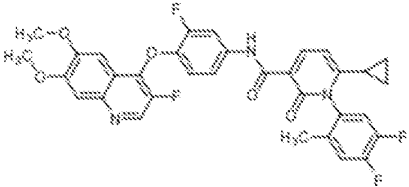
136	 2-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.14 (s, 1H), 8.80 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 7.96 (dd, J = 2.3, 13.3 Hz, 1H), 7.59 - 7.54 (m, 1H), 7.46 (s, 1H), 7.41 (dd, J = 3.0, 9.5 Hz, 1H), 7.37 - 7.27 (m, 3H), 7.08 (t, J = 9.3 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.10 (s, 3H), 1.43 - 1.38 (m, 1H), 1.25 - 1.20 (m, 2H), 1.13 - 1.04 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₃N₄O₅+H]⁺: 602.9, found: 603.2, tR= 5.401 min, [Method AC]	Atrop 2	-10.48
137	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 2.5, 13.3 Hz, 1H), 7.46 - 7.42 (m, 2H), 7.36 (dd, J = 2.8, 9.5 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.28 - 7.22 (m, 1H), 7.06 (t, J = 9.1 Hz, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.66 (s, 1H), 3.90 (s, 5H), 2.04 (s, 3H), 1.33 - 1.27 (m, 1H), 1.25 (s, 6H), 0.94 - 0.83 (m, 4H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₆H₃₂F₃N₃O₆+H]⁺: 660.6, found: 659.9, tR= 5.160 min, [Method W].	Atrop 1	37.88

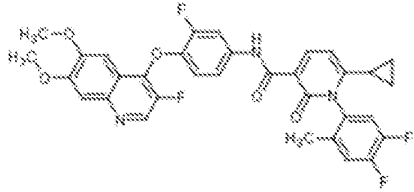
138	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.93 (s, 1H), 8.68 (d, J = 3.5 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 7.84 - 7.72 (m, 4H), 7.52 (dd, J = 2.8, 8.3 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 1.36 - 1.31 (m, 1H), 0.93 - 0.91 (m, 2H), 0.89 - 0.81 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₂ClF₄N₃O₅+H]⁺: 640.18, found: 639.9, tR= 5.435 min, [Method W].	Atrop 1	79.4
139	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (s, 1H), 8.75 (d, J = 2.7 Hz, 1H), 8.67 (d, J = 7.3 Hz, 1H), 7.99 (dd, J = 2.6, 13.1 Hz, 1H), 7.85 - 7.80 (m, 2H), 7.55 - 7.47 (m, 1H), 7.46 - 7.39 (m, 3H), 7.32 (s, 1H), 7.08 (t, J = 9.2 Hz, 1H), 4.67 (s, 1H), 3.90 (s, 5H), 1.25 (s, 6H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₃H₂₄ClF₆N₃O₆+H]⁺: 708.14, found: 707.80, tR= 5.350 min, [Method W].	Atrop 1	199.76

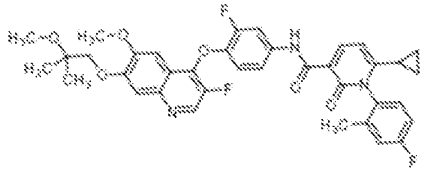
140	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-1-(2-oxo-1H-pyridin-3-yl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.29 (br s, 1H), 12.00 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.43 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.72 (dd, J = 1.7, 7.1 Hz, 1H), 7.60 (dd, J = 2.0, 6.4 Hz, 1H), 7.46 (s, 1H), 7.33 - 7.30 (m, 2H), 7.07 (t, J = 9.0 Hz, 1H), 6.44 (d, J = 7.3 Hz, 1H), 6.37 (t, J = 6.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 1.60 - 1.55 (m, 1H), 0.94 - 0.88 (m, 2H), 0.87 - 0.78 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄F₂N₄O₆+H]⁺: 587.55, found: 587.0, tR= 4.227 min, [Method W].	Atrop 1	61.68
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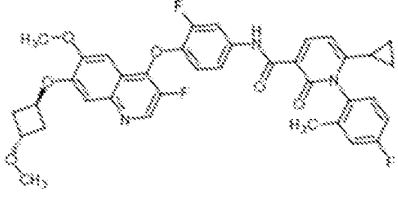
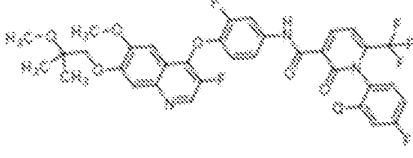
141	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-1-(2-oxo-1H-pyridin-3-yl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.28 (br s, 1H), 11.98 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.44 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.7 Hz, 1H), 7.74 (dd, J = 2.2, 7.1 Hz, 1H), 7.59 (d, J = 4.9 Hz, 1H), 7.46 (s, 1H), 7.33 - 7.30 (m, 2H), 7.07 (t, J = 9.3 Hz, 1H), 6.44 (d, J = 7.8 Hz, 1H), 6.39 (t, J = 6.6 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 1.60 - 1.55 (m, 1H), 0.94 - 0.81 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄F₂N₄O₆+H]⁺: 587.55, found: 587.0, tR = 4.220 min, [Method W]	Atrop 2	-32.24
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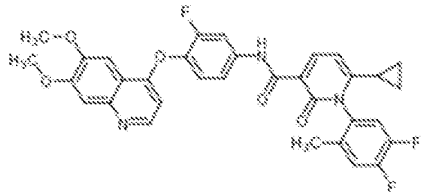
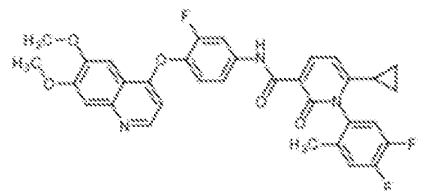
142	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-cyclopropyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.92 (s, 1H), 8.53 (d, J = 7.8 Hz, 1H), 8.49 (d, J = 5.4 Hz, 1H), 8.04 (dd, J = 2.4, 13.0 Hz, 1H), 7.83 (dd, J = 2.7, 8.6 Hz, 1H), 7.79 (dd, J = 5.6, 8.8 Hz, 1H), 7.71 (s, 1H), 7.56 - 7.49 (m, 3H), 7.45 - 7.39 (m, 1H), 6.53 (d, J = 7.8 Hz, 1H), 6.48 (d, J = 4.9 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.92 (s, 3H), 1.36 - 1.31 (m, 1H), 0.95 - 0.83 (m, 6H), 0.80 - 0.74 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₆ClF₂N₃O₅+H]⁺: 630.04, found: 629.8, tR= 4.467 min, [Method N]	Atrop 1	134.96
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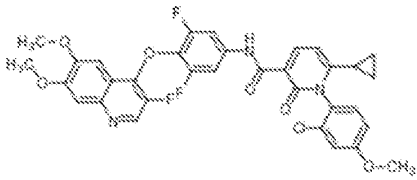
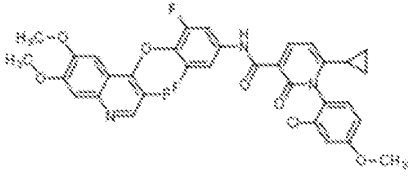
143	 6-cyclopropyl-1-(4,5-difluoro-2-methylphenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.89 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.7 Hz, 1H), 7.72 (dd, J = 7.8, 10.8 Hz, 1H), 7.62 (dd, J = 9.0, 11.0 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.29 (m, 2H), 7.07 (t, J = 9.0 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.00 (s, 3H), 1.37 - 1.31 (m, 1H), 0.95 - 0.90 (m, 2H), 0.89 - 0.85 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.17, found: 619.9, tR= 5.273 min, [Method W]	Atrop 1	43.84
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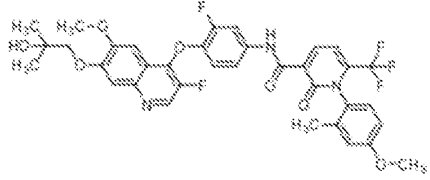
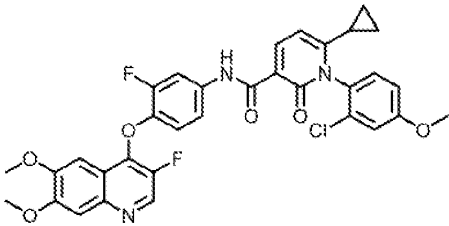
144	 6-cyclopropyl-1-(4,5-difluoro-2-methylphenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxopyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.89 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.5, 13.3 Hz, 1H), 7.72 (dd, J = 7.9, 10.9 Hz, 1H), 7.62 (dd, J = 8.6, 11.4 Hz, 1H), 7.46 (s, 1H), 7.36 - 7.25 (m, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.00 (s, 3H), 1.37 - 1.29 (m, 1H), 0.97 - 0.90 (m, 2H), 0.90 - 0.85 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₅F₄N₃O₅+H]⁺: 620.18, Found: 619.9, tR = 5.28 min, [Method W].	Atrop 2	-40.28
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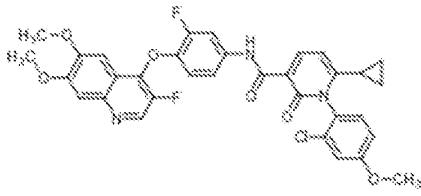
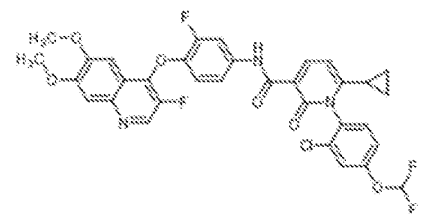
145	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.74 (d, J = 2.9 Hz, 1H), 8.47 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.48 (s, 1H), 7.44 (dd, J = 5.4, 8.8 Hz, 1H), 7.36 (dd, J = 2.9, 9.8 Hz, 1H), 7.33 - 7.30 (m, 2H), 7.29 - 7.22 (m, 1H), 7.06 (t, J = 9.0 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 4.03 (s, 2H), 3.90 (s, 3H), 3.19 (s, 3H), 2.03 (s, 3H), 1.33 - 1.27 (m, 1H), 1.26 (s, 6H), 0.94 - 0.89 (m, 2H), 0.88 - 0.82 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₇H₃₄F₃N₃O₆+H]⁺: 674.69, found: 674.1, tR = 5.494 min, [Method W].	Atrop 1	60.64
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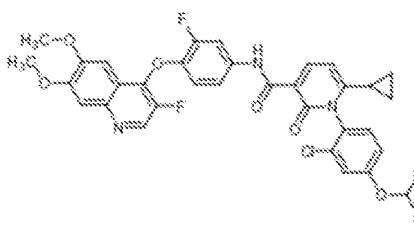
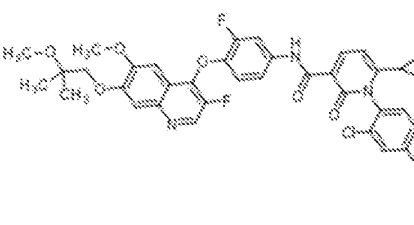
146	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(3-methoxycyclobutoxy)-4-quinolyl]oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.73 (d, J = 3.0 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.44 (dd, J = 5.5, 8.5 Hz, 1H), 7.36 (dd, J = 2.5, 9.5 Hz, 1H), 7.34 - 7.29 (m, 2H), 7.28 - 7.23 (m, 1H), 7.19 (s, 1H), 7.06 (t, J = 9.3 Hz, 1H), 6.46 (d, J = 7.5 Hz, 1H), 5.04 - 5.00 (m, 1H), 4.13 - 4.07 (m, 1H), 3.89 (s, 3H), 3.30 - 3.29 (m, 2H), 3.19 (s, 3H), 2.43 - 2.39 (m, 2H), 2.03 (s, 3H), 1.31 - 1.25 (m, 1H), 0.94 - 0.89 (m, 2H), 0.88 - 0.82 (m, 2H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₇H₃₂F₃N₃O₆+H]⁺: 672.18, found: 671.9, tR = 5.41 min, [Method W].	Atrop 1	26.64
147	 1-(2-chloro-4-fluoro-phenyl)-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.46 (s, 1H), 8.75 (d, J = 2.5 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.5, 13.0 Hz, 1H), 7.82 (dd, J = 2.8, 8.3 Hz, 2H), 7.54 - 7.48 (m, 2H), 7.44 - 7.38 (m, 2H), 7.32 (s, 1H), 7.08 (t, J = 9.3 Hz, 1H), 4.03 (s, 2H), 3.90 (s, 3H), 3.20 (s, 3H), 1.26 (s, 6H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₆ClF₆N₃O₆+H]⁺: 723.04 was found: 721.8, tR = 5.670 min, [Method W].	Atrop 1	116.56

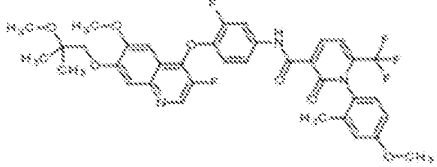
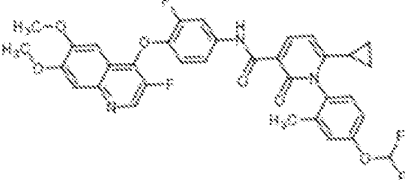
148	 6-cyclopropyl-1-(4,5-difluoro-2-methylphenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.00 (s, 1H), 8.51 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 5.3 Hz, 1H), 8.05 (dd, J = 2.4, 13.1 Hz, 1H), 7.74 (dd, J = 7.8, 11.0 Hz, 1H), 7.64 (dd, J = 8.8, 11.3 Hz, 1H), 7.56 - 7.51 (m, 2H), 7.47 - 7.39 (m, 2H), 6.52 - 6.44 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.02 (s, 3H), 1.38 - 1.32 (m, 1H), 0.96 - 0.91 (m, 2H), 0.91 - 0.86 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆F₃N₃O₅+H]⁺: 601.58, found: 602.0, t_R = 1.720 min, [Method N].	Atrop 1	47.6
149	 6-cyclopropyl-1-(4,5-difluoro-2-methylphenyl)-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.00 (s, 1H), 8.53 - 8.45 (m, 2H), 8.04 (dd, J = 2.5, 13.0 Hz, 1H), 7.74 (dd, J = 7.8, 10.8 Hz, 1H), 7.63 (dd, J = 8.5, 11.5 Hz, 1H), 7.55 - 7.50 (m, 2H), 7.44 - 7.39 (m, 2H), 6.51 - 6.45 (m, 2H), 3.95 (s, 6H), 2.02 (s, 3H), 1.38 - 1.31 (m, 1H), 0.96 - 0.92 (m, 2H), 0.91 - 0.87 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₇F₂N₃O₅+H]⁺: 601.58, found: 602.0, t_R = 4.196 min, [Method W].	Atrop 2	-90.16

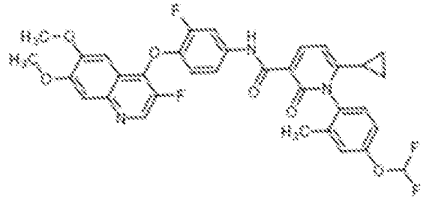
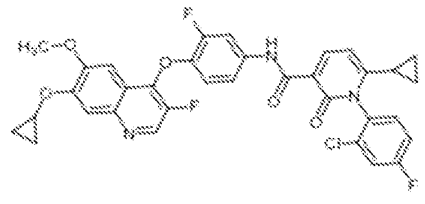
150	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.03 (s, 1H), 8.68 (d, J = 3.5 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 10.3 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.44 (s, 1H), 7.34 (d, J = 2.8 Hz, 1H), 7.15 (dd, J = 2.9, 8.9 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 1.38 - 1.30 (m, 1H), 0.95 - 0.81 (m, 4H). MS (ES⁺) m/z calc'd for [m+H]⁺ [C₃₃H₂₅ClF₃N₃O₆+H]⁺: 653.02, found: 652.2, tR= 5.702 min, [Method W].	Atrop 1	86.88
151	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.04 (s, 1H), 8.68 (d, J = 3.7 Hz, 1H), 8.48 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 10.3 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 2.9, 8.8 Hz, 1H), 6.48 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.87 (s, 3H), 1.38 - 1.31 (m, 1H), 0.95 - 0.84 (m, 4H). MS(ES)⁺ m/z calc'd for [m+H]⁺ [C₃₃H₂₅ClF₃N₃O₆+H]⁺: 653.02, found:., tR=5.701 min, [Method W].	Atrop 2	-22.8

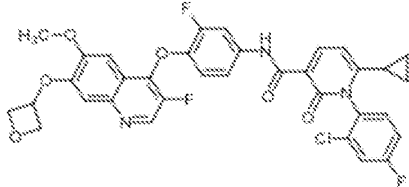
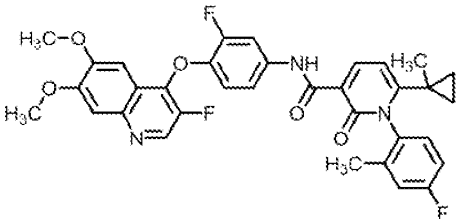
152	 N-[3-fluoro-4-[[3-fluoro-7-(2-hydroxy-2-methyl-propoxy)-6-methoxy-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.3, 13.6 Hz, 1H), 7.45 - 7.30 (m, 5H), 7.09 (t, J = 8.9 Hz, 1H), 6.99 (d, J = 2.4 Hz, 1H), 6.91 (dd, J = 2.7, 8.3 Hz, 1H), 4.68 (s, 1H), 3.90 (s, 5H), 3.81 (s, 3H), 1.99 (s, 3H), 1.25 (s, 6H). MS(ES)⁺ m/z calc'd for [M+H]⁺ [C₃₅H₃₀F₅N₃O₇+H]⁺: 700.63, found: 700.62, t_R = 4.71 min, [Method AD].	Atrop 1	30.72
153	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.6, 13.6 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.31 (m, 3H), 7.14 (dd, J = 2.7, 8.8 Hz, 1H), 7.07 (t, J = 8.9 Hz, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.86 (s, 3H), 1.35 - 1.30 (m, 1H), 0.93 - 0.85 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆ClF₂N₃O₆+H]⁺: 634.09, found: 634.2, t_R = 5.586 min, [Method AC].	Atrop 1	129.2

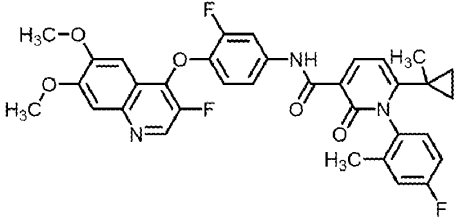
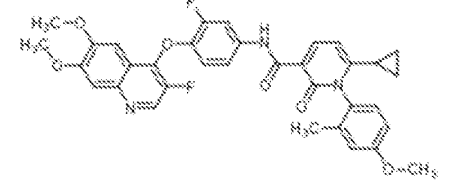
154	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.75 (d, J = 2.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.4 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.31 (m, 3H), 7.14 (dd, J = 2.6, 8.9 Hz, 1H), 7.09 - 7.04 (m, 1H), 6.47 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.87 (d, J = 8.5 Hz, 6H), 1.36 - 1.32 (m, 1H), 0.93 - 0.87 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₆ClF₂N₃O₆+H]⁺: 634.09, found: 633.9, tR = 5.308 min, [Method W].	Atrop 2	-27.4
155	 1-[2-chloro-4-(difluoromethoxy)phenyl]-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.82 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.2 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.49 - 7.25 (m, 5H), 7.06 (t, J = 9.3 Hz, 1H), 6.51 (d, J = 8.3 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 1.36 - 1.28 (m, 1H), 0.95 - 0.80 (m, 4H). MS (es⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₄ClF₄N₃O₆+H]⁺: 670.13, found: 669.8, tR = 5.355 min, [Method W]	Atrop 1	70.8

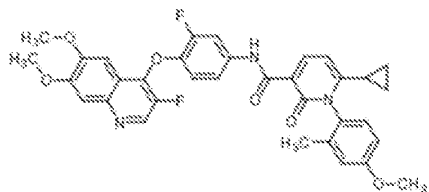
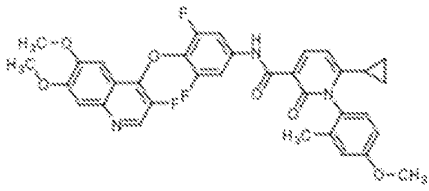
156	 1-[2-chloro-4-(difluoromethoxy)phenyl]-6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.82 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.7, 13.4 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.59 - 7.22 (m, 5H), 7.06 (t, J = 9.0 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 1.36 - 1.28 (m, 1H), 0.94 - 0.78 (m, 4H) MS (es+) m/z calc'd for [M+H]⁺ [C₃₃H₂₄ClF₄N₃O₆+H]⁺: 670.13, found: 669.8, tR=5.355 min,[Method W]	Atrop 2	-33.6
157	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.83 - 7.76 (m, J = 11.9 Hz, 2H), 7.52 - 7.48 (m, 2H), 7.35 - 7.31 (m, 2H), 7.06 (t, J = 9.1 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 4.03 (s, 2H), 3.90 (s, 3H), 3.19 (s, 3H), 1.33 - 1.29 (m, 1H), 1.26 (s, 6H), 0.91 (br d, J = 5.0 Hz, 2H), 0.86 - 0.80 (m, 2H). MS (ES+)m/z calc'd for [M+H]⁺ [C₃₆H₃₁ClF₃N₃O₆+H]⁺: 694.1 was found: 693.9, tR: 5.546 Min,[Method W]	Atrop 1	79.56

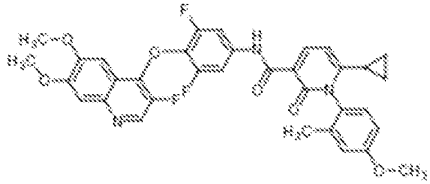
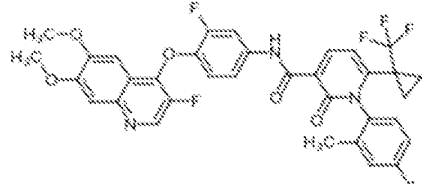
158	 N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxy-2-methyl-propoxy)-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (s, 1H), 8.75 (d, J = 2.8 Hz, 1H), 8.64 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.3, 13.3 Hz, 1H), 7.49 (s, 1H), 7.39 (br d, J = 9.0 Hz, 1H), 7.35 - 7.27 (m, 3H), 7.09 (t, J = 9.1 Hz, 1H), 6.99 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 2.6, 8.6 Hz, 1H), 4.03 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.20 (s, 3H), 2.00 (s, 3H), 1.26 (s, 6H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₆H₃₂F₅N₃O₇+H]⁺: 714.18, found: 713.9, tR = 5.41 min, [Method W]	Atrop 1	86.48
159	 6-cyclopropyl-1-[4-(difluoromethoxy)-2-methyl-phenyl]-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.97 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.54 - 7.39 (m, 2H), 7.39 - 7.25 (m, 4H), 7.25 - 7.15 (m, 1H), 7.06 (t, J = 9.0 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H), 1.33 - 1.23 (m, 1H), 0.97 - 0.82 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₇F₄N₃O₆+H]⁺: 650.60 found: 649.90, tR = 5.278 min, [Method W]	Atrop 1	35.84

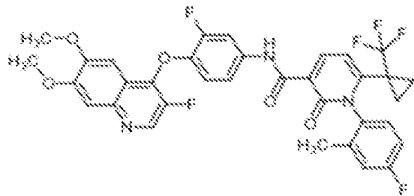
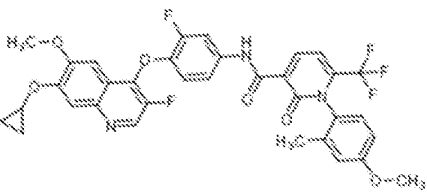
160	 6-cyclopropyl-1-[4-(difluoromethoxy)-2-methyl-phenyl]-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.97 (s, 1H), 8.75 (d, J = 2.4 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.55 - 7.41 (m, 2H), 7.41 - 7.28 (m, 4H), 7.28 - 7.15 (m, 1H), 7.06 (t, J = 9.0 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H), 1.31 - 1.23 (m, 1H), 0.95 - 0.83 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₇F₄N₃O₆+H]⁺: 650.60 found: 649.90, tR = 5.28 min.[Method W]	Atrop 2	-4.24
161	 1-(2-chloro-4-fluoro-phenyl)-N-[4-[[7-(cyclopropoxy)-3-fluoro-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-6-cyclopropyl-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.6, 13.3 Hz, 1H), 7.83 - 7.78 (m, 2H), 7.77 - 7.75 (m, 1H), 7.52 - 7.47 (m, 1H), 7.34 - 7.31 (m, 2H), 7.06 (t, J = 9.0 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.07 - 4.03 (m, 1H), 3.86 (s, 3H), 1.34 - 1.26 (m, 1H), 0.92 - 0.80 (m, 6H), 0.79 - 0.73 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₅ClF₃N₃O₅+H]⁺: 649.04, found: 647.8, tR = 5.502min.[Method W]	Atrop 1	205.36

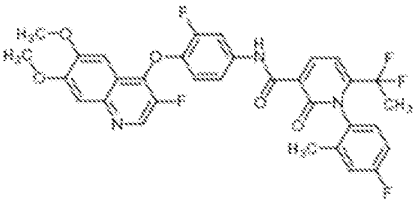
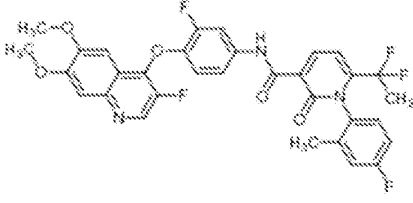
162	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(oxetan-3-yloxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.80 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.83 - 7.75 (m, 2H), 7.53 - 7.48 (m, 1H), 7.38 (s, 1H), 7.34 - 7.31 (m, 1H), 7.10 (s, 2H), 6.51 (d, J = 7.8 Hz, 1H), 5.51 - 5.47 (m, 1H), 5.03 (t, J = 6.9 Hz, 2H), 4.63 (dd, J = 5.0, 7.5 Hz, 2H), 3.92 (s, 3H), 1.35 - 1.28 (m, 1H), 0.93 - 0.81 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₅ClF₃N₃O₆+H]⁺: 665 found: 663.8, tR= 5.218 min, [Method W]	Atrop 1	84.96
163	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.52 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.55 (dd, J = 5.4, 8.6 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.30 (m, 3H), 7.27 - 7.21 (m, 1H), 7.06 (t, J = 9.1 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.00 (s, 3H), 1.07 - 1.02 (m, 1H), 0.97 (s, 3H), 0.94 - 0.90 (m, 1H), 0.56 - 0.48 (m, 2H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₅+H]⁺: 616.6 found: 615.9, tR= 5.430 min, [Method W]	Atrop 1	77.96

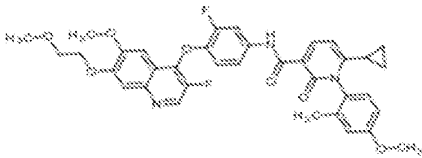
164	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-6-(1-methylcyclopropyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.52 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.55 (dd, J = 5.5, 8.8 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.30 (m, 3H), 7.27 - 7.21 (m, 1H), 7.06 (t, J = 9.3 Hz, 1H), 6.79 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.00 (s, 3H), 1.07 - 1.02 (m, 1H), 0.97 (s, 3H), 0.95 - 0.90 (m, 1H), 0.53 - 0.48 (m, 2H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₅+H]⁺: 616.6 found: 615.9, tR= 5.433 min, [Method W]	Atrop 2	-96.12
165	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.05 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.3, 13.3 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.27 (m, 2H), 7.24 (d, J = 9.0 Hz, 1H), 7.09 - 7.01 (m, 2H), 6.95 (dd, J = 3.0, 8.5 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H), 1.34 - 1.28 (m, 1H), 0.97 - 0.78 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₉F₂N₃O₆+H]⁺: 614.6 found: 613.9, tR= 5.271 min, [Method W]	Atrop 1	47.32

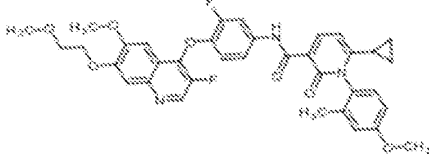
166	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.05 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.3, 13.3 Hz, 1H), 7.46 (s, 1H), 7.33 - 7.28 (m, 2H), 7.24 (d, J = 9.0 Hz, 1H), 7.09 - 7.02 (m, 2H), 6.95 (dd, J = 3.0, 8.5 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 2.00 (s, 3H), 1.35 - 1.27 (m, 1H), 0.93 - 0.81 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₉F₂N₃O₆+H]⁺: 614.6 found: 613.9, tR = 5.261 min, [Method W]	Atrop 2	-34.72
167	 6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.20 (s, 1H), 8.68 (d, J = 3.4 Hz, 1H), 8.46 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 10.3 Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.96 (dd, J = 2.7, 8.6 Hz, 1H), 6.42 (d, J = 7.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H), 1.36 - 1.28 (m, 1H), 0.98 - 0.86 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₆+H]⁺: 632.20, found: 631.9, tR = 5.42 min, [Method W]	Atrop 1	75.8

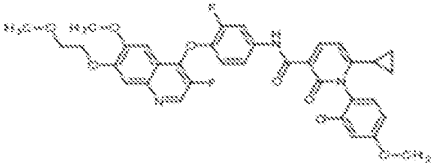
168	 6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.19 (s, 1H), 8.67 (d, J = 3.5 Hz, 1H), 8.46 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 10.5 Hz, 2H), 7.49 (s, 1H), 7.43 (s, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.04 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 3.0, 8.5 Hz, 1H), 6.42 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H), 2.00 (s, 3H), 1.35 - 1.28 (m, 1H), 0.99 - 0.86 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₆+H]⁺: 632.20, found: 631.9, t_R = 5.43 min, [Method W]	Atrop 2	-8.6
169	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-6-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.82 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.60 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.48 - 7.43 (m, 2H), 7.37 - 7.29 (m, 3H), 7.27 - 7.22 (m, 1H), 7.09 - 7.04 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 1.94 (s, 3H), 1.54 (dd, J = 5.8, 9.0 Hz, 1H), 1.34 - 1.27 (m, 1H), 1.25 - 1.19 (m, 1H), 0.98 - 0.93 (m, 1H) ms (es⁺) m/z calc'd for [m+H]⁺ [C₃₄H₂₅F₆N₃O₅+H]⁺: 670.58, found: 669.9, t_R = 5.448 min, [Method W]	Atrop 1	274.16

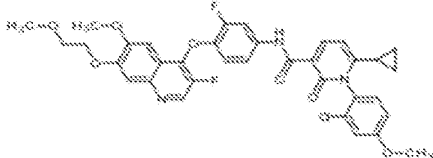
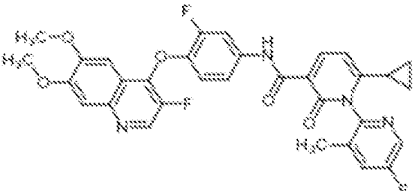
170	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-6-[1-(trifluoromethyl)cyclopropyl]pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.82 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.60 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.0 Hz, 1H), 7.47 - 7.42 (m, 2H), 7.38 - 7.28 (m, 3H), 7.27 - 7.21 (m, 1H), 7.10 - 7.03 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 1.94 (s, 3H), 1.58 - 1.50 (m, 1H), 1.34 - 1.26 (m, 1H), 1.25 - 1.18 (m, 1H), 0.99 - 0.89 (m, 1H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₅F₆N₃O₅+H]⁺: 670.58, found: 669.9, tR = 5.447 min, [Method W]	Atrop 2	-219
171	 N-[4-[[7-(cyclopropoxy)-3-fluoro-6-methoxy-4-quinolyl]oxy]-3-fluoro-phenyl]-1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.71 (s, 1H), 8.77 (d, J = 2.6 Hz, 1H), 8.64 (d, J = 7.6 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.76 (s, 1H), 7.41 - 7.37 (m, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.32 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.12 - 7.07 (m, 1H), 6.99 (d, J = 2.6 Hz, 1H), 6.91 (dd, J = 2.9, 8.9 Hz, 1H), 4.07 - 4.04 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H), 0.92 - 0.90 (m, 4H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₆F₅N₃O₆+H]⁺: 668.59, found: 667.9 tR = 5.568min, [Method W]	Atrop 1	44.4

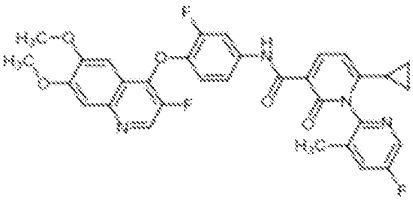
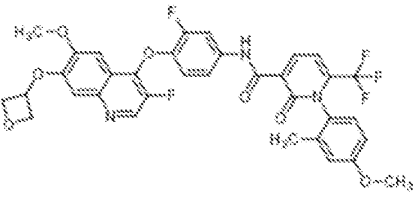
172	 6-(1,1-difluoroethyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (s, 1H), 8.75 (d, J = 2.8 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.1 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.37 (d, J = 8.3 Hz, 1H), 7.33 - 7.25 (m, 2H), 7.23 - 7.17 (m, 1H), 7.14 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.01 (s, 3H), 1.82 (t, J = 19.6 Hz, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₅N₃O₅+H]⁺: 625.16 was found: 625.8, tR: 5.295 Min, [Method W]	Atrop 1	88.72
173	 6-(1,1-difluoroethyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methylphenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.72 (s, 1H), 8.75 (d, J = 3.0 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 2.3, 13.3 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.40 - 7.35 (m, 1H), 7.32 - 7.28 (m, 2H), 7.23 - 7.17 (m, 1H), 7.14 (d, J = 7.5 Hz, 1H), 7.08 (t, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.01 (s, 3H), 1.82 (t, J = 19.5 Hz, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₅N₃O₅+H]⁺: 626.15 was found: 625.8, tR: 5.295 Min, [Method W]	Atrop 2	-143.8

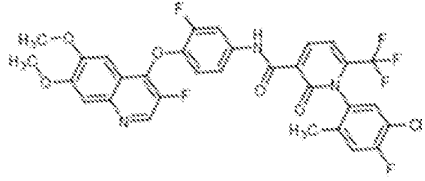
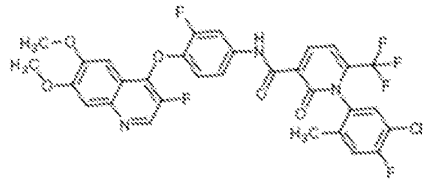
174	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.05 (s, 1H), 8.73 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.47 (s, 1H), 7.33 - 7.29 (m, 2H), 7.24 (d, J = 9.0 Hz, 1H), 7.09 - 7.02 (m, 2H), 6.95 (dd, J = 2.8, 8.8 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 4.28 (br dd, J = 3.3, 5.3 Hz, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.77 - 3.72 (m, 2H), 3.34 (s, 3H), 1.99 (s, 3H), 1.33 - 1.26 (m, 1H), 0.93 - 0.80 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₆H₃₃F₂N₃O₇+H]⁺: 658.67, found: 657.9 tR = 5.252 min. [Method W]	Atrop 1	76
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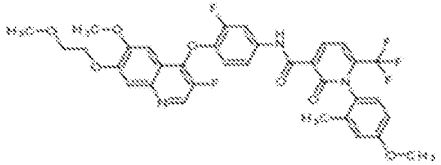
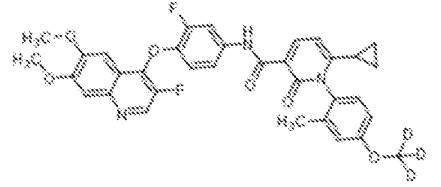
175	 6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 12.06 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.45 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.5, 13.5 Hz, 1H), 7.47 (s, 1H), 7.34 - 7.28 (m, 2H), 7.24 (d, J = 8.8 Hz, 1H), 7.10 - 7.02 (m, 2H), 6.95 (dd, J = 2.8, 8.5 Hz, 1H), 6.41 (d, J = 8.0 Hz, 1H), 4.30 - 4.25 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.76 - 3.73 (m, 2H), 3.34 (s, 3H), 1.99 (s, 3H), 1.34 - 1.28 (m, 1H), 0.93 - 0.85 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₆H₃₃F₂N₃O₇+H]⁺: 658.67, found: 657.9, tR = 5.244 min. [Method W]	Atrop 2	-2.08
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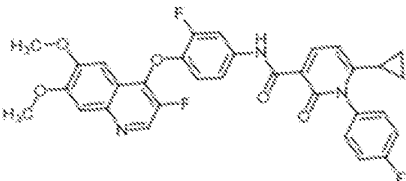
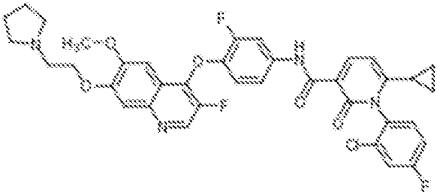
176	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.48 (d, J = 8.0 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.48 (s, 1H), 7.35 - 7.30 (m, 3H), 7.15 - 7.12 (m, 1H), 7.10 - 7.04 (m, 1H), 6.47 (d, J = 8.0 Hz, 1H), 4.30 - 4.27 (m, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.76 - 3.73 (m, 2H), 3.34 (s, 3H), 1.33 (s, 1H), 0.93 - 0.82 (m, 4H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₅H₃₀ClF₂N₃O₇+H]⁺: 679.09, found: 677.9, tR = 5.298 min, [Method W]	Atrop 1	60.24
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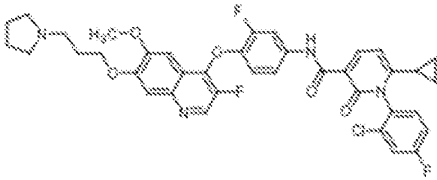
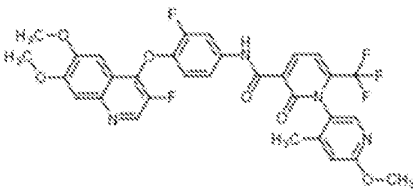
177	 1-(2-chloro-4-methoxy-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.91 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.5, 13.3 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.48 (s, 1H), 7.34 - 7.30 (m, 3H), 7.14 (dd, J = 2.9, 8.9 Hz, 1H), 7.09 - 7.03 (m, 1H), 6.47 (d, J = 7.8 Hz, 1H), 4.28 (dd, J = 3.6, 5.4 Hz, 2H), 3.89 (s, 3H), 3.86 (s, 3H), 3.77 - 3.73 (m, 2H), 3.34 (s, 3H), 1.36 - 1.31 (m, 1H), 0.94 - 0.83 (m, 4H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₅H₃₀ClF₂N₃O₇+H]⁺: 679.09, found: 677.9, tR = 5.310 min, [Method W]	Atrop 2	-71.28
178	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(5-fluoro-3-methyl-2-pyridyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.55 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.03 - 7.95 (m, 2H), 7.46 (s, 1H), 7.34 - 7.28 (m, 2H), 7.06 (t, J = 9.3 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.14 (s, 3H), 1.30 - 1.22 (m, 1H), 1.03 - 0.94 (m, 1H), 0.93 - 0.78 (m, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₃N₄O₅+H]⁺: 603 found: 602.9, tR: 4.99, [Method W]	Atrop 1	90.4

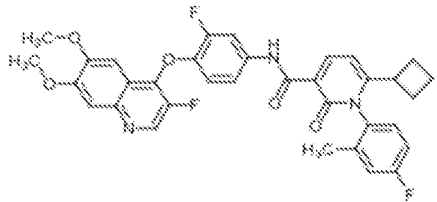
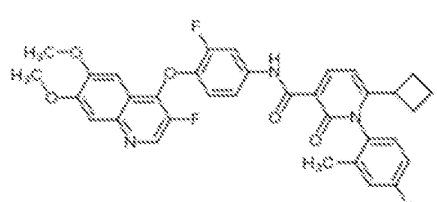
179	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(5-fluoro-3-methyl-2-pyridyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), 8.74 (d, J = 3.0 Hz, 1H), 8.55 (d, J = 3.0 Hz, 1H), 8.50 (d, J = 8.0 Hz, 1H), 8.03 - 7.93 (m, 2H), 7.46 (s, 1H), 7.34 - 7.28 (m, 2H), 7.06 (t, J = 9.0 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.14 (s, 3H), 1.27 - 1.23 (m, 1H), 0.90 - 0.76 (m, 4H). MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₃N₄O₅+H]⁺: 603 found: 602.9, tR: 4.988, [Method W]	Atrop 2	-99.52
180	 N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(oxetan-3-yl)oxy]-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.70 (s, 1H), 8.75 (d, J = 2.5 Hz, 1H), 8.64 (d, J = 7.5 Hz, 1H), 7.98 (dd, J = 2.5, 13.0 Hz, 1H), 7.41 - 7.37 (m, 2H), 7.34 (d, J = 7.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.13 - 7.08 (m, 2H), 6.99 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 3.0, 8.5 Hz, 1H), 5.52 - 5.47 (m, 1H), 5.06 - 5.01 (m, 2H), 4.66 - 4.61 (m, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 1.99 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₄H₂₆F₅N₃O₇+H]⁺: 684.59 was found: 683.8, tR: 5.291 Min, [Method W]	Atrop 1	154.8

181	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.54 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.66 (d, J = 7.3 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.89 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 10.3 Hz, 1H), 7.46 (s, 1H), 7.43 - 7.34 (m, 2H), 7.32 (s, 1H), 7.09 (t, J = 8.8 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.05 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₀ClF₆N₃O₅+H]⁺: 664.96 was found: 663.8, tR: 5.549 Min, [Method W]	Atrop 1	34.8
182	 1-(5-chloro-4-fluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.54 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.66 (d, J = 7.8 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.89 (d, J = 6.8 Hz, 1H), 7.60 (d, J = 10.3 Hz, 1H), 7.46 (s, 1H), 7.42 - 7.36 (m, 2H), 7.32 (s, 1H), 7.09 (t, J = 9.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.05 (s, 3H) MS (ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₀ClF₆N₃O₅+h]⁺: 664.96 was found: 663.8, tR: 5.554 min, [Method W]	Atrop 2	-66

183	 N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-methoxyethoxy)-4-quinolyl]oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.7 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.64 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.2 Hz, 1H), 7.47 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.35 - 7.27 (m, 3H), 7.09 (t, J = 9.2 Hz, 1H), 7.00 - 6.98 (m, 1H), 6.91 (dd, J = 3.2, 8.8 Hz, 1H), 4.30 - 4.27 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.78 - 3.73 (m, 2H), 3.33 (s, 3H), 1.99 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₄H₂₈F₅N₃O₇+H]⁺: 686.6, found: 685.9 tR = 5.365min [Method W]	Atrop 1	5.6
184	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-[2-methyl-4-(trideuteriomethoxy)phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (500 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.76 (br d, J = 2.7 Hz, 1H), 8.65 (br d, J = 7.6 Hz, 1H), 8.19 (s, 1H), 7.99 (br dd, J = 2.6, 13.0 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.34 (m, 2H), 7.32 (s, 1H), 7.10 (br t, J = 9.3 Hz, 1H), 6.94 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 2.04 (s, 3H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₃F₅N₄O₆+H]⁺: 643.54, found: 643.60 tR = 4.62min [Method W]	Atrop 1	75.2

185	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluorophenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.98 (s, 1H), 8.75 (d, J = 2.9 Hz, 1H), 8.45 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 13.3, 2.4 Hz, 1H), 7.55-7.49 (m, 2H), 7.47-7.39 (m, 3H), 7.34-7.28 (m, 2H), 7.06 (t, J = 9.2 Hz, 1H), 6.46 (d, J = 7.8 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 1.41-1.27 (m, 1H), 0.90 (dd, J = 5.3, 2.0 Hz, 2H), 0.85-0.79 (m, 2H) MS (ES+) m/z calc'd for [M+H]⁺ [C₃₂H₂₄F₃N₃O₅+H]⁺: 588.17, found: 588.2, t_R = 4.945 min [Method W]	NA	NA
186	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(2-pyrrolidin-1-ylethoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (500 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.74 (d, J = 2.7 Hz, 1H), 8.50 (d, J = 7.6 Hz, 1H), 7.99 (dd, J = 2.4, 13.4 Hz, 1H), 7.82 (dd, J = 2.9, 8.4 Hz, 1H), 7.77 (dd, J = 5.6, 8.7 Hz, 1H), 7.52 - 7.48 (m, 1H), 7.47 (s, 1H), 7.35 - 7.31 (m, 2H), 7.06 (t, J = 9.2 Hz, 1H), 6.52 (d, J = 7.6 Hz, 1H), 4.25 (t, J = 5.8 Hz, 2H), 3.88 (s, 3H), 2.87 (t, J = 6.0 Hz, 2H), 2.56 - 2.54 (m, 4H), 1.72 - 1.67 (m, 4H), 1.34 - 1.29 (m, 1H), 0.91 - 0.79 (m, 4H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₇H₃₂ClF₃N₄O₅+H]⁺: 705.13 was found: 705.0, t_R: 4.151 min [Method W]	Atrop 1	88.72

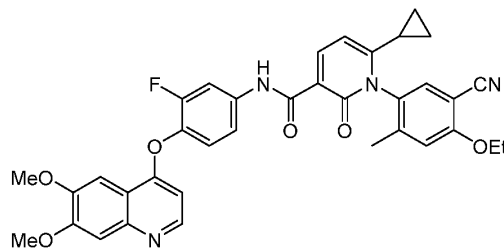
187	 1-(2-chloro-4-fluoro-phenyl)-6-cyclopropyl-N-[3-fluoro-4-[[3-fluoro-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy)-4-quinolyl]oxy]phenyl]-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.81 (s, 1H), 8.74 (d, J = 2.8 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 7.98 (dd, J = 2.4, 13.4 Hz, 1H), 7.82 - 7.77 (m, 2H), 7.53 - 7.48 (m, 1H), 7.44 (s, 1H), 7.35 - 7.29 (m, 2H), 7.06 (t, J = 9.4 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 4.20 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 2.58 - 2.54 (m, 2H), 2.46 (br d, J = 6.8 Hz, 4H), 1.97 (t, J = 1.0 Hz, 2H), 1.73 - 1.65 (m, 4H), 1.35 - 1.29 (m, 1H), 0.92 - 0.81 (m, 4H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₈H₃₄ClF₃N₄O₅+H]⁺: 720.16 found: 718.9, tR = 4.223 min. [Method W]	Atrop 1	145.6
188	 N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹H NMR (500 MHz, DMSO-d₆): δ 11.56 (s, 1H), 8.76 (br d, J = 2.7 Hz, 1H), 8.65 (br d, J = 7.6 Hz, 1H), 8.19 (s, 1H), 7.99 (br dd, J = 2.6, 13.0 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.34 (m, 2H), 7.32 (s, 1H), 7.10 (br t, J = 9.3 Hz, 1H), 6.94 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 2.04 (s, 3H). MS (ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₃F₅N₄O₆+H]⁺: 643.54, found: 643.60, tR = 4.62 min. [Method AD]	Atrop 1	75.2

189	 6-cyclobutyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, <i>J</i> = 2.9 Hz, 1H), 8.57 (d, <i>J</i> = 7.3 Hz, 1H), 7.99 (dd, <i>J</i> = 2.4, 13.7 Hz, 1H), 7.46 (s, 1H), 7.39 - 7.31 (m, 4H), 7.26 - 7.20 (m, 1H), 7.07 (t, <i>J</i> = 9.3 Hz, 1H), 6.76 (d, <i>J</i> = 7.3 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.09 (br d, <i>J</i> = 9.3 Hz, 1H), 2.17 - 2.12 (m, 1H), 2.09 - 2.04 (m, 1H), 1.98 (s, 3H), 1.82 - 1.77 (m, 1H), 1.72 (br d, <i>J</i> = 9.8 Hz, 1H), 1.65 - 1.57 (m, 2H). MS (ES+) <i>m/z</i> calc'd for [M+H]⁺ [C₃₄H₂₈F₃N₃O₅]: 620.61, found : 615.9, tR = 5.486min. [Method W]	Atrop 2	-40.8
190	 6-cyclobutyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-fluoro-2-methyl-phenyl)-2-oxo-pyridine-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.96 (s, 1H), 8.75 (d, <i>J</i> = 2.7 Hz, 1H), 8.57 (d, <i>J</i> = 8.1 Hz, 1H), 7.97 (br d, <i>J</i> = 2.7 Hz, 1H), 7.46 (s, 1H), 7.39 - 7.29 (m, 4H), 7.26 - 7.21 (m, 1H), 7.07 (t, <i>J</i> = 9.3 Hz, 1H), 6.76 (d, <i>J</i> = 7.8 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.12 - 3.08 (m, 1H), 2.14 - 2.05 (m, 2H), 1.98 (s, 3H), 1.74 - 1.57 (m, 4H). MS (ES+) <i>m/z</i> calc'd for [M+H]⁺ [C₃₁H₂₅F₂N₃O₅]: 620.61, found : 615.9, tR = 5.492min. [Method W]	Atrop 1	20.2

^aSOR: Specific optical rotation; ND: Not determined; NA: Not applicable.

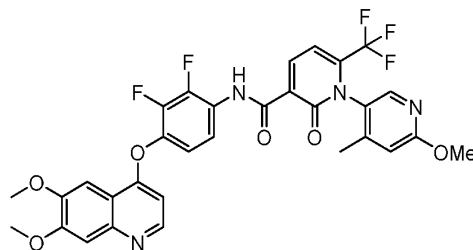
Method 1:

[1100] Synthesis of 1-(5-cyano-4-ethoxy-2-methyl-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide [Example A-1]:

**Example A-1**

[1101] To a solution of 1-(5-cyano-4-ethoxy-2-methyl-phenyl)-6-cyclopropyl-2-oxo-pyridine-3-carboxylic acid (30.00 mg, 88.66 μmol , 1.00 eq) in DMF (0.6 mL) was added HATU (50.57 mg, 133.00 μmol , 1.50 eq), the mixture was stirred at 25 °C for 0.5 hr. Then 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-aniline (27.87 mg, 88.66 μmol , 1.00 eq) and TEA (26.92 mg, 265.99 μmol , 37.02 μL , 3.00 eq) was added. The mixture was stirred at 25 °C for 0.5 hr. LC-MS showed the reaction was completed. The mixture was quenched with water (50 mL) and extracted with EtOAc (3 $\times$ 30 mL). The combined organic phase was washed with brine (5 $\times$ 30 mL), dried with anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (Formic acid condition; column: Phenomenex luna C18 100 $\times$ 40mm $\times$ 5 μm ; mobile phase: [H_2O (0.2% Formic acid)-MeCN]; gradient: 35%-65% B over 8.0 min), after purification, fractions were lyophilized to afford 1-(5-cyano-4-ethoxy-2-methyl-phenyl)-6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-2-oxo-pyridine-3-carboxamide (27 mg, 47.65% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 12.03 (s, 1 H) 8.53 (d, $J=5.38$ Hz, 1 H) 8.51 (d, $J=7.88$ Hz, 1 H) 8.06 (dd, $J=13.01, 2.25$ Hz, 1 H) 7.91 (s, 1 H) 7.56 (s, 1 H) 7.54 (dd, $J=9.32, 1.81$ Hz, 1 H) 7.43 - 7.48 (m, 1 H) 7.42 (s, 1 H) 7.40 (s, 1 H) 6.55 (br d, $J=5.25$ Hz, 1 H) 6.49 (d, $J=7.88$ Hz, 1 H) 4.24 - 4.32 (m, 2 H) 3.96 (d, $J=2.63$ Hz, 6 H) 2.11 (s, 3 H) 1.42 (t, $J=6.94$ Hz, 3 H) 1.30 - 1.37 (m, 1 H) 0.91 - 0.97 (m, 2 H) 0.84 - 0.90 (m, 2 H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ [$\text{C}_{36}\text{H}_{31}\text{FN}_4\text{O}_6+\text{H}$] $^+$: 635.22, found: 635.2, $t_R=3.158$ min.

[1102] Synthesis of *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2,3-difluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide [Example A-17].

**Example A-17**

[1103] To a stirred solution of 6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxylic acid (TFA salt) (153 mg, 0.361 mmol, 1.2 eq) in a pyridine (3mL), EDC.HCl (117 mg, 0.607 mmol, 2.0 eq) followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (100 mg, 0.300 mmol, 1.00 eq) was added at 0 °C. The reaction mixture was stirred for 5 h at room temperature. After completion of the reaction, the reaction mixture was diluted with ice water (30 mL) and extracted with EtOAc (3x50 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated under reduced pressure to get crude compound which was further purified by Prep-HPLC to afford *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)-2,3-difluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide (69 mg, 35% yield) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) =12.03 (s, 1H), 8.73 (d, *J* = 7.6 Hz, 1H), 8.50 (d, *J* = 5.2 Hz, 1H), 8.34 (t, *J* = 10 Hz, 1H), 8.21 (s, 1H), 7.51 (s, 1H), 7.42 (m, 2H), 7.35 (t, *J* = 10 Hz, 1H), 6.96 (s, 1H), 6.62 (d, *J* = 4.8 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 2.05 (s, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₁H₂₃F₅N₄O]⁺: 642.54, found: 643.48, *t_R* = 3.92 min.

[1104] Prep-HPLC Method: Column X BRIDGE C18 (250*30) mm, 5 μ m, Mobile Phase A 10 mm ABC IN WATER, Mobile Phase B 100% MeCN, Flow rate 22ml/min, Instrument ID PREP-28, Gradient (Time/%B) 0/40, 2/40, 25/100.

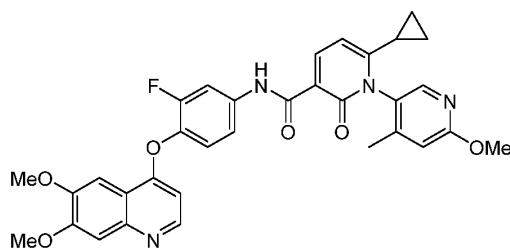
[1105] Chiral HPLC purity: 99.45%, *t_R* = 5.74 min, ee = 99.45 %. Method: CHIRALPAK-1K (250 x 4.6 mm, 5 μ m), Mobile Phase B: MeCN A/B: 20/80 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-027.

[1106] Specific optical rotation (SOR): 11.84, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1; solvent-methanol.

[1107] Using Method 1, **A-1** to **A-3**, **A-7** to **A-17**, **A-23** to **A-29**, **32**, and **A-35** to **A-40** were prepared.

Method 2:

[1108] Synthesis of 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide [Examples A-4, A-5, A-6]:



Racemic: Example A-4
Atropisomer 1: Example A-5
Atropisomer 2: Example A-6

[1109] To a solution of 6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxylic acid (698.44 mg, 2.33 mmol, 1.70 eq), 4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-aniline (300.00 mg, 954.47 μ mol, 1.00 eq) in DCM (18 mL) was added DIEA (442.03 mg, 3.42 mmol, 595.73 μ L, 2.50 eq) and DMTMM (416.43 mg, 1.50 mmol, 1.10 eq). The mixture was stirred at 25 °C for 12 hr. LC-MS showed ~11.0% of starting material amine remained and ~81.3% of desired compound was detected. The residue was poured into water (50 mL). The aqueous phase was extracted with DCM (3 $\times$ 30 mL). The combined organic phase was washed with brine (50 mL), dried with anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=100/1 to 0/1), then purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN]; gradient: 40%-85% B over 8.0 min) to afford 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (418 mg, 72.04% yield) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₉FN₄O₆ +H]⁺: 597.20, found: 597.4, *t*_R= 1.547 min.

[1110] Atropisomer mixture (530 mg, combined with pilot reaction) was purified by SFC (column: DAICEL CHIRALPAK IC (250mm*30mm, 10 μ m); mobile phase: [CO₂-EtOH:MeCN=1:1 (0.1% NH₃H₂O)]; B%:70%, isocratic elution mode) which afforded 199.8 mg of Atropisomer 1 and 226.2 mg of Atropisomer 2 as an off white solid.

[1111] Atropisomer 1: 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide [Example A-5]:
¹H NMR (400 MHz, DMSO-*d*₆): δ 12.02 (s, 1 H) 8.51 (d, *J*=7.75 Hz, 1 H) 8.48 (d, *J*=5.25 Hz, 1 H) 8.17 (s, 1 H) 8.04 (dd, *J*=13.01, 2.38 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.40 (s, 2 H) 6.98 (s, 1 H) 6.50 (d, *J*=7.88 Hz, 1 H) 6.47 (d, *J*=5.13 Hz, 1 H) 3.94 (d, *J*=1.88 Hz, 6 H) 3.91 (s, 3 H) 2.05 (s,

3 H) 1.38 (s, 1 H) 0.91 - 0.97 (m, 2 H) 0.85 - 0.91 (m, 2 H); MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{33}H_{29}FN_4O_6 + H]^+$: 597.20, found: 597.3, t_R = 1.995 min, Chiral HPLC purity: 100%, t_R = 1.820, ee = 100%.

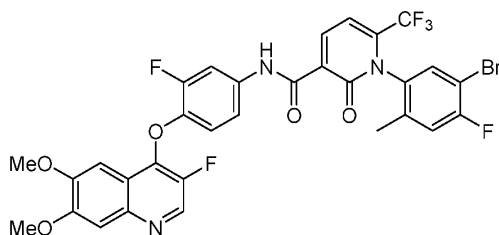
[1112] Atropisomer 2: 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide [Example A-6]:

1H NMR (400 MHz, DMSO- d_6): δ 12.02 (s, 1 H) 8.49 - 8.54 (m, 1 H) 8.45 - 8.49 (m, 1 H) 8.17 (s, 1 H) 8.04 (dd, J = 13.01, 2.38 Hz, 1 H) 7.49 - 7.56 (m, 2 H) 7.38 - 7.47 (m, 2 H) 6.98 (s, 1 H) 6.50 (d, J = 7.88 Hz, 1 H) 6.44 - 6.48 (m, 1 H) 3.93 - 3.97 (m, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.38 (s, 1 H) 0.91 - 0.96 (m, 2 H) 0.85 - 0.91 (m, 2 H); MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{33}H_{29}FN_4O_6 + H]^+$: 597.20, found: 597.3, t_R = 1.991 min, Chiral HPLC purity: 100%, t_R = 3.645, ee = 100%.

[1113] Using Method 2, **A-18** to **A-22**, **A-30**, and **A-33** to **A-34** were prepared.

Method 3:

[1114] Synthesis of 1-(5-bromo-4-fluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-47]:



Example A-47

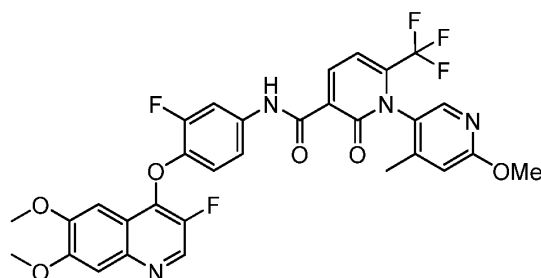
[1115] To a solution of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (30.00 mg, 90.28 μ mol, 1.00 eq) and 1-(5-bromo-4-fluoro-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (53.37 mg, 135.42 μ mol, 1.50 eq) in pyridine (1 mL) was added EDCI (25.96 mg, 135.42 μ mol, 1.50 eq). The mixture was stirred at 25 °C for 4 h. LC-MS showed starting material amine was consumed completely and one main peak with desired m/z mass was detected. After completion, the solvent was removed by concentration to give the crude. The crude was purified by prep-HPLC (Formic acid condition, column: Phenomenex luna C18 100*40mm*5 μ m; mobile phase: $[H_2O(0.2\% \text{ Formic acid}) - MeCN]$; gradient: 55%-85% B over 8.0 min). After purification, lyophilized to afford 1-(5-bromo-4-fluoro-2-methyl-phenyl)-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (30.9 mg, 48.32% yield) as a yellow solid. 1H NMR (400 MHz, DMSO- d_6): δ 11.54 (s, 1 H) 8.75 (d, J = 3.00 Hz, 1 H) 8.65

(d, $J=7.63$ Hz, 1 H) 7.93 - 8.03 (m, 2 H) 7.56 (d, $J=9.51$ Hz, 1 H) 7.46 (s, 1 H) 7.36 - 7.42 (m, 2 H) 7.32 (s, 1 H) 7.09 (t, $J=9.13$ Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.03 (s, 3 H). MS(ES⁺) m/z calc'd for $[M+H]^+$ $[C_{31}H_{20}N_3O_5F_6Br+H]^+$: 708.05, found: 708.1/710.0, $t_R=3.595$ min.

[1116] Using Method 3, **A-41** to **A-56** were prepared.

Method 4:

[1117] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6, 7-dimethoxy-4-quinolyl)oxy] phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxamide [Example **A-70** (Atropisomer-1)]:



Example A-70

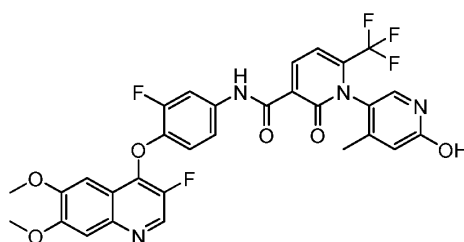
[1118] To a stirred solution of 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (Atropisomer-1 (P1) 106 mg, 0.325 mmol, 1.2 eq) in pyridine (10 mL) was added EDC.HCl (104.9 mg, 0.5417 mmol, 2.0 eq) followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (90 mg, 0.270 mmol, 1.0 eq) at room temperature and stirred for 16 h at 25 °C. After completion of the reaction, diluted with water (50 mL) and extracted with EtOAc (3x30 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure to get crude. Crude was purified by Prep-HPLC and pure fractions were lyophilized to afford *N*-[3-fluoro-4-[(3-fluoro-6, 7-dimethoxy-4-quinolyl)oxy] phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxamide (55 mg, 31.29% yield) as an off-White solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.56 (s, 1H), 8.76 (d, $J=2.9$ Hz, 1H), 8.65 (d, $J=7.6$ Hz, 1H), 8.18 (s, 1H), 7.99 (dd, $J=2.4$, 13.2 Hz, 1H), 7.46 (s, 1H), 7.38 (d, $J=7.6$ Hz, 2H), 7.32 (s, 1H), 7.10 (t, $J=9.1$ Hz, 1H), 6.94 (s, 1H), 3.95 (s, 3H), 3.89 (d, $J=6.3$ Hz, 6H), 2.04 (s, 3H). MS(ES⁺) m/z calc'd for $[M+H]^+$ $[C_{31}H_{23}F_5N_4O_6+H]^+$: 642.1, found: 643.3, $t_R=2.25$ min.

[1119] Prep-HPLC Method: Column: X-Select CSH C18 (250*30)mm, 5 μ m, Mobile Phase A: 10 mm ABC in water, Mobile Phase B: 100%MeCN, Flowrate: 25ml/min, Instrument: IDPREP2, Gradient:(Time/%B)0/35,3/35,5/60,20/90,22/100].

[1120] Chiral HPLC purity: 99.97%, t_R = 6.654 min, ee = 99.94 %. Method: CHIRALPAK IK (250X4.6mm, 5 μ m), Mobile Phase A: MeCN, Mobile Phase B: ETOH: MEOH (1:1), A B: 20:80, Flow rate: 1.00mL/min, Column ID: M-ARD-CAL/OLD-028.

[1121] Specific optical rotation (SOR): 76.77, Light Source: Na, Monitor wavelength: 589 nm, D.I.T: 5 sec, No. of cycle: 5, Cycle interval-5 sec, Temp. Monitor- Holder, Temp. Corr. Factor- None, Aperture(S)- 8.0mm, Aperture(L)- Auto, Mode Specific O.R., Path Length-10 mm, Concentration 0.1055 w/v%. Water content of sample 0 %, Factor 1.

[1122] **Synthesis of *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide**
[Example A-71 (Atropisomer 1), Example A-72 (Atropisomer 2)]:

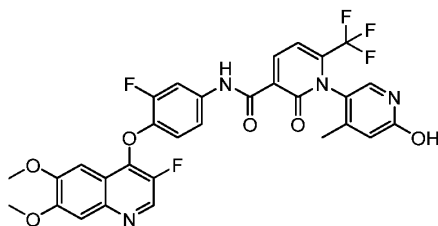


Atropisomer 1: Example A-71
Atropisomer 2: Example A-72

[1123] To a stirred solution of 1-(6-hydroxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (250.00 mg, 0.795 mmol, 1.0 eq) in pyridine (2 mL) was added EDC.HCl (466.9 mg, 2.387 mmol, 3.0 eq) followed by 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (264.4 mg, 0.795 mmol, 1.0 eq). The reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2x30 mL). The combined organic layers, dried over Na₂SO₄, and concentrated to get crude. The crude compound was purified by combi flash using YMC 80 g cartridge, eluting with 0-40% ethyl acetate/heptane to afford *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide (400.00 mg, 72.89 % yield) as an off white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.84 (s, 1H), 11.60 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.63 (d, J = 7.5 Hz, 1H), 8.01 (dd, J = 2.4, 13.1 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.42 (d, J = 8.9 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.11 (t, J = 9.2 Hz, 1H), 6.37 (s, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 1.88 (s, 3H). MS(ES+) m/z calc'd for [M+H]⁺ [C₃₀H₂₁F₅N₄O₆+H]⁺: 628.1, found: 629.0, t_R = 4.46 min. The racemic compound was submitted for Chiral SFC purification, separate both the peaks and evaporated under vacuum to afford Peak-1 & Peak-2.

[1124] Purification of *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide

[Example A-71 (Atropisomer-1, Peak-1)]:



Atropisomer 1
Example A-71

[1125] 400 mg of racemic compound was submitted for chiral separation and isolated P1 (Atrope-1) = 75 mg and P2 (Atrope-2) = 65 mg. Atropisomer was separated by chiral SFC (instrument name: waters-2767, prep-SFC 100) method to afford 75 mg of the titled compound as a pale-yellow solid.

[1126] SFC Purification method: No. of Injections 17 inj (22 mg/Inj /6.5 min), Column IA (20X250*mm, 5 μ m), Mobile phase A 0.1% Formic acid in DCM, Mobile phase B MEOH, Eluent A: B: 60:40, Total Flow rate (mL/min) 20 ml/min Diluent MP, Detection 245 nm.

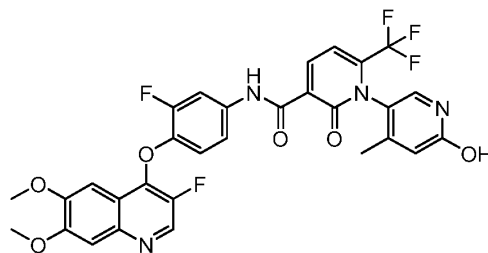
[1127] ^1H NMR (400 MHz, DMSO- d_6) δ = 11.84 (s, 1H), 11.60 (s, 1H), 8.76 (d, J = 2.8 Hz, 1H), 8.63 (d, J = 7.5 Hz, 1H), 8.01 (dd, J = 2.1, 13.1 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.11 (t, J = 9.1 Hz, 1H), 6.37 (s, 1H), 3.97 - 3.88 (m, 6H), 1.88 (s, 3H). MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ [$\text{C}_{30}\text{H}_{21}\text{F}_5\text{N}_4\text{O}_6+\text{H}$] $^+$: 628.1, found: 629.3, t_R = 4.42 min.

[1128] Chiral HPLC purity: 100 %, t_R = 3.998 min. ee = 100 %. (CHIRALPAK IK (250 X 4.6mm, 5 μ m), Mobile Phase A: ETOH: MEOH (1:1), Mobile Phase B: MeCN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL/OLD-028.

[1129] Specific optical rotation (SOR): -15.01, Light Source WI, Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.050 w/v%. Water content of sample 0% Factor 1.

[1130] Purification of *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide:

[Example A-72 (Atropisomer-2, Peak-2)]:



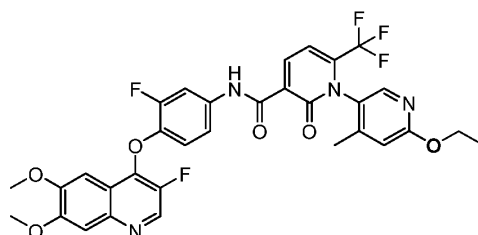
Atropisomer 2
Example A-72

[1131] ^1H NMR (400 MHz, DMSO- d_6) δ = 11.82(s, 1H), 11.60 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.63 (d, J = 7.5 Hz, 1H), 8.01 (dd, J = 2.4, 13.1 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.42 (d, J = 9.5 Hz, 1H), 7.38 - 7.30 (m, 2H), 7.11 (t, J = 9.1 Hz, 1H), 6.37 (s, 1H), 3.99 - 3.87 (m, 6H), 1.88 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{30}\text{H}_{21}\text{F}_5\text{N}_4\text{O}_6+\text{H}]^+$: 628.1, found: 629.3, t_R = 4.43 min.

[1132] Chiral HPLC purity: 99.79 %, t_R = 4.274 min. ee = 99.5 %. (CHIRALPAK IK (250 X 4.6mm, 5 μ m), Mobile Phase A: ETOH: MEOH (1:1), Mobile Phase B: MeCN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL/OLD-028.

[1133] Specific optical rotation (SOR): 22.97, Light Source WI, Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.0505 w/v%. Water content of sample 0% Factor 1.

[1134] **Synthesis of 6'-ethoxy-N-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide [Example A-76 (Atropisomer 1) and Example A-77 (Atropisomer 2)]**



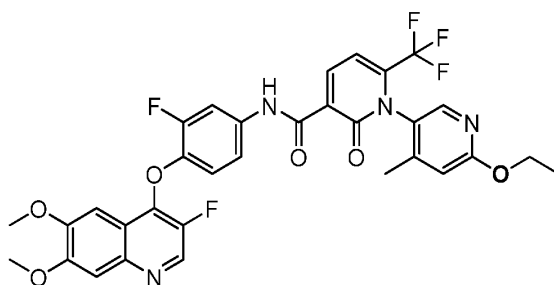
Atropisomer 1: Example A-76
Atropisomer 2: Example A-77

[1135] To a stirred solution of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (150 mg, 0.4514 mmol) in pyridine (2 mL) was added EDAC (135.00 mg, 0.69013 mmol) and stirred for 5 minutes at room temperature. Then, 1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (185 mg, 0.5405 mmol) was added and resulting mixture was stirred at same temperature for a period of 16 h. Progress of the reaction was

monitored by TLC and after completion of the reaction, the reaction mixture was diluted with water (30mL) and extracted with EtOAc (2X30mL). The combined organic layers, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product obtained was subjected to combi flash chromatography using a gradient 50-60% EtOAc in heptane. The pure fractions containing the product were combined and concentrated under reduced pressure to obtain 220 mg, 874% yield of the title compound (racemic) as pale brown solid.

[1136] The racemic compound (220 mg) was separated through Chiral HPLC purification. Collected fractions were concentrated under vacuum to afford both peaks.

[1137] **Purification of 6'-ethoxy-N-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide [Example A-76 (Atropisomer 1)]:**



Atropisomer 1
Example A-76

[1138] 220 mg of racemic compound was purified by chiral SFC and isolated 62.8 mg of Peak-1 (Atrope-1) as an off-white solid.

[1139] SFC Purification method: No. of Injections 7 inj (35 mg/Inj /12 min) Column IG (30X250*mm,5μm) Mobile phase A DCM Mobile phase B MeOH Eluent A: B:50:50 Total Flow rate (mL/min) 42 ml/min Diluent MP Detection 330 nm.

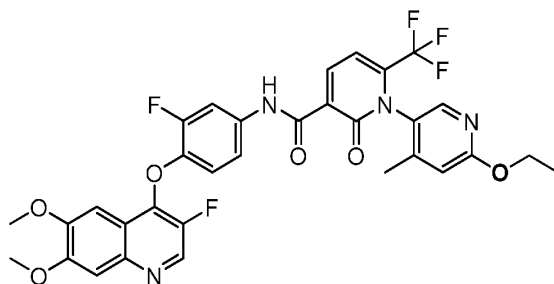
[1140] ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm): 11.56 (s, 1H), 8.76 (d, *J* = 2.9 Hz, 1H), 8.66 - 8.63 (m, 1H), 8.16 (s, 1H), 7.99 (dd, *J* = 2.5, 13.1 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.37 (m, 2H), 7.32 (s, 1H), 7.10 (t, *J* = 9.1 Hz, 1H), 6.90 (s, 1H), 4.35 (dq, *J* = 2.9, 6.9 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.36 - 1.32 (m, 3H). LCMS MS(ES+) *m/z* calc'd for [M+H]⁺ [C₃₂H₂₅F₅N₄O₆+H]⁺: 657.17, found: 657.35, *t*_R = 5.44 min.

[1141] Chiral HPLC purity: 98.47%, *t*_R = 4.239 min, ee = 96.94 %. Method: CHIRALPAK IG (250X4.6mm,5μm) Mobile Phase A: DCM, Mobile Phase B: MeOH Flow: 1.0 ml/MIN, Column ID: M-ARD-CAL-025

[1142] Specific optical rotation (SOR): 12.48, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor None

Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[1143] Purification of 6'-ethoxy-N-(3-fluoro-4-((3-fluoro-6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide [Example A-77 (Atropisomer 1)]:



Atropisomer 2
Example A-77

[1144] 220 mg of racemic compound was purified by chiral SFC and isolated 32.5 mg of Peak-2 (Atrope-2) as an off-white solid.

[1145] SFC Purification method: No. of Injections: 7 (35 mg/Inj /12 min), Column: IG (30X250*mm, 5 μ m) Mobile phase A: DCM, Mobile phase B: ME OH. Eluent A: B: 50:50 Total Flow rate (mL/min) 42 ml/min Diluent MP Detection 330 nm.

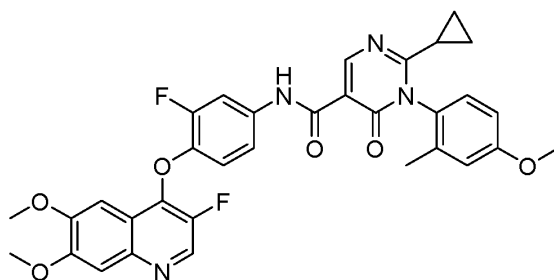
[1146] ^1H NMR (400 MHz, DMSO- d_6) δ (ppm): 11.57 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.68 - 8.64 (m, 1H), 8.16 (s, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.47 (s, 1H), 7.42 - 7.37 (m, 2H), 7.32 (s, 1H), 7.10 (t, J = 9.2 Hz, 1H), 6.91 (s, 1H), 4.35 (dq, J = 3.0, 6.8 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.04 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{32}\text{H}_{25}\text{F}_5\text{N}_4\text{O}_6+\text{H}]^+$: 657.17, found: 657.35, t_R = 5.43 min.

[1147] Chiral HPLC purity: 99.55%, t_R = 5.393 min, ee = 99.1%. Method CHIRALPAK IG (250X4.6mm, 5 μ m) Mobile Phase A: DCM Mobile Phase B: MeOH, Flow: 1.0 ml/MIN, Column ID: M-ARD-CAL--025

[1148] MobilePhase A: DCM MobilePhase B: ME OH Column Name: CHIRALPAK IG (250X4.6mm, 5 μ m) A B: 50:50 Column ID: M-ARD-CAL--025 System Name : AMC_HPLC_1

[1149] Specific optical rotation (SOR): -12.63, Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec, Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[1150] Synthesis of 2-cyclopropyl- $\{N\}$ -[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide [Example A-85 (Atropisomer 1) and Example A-86 (Atropisomer 2)]:

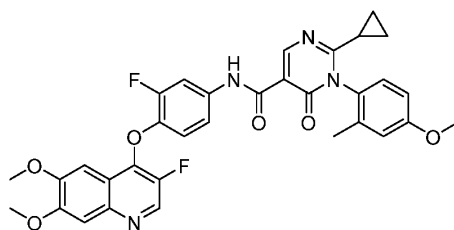


Atropisomer 1: Example A-85
Atropisomer 2: Example A-86

[1151] To a stirred solution of 2-cyclopropyl-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxylic acid (135.6 mg, 0.451 mmol, 1.0 eq) in pyridine (1.5 mL ca) was added EDAC (131.1 mg, 0.677 mmol, 1.5 eq) at 0° C. Then, 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]aniline (150 mg, 0.4514 mmol, 1.0 eq) was added and the mixture was stirred at room temperature for 16 hours. After completion of the reaction, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated under reduced pressure to afford 2-cyclopropyl- $\{N\}$ -[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide (250 mg (82.0 % yield) as a pale brown gummy solid.

[1152] The obtained racemic product (250 mg) was separated by SFC.

[1153] Purification of 2-cyclopropyl- $\{N\}$ -[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide [Example A-85 (Atropisomer-1)]:



Atropisomer 1
Example A-85

[1154] 250 mg of racemic compound was separated by chiral SFC and isolated Peak-1 (Atrope-1) = 70 mg and Peak-2 (Atrope-2) = 55 mg.

[1155] Atropisomers were separated by chiral SFC (instrument name: waters-2767, prep-SFC 100) to afford Peak-1 (Atrope-1, 70 mg, 0.109 mmol) as pale yellow solid.

[1156] SFC Purification method: No of Injections 6(40.0 mg/ inj /8.0 min) Column R,R WHELK (30*250mm,5 μ m) MP(A)C02 60.0 g/min MP(B)Co-Solvent 30.0 ml/min (0.1% MeONH₂ in MeOH:MeCN) Total Flow rate (mL/min) 60g-40% ,100 bar Diluent MeOH Detection 254 nm.

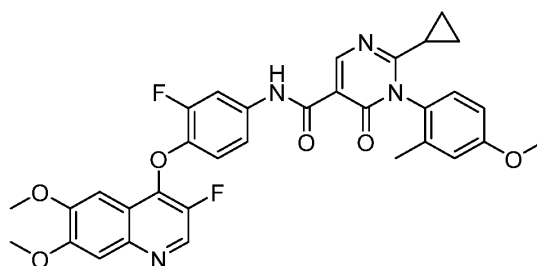
[1157] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm: 11.22 (s, 1 H) 8.79 (s, 1 H) 8.75 (d, *J*=2.75 Hz, 1 H) 7.96 (dd, *J*=13.20, 2.31 Hz, 1 H) 7.46 (s, 1 H) 7.30 - 7.40 (m, 3 H) 7.05 - 7.12 (m, 2 H) 6.99 (dd, *J*=8.63, 2.63 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 3.82 (s, 3 H) 2.06 (s, 3 H) 1.45 (td, *J*=8.00, 4.25 Hz, 1 H) 1.16 - 1.26 (m, 2 H) 1.00 - 1.12 (m, 2 H). MS(ES+) *m/z* calc'd for [M+H]⁺ [C₃₃H₂₈F₂N₄O₆+H]⁺ : 615.6, found: 615.43, *t*_R = 4.65 min.

[1158] Chiral HPLC purity: 100 %, *t*_R = 4.992 min, ee = 100 %; Method: CHIRALPAK IK (250*4.6mm, 5 μ m) Mobile Phase A: MeCN ETOH:MEOH(1:1) Mobile Phase B: MeCN ETOH:MEOH(1:1) A B: 80:20 Flow: 1.5 ml/MIN Column ID : M-ARD\CAL-028

[1159] Chiral HPLC purity: 99.1 %, *t*_R = 6.128 min. ee = 98.2 %. (as per RR WHELK method).

[1160] Specific optical rotation (SOR): -74.2, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5N Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1; solvent-methanol.

[1161] Purification of 2-cyclopropyl-~{N}-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(4-methoxy-2-methyl-phenyl)-6-oxo-pyrimidine-5-carboxamide [Example A-86 (Atropisomer-2)]:



Atropisomer 2
Example A-86

[1162] 250 mg of racemic compound was separated by chiral SFC and isolated Peak-1 (Atrope-1) =70 mg and Peak-2 (Atrope-2) = 55 mg.

[1163] Atropisomers were separated by chiral SFC (instrument name: waters-2767, prep-SFC 100) to afford Peak-2 (Atrope-2, 55 mg, 0.089 mmol) as pale yellow solid.

[1164] SFC Purification method: No of Injections 6(40.0 mg/ inj /8.0 min) Column R,R WHELK (30*250mm,5 μ m) MP(A)C02 60.0 g/min MP(B)Co-Solvent 30.0 ml/min (0.1%

MEONH₂ in MeOH:MeCN) Total Flow rate (mL/min) 60g-40% ,100 bar Diluent MeOH

Detection 254 nm

[1165] ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.22 (s, 1 H) 8.79 (s, 1 H) 8.75 (d, *J*=2.75 Hz, 1 H) 7.96 (dd, *J*=13.26, 2.13 Hz, 1 H) 7.46 (s, 1 H) 7.29 - 7.40 (m, 3 H) 7.04 - 7.12 (m, 2 H) 6.99 (dd, *J*=8.75, 2.50 Hz, 1 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 3.82 (s, 3 H) 2.06 (s, 3 H) 1.41 - 1.49 (m, 1 H) 1.16 - 1.26 (m, 2 H) 0.99 - 1.10 (m, 2 H). MS(ES+) *m/z* calc'd for [M+H]⁺

[C₃₃H₂₈F₂N₄O₆+H]⁺ : 615.6, found: 615.40, *t*_R=5.33 min. [Method AT].

[1166] Chiral HPLC purity: 100 %, *t*_R= 4.615 min. ee = 100 %. CHIRALPAK IK

(250*4.6mm, 5μm) MobilePhase A: MeCN ETOH:MEOH(1:1) MobilePhase B : MeCN

ETOH:MEOH(1:1) A B : 80:20 Flow: 1.5 ml/MIN Column ID : M-ARD\CAL-028

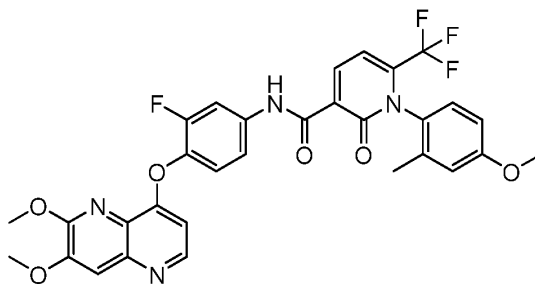
[1167] Chiral HPLC purity: 99.78 %, *t*_R = 7.527 min. ee = 99.56 %. (as per RR WHELK method).

[1168] Specific optical rotation (SOR): 24.88, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5N Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1; solvent-methanol.

[1169] Using Method 4, examples A-57 to A-89 were prepared.

Method 5:

[1170] Synthesis of *N*-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide [Example A-90]:



Example A-90

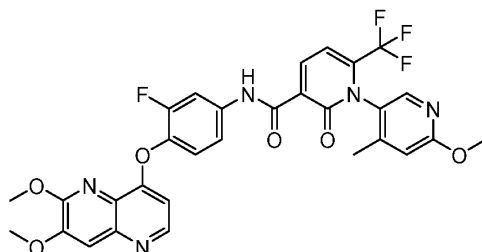
[1171] To a stirred solution 1-(4-methoxy-2-methyl-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (3.01 g, atropisomer-1, 9.20 mmol, 1.0 eq) in pyridine (45 mL, 10 vol), EDC.HCl (3.60 g, 1.903 mmol, 2.0 eq) followed by 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-aniline (2.90 g, 9.20 mmol, 1.0 eq) was added at 25 °C. The resulting mixture was stirred for 16 h at 25 °C. After completion of the reaction, the

reaction mixture was diluted with ice water (50 mL) and extracted with EtOAc (3x150 mL). The combined organic layer was dried over Na₂SO₄ and concentrated to obtain crude. The crude was purified by combi-flash by using YMC 24 g column with 80-100% ethyl acetate in heptane to afford *N*-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide (3.05 g, 52.6 % yield) as an off white solid. ¹H NMR (400 MHz, DMSO-d₆): δ 11.76 (s, 1H), δ 8.66 (d, *J* = 7.5 Hz, 1H), δ 8.55 (d, *J* = 5.3 Hz, 1H), δ 8.01 (dd, *J* = 2.4, 12.9 Hz, 1H), δ 7.65 (s, 1H), δ 7.52 (dd, *J* = 1.1, 9.0 Hz, 1H), δ 7.33 (dd, *J* = 8.3, 15.8 Hz, 3H), 7.01 (d, *J* = 2.6 Hz, 1H), 6.93 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.84 (d, *J* = 5.1 Hz, 1H), δ 3.96 (s, 3H), δ 3.91 (s, 3H), δ 3.82 (s, 3H), δ 2.01 (s, 3H). MS(ES⁺) *m/z* calc'd for [M+H]⁺[C₃₁H₂₄F₄N₄O₆]⁺: 624.1, found: 625.42, *t_R* = 4.24 min.

[1172] Chiral HPLC purity: 100 %, *t_R* = 4.176 min, ee = 100 %. Method: CHIRALPAK-IK (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: MeCN A/B: 80/20 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028.

[1173] Specific optical rotation (SOR): 89.5, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture (L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.1 w/v% Water content of sample 0 % Factor 1.

[1174] **Synthesis of *N*-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide [Example A-95 (Atropisomer 1)]:**



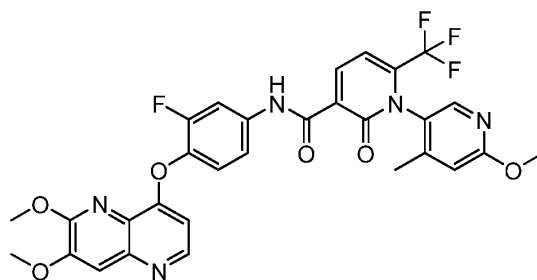
Atropisomer 1: Example A-95

Atropisomer 2: Example A-95A

[1175] To a stirred solution of 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (234.2 mg, 0.713 mmol, 1.5 eq) in Pyridine (1.50 mL) at 0 °C was added EDAC (372.2 mg, 1.903 mmol, 4 eq) portion wise and stirred for 30 minutes. Then added 4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-aniline (150.00 mg, 0.4757 mmol, 1.0 eq) portion wise and the reaction mixture was stirred at room temperature for 12 hours. After completion of reaction, the reaction mixture was treated with ice water (10 mL) at 0 °C and stirred for 20 minutes. The resulting solid was filtered and washed with water (10

mL) and dried under vacuum to obtain N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2H-[1,3'-bipyridine]-3-carboxamide (170 mg, 57.13 % yield) as a brown color solid. The crude compound was further purified.

[1176] Peak-1: N-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-95 (Atropisomer 1)]:



Atropisomer 1
Example A-95

[1177] 170 mg of racemic mixture was submitted for chiral separation and isolated Peak-1 (Atrope-1) = 41.39 mg.

[1178] The racemic mixture was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 41.39 mg of the of title compound as an off white solid.

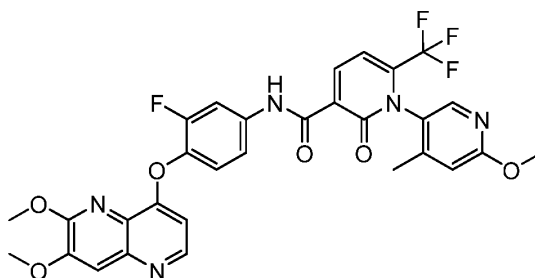
[1179] SFC purification Method: Mobile Phase A: ETOH: MeOH (1:1) Mobile Phase B: CAN, Column: CHIRALPAK IK (250 X 4.6 mm ,5 μ m) A B: 80:20 Column ID: M-ARD-CAL-028 , Flow rate : 1.00 mL/min).

[1180] ^1H NMR (400 MHz, DMSO- d_6): δ 11.62 (s, 1H), 8.66 (d, J = 7.6 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.20 (s, 1H), 8.01 (dd, J = 2.0 Hz, J=2.4Hz, 1H), 7.65 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 9.2 Hz, 1H), 6.95 (s, 1H), 6.85 (d, J = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 6H), 2.05 (s, 3H). MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{30}\text{H}_{23}\text{F}_4\text{N}_5\text{O}_6+\text{H}]^+$: 625.1, find: 626.41, t_R = 4.15 min.

[1181] Chiral HPLC purity: 100 %, t_R = 4.675 min, ee = 100 %. Method: Column: CHIRALPAK- IK (250 $\times$ 4.6mm, 5 μ m) Mobile Phase A: MeOH: EtOH (50:50) Mobile Phase B: MeCN A/B: 80:20 Flow: 1.0 mL/min COLUMN ID: PDA: IK-028.

[1182] Specific Optical Rotation (SOR): +16.26, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor Concentration 0.05 w/v% Water content of sample 0% Factor 1.

[1183] Peak-2: *N*-[4-[(6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide, [Example A-95A (Atropisomer 2)]:



Atropisomer 2
Example: A-95A

[1184] 170 mg of racemic mixture was submitted for chiral separation and isolated Peak-2 (Atrope-2) = 35.39 mg.

[1185] The racemic mixture was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 35.39 mg of the of title compound as an off white solid.

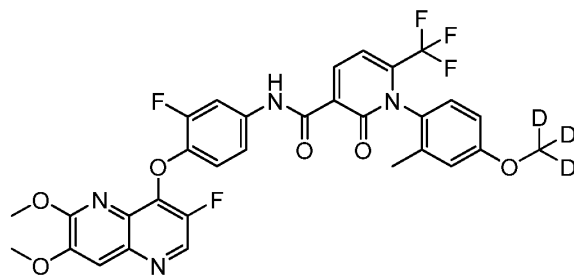
[1186] SFC purification Method: Mobile Phase A: ETOH: MeOH (1:1), Mobile Phase B: MeCN, Column: CHIRALPAK IK (250 X 4.6 mm ,5 μ m) A B: 80:20 Column ID: M-ARD-CAL-028, Flow rate: 1.00 mL/min).

[1187] ^1H NMR (400 MHz, DMSO- d_6): δ 11.62 (s, 1H), 8.66 (d, J = 7.6 Hz, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.20 (s, 1H), 8.01 (dd, J = 2.0 Hz, J = 2.4 Hz, 1H), 7.65 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 9.2 Hz, 1H), 6.95 (s, 1H), 6.85 (d, J = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 6H), 2.05 (s, 3H). MS(ES $^+$) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{30}\text{H}_{23}\text{F}_4\text{N}_5\text{O}_6+\text{H}]^+$: 625.1, find: 626.45, t_R = 4.15 min.

[1188] Chiral HPLC purity: 96.71 %, t_R = 5.52 min, ee = 93.42 %. Method: Column: CHIRALPAK- IK (250 $\times$ 4.6mm, 5 μ m) Mobile Phase A: MeOH: EtOH (50:50) Mobile Phase B: MeCN A/B: 80:20 Flow: 1.0 mL/min COLUMN ID: PDA: IK-028.

[1189] Specific Optical Rotation (SOR): -16.96, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor Concentration 0.05 w/v% Water content of sample 0% Factor 1.

[1190] Synthesis of 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-[2-methyl-4-(trideuteriomethoxy)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-119]:

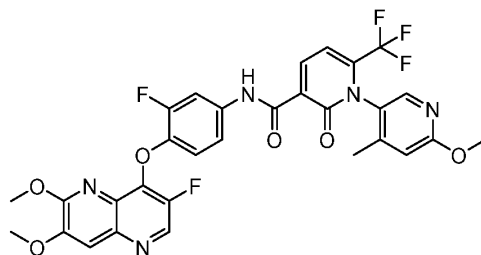
**Example A-119**

[1191] To a stirred solution of 1-[2-methyl-4-(trideuteriomethoxy)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (118, 2 mg, 0.358 mmol, 2.2 eq) in pyridine (1 mL) was added EDC.HCl (116.2 mg, 0.600 mmol, 4 eq) and 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]aniline (50.00 mg, 0.150 mmol, 1.0 eq) at 0°C and stirred at room temperature for 16 hours. After completion of the reaction, reaction mass was diluted with water (5 mL), the resulting solid was filtered and purified by combi flash using YMC 12 g cartridge, eluting with 0-50% ethyl acetate/heptane to afford 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-[2-methyl-4-(trideuteriomethoxy)phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (30.24 mg, 28.10 % yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 11.7 (s, 1 H), 8.90 (d, *J*=2 Hz, 1 H), 8.63 (d, *J*=7.6 Hz, 1 H), 7.93 (dd, *J*=13.2, 2.4 Hz, 1 H), 7.68 (s, 1 H), 7.34- 7.33 (m, 2 H), 7.28 (d, *J*=8.8 Hz, 1 H), 7.09 (t, *J*=9.2, 1 H), 6.99-6.98 (m 1 H), 6.92=6.89 (m, 1 H), 3.93 (s, 3 H), 3.60 (s, 3 H), 1.99 (s, 3 H). MS(ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₁D₃H₂₀F₅N₄O₆+H]⁺ : 646.1, found: 646.37, *t*_R= 5.63 min.

[1192] Chiral HPLC purity: 99.56%, *t*_R= 3.62 min, ee= 99.42 %. Method: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: MeCN A/B: 80/20 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028.

[1193] Specific optical rotation (SOR): 87.78, Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 10 mm Concentration 0.1 w/v% Water content of sample 0 % Factor 1.

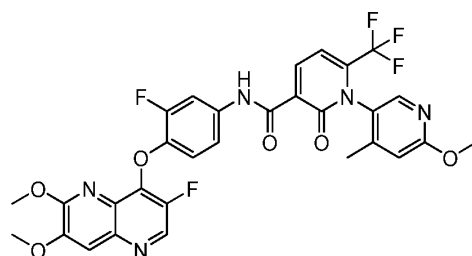
[1194] Synthesis of *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)phenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide [Example A-120 (Atropisomer 1) and Example A-121 (Atropisomer 2)]:

**Atropisomer A-1: Example 120****Atropisomer A-2: Example 121**

[1195] To a solution of 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (68.93 mg, 0.210 mmol, 1.0 eq) in pyridine (1 mL) was added and EDC.HCl (79.81 mg, 0.420 mmol, 2.0 eq) and 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]aniline (70 mg, 0.210 mmol, 1.0 eq) at room temperature and the mixture was stirred for 16 h. The reaction mixture was treated with ice water (5 mL) at 0 °C and stirred for 5 minutes. The resulting solid was filtered and washed with water (5 mL) and dried under vacuum to get crude product. The crude was purified by comb flash using 24 g column cartridge and eluted with 0-70% ethyl acetate/heptane to afford racemic *N*-(3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)phenyl)-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-2*H*-[1,3'-bipyridine]-3-carboxamide (70 mg, 51.79 % yield) as a brown color solid.

[1196] The racemic compound was submitted for chiral SFC purification, separated both the peaks and evaporated under vacuum to afford Peak-1 & Peak-2.

[1197] Purification of *N*-(3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl)-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide, [Example A-120 (Atropisomer-1, P1)]:

**Atropisomer 1****Example A-120**

[1198] 70 mg of racemic compound was submitted for chiral separation and isolated Peak-1 (Atrope-1) = 18.01 mg.

[1199] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 18.01 mg of the of title compound as an off white solid.

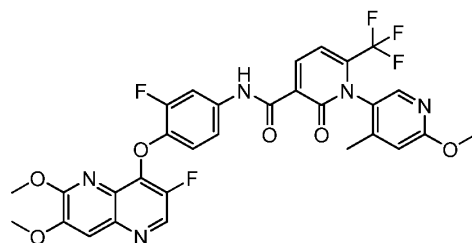
[1200] Preparative NP-Chiral prep Method: Column IG (30X250*mm,5 μ m) Mobile phase A 0.1% IPA mine in Hexane Mobile phase B DCM: MEOH (80:20) Eluent A: B: 60:40 Total Flow rate (mL/min) 42 ml/min Diluent MP Detection 325 nm.

[1201] ^1H NMR (400 MHz, DMSO- d_6): 11.55 (s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.64 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 7.92 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 7.68 (s, 1H), 7.36 (dd, J = 7.6 Hz, J = 15.6 Hz, 2H), 7.09 (t, J = Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.60 (s, 3H), 2.04 (s, 3H). MS(ES+) m/z calc'd for $[\text{M}+\text{H}]^+$ $[\text{C}_{30}\text{H}_{22}\text{F}_5\text{N}_5\text{O}_6+\text{H}]^+$: 644.10, found: 644.43, t_R = 4.70 min.

[1202] Chiral HPLC purity: 100%, t_R = 4.47 min, ee = 100%. Method: Column: CHIRALPAK IG (250X4.6 mm, 5 μ m) A B: 25:75, Column ID: M-ARD-CAL-025, Flow rate: 1.00 ml/min.

[1203] Specific Optical Rotation (SOR): +9.7, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

[1204] Purification of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide, [Example A-121 (Atropisomer-2, P2)]:



Atropisomer 2
Example A-121

[1205] 70 mg of racemic compound was submitted for chiral separation and isolated Peak-2 (Atrope-2) = 15.82 mg.

[1206] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 15.82 mg of the title compound as an off-white solid.

[1207] Preparative NP-Chiral prep Method: Column IG (30X250*mm,5 μ m) Mobile phase A 0.1% IPA mine in Hexane Mobile phase B DCM: MEOH (80:20) Eluent A: B: 60:40 Total Flow rate (mL/min) 42 ml/min Diluent MP Detection 325 nm.

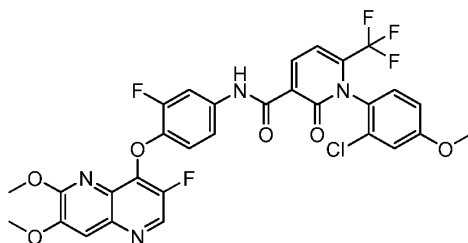
[1208] ^1H NMR (400 MHz, DMSO- d_6): 11.54 (s, 1H), 8.90 (d, J = 1.6 Hz, 1H), 8.64 (d, J = 7.6 Hz, 1H), 8.17 (s, 1H), 7.92 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 7.68 (s, 1H), 7.36 (dd, J = 7.6 Hz, J = 15.6 Hz, 2H), 7.09 (t, J = Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.60 (s, 3H),

2.04 (s,3H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{30}H_{22}F_5N_5O_6+H]^+$: 644.10, found: 644.43, t_R = 4.70 min.

[1209] Chiral HPLC purity: 98.68%, t_R = 6.22 min, ee= 97.31%. Method: Column: CHIRALPAK IG (250X4.6 mm ,5 μ m) A B: 25:75, Column ID: M-ARD-CAL-025, Flow rate: 1.00 ml/min.

[1210] Specific Optical Rotation (SOR): -15, Method: Light Source WI Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor None Aperture(S) 8.0mm Aperture(L) Auto Mode Specific O.R. Path Length 50 mm Concentration 0.05 w/v% Water content of sample 0 % Factor 1.

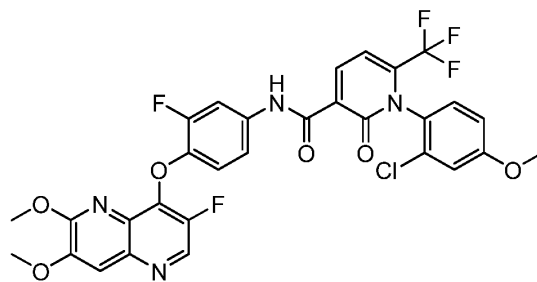
[1211] Synthesis 1-(2-chloro-4-methoxy-phenyl)-{N}-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-133 (Atropisomer 1) and Example A-134 (Atropisomer 2)]:



Atropisomer 1: Example A-133
Atropisomer 2: Example A-134

[1212] To a stirred solution of 1-(2-chloro-4-methoxy-phenyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (149 mg, 0.429 mmol, 1.1 eq) in pyridine (3 mL) was added EDAC (152 mg, 0.780 mmol, 2.0 eq) at 0° C. Then, 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]aniline (130 mg, 0.390 mmol, 1.0 eq) was added and resulting mixture was stirred at room temperature for 16 h. After completion of the reaction, the mixture was diluted with water (10mL) and extracted with EtOAc (20mL). The organic layer was separated, dried over Na₂SO₄, and concentrated under reduced pressure to get crude product. The crude product obtained was purified by flash column chromatography to afford racemic 1-(2-chloro-4-methoxy-phenyl)-~{N}-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy]phenyl]-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (80.00 mg, 30.94% yield) as an off-white solid which was further separated by SFC.

[1213] 1-(2-Chloro-4-methoxyphenyl)-N-(3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)phenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide [Example A-133 (Atropisomer-1)]:



Atropisomer 1
Example A-133

[1214] 80 mg of racemic compound was submitted for chiral separation and isolated Peak-1 (Atrope-1) = 26 mg.

[1215] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 26 mg of the title compound as an off-white solid.

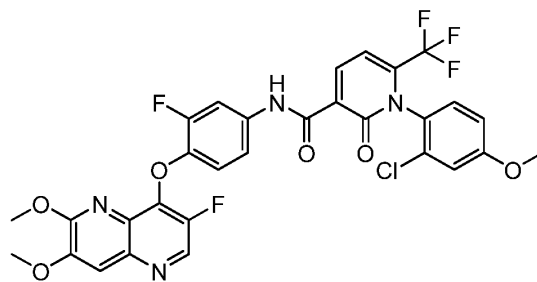
[1216] SFC purification Method: Mobile Phase A: CO₂ Mobile Phase B: (0.1% MEONH₂ IN MeCN:MeOH), Column: CHIRALCEL-OX-H (20*250mm, 5 μ m) A B : 82:18 Column ID : M-ARD-CAL-028 , Flow rate : 60g-30% , 100 bar.

[1217] ¹H NMR (400 MHz, DMSO-d₆) δ = 11.53 (s, 1H), 8.91 (d, *J* = 1.9 Hz, 1H), 8.66 (d, *J* = 7.5 Hz, 1H), 7.93 (dd, *J* = 2.5, 13.1 Hz, 1H), 7.69 (s, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.39 - 7.31 (m, 3H), 7.15 - 7.06 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H).

[1218] Chiral HPLC purity: 99.90 %, *t_R* = 2.061 min, ee = 99.8 %. Method: Column: CHIRALCEL OX-H (150*4.6mm, 5 μ m) Mobile Phase A: CO₂ Mobile Phase B: 0.1% MeONH₃ in MeCN:MeOH(1:1) Flow: 3g-30% COLUMN ID: M-ARD-CAL-051.

[1219] Specific Optical Rotation (SOR): +201.6800, Method: Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Concentration 0.05 w/v% Water content of sample 0% Factor 1; solvent-methanol.

[1220] 1-(2-Chloro-4-methoxyphenyl)-N-(3-fluoro-4-((3-fluoro-6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)phenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide [Example A-134 (Atropisomer 2)]:



Atropisomer 2
Example A-134

[1221] 80 mg of racemic compound was submitted for chiral separation and isolated Peak-1 (Atrope-1) = 18 mg.

[1222] Atropisomer was separated by chiral SFC (instrument name: Waters-2767, prep-SFC 100) method to afford 18 mg of the of title compound as an off white solid.

[1223] SFC purification Method: Mobile Phase A: CO₂ Mobile Phase B: (0.1% MEONH₂ IN MeCN:MeOH), Column: CHIRALCEL-OX-H (20*250mm, 5 μ m) A B : 82:18 Column ID : M-ARD-CAL-028 , Flow rate : 60g-30% , 100 bar.

[1224] ¹H NMR (400 MHz, DMSO-d₆) δ = 11.54 (s, 1H), 8.91 (d, *J* = 1.8 Hz, 1H), 8.66 (d, *J* = 7.5 Hz, 1H), 7.94 (dd, *J* = 2.4, 13.2 Hz, 1H), 7.69 (s, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.42 - 7.31 (m, 4H), 7.21 - 7.01 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.60 (s, 3H).

[1225] Chiral HPLC purity: 100 %, *t_R* = 3.072 min, ee = 100 %. Method: Column:

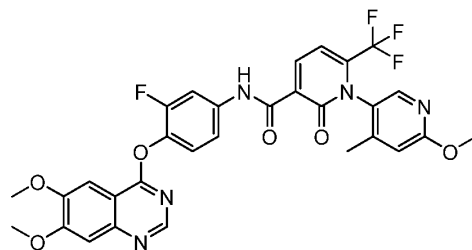
CHIRALCEL OX-H (150*4.6mm, 5 μ m) Mobile Phase A: CO₂ Mobile Phase B: : 0.1%MeONH₃ in MeCN:MeOH(1:1) Flow: 3g-30% COLUMN ID: M-ARD-CAL-052.

[1226] Specific Optical Rotation (SOR): -140.6400, Method: Light Source Na Monitor wavelength 589 nm D.I.T. 5 sec No. of cycle 5 Cycle interval 5 sec Temp. Monitor Holder Temp. Corr. Factor 0 at 20 C Concentration 0.05 w/v% Water content of sample 0% Factor 1; solvent-methanol.

[1227] Using Method 5, **A-90** to **A-142** and **A-177** to **A-183** were prepared.

Method 6:

[1228] Synthesis of {*N*}-[4-(6, 7-dimethoxyquinazolin-4-yl) oxy-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxamide [Example A-143 (Atropisomer 1)]:



Atropisomer 1
Example A-143

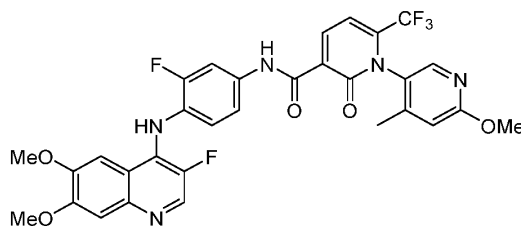
[1229] To a stirred solution of Atropisomer 1 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (124.9 mg, 0.380 mmol, 1.2 eq) in a pyridine (2 mL) was added EDC.HCl (122.8 mg, 0.634 mmol, 2.0 eq) followed by 4-(6,7-dimethoxyquinazolin-4-yl)oxy-3-fluoro-aniline (100 mg, 0.317 mmol, 1.00 eq) at room temperature. The reaction mixture was stirred for 16 h at 25 °C. After completion of the reaction, the reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3x30 mL). The crude compound was purified by combi flash using YMC 80 g cartridge, eluting with 0-50% ethyl acetate/heptane to afford {*N*}-[4-(6, 7-dimethoxyquinazolin-4-yl) oxy-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl) pyridine-3-carboxamide (96 mg, 48.3 % yield) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 11.64 (s, 1H), 8.69 (d, *J* = 7.5 Hz, 1H), 8.57 (s, 1H), 8.21 (s, 1H), 7.99 (dd, *J* = 2.3, 12.5 Hz, 1H), 7.58 (s, 1H), 7.56 (d, *J* = 1.3 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.43 - 7.37 (m, 2H), 6.96 (s, 1H), 4.00 (d, *J* = 6.3 Hz, 6H), 3.92 (s, 3H), 2.10 - 2.04 (m, 3H). MS (ES⁺) *m/z* calc'd for [M+H]⁺ [C₃₀H₂₃F₄N₅O₆+H]⁺: 626.1, found: 626.4, *t_R* = 4.49 min.

[1230] Chiral HPLC purity: 98.9%, *t_R* = 5.507 min, ee = 97.98 %. CHIRALPAK IK (250X4.6mm, 5μm), Mobile Phase A: ETOH: MEOH (1:1), Mobile Phase B: MeCN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL-028

[1231] Specific optical rotation (SOR): 247.6, Light Source- Na, Monitor wavelength- 589 nm, D.I.T-5 sec, No. of cycle-5, Cycle interval-5 sec, Temp. Monitor- Holder, Temp. Corr. Factor- None, Aperture(S)- 8.0mm, Aperture(L)- Auto, Mode Specific O.R. Path Length-10 mm, Concentration 0.1 w/v%. Water content of sample 0 %, Factor 1

Method 7:

[1232] Synthesis of *N*-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)amino]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-150 (Racemic), Example A-151 (Atropisomer 1), and Example A-152 (Atropisomer 2)]:



Racemic: Example A-150
Atropisomer 1: Example A-151
Atropisomer 2: Example A-152

[1233] To a solution of 2-fluoro-N1-(3-fluoro-6,7-dimethoxy-4-quinolyl)benzene-1,4-diamine (50.00 mg, 150.91 μ mol, 1.00 eq) and 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (74.30 mg, 226.37 μ mol, 1.50 eq) in pyridine (1 mL) was added EDCI (43.40 mg, 226.37 μ mol, 1.50 eq). The mixture was stirred at 25 °C for 4 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. After completion, the solvent was removed by concentration to give the crude. The residue was purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN];gradient:40%-75% B over 8.0 min), after purification pure fractions were lyophilized to afford N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)amino]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (35.10 mg, 35.82% yield) as a yellow solid as a racemic mixture. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.50 Hz, 1 H) 8.53 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.38, 2.25 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.10 (s, 1 H) 6.95 (s, 1 H) 3.90 - 3.93 (m, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄N₅F₅O₅+H]⁺: 642.54, found: 642.2, *t*_R= 3.177 min.

[1234] The racemic mixture (30 mg) was purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10 μ m); mobile phase: [CO₂-IPA(0.1% NH₃H₂O)];B%:50%, isocratic elution mode) which afforded 5.7 mg of Atropisomer 1 and 6.5 mg of Atropisomer 2 as a yellow solid.

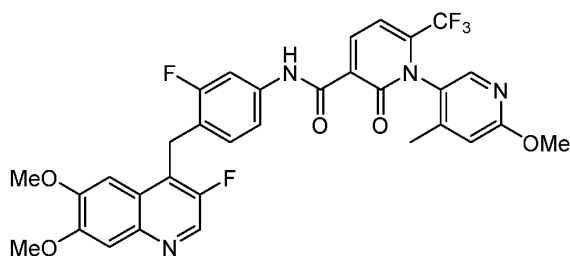
[1235] N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)amino]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-151 (Atropisomer 1)]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 8.55 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.45, 2.19 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.11 (t, J=9.19 Hz, 1 H) 6.95 (s, 1 H) 3.91 (s, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₁H₂₄N₅F₅O₅+H]⁺: 642.54, found: 642.2, *t*_R= 3.185 min, Chiral HPLC purity: 100%, *t*_R= 0.762, ee= 100%.

[1236] N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)amino]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide[Example A-152

(Atropisomer 2)]: ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 8.55 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.45, 2.19 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.11 (t, J=9.19 Hz, 1 H) 6.95 (s, 1 H) 3.91 (s, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H). MS(ES+) m/z calc'd for [M+H]⁺ [C₃₁H₂₄N₅F₅O₅+H]⁺: 642.54, found: 642.2, t_R= 3.186 min, Chiral HPLC purity: 100%, t_R= 1.389, ee= 99.52%.

Method 8:

[1237] Synthesis of N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-161]:



Example A-161

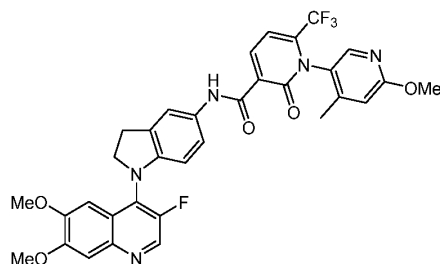
[1238] To a solution of 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (28.32 mg, 86.28 μmol, 1.50 eq) and 3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]aniline (19.00 mg, 57.52 μmol, 1.00 eq) in DCM (2 mL) was added DIEA (14.87 mg, 115.04 μmol, 20.04 μL, 2.00 eq) and BOP-Cl (21.96 mg, 86.28 μmol, 1.50 eq). The mixture was stirred at 25 °C for 1 hr. LC-MS showed starting material was consumed completely and one main peak with desired m/z was detected. The mixture was quenched with water (50 mL) and extracted with DCM (3×30 mL). The combined organic phase was washed with brine (2×30 mL), dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by prep-HPLC (neutral condition; column: WePure Biotech XP tC18 150*40*7μm; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN]; gradient: 55%-85% B over 8.0 min) after purification, fractions were lyophilized to afford N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (16 mg, 43.2% yield) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.53 (s, 1 H) 8.69 (s, 1 H) 8.62 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.79 (dd, J=12.51, 1.88 Hz, 1 H) 7.33 - 7.41 (m, 3 H) 7.27 (dd, J=8.50, 1.88 Hz, 1 H) 7.13 (t, J=8.50 Hz, 1 H) 6.92 (s, 1 H)

4.41 (s, 2 H) 3.90 (d, J=4.00 Hz, 6 H) 3.86 (s, 3 H) 2.02 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₅F₅N₄O₅+H]⁺: 641.17, found: 641.2, *t_R* = 3.374 min.

[1239] Using Method 8, **A-162** was prepared.

Method 9:

[1240] Synthesis of N-[1-(3-fluoro-6,7-dimethoxy-4-quinolyl)indolin-5-yl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-163]:



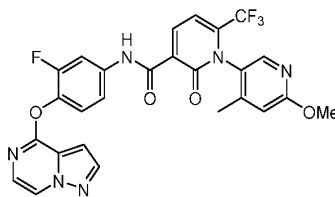
Example A-163

[1241] To a stirred solution of 1-(3-fluoro-6,7-dimethoxy-4-quinolyl) indolin-5-amine (40.00 mg, 117.87 μ mol, 1.00 eq), 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (58.03 mg, 176.80 μ mol, 1.50 eq) in DCM (1 mL) was added DIEA (45.70 mg, 353.60 μ mol, 61.59 μ L, 3.00 eq), DMTMM (97.85 mg, 353.60 μ mol, 3.00 eq). The mixture was stirred at 25 °C for 12 hr under N₂. LCMS showed the reaction was completed. The reaction mixture was poured into 30 mL H₂O and followed by EtOAc (30 mL). The solution was stirred for 1 h. After that, the aqueous phase was separated and extracted with EtOAc (2x30 mL). The combined organic layer was washed successively with water (2x50 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-HPLC: We Pure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-MeCN]; gradient: 50%-85% B over 8.0 min. After purification, fractions were lyophilized to afford N-[1-(3-fluoro-6,7-dimethoxy-4-quinolyl)indolin-5-yl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (24.6 mg, 32.13% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.38 (d, J=1.75 Hz, 1 H) 8.72 (d, J=3.00 Hz, 1 H) 8.64 (d, J=7.50 Hz, 1 H) 8.19 (s, 1 H) 7.71 (br d, J=6.38 Hz, 1 H) 7.44 (s, 1 H) 7.38 (d, J=7.75 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.16 (d, J=4.25 Hz, 1 H) 6.95 (s, 1 H) 6.17 (dd, J=8.44, 1.69 Hz, 1 H) 4.22 (br dd, J=4.13, 2.00 Hz, 1 H) 3.96 - 4.04 (m, 1 H) 3.94 (s, 3 H) 3.91 (s, 3 H) 3.78 (d, J=3.50 Hz, 3 H) 3.22 - 3.32 (m, 2 H) 2.05 (s, 3 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₂₇N₅O₅F₄+H]⁺: 650.20, found: 650.2, *t_R* = 3.349 min.

[1242] Using Method 9, **A-164** was prepared.

Method 10:

[1243] Synthesis of N-(3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-phenyl)-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide [Example A-175]:



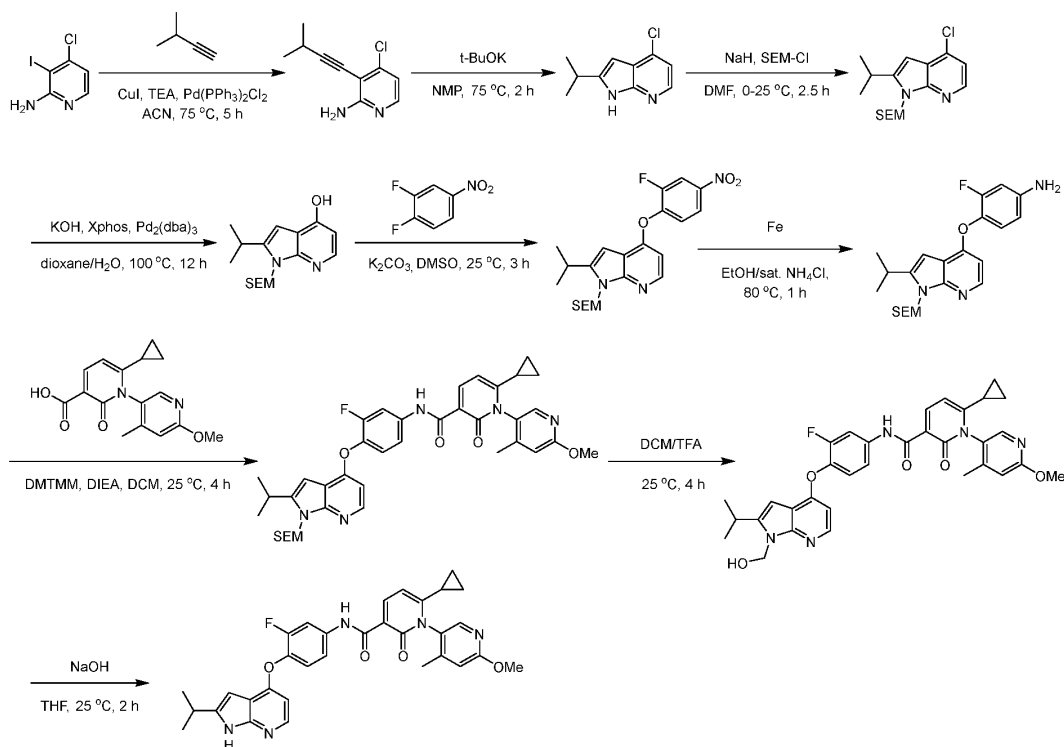
Example A-175

[1244] To a mixture of 3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-aniline (40.00 mg, 163.78 μ mol, 1.00 eq) in DCM (2 mL) was added DMTMM (135.97 mg, 491.35 μ mol, 3.00 eq), DIEA (63.50 mg, 491.35 μ mol, 85.58 μ L, 3.00 eq), 1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid (80.64 mg, 245.68 μ mol, 1.50 eq) at 25 °C. The mixture was stirred at 25 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired m/z was detected. The reaction mixture was poured into 30 mL H₂O. After that, the aqueous phase was separated and extracted with EtOAc (2×30 mL). The combined organic layer was washed successively with water (2×50 mL) and brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated to give a residue. The residue was purified by prep-HPLC: WePure Biotech XP tC18 150*40*7 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-MeCN]; gradient: 45%-80% B over 8.0 min, after purification, fractions were lyophilized to afford N-(3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-phenyl)-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide (28.5 mg, 31.38% yield) as a white solid.

[1245] Using Method 10 these compounds, **A-165 to A-175** were prepared.

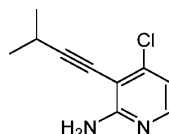
Method 11:

[1246] Synthesis of 6-cyclopropyl-N-[3-fluoro-4-[(2-isopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide [Example A-176]:



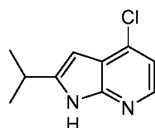
Example A-176

[1247] Synthesis of 4-chloro-3-(3-methylbut-1-ynyl)pyridin-2-amine:



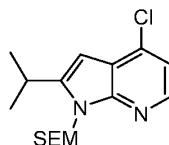
[1248] A mixture of 4-chloro-3-iodo-pyridin-2-amine (1.40 g, 5.50 mmol, 1.00 eq), 3-methylbut-1-yne (749.55 mg, 11.00 mmol, 1.13 mL, 2.00 eq), CuI (104.78 mg, 550.19 μ mol, 0.10 eq), TEA (3.90 g, 38.51 mmol, 5.36 mL, 7.00 eq) and Pd(PPh₃)₂Cl₂ (386.18 mg, 550.19 μ mol, 0.10 eq) in MeCN (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 75 °C for 5 h under N₂ atmosphere. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by an addition of H₂O 50 mL, and then extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine 50 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/EtOAc=1/0 to 90/10, pet.ether/EtOAc=3/1, TM/R_f=0.42) to afford 4-chloro-3-(3-methylbut-1-ynyl)pyridin-2-amine (1.00 g, 84.03% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 7.84 (br s, 1 H) 6.67 (d, J=5.38 Hz, 1 H) 6.34 (br s, 2 H) 2.83 - 2.94 (m, 1 H) 1.24 (d, J=6.88 Hz, 6 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₀H₁₁N₂Cl+H]⁺: 195.06, found: 195.1, *t*_R= 0.352 min.

[1249] Synthesis of 4-chloro-2-isopropyl-1H-pyrrolo[2,3-b]pyridine:



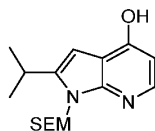
[1250] To a solution of 4-chloro-3-(3-methylbut-1-ynyl)pyridin-2-amine (900.00 mg, 4.62 mmol, 1.00 eq) in NMP (10 mL) was added *tert*-BuOK (1 M, 9.25 mL, 2.00 eq). The mixture was stirred at 75 °C for 2 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (30 mL) and then extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine 30 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/EtOAc=1/0 to 90/10, pet.ether/EtOAc=1/1, TM/R_f=0.58) to afford 4-chloro-2-isopropyl-1H-pyrrolo[2,3-b]pyridine (700.00 mg, 77.78% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.89 (br s, 1 H) 8.07 (br s, 1 H) 7.11 (d, J=5.13 Hz, 1 H) 6.20 (d, J=1.13 Hz, 1 H) 2.99 - 3.11 (m, 1 H) 1.31 (d, J=6.88 Hz, 6 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₀H₁₁N₂Cl+H]⁺: 195.06, found: 195.2, *t*_R= 0.448 min.

[1251] Synthesis of 2-[(4-chloro-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane:



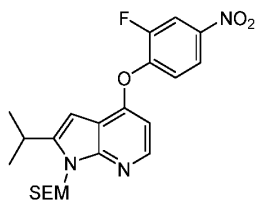
[1252] To a solution of 4-chloro-2-isopropyl-1H-pyrrolo[2,3-b]pyridine (500.00 mg, 2.57 mmol, 1.00 eq) in DMF (8 mL) was added NaH (308.20 mg, 7.71 mmol, 60% purity, 3.00 eq) at 0 °C for 1 h, then SEM-Cl (513.88 mg, 3.08 mmol, 545.52 μL, 1.20 eq) was added at 0 °C. The mixture was stirred at 25 °C for 1.5 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL) and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/ethyl acetate=1/0 to 90/10, PE/ETOAC=4/1, TM/R_f=0.44) to afford 2-[(4-chloro-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (750.00 mg, 89.87% yield) as a yellow oil. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₂₅N₂ClSiO+H]⁺: 325.14, found: 325.3, *t*_R= 0.765 min.

[1253] Synthesis of 2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol:



[1254] To a solution of 2-[(4-chloro-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl)methoxy]ethyl-trimethyl-silane (700.00 mg, 2.15 mmol, 1.00 eq) in dioxane (5 mL) and H₂O (5 mL) was added Xphos (205.41 mg, 430.88 μ mol, 0.20 eq), then KOH (362.65 mg, 6.46 mmol, 3.00 eq) and Pd₂(dba)₃ (197.28 mg, 215.44 μ mol, 0.10 eq) was added. The mixture was stirred at 100 °C for 12 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL) and then extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, pet. ether/EtOAc=1/0 to 90/10, pet.ether/EtOAc=3/1, TM/R_f=0.35) to afford 2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol (420.00 mg, 63.61% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.46 (br s, 1 H) 7.89 (d, J=5.38 Hz, 1 H) 6.46 (d, J=5.38 Hz, 1 H) 6.31 (s, 1 H) 5.59 (s, 2 H) 3.48 (t, J=8.00 Hz, 2 H) 3.14 - 3.21 (m, 1 H) 1.29 (d, J=6.88 Hz, 6 H) 0.78 - 0.83 (m, 2 H) -0.11 (s, 9 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₁₆H₂₆N₂O₂Si +H]⁺: 307.18, found: 307.3, *t*_R= 0.442 min.

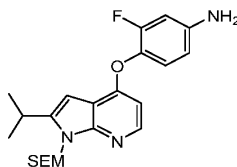
[1255] Synthesis of 2-[[4-(2-fluoro-4-nitro-phenoxy)-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl]methoxy]ethyl-trimethyl-silane:



[1256] To a solution of 2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-ol (200.00 mg, 652.58 μ mol, 1.00 eq) and 1,2-difluoro-4-nitro-benzene (114.20 mg, 717.84 μ mol, 79.47 μ L, 1.10 eq) in DMSO (2 mL) was added K₂CO₃ (360.76 mg, 2.61 mmol, 4.00 eq). The mixture was stirred at 25 °C for 3 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, pet. ether:EtOAc = 3:1, TM/R_f=0.48) to afford 2-[[4-(2-fluoro-4-nitro-phenoxy)-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl]methoxy]ethyl-trimethyl-silane (200.00 mg, 68.78% yield) as a

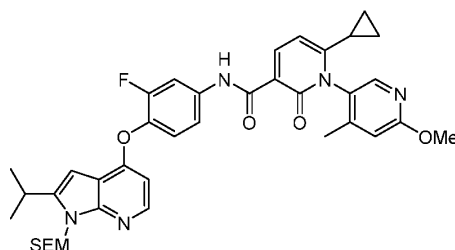
yellow oil. MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{22}H_{28}O_4N_3FSi + H]^+$: 446.18, found: 445.9, t_R = 0.826 min.

[1257] Synthesis of 3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline:



[1258] To a solution of 2-[[4-(2-fluoro-4-nitro-phenoxy)-2-isopropyl-pyrrolo[2,3-b]pyridin-1-yl]methoxy]ethyl-trimethyl-silane (200.00 mg, 448.88 μ mol, 1.00 eq) in EtOH (4 mL) and saturated NH_4Cl (1 mL) was added Fe (125.34 mg, 2.24 mmol, 5.00 eq) at 80 °C. The mixture was stirred at 80 °C for 1 h. LC-MS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was filtered through Celite and the filter cake was washed with EtOAc (2 $\times$ 20 mL). The resulting filtrate was extracted with EtOAc (2 $\times$ 20 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 , filtered, and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , pet. ether/EtOAc=1/0 to 1/1, pet. ether: EtOAc = 1:1, TM/R_f =0.51) to afford 3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline (150.00 mg, 80.41% yield) as a yellow oil. 1H NMR (400 MHz, $DMSO-d_6$): δ 8.00 (d, J =5.50 Hz, 1 H) 7.01 (t, J =9.01 Hz, 1 H) 6.52 (dd, J =13.20, 2.44 Hz, 1 H) 6.43 (dd, J =8.44, 2.06 Hz, 1 H) 6.22 - 6.31 (m, 2 H) 5.65 (s, 2 H) 5.43 (s, 2 H) 3.47 - 3.54 (m, 2 H) 3.22 (br dd, J =13.57, 6.94 Hz, 1 H) 1.30 (d, J =6.75 Hz, 6 H) 0.79 - 0.85 (m, 2 H) -0.12 - -0.08 (m, 9 H). MS(ES+) m/z calc'd for $[M+H]^+$ $[C_{22}H_{30}O_2N_3FSi + H]^+$: 416.21, found: 416.3, t_R = 0.581 min.

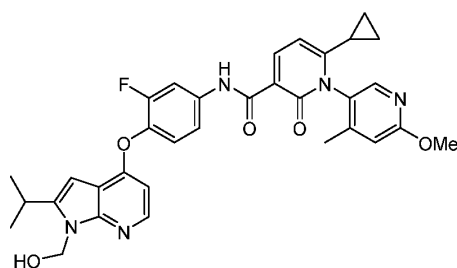
[1259] Synthesis of 6-cyclopropyl-N-[3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl) pyrrolo[2,3-b]pyridin-4-yl]oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide:



[1260] To a solution of 3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl)pyrrolo[2,3-b]pyridin-4-yl]oxy-aniline (70.00 mg, 168.44 μ mol, 1.00 eq) and 6-cyclopropyl-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxylic acid (60.70 mg, 202.13 μ mol, 1.20 eq) in DCM

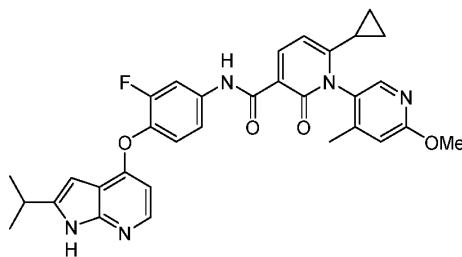
(2 mL) was added DIEA (65.31 mg, 505.32 μ mol, 88.02 μ L, 3.00 eq) and DMTMM (139.83 mg, 505.32 μ mol, 3.00 eq). The mixture was stirred at 25 °C for 4 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, pet. ether: EtOAc = 1:1, TM/R_f=0.47) to afford 6-cyclopropyl-N-[3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl) pyrrolo[2,3-b]pyridin-4-yl]oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (80.00 mg, 68.06% yield) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₈H₄₄O₅N₅FSi+H]⁺: 698.31, found: 698.4, t_R= 0.712 min.

[1261] Synthesis of 6-cyclopropyl-N-[3-fluoro-4-[1-(hydroxymethyl)-2-isopropyl-pyrrolo[2,3-b]pyridin-4-yl]oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide:



[1262] To a solution of 6-cyclopropyl-N-[3-fluoro-4-[2-isopropyl-1-(2-trimethylsilylethoxymethyl) pyrrolo[2,3-b] pyridin-4-yl] oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (70.00 mg, 100.31 μ mol, 1.00 eq) in DCM (2 mL) and TFA (0.5 mL). The mixture was stirred at 25 °C for 4 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was poured onto H₂O (10 mL) and then adjusted the pH to 7 with sat. Na₂CO₃. Then, the resulting solution was extracted with DCM (2 $\times$ 10 mL). The combined organic layer was washed successively with water (2 $\times$ 20 mL) and brine (20 ml), dried over anhydrous Na₂SO₄, filtered, and concentrated to afford 6-cyclopropyl-N-[3-fluoro-4-[1-(hydroxymethyl)-2-isopropyl-pyrrolo[2,3-b]pyridin-4-yl]oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (70.00 mg, crude) as a yellow solid. MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₃H₃₂O₅N₅F +H]⁺: 598.24, found: 598.4, t_R= 0.526 min.

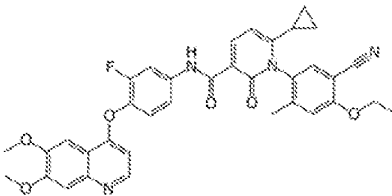
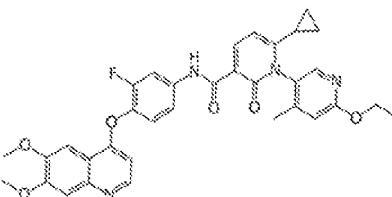
[1263] Synthesis of 6-cyclopropyl-N-[3-fluoro-4-[(2-isopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl]oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide [Example A-176]:

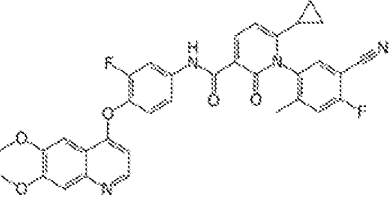
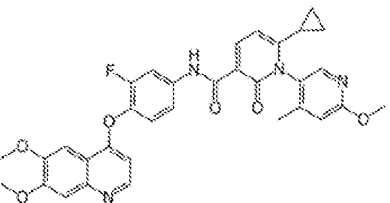
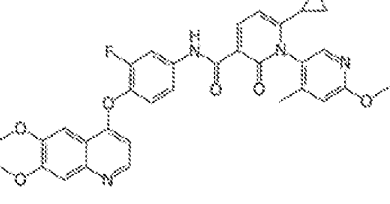
**Example A-176**

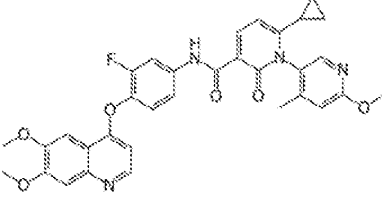
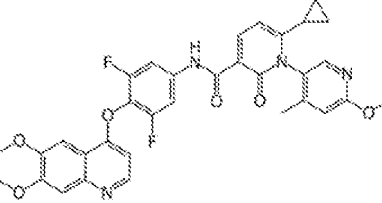
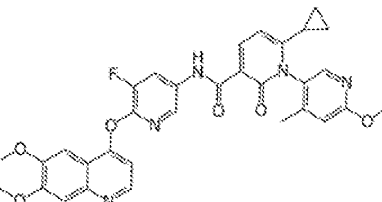
[1264] To a solution of 6-cyclopropyl-N-[3-fluoro-4-[1-(hydroxymethyl)-2-isopropyl-pyrrolo[2,3-b]pyridin-4-yl]oxy-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (70.00 mg, 117.13 μmol , 1.00 eq) in THF (1 mL) was added NaOH (4 M, 1 mL, 34.15 eq). The mixture was stirred at 25 °C for 2 h. LCMS showed starting material was consumed completely and one main peak with desired m/z mass was detected. The reaction mixture was quenched by addition H₂O (20 mL), and then extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: WePure Biotech XP tC18 150*40*7 μm ; mobile phase: [H₂O(10mM NH₄HCO₃)-MeCN]; gradient: 50%-80% B over 8.0 min), after purification, fractions were lyophilized to afford 6-cyclopropyl-N-[3-fluoro-4-[(2-isopropyl-1H-pyrrolo[2,3-b]pyridin-4-yl)oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide (19.10 mg, 28.73% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆): δ 11.98 (s, 1 H) 11.64 (s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.17 (s, 1 H) 7.93 - 8.03 (m, 2 H) 7.45 (br d, J=8.75 Hz, 1 H) 7.30 (t, J=8.94 Hz, 1 H) 6.97 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.30 (d, J=5.38 Hz, 1 H) 6.00 (d, J=1.50 Hz, 1 H) 3.91 (s, 3 H) 2.96 - 3.04 (m, 1 H) 2.04 (s, 3 H) 1.34 - 1.41 (m, 1 H) 1.27 (d, J=6.88 Hz, 6 H) 0.85 - 0.97 (m, 4 H). MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₃₀O₄N₃F+H]⁺: 568.23, found: 568.3, t_R= 3.320 min.

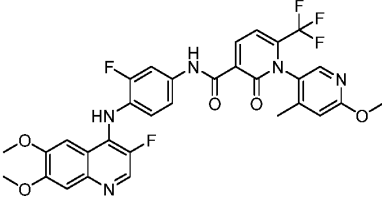
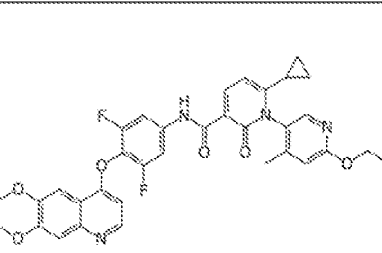
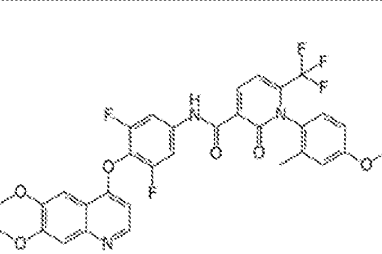
[1265] The following compounds in **TABLE 2** were referenced above or made following similar procedures as described above.

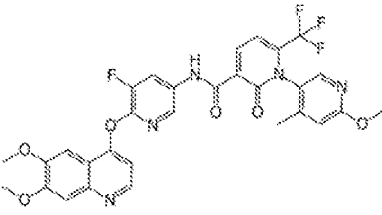
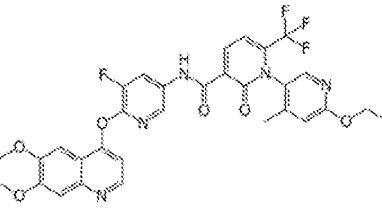
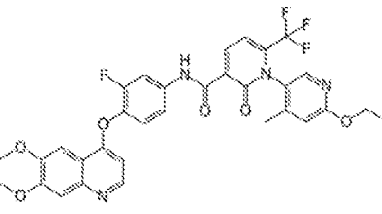
TABLE 2

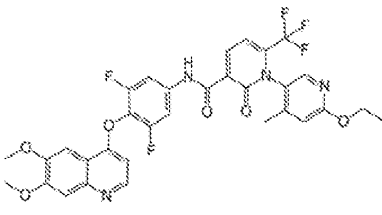
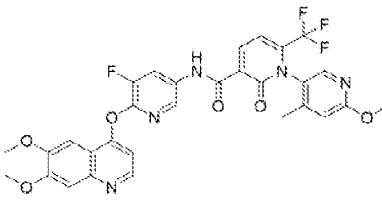
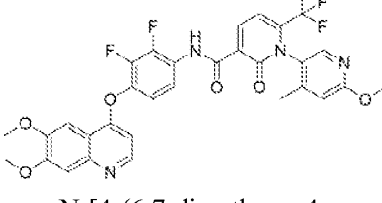
Ex. No.	STRUCTURE	H-NMR / LCMS:	Stereo Note	SOR ^c
A-1	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(5-cyano-4-ethoxy-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.03 (s, 1 H) 8.53 (d, J=5.38 Hz, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.06 (dd, J=13.01, 2.25 Hz, 1 H) 7.91 (s, 1 H) 7.56 (s, 1 H) 7.54 (dd, J=9.32, 1.81 Hz, 1 H) 7.43 - 7.48 (m, 1 H) 7.42 (s, 1 H) 7.40 (s, 1 H) 6.55 (br d, J=5.25 Hz, 1 H) 6.49 (d, J=7.88 Hz, 1 H) 4.24 - 4.32 (m, 2 H) 3.96 (d, J=2.63 Hz, 6 H) 2.11 (s, 3 H) 1.42 (t, J=6.94 Hz, 3 H) 1.30 - 1.37 (m, 1 H) 0.91 - 0.97 (m, 2 H) 0.84 - 0.90 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₆ H ₃₁ FN ₄ O ₆ +H] ⁺ : 635.22, found: 635.2, t _R = 3.158 min. [Method 1]	Racemic	NA
A-2	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.03 (s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.15 (s, 1 H) 8.05 (dd, J=13.01, 2.25 Hz, 1 H) 7.51 - 7.55 (m, 2 H) 7.39 - 7.46 (m, 2 H) 6.94 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.47 (d, J=5.25 Hz, 1 H) 4.31 - 4.40 (m, 2 H) 3.94 (d, J=1.63 Hz, 6 H) 2.04 (s, 3 H) 1.37 - 1.42 (m, 1 H) 1.37 (s, 3 H) 0.86 - 0.96 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₃₁ N ₄ O ₆ F+H] ⁺ : 611.22, found: 611.3, t _R = 3.285 min. [Method 1]	Racemic	NA

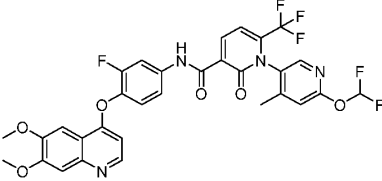
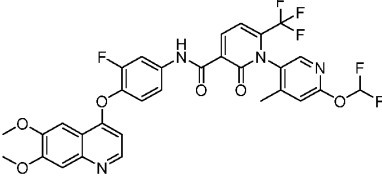
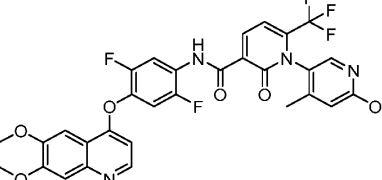
A-3	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.91 (s, 1 H) 8.53 (d, J=7.88 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.19 (d, J=6.25 Hz, 1 H) 8.04 (dd, J=13.01, 2.38 Hz, 1 H) 7.77 (d, J=10.13 Hz, 1 H) 7.50 - 7.55 (m, 2 H) 7.40 - 7.45 (m, 2 H) 6.53 (d, J=7.88 Hz, 1 H) 6.47 (dd, J=5.19, 0.94 Hz, 1 H) 3.95 (d, J=2.25 Hz, 6 H) 2.15 (s, 3 H) 1.35 (s, 1 H) 0.91 - 0.97 (m, 2 H) 0.86 (dd, J=8.38, 1.75 Hz, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₂₆ F ₂ N ₄ O ₅ +H] ⁺ : 609.18, found: 609.2, t _R = 3.054 min. [Method 1]	Racemic	NA
A-4	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 12.07 (s, 1 H) 8.68 (br d, J=5.88 Hz, 1 H) 8.52 (d, J=7.88 Hz, 1 H) 8.17 (s, 1 H) 8.09 (dd, J=13.01, 2.25 Hz, 1 H) 7.66 (s, 1 H) 7.55 - 7.60 (m, 1 H) 7.51 (d, J=8.88 Hz, 1 H) 7.47 (s, 1 H) 6.98 (s, 1 H) 6.77 (br d, J=5.00 Hz, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 4.00 (d, J=4.00 Hz, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.34 - 1.41 (m, 1 H) 0.92 - 0.97 (m, 2 H) 0.86 - 0.92 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ FN ₄ O ₆ +H] ⁺ : 597.20, found: 597.2, t _R = 3.088 min. [Method 2]	Racemic	NA
A-5	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.02 (s, 1 H) 8.51 (d, J=7.75 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.17 (s, 1 H) 8.04 (dd, J=13.01, 2.38 Hz, 1 H) 7.48 - 7.56 (m, 2 H) 7.40 (s, 2 H) 6.98 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.47 (d, J=5.13 Hz, 1 H) 3.94 (d, J=1.88 Hz, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.38 (s, 1 H) 0.91 - 0.97 (m, 2 H) 0.85 - 0.91 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ FN ₄ O ₆ +H] ⁺ : 597.20, found: 597.52, t _R = 1.995 min. [Method 2]	Atrop 1	22.0

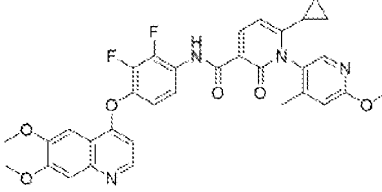
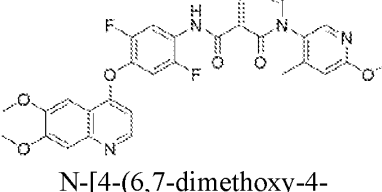
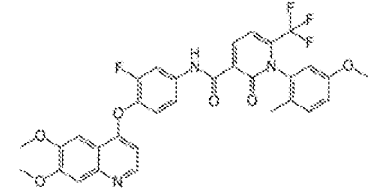
A-6	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.02 (s, 1 H) 8.49 - 8.54 (m, 1 H) 8.45 - 8.49 (m, 1 H) 8.17 (s, 1 H) 8.04 (dd, J=13.01, 2.38 Hz, 1 H) 7.49 - 7.56 (m, 2 H) 7.38 - 7.47 (m, 2 H) 6.98 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.44 - 6.48 (m, 1 H) 3.93 - 3.97 (m, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.38 (s, 1 H) 0.91 - 0.96 (m, 2 H) 0.85 - 0.91 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ FN ₄ O ₆ +H] ⁺ : 597.20, found: 597.3, <i>t</i> _R = 1.991 min. [Method 2]	Atrop 2	ND
A-7	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.12 (s, 1 H) 8.46 - 8.54 (m, 2 H) 8.18 (s, 1 H) 7.83 (d, J=10.26 Hz, 2 H) 7.53 (s, 1 H) 7.42 (s, 1 H) 6.98 (s, 1 H) 6.58 (d, J=5.25 Hz, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.95 (s, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.39 (s, 1 H) 0.85 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.19, found: 615.2, <i>t</i> _R = 2.095 min. [Method 1]	Racemic	NA
A-8	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.08 (s, 1 H) 8.56 (d, J=5.13 Hz, 1 H) 8.49 - 8.55 (m, 2 H) 8.41 (d, J=2.25 Hz, 1 H) 8.17 (s, 1 H) 7.42 (s, 1 H) 7.39 (s, 1 H) 6.97 (s, 1 H) 6.86 (d, J=5.13 Hz, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.95 (s, 3 H) 3.90 (d, J=2.88 Hz, 6 H) 2.04 (s, 3 H) 1.34 - 1.43 (m, 1 H) 0.93 - 0.98 (m, 2 H) 0.86 - 0.92 (m, 2 H); MS (ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ FN ₅ O ₆ +H] ⁺ : 598.20, found: 598.3, <i>t</i> _R = 1.966 min. [Method 1]	Racemic	NA

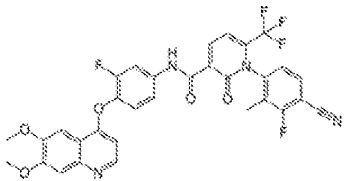
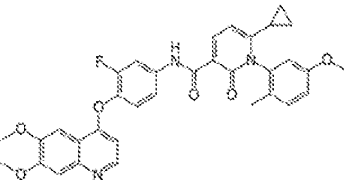
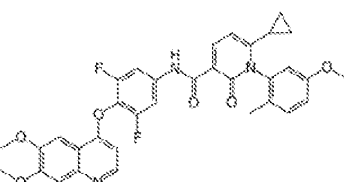
A-9	 N-[6-(3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-quinolylamino)phenyl]-6'-ethoxymethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 8.55 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.45, 2.19 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.11 (t, J=9.19 Hz, 1 H) 6.95 (s, 1 H) 3.91 (s, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 642.54, found: 642.2, t _R = 3.185 min. [Method 7]	Atrop 1	+5.96
A-10	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.12 (s, 1 H) 8.42 - 8.60 (m, 2 H) 8.15 (s, 1 H) 7.83 (d, J=10.26 Hz, 2 H) 7.54 (s, 1 H) 7.42 (s, 1 H) 6.94 (s, 1 H) 6.58 (d, J=5.13 Hz, 1 H) 6.51 (d, J=8.00 Hz, 1 H) 4.36 (br dd, J=7.00, 4.25 Hz, 2 H) 3.95 (s, 6 H) 2.04 (s, 3 H) 1.35 (t, J=7.00 Hz, 4 H) 0.82 - 1.00 (m, 4 H); MS (ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ F ₂ N ₄ O ₆ +H] ⁺ : 629.21, found: 629.3, t _R = 2.141 min. [Method 3]	Racemic	NA
A-11	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.90 (s, 1 H) 8.67 (d, J=7.50 Hz, 1 H) 8.50 (d, J=5.25 Hz, 1 H) 7.87 (d, J=10.01 Hz, 2 H) 7.53 (s, 1 H) 7.42 (s, 1 H) 7.36 (d, J=7.75 Hz, 1 H) 7.32 (d, J=8.88 Hz, 1 H) 7.01 (d, J=2.75 Hz, 1 H) 6.93 (dd, J=8.69, 2.81 Hz, 1 H) 6.58 (d, J=5.25 Hz, 1 H) 3.95 (s, 6 H) 3.82 (s, 3 H) 2.01 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₄ F ₃ N ₃ O ₆ +H] ⁺ : 642.15, found: 642.2, t _R = 2.257 min. [Method 1]	Racemic	NA

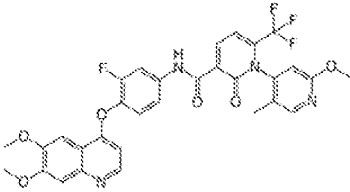
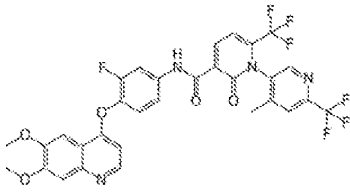
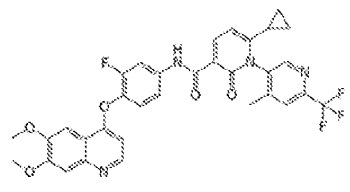
A-12	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.69 (s, 1 H) 8.68 (d, J=7.63 Hz, 1 H) 8.57 (d, J=5.25 Hz, 1 H) 8.52 (dd, J=11.63, 2.13 Hz, 1 H) 8.45 (d, J=2.25 Hz, 1 H) 8.20 (s, 1 H) 7.43 (s, 1 H) 7.40 (d, J=7.75 Hz, 1 H) 7.38 (s, 1 H) 6.95 (s, 1 H) 6.90 (d, J=5.13 Hz, 1 H) 3.95 (s, 3 H) 3.90 (d, J=4.75 Hz, 6 H) 2.05 (s, 3 H); MS (ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₃ F ₄ N ₅ O ₆ +H] ⁺ : 626.16, found: 626.1, t _R = 2.057 min. [Method 1]	Racemic	NA
A-13	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.70 (s, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.57 (d, J=5.25 Hz, 1 H) 8.52 (dd, J=11.69, 2.19 Hz, 1 H) 8.46 (d, J=2.25 Hz, 1 H) 8.17 (s, 1 H) 7.43 (s, 1 H) 7.36 - 7.41 (m, 2 H) 6.87 - 6.95 (m, 2 H) 4.29 - 4.40 (m, 2 H) 3.95 (s, 3 H) 3.87 - 3.89 (m, 1 H) 3.89 (s, 3 H) 2.05 (s, 3 H) 1.34 (t, J=7.00 Hz, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₅ F ₄ N ₅ O ₆ +H] ⁺ : 640.17, found: 640.2, t _R = 3.298 min. [Method 1]	Racemic	NA
A-14	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.66 (s, 1 H) 8.67 (d, J=7.63 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.18 (s, 1 H) 8.05 (dd, J=12.82, 2.31 Hz, 1 H) 7.59 (s, 1 H) 7.52 (s, 1 H) 7.44 - 7.49 (m, 1 H) 7.37 - 7.42 (m, 2 H) 6.92 (s, 1 H) 6.47 (d, J=5.13 Hz, 1 H) 4.35 (br dd, J=7.00, 2.88 Hz, 2 H) 3.95 (d, J=2.00 Hz, 6 H) 2.05 (s, 3 H) 1.34 (t, J=7.07 Hz, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ N ₄ O ₆ F ₄ +H] ⁺ : 639.27, found: 639.2, t _R = 3.397 min. [Method 3]	Racemic	NA

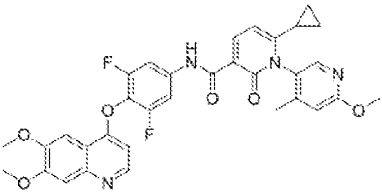
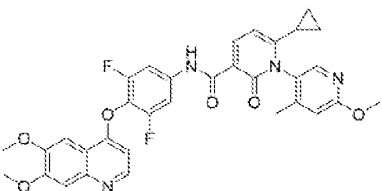
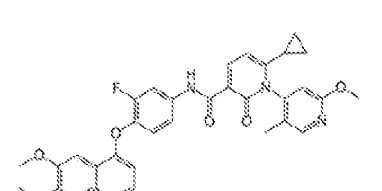
A-15	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.75 (s, 1 H) 8.68 (d, <i>J</i> =7.63 Hz, 1 H) 8.50 (d, <i>J</i> =5.25 Hz, 1 H) 8.19 (s, 1 H) 7.88 (d, <i>J</i> =10.01 Hz, 2 H) 7.54 (s, 1 H) 7.35 - 7.45 (m, 2 H) 6.93 (s, 1 H) 6.59 (d, <i>J</i> =5.13 Hz, 1 H) 4.36 (br dd, <i>J</i> =7.07, 2.69 Hz, 2 H) 3.96 (s, 6 H) 2.06 (s, 3 H) 1.35 (t, <i>J</i> =7.00 Hz, 3 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 657.16, found: 657.3, <i>t</i> _R = 2.264 min. [Method 1]	Racemic	NA
A-16	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.70 (s, 1 H) 8.68 (d, <i>J</i> =7.63 Hz, 1 H) 8.57 (d, <i>J</i> =5.13 Hz, 1 H) 8.52 (dd, <i>J</i> =11.63, 2.25 Hz, 1 H) 8.45 (d, <i>J</i> =2.25 Hz, 1 H) 8.20 (s, 1 H) 7.43 (s, 1 H) 7.40 (d, <i>J</i> =7.63 Hz, 1 H) 7.38 (s, 1 H) 6.95 (s, 1 H) 6.90 (d, <i>J</i> =5.13 Hz, 1 H) 3.95 (s, 3 H) 3.90 (d, <i>J</i> =4.25 Hz, 6 H) 2.05 (s, 3 H); MS (ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₃ F ₄ N ₅ O ₆ +H] ⁺ : 626.16, found: 626.3, <i>t</i> _R = 2.023 min. [Method 1]	Atrop 1	ND
A-17	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-2,3-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) =12.03 (s, 1H), 8.73 (d, <i>J</i> = 7.6 Hz, 1H), 8.50 (d, <i>J</i> = 5.2 Hz, 1H), 8.34 (t, <i>J</i> = 10 Hz, 1H), 8.21 (s, 1H), 7.51 (s, 1H), 7.42 (m, 2H), 7.35 (t, <i>J</i> = 10 Hz, 1H), 6.96 (s, 1H), 6.62 (d, <i>J</i> = 4.8 Hz, 1H), , , 3.95 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H), 2.05 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₃ F ₅ N ₄ O] ⁺ : 642.54, found: 643.48 , <i>t</i> _R = 3.92 min. [Method 1]	Atrop 1	ND

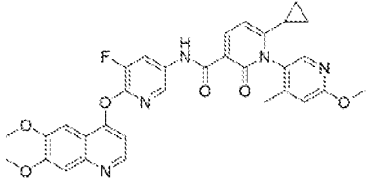
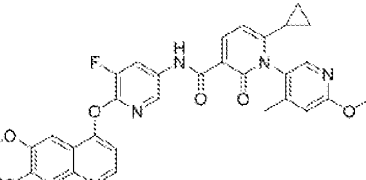
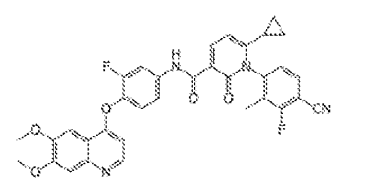
A-18	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.61 (s, 1H), 8.69 (d, <i>J</i> = 7.6 Hz, 1H), 8.48 (d, <i>J</i> = 5.2 Hz, 1H), 8.38 (s, 1H), 8.04 (dd, <i>J</i> = 12.8 Hz, <i>J</i> = 12.8 Hz, 1H), 7.97-7.59 (m, 2H), 7.52-7.41 (m, 4H), 7.28 (s, 1H), 6.51 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.15 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₂ F ₆ N ₄ O ₆ +H] ⁺ : 660.53, found: 661.41, <i>t_R</i> = 4.05 min. [Method 2]	Atrop 1	+53.92
A-19	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.61 (s, 1H), 8.69 (d, <i>J</i> = 7.6 Hz, 1H), 8.48 (d, <i>J</i> = 5.2 Hz, 1H), 8.38 (s, 1H), 8.04 (dd, <i>J</i> = 12.8 Hz, <i>J</i> = 12.8 Hz, 1H), 7.97-7.59 (m, 2H), 7.52-7.41 (m, 4H), 7.28 (s, 1H), 6.51 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.15 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₂ F ₆ N ₄ O ₆ +H] ⁺ : 660.53, found: 661.41, <i>t_R</i> = 4.10 min. [Method 1]	Atrop 2	-62.96
A-20	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-2,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm = 12.15 - 11.95 (m, 1H), 8.77 - 8.70 (m, 1H), 8.60 - 8.52 (m, 1H), 8.52 - 8.47 (m, 1H), 8.25 - 8.18 (m, 1H), 7.76 - 7.67 (m, 1H), 7.53 - 7.49 (m, 1H), 7.46 - 7.40 (m, 2H), 6.98 - 6.94 (m, 1H), 6.62 - 6.56 (m, 1H), 3.99 - 3.88 (m, 9H), 2.08 - 2.01 (m, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ FN ₅ O ₆ +H] ⁺ : 642.1, found: 643.3, <i>t_R</i> = 4.95 min. [Method 1]	Atrop 1	+12.8

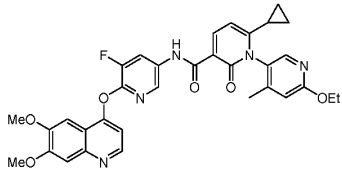
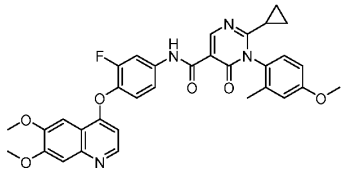
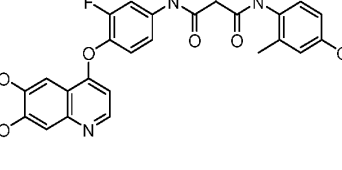
A-21	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-2,3-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.28 (s, 1H), 8.53 (d, <i>J</i> = 7.9 Hz, 1H), 8.51 - 8.48 (m, 1H), 8.41 - 8.36 (m, 1H), 8.18 (s, 1H), 7.52 (s, 1H), 7.42 (s, 1H), 7.36 - 7.30 (m, 1H), 6.99 (s, 1H), 6.61 (d, <i>J</i> = 5.1 Hz, 1H), 6.52 (d, <i>J</i> = 7.9 Hz, 1H), 3.95 (d, <i>J</i> = 3.1 Hz, 6H), 3.92 (s, 3H), 2.04 (s, 3H), 1.41 - 1.34 (m, 1H), 0.98 - 0.87 (m, 4H); MS(ES+) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ F ₆ N ₃ O ₆] ⁺ : 615.1, found: 615.43 <i>t</i> _R = 3.84 min. [Method 1]	Atrop 1	+26.08
A-22	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-2,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 12.34 (s, 1 H), 8.63-8.58 (m, 1 H), 8.54 (d, <i>J</i> =2 Hz, 1 H), 8.50 (d, <i>J</i> =5.2 Hz, 1 H), 8.18 (s, 1 H), 7.72- 7.67 (m, 2 H), 7.51 (s, 1 H), 7.42 (s, 1 H), 6.99 (s, 1 H), 6.87 (d, <i>J</i> = 4.8 Hz, 1 H), 6.53 (d, <i>J</i> = 7.6 Hz, 1 H), 3.95 (s, 3 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 1.99 (s, 3 H); MS(ES+) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.0, found: 615.1, <i>t</i> _R = 4.06 min. [Method 1]	Atrop 1	-5.84
A-23	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(5-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.78 (s, 1 H) 8.68 (d, <i>J</i> =7.50 Hz, 1 H) 8.48 (d, <i>J</i> =5.25 Hz, 1 H) 8.05 (dd, <i>J</i> =12.88, 2.38 Hz, 1 H) 7.61 (dd, <i>J</i> =8.88, 1.25 Hz, 1 H) 7.52 (s, 1 H) 7.46 (t, <i>J</i> =8.94 Hz, 1 H) 7.41 (s, 1 H) 7.37 (d, <i>J</i> =7.63 Hz, 1 H) 7.34 (d, <i>J</i> =8.50 Hz, 1 H) 7.09 (s, 1 H) 7.03 - 7.07 (m, 1 H) 6.47 (dd, <i>J</i> =5.19, 0.81 Hz, 1 H) 3.94 (d, <i>J</i> =2.50 Hz, 6 H) 3.75 (s, 3 H) 1.96 (s, 3 H); MS(ES+) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₅ F ₄ N ₃ O ₆ +H] ⁺ : 624.17, found: 624.3, <i>t</i> _R = 2.183 min. [Method 1]	Racemic	NA

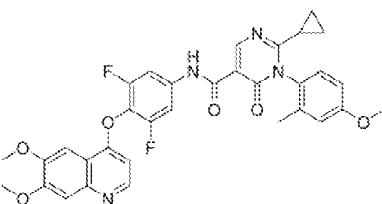
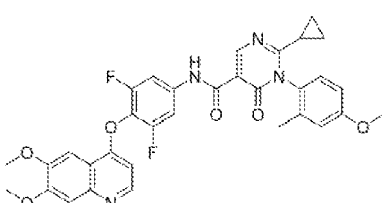
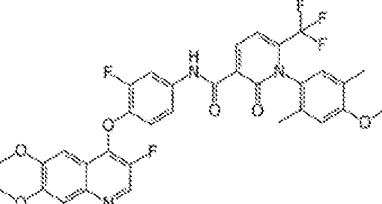
A-24	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(4-cyano-3-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.51 (s, 1 H) 8.69 (d, J=7.50 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 7.99 - 8.13 (m, 2 H) 7.67 (d, J=8.38 Hz, 1 H) 7.58 (br d, J=1.38 Hz, 1 H) 7.52 (s, 1 H) 7.45 (s, 2 H) 7.41 (s, 1 H) 6.47 (d, J=5.25 Hz, 1 H) 3.94 (d, J=2.63 Hz, 6 H) 2.07 (d, J=1.50 Hz, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ N ₄ O ₅ F ₅ +H] ⁺ : 637.14, found: 637.2, t _R = 3.290 min. [Method 1]	Racemic	NA
A-25	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-1-(5-methoxy-2-tolyl)-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.15 (s, 1 H) 8.46 - 8.52 (m, 2 H) 8.05 (dd, J=13.01, 2.38 Hz, 1 H) 7.50 - 7.56 (m, 2 H) 7.36 - 7.45 (m, 3 H) 7.00 - 7.05 (m, 2 H) 6.43 - 6.49 (m, 2 H) 3.94 (d, J=1.88 Hz, 6 H) 3.77 (s, 3 H) 1.96 (s, 3 H) 1.30 - 1.39 (m, 1 H) 0.86 - 0.98 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ FN ₃ O ₆ +H] ⁺ : 596.21, found: 596.4, t _R = 2.104 min. [Method 1]	Racemic	NA
A-26	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6-cyclopropyl-1-(5-methoxy-2-tolyl)-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.25 (s, 1 H) 8.50 (d, J=1.25 Hz, 1 H) 8.49 (s, 1 H) 7.78 - 7.87 (m, 2 H) 7.53 (s, 1 H) 7.42 (s, 1 H) 7.36 - 7.40 (m, 1 H) 7.00 - 7.05 (m, 2 H) 6.58 (d, J=5.25 Hz, 1 H) 6.45 (d, J=8.00 Hz, 1 H) 3.95 (s, 6 H) 3.77 (s, 3 H) 1.96 (s, 3 H) 1.32 - 1.40 (m, 1 H) 0.88 - 1.01 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₂₉ F ₂ N ₃ O ₆ +H] ⁺ : 614.20, found: 614.2, t _R = 2.178 min. [Method 1]	Racemic	NA

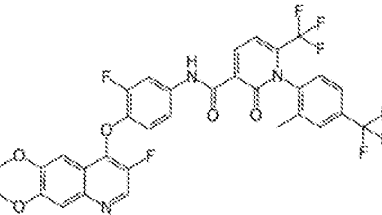
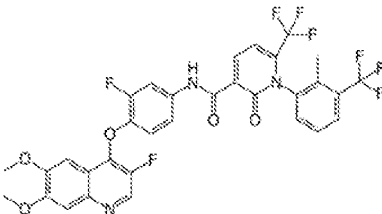
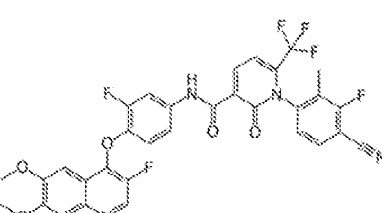
A-27	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-2'-methoxy-5'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,4'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.60 (s, 1 H) 8.68 (d, J=7.38 Hz, 1 H) 8.48 (d, J=5.13 Hz, 1 H) 8.27 (s, 1 H) 8.04 (dd, J=12.76, 2.38 Hz, 1 H) 7.61 (d, J=8.88 Hz, 1 H) 7.52 (s, 1 H) 7.46 (t, J=8.94 Hz, 1 H) 7.37 - 7.43 (m, 2 H) 7.11 (s, 1 H) 6.47 (d, J=5.25 Hz, 1 H) 3.92 - 3.96 (m, 6 H) 3.90 (s, 3 H) 1.98 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ F ₄ N ₄ O ₆ +H] ⁺ : 625.16, found: 625.3, t _R = 2.070 min. [Method 1]	Racemic	NA
A-28	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-4'-methyl-2-oxo-6,6'-bis(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.49 (s, 1 H) 8.89 (s, 1 H) 8.71 (d, J=7.50 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.19 (s, 1 H) 8.04 (dd, J=12.82, 2.31 Hz, 1 H) 7.61 (dd, J=9.07, 1.19 Hz, 1 H) 7.52 (s, 1 H) 7.43 - 7.49 (m, 2 H) 7.41 (s, 1 H) 6.47 (d, J=5.13 Hz, 1 H) 3.95 (d, J=2.63 Hz, 6 H) 2.28 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₁ N ₄ O ₅ F ₇ +H] ⁺ : 663.14, found: 663.2, t _R = 3.329. [Method 1]	Racemic	NA
A-29	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-4'-methyl-2-oxo-6'-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.84 (s, 1 H) 8.85 (s, 1 H) 8.56 (d, J=7.75 Hz, 1 H) 8.48 (d, J=5.13 Hz, 1 H) 8.18 (s, 1 H) 8.04 (dd, J=13.01, 2.38 Hz, 1 H) 7.50 - 7.56 (m, 2 H) 7.39 - 7.46 (m, 2 H) 6.59 (d, J=7.88 Hz, 1 H) 6.46 (d, J=5.00 Hz, 1 H) 3.94 (d, J=2.38 Hz, 6 H) 2.25 (s, 3 H) 1.34 (s, 1 H) 0.96 (br d, J=4.88 Hz, 2 H) 0.80 - 0.89 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₆ N ₄ O ₅ F ₄ +H] ⁺ : 635.18, found: 635.2, t _R = 3.245 min. [Method 1]	Racemic	NA

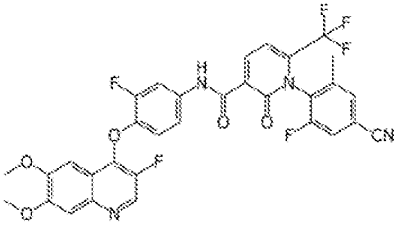
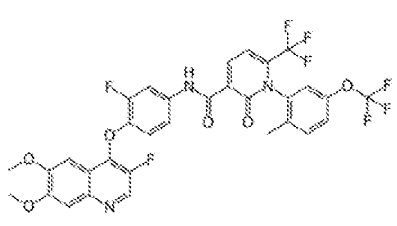
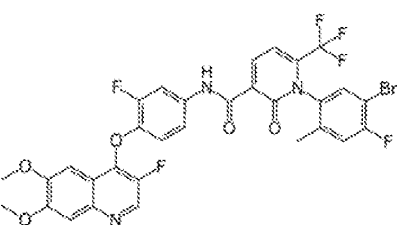
A-30	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 12.12 (s, 1 H) 8.44 - 8.58 (m, 2 H) 8.18 (s, 1 H) 7.83 (d, J=10.13 Hz, 2 H) 7.53 (s, 1 H) 7.42 (s, 1 H) 6.98 (s, 1 H) 6.58 (d, J=5.13 Hz, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.95 (s, 6 H) 3.88 - 3.92 (m, 3 H) 2.04 (s, 3 H) 1.38 (s, 1 H) 0.82 - 1.00 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.19, found: 615.2, t _R = 3.228 min., Chiral HPLC purity: 100%, t _R = 0.806, ee= 100% [Method 2]	Atrop 1	-2.45
A-31	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 12.12 (s, 1 H) 8.41 - 8.61 (m, 2 H) 8.18 (s, 1 H) 7.83 (d, J=10.13 Hz, 2 H) 7.53 (s, 1 H) 7.42 (s, 1 H) 6.98 (s, 1 H) 6.58 (d, J=5.25 Hz, 1 H) 6.45 - 6.54 (m, 1 H) 3.95 (s, 6 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.31 - 1.43 (m, 1 H) 0.86 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.19, found: 615.2, t _R = 3.234 min., Chiral HPLC purity: 100%, t _R = 1.566, ee= 100%. [Method 2]	Atrop 2	+0.33
A-32	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6-cyclopropyl-2'-methoxy-5'-methyl-2-oxo-1,2-dihydro[1,4'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.95 (s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.48 (d, J=5.25 Hz, 1 H) 8.30 (s, 1 H) 8.04 (dd, J=13.01, 2.38 Hz, 1 H) 7.50 - 7.56 (m, 2 H) 7.39 - 7.46 (m, 2 H) 7.07 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.47 (d, J=5.13 Hz, 1 H) 3.95 (d, J=2.13 Hz, 6 H) 3.91 (s, 3 H) 1.97 (s, 3 H) 1.32 - 1.41 (m, 1 H) 0.92 - 0.99 (m, 2 H) 0.87 - 0.92 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₃ H ₂₉ FN ₄ O ₆ +H] ⁺ : 597.20, found: 597.2, t _R = 3.146 min. [Method 1]	Racemic	NA

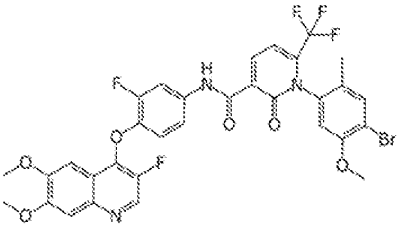
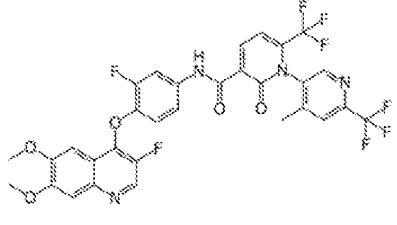
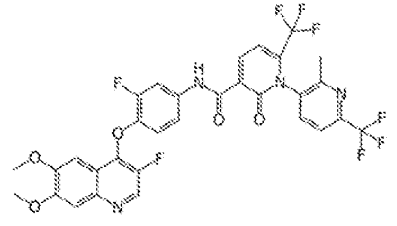
A-33	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.07 (s, 1 H) 8.55 - 8.59 (m, 1 H) 8.49 - 8.55 (m, 2 H) 8.41 (d, J=1.50 Hz, 1 H) 8.17 (s, 1 H) 7.42 (s, 1 H) 7.39 (s, 1 H) 6.97 (s, 1 H) 6.86 (d, J=5.13 Hz, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 3.95 (s, 3 H) 3.90 (d, J=3.25 Hz, 6 H) 2.04 (s, 3 H) 1.29 - 1.42 (m, 1 H) 0.84 - 1.01 (m, 4 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ FN ₅ O ₆ +H] ⁺ : 598.20, found: 598.3, t _R = 1.969 min, Chiral HPLC purity: 100%, t _R = 1.285, ee= 100%. [Method 2]	Atrop 2	NA
A-34	 N-[6-(6,7-dimethoxy-4-quinolyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.07 (s, 1 H) 8.57 (d, J=5.13 Hz, 1 H) 8.49 - 8.56 (m, 2 H) 8.42 (d, J=1.63 Hz, 1 H) 8.17 (s, 1 H) 7.43 (s, 1 H) 7.40 (s, 1 H) 6.97 (s, 1 H) 6.88 (d, J=5.13 Hz, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 3.95 (s, 3 H) 3.90 (s, 6 H) 2.04 (s, 3 H) 1.33 - 1.43 (m, 1 H) 0.84 - 1.00 (m, 4 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ FN ₅ O ₆ +H] ⁺ : 598.20, found: 598.4, t _R = 1.952 min, Chiral HPLC purity: 99.76%, t _R = 1.497, ee= 99.52%. [Method 2]	Atrop 1	NA
A-35	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(4-cyano-3-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.86 (s, 1 H) 8.53 (d, J=7.88 Hz, 1 H) 8.48 (br d, J=5.25 Hz, 1 H) 8.00 - 8.09 (m, 2 H) 7.61 (br d, J=8.38 Hz, 1 H) 7.52 (br s, 2 H) 7.38 - 7.46 (m, 2 H) 6.54 (br d, J=7.88 Hz, 1 H) 6.46 (br d, J=4.38 Hz, 1 H) 3.92 - 3.97 (m, 6 H) 2.04 (s, 3 H) 1.29 - 1.38 (m, 1 H) 0.90 - 0.96 (m, 2 H) 0.79 - 0.89 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₂₆ N ₄ O ₅ F ₂ +H] ⁺ : 609.19, found: 609.3, t _R = 2.089 min. [Method 1]	Racemic	NA

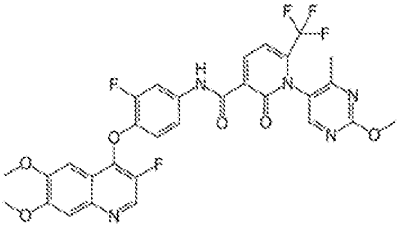
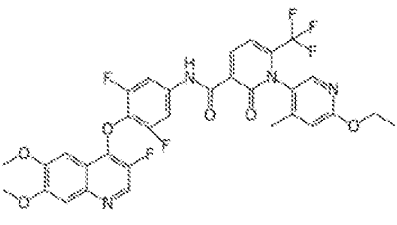
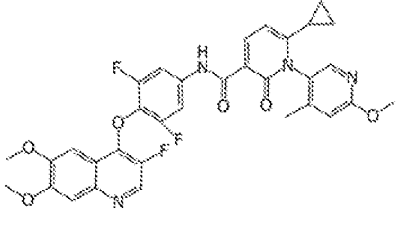
A-36	 6-cyclopropyl-N-[6-[(6,7-dimethoxy-4-quinolyl)oxy]-5-fluoro-3-pyridyl]-1-(6-ethoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.07 (s, 1 H) 8.56 (d, J=5.13 Hz, 1 H) 8.53 - 8.53 (m, 1 H) 8.49 - 8.55 (m, 1 H) 8.41 (d, J=2.25 Hz, 1 H) 8.14 (s, 1 H) 7.42 (s, 1 H) 7.39 (s, 1 H) 6.94 (s, 1 H) 6.86 (d, J=5.13 Hz, 1 H) 6.50 (d, J=8.00 Hz, 1 H) 4.35 (qd, J=7.09, 3.63 Hz, 2 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 2.03 (s, 3 H) 1.30 - 1.40 (m, 4 H) 0.92 - 0.99 (m, 2 H) 0.83 - 0.92 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C33H30FN5O6+H] ⁺ : 612.22, found: 612.3, t _R = 2.054 min. [Method 1]	Racemic	NA
A-37	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.33 (s, 1 H) 8.82 (s, 1 H) 8.48 (d, J=5.13 Hz, 1 H) 8.03 (dd, J=12.82, 2.06 Hz, 1 H) 7.52 - 7.56 (m, 2 H) 7.44 - 7.48 (m, 1 H) 7.38 - 7.43 (m, 2 H) 7.09 (d, J=2.38 Hz, 1 H) 7.01 (dd, J=8.69, 2.69 Hz, 1 H) 6.47 (d, J=5.13 Hz, 1 H) 3.95 (s, J=1.75 Hz, 6 H) 3.84 (s, 3 H) 2.08 (s, 3 H) 1.47 (td, J=8.00, 4.00 Hz, 1 H) 1.20 - 1.28 (m, 2 H) 1.03 - 1.10 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C33H29FN4O6+H] ⁺ : 597.4, found: 597.41, t _R = 4.66 min. [Method 1]	Atrop 1	+6.0
A-38	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.33 (s, 1 H) 8.82 (s, 1 H) 8.48 (d, J=5.13 Hz, 1 H) 8.03 (dd, J=12.88, 2.13 Hz, 1 H) 7.51 - 7.57 (m, 2 H) 7.37 - 7.47 (m, 3 H) 7.09 (d, J=2.50 Hz, 1 H) 7.01 (dd, J=8.76, 2.75 Hz, 1 H) 6.47 (d, J=5.00 Hz, 1 H) 3.95 (s, 6 H) 3.84 (s, 3 H) 2.08 (s, 3 H) 1.47 (td, J=7.85, 4.19 Hz, 1 H) 1.19 - 1.28 (m, 2 H) 1.02 - 1.13 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C33H29FN4O6+H] ⁺ : 597.4, found: 597.41, t _R = 4.65 min. [Method 1]	Atrop 2	-22.64

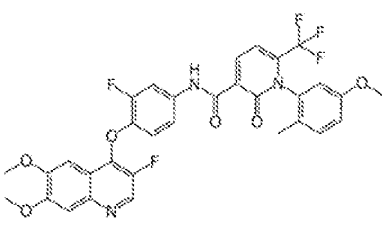
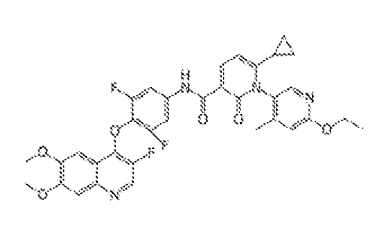
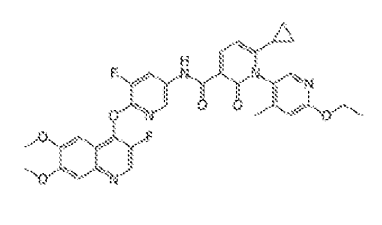
A-39	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.41 (s, 1 H) 8.82 (s, 1 H) 8.50 (d, <i>J</i> =5.25 Hz, 1 H) 7.83 (br d, <i>J</i> =10.26 Hz, 2 H) 7.54 (s, 1 H) 7.42 (s, 1 H) 7.37 - 7.41 (m, 1 H) 7.05 - 7.12 (m, 1 H) 6.97 - 7.05 (m, 1 H) 6.58 (d, <i>J</i> =5.13 Hz, 1 H) 3.95 (s, 6 H) 3.83 (s, 3 H) 2.08 (s, 3 H) 1.42 - 1.54 (m, 1 H) 1.19 - 1.29 (m, 2 H) 1.00 - 1.15 (m, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.1, found :615.2, t _R = 6.05 min. [Method 1]	Atrop 1	+23.76
A-40	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.41 (s, 1 H) 8.82 (s, 1 H) 8.51 (d, <i>J</i> =5.25 Hz, 1 H) 7.83 (br d, <i>J</i> =10.26 Hz, 2 H) 7.54 (s, 1 H) 7.43 (s, 1 H) 7.39 (d, <i>J</i> =8.76 Hz, 1 H) 7.09 (d, <i>J</i> =2.38 Hz, 1 H) 7.01 (dd, <i>J</i> =8.69, 2.56 Hz, 1 H) 6.60 (br d, <i>J</i> =5.00 Hz, 1 H) 3.96 (s, 6 H) 3.83 (s, 3 H) 2.08 (s, 3 H) 1.44 - 1.52 (m, 1 H) 1.20 - 1.29 (m, 2 H) 1.03 - 1.11 (m, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.1, found :615.2, t _R = 6.05 min. [Method 1]	Atrop 2	-33.04
A-41	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-methoxy-2,5-xylyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.73 (s, 1 H) 8.76 (d, <i>J</i> =2.88 Hz, 1 H) 8.64 (d, <i>J</i> =7.63 Hz, 1 H) 7.99 (dd, <i>J</i> =13.20, 2.44 Hz, 1 H) 7.47 (s, 1 H) 7.36 - 7.41 (m, 1 H) 7.31 - 7.35 (m, 2 H) 7.13 (s, 1 H) 7.07 - 7.12 (m, 1 H) 6.98 (s, 1 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 3.86 (s, 3 H) 2.13 (s, 3 H) 1.99 (s, 3 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₆ F ₃ N ₃ O ₆ +H] ⁺ : 656.14, found: 656.2, t _R = 3.578 min. [Method 3]	Racemic	NA

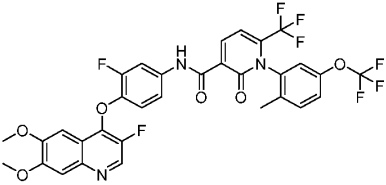
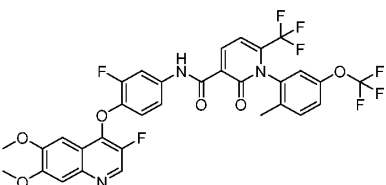
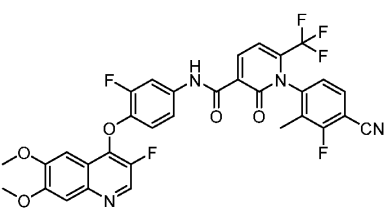
A-42	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-oxo-6-(trifluoromethyl)-1-[4-(trifluoromethyl)-2-tolyl]-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.54 (s, 1 H) 8.76 (d, <i>J</i> =2.88 Hz, 1 H) 8.68 (d, <i>J</i> =7.50 Hz, 1 H) 7.99 (dd, <i>J</i> =13.13, 2.50 Hz, 1 H) 7.90 (s, 1 H) 7.78 - 7.83 (m, 1 H) 7.70 - 7.74 (m, 1 H) 7.46 (s, 1 H) 7.38 - 7.43 (m, 2 H) 7.32 (s, 1 H) 7.09 (t, <i>J</i> =9.13 Hz, 1 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 2.15 (s, 3 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ F ₈ N ₃ O ₅ +H] ⁺ : 680.14, found: 680.1, <i>t</i> _R = 3.589 min. [Method 3]	Racemic	NA
A-43	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-oxo-6-(trifluoromethyl)-1-[3-(trifluoromethyl)-2-tolyl]-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.13 (s, 1H), 8.62 - 8.58 (m, 1H), 8.48 (d, <i>J</i> = 5.3 Hz, 1H), 8.16 - 8.13 (m, 1H), 8.08 - 8.03 (m, 1H), 7.64 - 7.59 (m, 2H), 7.55 - 7.51 (m, 2H), 7.47 - 7.41 (m, 4H), 6.74 (t, <i>J</i> = 7.0 Hz, 1H), 6.48 (d, <i>J</i> = 4.6 Hz, 1H), 3.95 (d, <i>J</i> = 1.5 Hz, 6H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ N ₃ O ₅ F ₈ +H] ⁺ : 679.5, found: 680.2, <i>t</i> _R = 3.597 min. [Method 3]	Racemic	NA
A-44	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-cyano-3-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.41 (s, 1 H) 8.75 (d, <i>J</i> =2.88 Hz, 1 H) 8.66 (d, <i>J</i> =7.50 Hz, 1 H) 8.05 (t, <i>J</i> =7.63 Hz, 1 H) 7.98 (dd, <i>J</i> =13.20, 2.31 Hz, 1 H) 7.65 (d, <i>J</i> =8.38 Hz, 1 H) 7.46 (s, 1 H) 7.42 (d, <i>J</i> =7.75 Hz, 1 H) 7.38 (br d, <i>J</i> =9.13 Hz, 1 H) 7.31 (s, 1 H) 7.09 (t, <i>J</i> =9.13 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.06 (s, 3 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₀ N ₄ O ₅ F ₆ +H] ⁺ : 654.5, found: 655.2, <i>t</i> _R = 3.377 min. [Method 3]	Racemic	NA

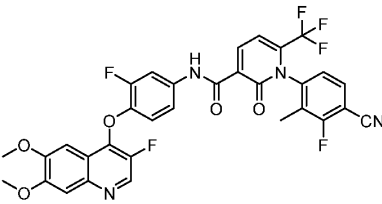
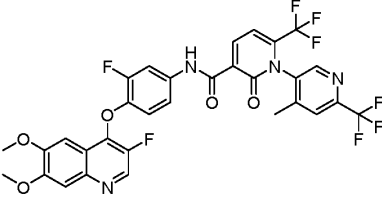
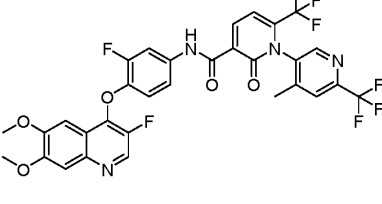
A-45	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-cyano-2-fluoro-6-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.21 (s, 1 H) 8.75 (d, J=2.88 Hz, 1 H) 8.66 (d, J=7.50 Hz, 1 H) 8.09 (d, J=9.13 Hz, 1 H) 7.92 - 7.99 (m, 2 H) 7.44 - 7.51 (m, 2 H) 7.36 - 7.42 (m, 1 H) 7.31 (s, 1 H) 7.10 (t, J=9.07 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.17 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₀ F ₆ N ₄ O ₅ +H] ⁺ : 655.13, found: 655.2, t _R = 3.390 min. [Method 3]	Racemic	NA
A-46	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-oxo-1-(5-trifluoromethoxy-2-tolyl)-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.57 (s, 1 H) 8.75 (d, J=2.75 Hz, 1 H) 8.66 (d, J=7.63 Hz, 1 H) 7.99 (dd, J=13.20, 2.31 Hz, 1 H) 7.66 (br s, 1 H) 7.56 - 7.61 (m, 1 H) 7.52 (s, 1 H) 7.46 (s, 1 H) 7.36 - 7.44 (m, 2 H) 7.31 (s, 1 H) 7.09 (s, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.06 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ F ₈ N ₃ O ₆ +H] ⁺ : 696.13, found: 696.2, t _R = 2.752 min. [Method 3]	Racemic	NA
A-47	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-bromo-4-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.54 (s, 1 H) 8.75 (d, J=3.00 Hz, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 7.93 - 8.03 (m, 2 H) 7.56 (d, J=9.51 Hz, 1 H) 7.46 (s, 1 H) 7.36 - 7.42 (m, 2 H) 7.32 (s, 1 H) 7.09 (t, J=9.13 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.03 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₀ N ₃ O ₅ F ₆ Br+H] ⁺ : 708.05, found: 708.1/710.0, t _R = 3.595 min. [Method 3]	Racemic	NA

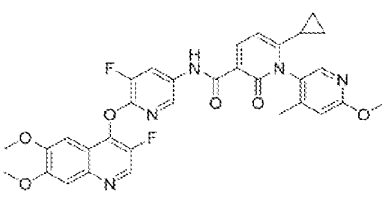
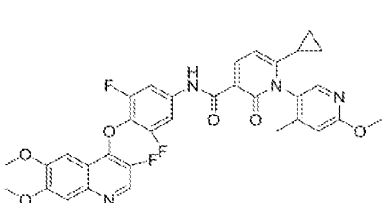
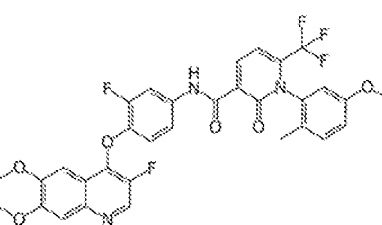
A-48	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-bromo-5-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.63 (s, 1 H) 8.75 (d, J=2.75 Hz, 1 H) 8.66 (d, J=7.63 Hz, 1 H) 7.99 (dd, J=13.13, 2.38 Hz, 1 H) 7.70 (s, 1 H) 7.46 (s, 1 H) 7.36 - 7.41 (m, 2 H) 7.33 - 7.35 (m, 1 H) 7.32 (s, 1 H) 7.10 (t, J=9.13 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 3.78 (s, 3 H) 1.96 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ N ₃ O ₆ F ₅ Br+H] ⁺ : 719.1& 721.1, found: 720.1& 722.0, t _R = 3.590 min. [Method 3]	Racemic	NA
A-49	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-4'-methyl-2-oxo-6,6'-bis(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.39 (s, 1 H) 8.87 (s, 1 H) 8.75 (d, J=2.88 Hz, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.98 (dd, J=13.20, 2.44 Hz, 1 H) 7.42 - 7.49 (m, 2 H) 7.37 - 7.41 (m, 1 H) 7.31 (s, 1 H) 7.04 - 7.13 (m, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.26 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₀ N ₃ O ₅ F ₆ Br+H] ⁺ : 681.13, found: 681.1, t _R = 3.415 min. [Method 3]	Racemic	NA
A-50	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2'-methyl-2-oxo-6,6'-bis(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.41 (s, 1 H) 8.75 (d, J=2.88 Hz, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.31 (d, J=8.00 Hz, 1 H) 8.06 (d, J=8.13 Hz, 1 H) 7.98 (dd, J=13.19, 2.44 Hz, 1 H) 7.43 - 7.47 (m, 2 H) 7.37 - 7.42 (m, 1 H) 7.31 (s, 1 H) 7.10 (t, J=9.19 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.37 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₀ F ₈ N ₄ O ₅ +H] ⁺ : 681.13, found: 681.2, t _R = 2.579 min. [Method 3]	Racemic	NA

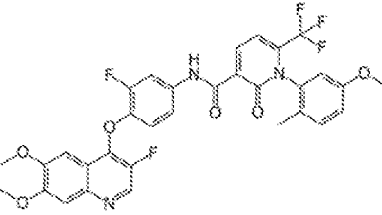
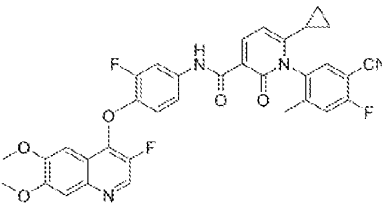
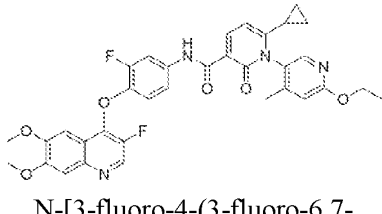
A-51	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(2-methoxy-4-methyl-5-pyrimidinyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.44 (s, 1 H) 8.75 (d, J=2.88 Hz, 1 H) 8.68 (s, 1 H) 8.65 (d, J=7.50 Hz, 1 H) 7.98 (dd, J=13.13, 2.50 Hz, 1 H) 7.46 (s, 1 H) 7.42 (d, J=7.88 Hz, 1 H) 7.38 (br d, J=1.13 Hz, 1 H) 7.32 (s, 1 H) 7.10 (t, J=9.13 Hz, 1 H) 3.99 (s, 3 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 2.24 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₀ H ₂₂ F ₅ N ₅ O ₆ +H] ⁺ : 644.14, found: 644.3, t _R = 2.330 min. [Method 3]	Racemic	NA
A-52	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 11.68 (s, 1 H) 8.68 (d, J=3.50 Hz, 1 H) 8.65 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.78 (d, J=10.38 Hz, 2 H) 7.49 (s, 1 H) 7.44 (s, 1 H) 7.39 (d, J=7.63 Hz, 1 H) 6.91 (s, 1 H) 4.35 (br dd, J=7.00, 2.63 Hz, 2 H) 3.94 (d, J=3.38 Hz, 6 H) 2.04 (s, 3 H) 1.34 (t, J=7.00 Hz, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₂ H ₂₄ F ₆ N ₄ O ₆ +H] ⁺ : 675.16, found: 675.2, t _R = 3.557 min. [Method 3]	Racemic	NA
A-53	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.05 (s, 1 H) 8.68 (d, J=3.63 Hz, 1 H) 8.49 (d, J=7.88 Hz, 1 H) 8.17 (s, 1 H) 7.74 (d, J=10.51 Hz, 2 H) 7.49 (s, 1 H) 7.43 (s, 1 H) 6.97 (s, 1 H) 6.50 (d, J=8.00 Hz, 1 H) 3.94 (d, J=3.38 Hz, 6 H) 3.90 (s, 3 H) 2.03 (s, 3 H) 1.34 - 1.41 (m, 1 H) 0.92 - 0.97 (m, 2 H) 0.86 - 0.91 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ : [C ₃₃ H ₂₇ F ₃ N ₄ O ₆ +H] ⁺ : 633.19, found: 633.3, t _R = 2.459 min. [Method 3]	Racemic	NA

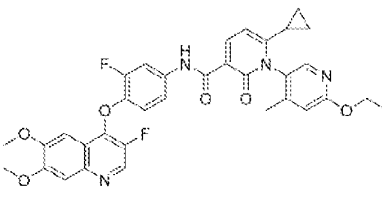
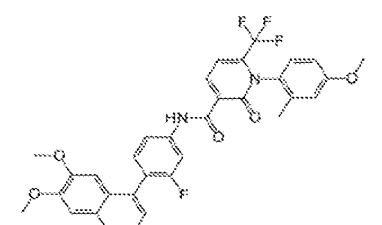
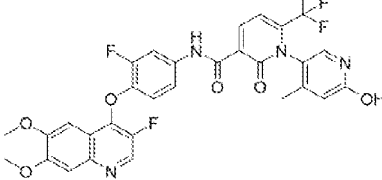
A-54	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.63 (s, 1H), 8.77 (d, <i>J</i> = 2.9 Hz, 1H), 8.67 (d, <i>J</i> = 7.6 Hz, 1H), 8.01 (dd, <i>J</i> = 2.6, 13.1 Hz, 1H), 7.54 - 7.49 (m, 2H), 7.43 - 7.34 (m, 4H), 7.28 - 7.24 (m, 1H), 7.14 - 7.09 (m, 1H), 4.32 - 4.28 (m, 2H), 3.91 (s, 3H), 3.78 - 3.75 (m, 2H), 3.36 (s, 3H), 2.06 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ : [C ₃₂ H ₂₄ F ₅ N ₃ O ₆ +H] ⁺ : 642.16, found: 642.2, <i>t_R</i> = 2.594 min. [Method 3]	Racemic	NA
A-55	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 12.04 (s, 1 H) 8.67 (d, <i>J</i> =3.50 Hz, 1 H) 8.48 (d, <i>J</i> =7.88 Hz, 1 H) 8.13 (s, 1 H) 7.72 (d, <i>J</i> =10.51 Hz, 2 H) 7.49 (s, 1 H) 7.43 (s, 1 H) 6.93 (s, 1 H) 6.49 (d, <i>J</i> =7.88 Hz, 1 H) 4.35 (td, <i>J</i> =7.13, 3.13 Hz, 2 H) 3.94 (d, <i>J</i> =3.75 Hz, 6 H) 2.03 (s, 3 H) 1.31 - 1.39 (m, 4 H) 0.91 - 0.97 (m, 2 H) 0.82 - 0.91 (m, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ : [C ₃₄ H ₂₉ F ₃ N ₄ O ₆ +H] ⁺ : 647.20, found: 647.3, <i>t_R</i> = 2.570 min. [Method 3]	Racemic	NA
A-56	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 11.95 (s, 1 H) 8.80 (d, <i>J</i> =2.00 Hz, 1 H) 8.46 - 8.53 (m, 2 H) 8.17 (d, <i>J</i> =2.13 Hz, 1 H) 8.12 (s, 1 H) 7.47 (s, 1 H) 7.24 (s, 1 H) 6.92 (s, 1 H) 6.49 (d, <i>J</i> =7.88 Hz, 1 H) 4.28 - 4.40 (m, 2 H) 3.94 (s, 3 H) 3.86 (s, 3 H) 2.01 (s, 3 H) 1.30 - 1.39 (m, 4 H) 0.85 - 0.96 (m, 4 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ : [C ₃₃ H ₂₉ F ₂ N ₅ O ₆ +H] ⁺ : 630.21, found: 630.3, <i>t_R</i> = 2.472 min. [Method 3]	Racemic	NA

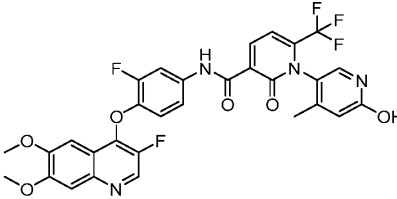
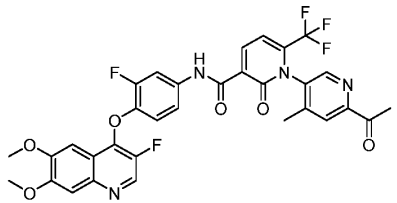
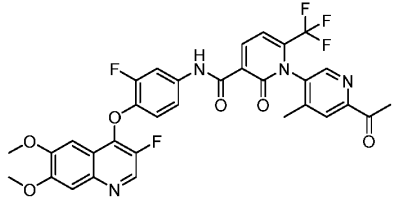
A-57	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-oxo-1-(5-trifluoromethoxy-2-tolyl)-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.57 (s, 1 H) 8.76 (d, J=2.88 Hz, 1 H) 8.66 (d, J=7.63 Hz, 1 H) 8.00 (dd, J=13.13, 2.25 Hz, 1 H) 7.67 (br s, 1 H) 7.56 - 7.61 (m, 1 H) 7.49 - 7.54 (m, 1 H) 7.46 (s, 1 H) 7.37 - 7.44 (m, 2 H) 7.32 (s, 1 H) 7.09 (t, J=9.07 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.07 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ F ₈ N ₃ O ₆ +H] ⁺ : 696.13, found: 696.2, t _R = 2.717 min. Chiral HPLC purity: 100%, t _R = 1.522, ee= 100%. [Method 4]	Atrop 1	NA
A-58	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-oxo-1-(5-trifluoromethoxy-2-tolyl)-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.57 (s, 1 H) 8.76 (d, J=2.88 Hz, 1 H) 8.66 (d, J=7.50 Hz, 1 H) 8.00 (dd, J=13.13, 2.25 Hz, 1 H) 7.67 (s, 1 H) 7.56 - 7.61 (m, 1 H) 7.49 - 7.54 (m, 1 H) 7.46 (s, 1 H) 7.36 - 7.44 (m, 2 H) 7.32 (s, 1 H) 7.09 (t, J=9.19 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.07 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₁ F ₈ N ₃ O ₆ +H+H] ⁺ : 696.13, found: 696.3, t _R = 2.718 min. Chiral HPLC purity: 99.92%, t _R = 1.852 ee= 99.84%. [Method 4]	Atrop 2	NA
A-59	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-cyano-3-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.42 (s, 1 H) 8.76 (d, J=2.88 Hz, 1 H) 8.66 (d, J=7.50 Hz, 1 H) 8.05 (t, J=7.57 Hz, 1 H) 7.99 (dd, J=13.07, 2.44 Hz, 1 H) 7.65 (d, J=8.25 Hz, 1 H) 7.46 (s, 1 H) 7.43 (d, J=7.63 Hz, 1 H) 7.38 (br d, J=9.38 Hz, 1 H) 7.31 (s, 1 H) 7.09 (t, J=9.13 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.03 - 2.08 (m, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 655.13, found: 655.1, t _R = 3.381 min, Chiral HPLC purity: 100%, t _R = 1.319, ee= 100%. [Method 4]	Atrop 1	NA

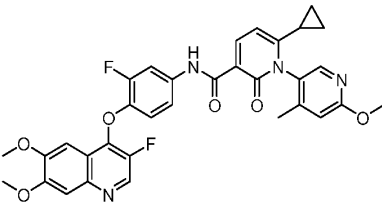
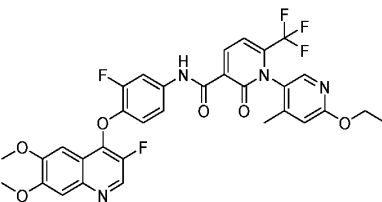
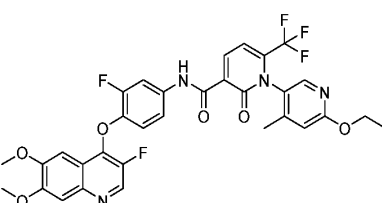
A-60	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-cyano-3-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.42 (s, 1 H) 8.76 (d, J=2.75 Hz, 1 H) 8.66 (d, J=7.50 Hz, 1 H) 8.05 (t, J=7.57 Hz, 1 H) 7.99 (dd, J=13.13, 2.38 Hz, 1 H) 7.65 (d, J=8.25 Hz, 1 H) 7.46 (s, 1 H) 7.43 (d, J=7.63 Hz, 1 H) 7.38 (br d, J=9.26 Hz, 1 H) 7.31 (s, 1 H) 7.09 (t, J=9.13 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.02 - 2.08 (m, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ : [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 655.13, found: 655.2, t _R = 3.382 min, Chiral HPLC purity: 99.76%, t _R = 1.678, ee= 99.52%. [Method 4]	Atrop 2	NA
A-61	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-4'-methyl-2-oxo-6,6'-bis(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.39 (s, 1 H) 8.87 (s, 1 H) 8.76 (d, J=2.75 Hz, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.98 (dd, J=13.13, 2.38 Hz, 1 H) 7.44 - 7.48 (m, 2 H) 7.39 (br d, J=9.26 Hz, 1 H) 7.31 (s, 1 H) 7.10 (t, J=9.19 Hz, 1 H) 3.94 (s, 3 H) 3.86 - 3.90 (m, 3 H) 2.24 - 2.28 (m, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ : [C ₃₁ H ₂₀ N ₄ O ₅ F ₈ +H] ⁺ : 681.13, found: 681.1, t _R = 3.419 min, Chiral HPLC purity: 99.9%, t _R = 3.419, ee= 99.74%. [Method 4]	Atrop 1	NA
A-62	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-4'-methyl-2-oxo-6,6'-bis(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.39 (s, 1 H) 8.87 (s, 1 H) 8.76 (d, J=2.88 Hz, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.98 (dd, J=13.13, 2.38 Hz, 1 H) 7.43 - 7.48 (m, 2 H) 7.36 - 7.42 (m, 1 H) 7.31 (s, 1 H) 7.10 (t, J=9.32 Hz, 1 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 2.26 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ : [C ₃₁ H ₂₀ N ₄ O ₅ F ₈ +H] ⁺ : 681.13, found: 681.2, t _R = 3.417 min, Chiral HPLC purity: 99.8%, t _R = 3.417, ee= 99.64%. [Method 4]	Atrop 2	NA

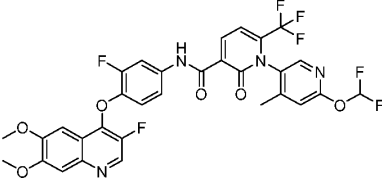
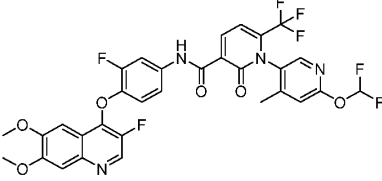
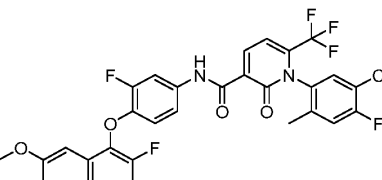
A-63	 6-cyclopropyl-N-[5-fluoro-6-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]-3-pyridyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) : δ 11.95 (s, 1 H) 8.80 (d, <i>J</i> =2.00 Hz, 1 H) 8.46 - 8.53 (m, 2 H) 8.16 (d, <i>J</i> =6.03 Hz, 2 H) 7.46 (s, 1 H) 7.24 (s, 1 H) 6.95 (s, 1 H) 6.48 (d, <i>J</i> =7.88 Hz, 1 H) 3.92 - 3.97 (m, 3 H) 3.85 - 3.91 (m, 6 H) 2.02 (s, 3 H) 1.32 - 1.41 (m, 1 H) 0.84 - 0.95 (m, 4 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₂ N ₅ O ₆ +H] ⁺ : 616.19, found: 616.3, <i>t</i> _R = 2.366 min. [Method 4]	Atrop 1	+2.95
A-64	 6-cyclopropyl-N-[3,5-difluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)oxy]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.04 (s, 1 H) 8.68 (d, <i>J</i> =3.50 Hz, 1 H) 8.49 (d, <i>J</i> =7.88 Hz, 1 H) 8.17 (s, 1 H) 7.73 (d, <i>J</i> =10.38 Hz, 2 H) 7.49 (s, 1 H) 7.43 (s, 1 H) 6.97 (s, 1 H) 6.50 (d, <i>J</i> =7.88 Hz, 1 H) 3.94 (d, <i>J</i> =3.50 Hz, 6 H) 3.90 (s, 3 H) 2.03 (s, 3 H) 1.28 - 1.44 (m, 1 H) 0.85 - 0.95 (m, 4 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₇ F ₃ N ₄ O ₆ +H] ⁺ : 633.18, found: 633.4, <i>t</i> _R = 2.449 min. [Method 4]	Atrop 1	+1.35
A-65	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.61 (s, 1H), 8.75 (d, <i>J</i> = 2.7 Hz, 1H), 8.65 (d, <i>J</i> = 7.6 Hz, 1H), 7.99 (dd, <i>J</i> = 2.4, 13.4 Hz, 1H), 7.52 - 7.47 (m, 1H), 7.46 (s, 1H), 7.37 (d, <i>J</i> = 8.1 Hz, 3H), 7.33 - 7.31 (m, 1H), 7.27 - 7.21 (m, 1H), 7.09 (t, <i>J</i> = 8.9 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.04 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₄ F ₅ N ₃ O ₆ +H] ⁺ : 642.16 found: 642.3, <i>t</i> _R = 2.556 min. [Method 4]	Atrop 1	ND

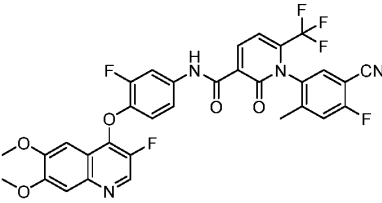
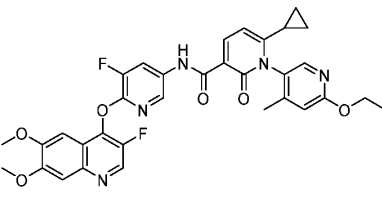
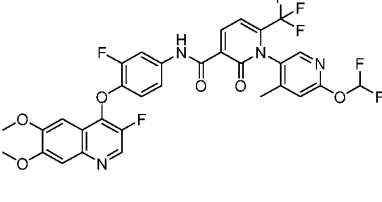
A-66	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.69 (s, 1 H) 8.75 (d, <i>J</i> =2.88 Hz, 1 H) 8.65 (d, <i>J</i> =7.63 Hz, 1 H) 7.99 (dd, <i>J</i> =13.20, 2.44 Hz, 1 H) 7.46 (s, 1 H) 7.40 (br d, <i>J</i> =9.63 Hz, 1 H) 7.36 (d, <i>J</i> =7.63 Hz, 1 H) 7.30 - 7.34 (m, 2 H) 7.02 - 7.13 (m, 3 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 3.74 (s, 3 H) 1.94 (s, 3 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₄ F ₅ N ₃ O ₆ +H] ⁺ : 642.16, found: 642.3, <i>t</i> _R = 2.564 min. [Method 4]	Atrop 2	ND
A-67	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.91 (s, 1H), 8.76 (d, <i>J</i> = 3.2 Hz, 1H), 8.50 (d, <i>J</i> = 8.0 Hz, 1H), 8.18 (d, <i>J</i> = 6.0 Hz, 1H), 8.00 (dd, <i>J</i> = 2.4, 13.2 Hz, 1H), 7.76 (d, <i>J</i> = 10.4 Hz, 1H), 7.46 (s, 1H), 7.32 - 7.31 (m, 2H), 7.07 (t, <i>J</i> = 8.8 Hz, 1H), 6.52 (s, <i>J</i> = 7.6 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.34 (m, 1H), 0.93 - 0.84 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₄ H ₂₅ F ₃ N ₄ O ₅ +H] ⁺ : 627.16, found: 627.44, <i>t</i> _R = 4.50 min. [Method 3]	Racemic	NA
A-68	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.91 (s, 1H), 8.75 (d, <i>J</i> = 3.0 Hz, 1H), 8.48 (d, <i>J</i> = 8.0 Hz, 1H), 8.12 (s, 1H), 7.98 (dd, <i>J</i> = 2.6, 13.4 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.23 (m, 2H), 7.07 (t, <i>J</i> = 9.3 Hz, 1H), 6.93 (s, 1H), 6.49 (d, <i>J</i> = 7.8 Hz, 1H), 4.41 - 4.26 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.02 (s, 3H), 1.42 - 1.17 (m, 4H), 0.99 - 0.61 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ F ₂ N ₄ O ₆ +H] ⁺ : 629.21, found: 628.49, <i>t</i> _R = 5.27 min. [Method 4]	Atrop 1	+70.00

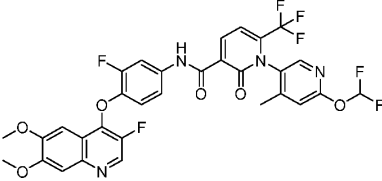
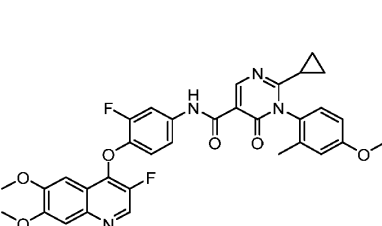
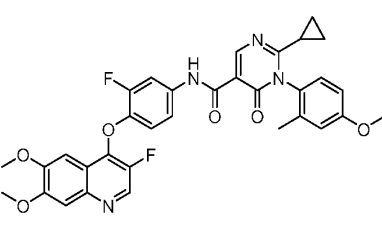
A-69	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.91 (s, 1H), 8.75 (d, <i>J</i> = 3.0 Hz, 1H), 8.48 (d, <i>J</i> = 8.0 Hz, 1H), 8.12 (s, 1H), 7.98 (dd, <i>J</i> = 2.6, 13.4 Hz, 1H), 7.46 (s, 1H), 7.34 - 7.25 (m, 2H), 7.07 (t, <i>J</i> = 9.3 Hz, 1H), 6.93 (s, 1H), 6.49 (d, <i>J</i> = 7.8 Hz, 1H), 4.38 - 4.29 (m, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.02 (s, 3H), 1.42 - 1.17 (m, 4H), 0.97 - 0.73 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ F ₂ N ₄ O ₆ +H] ⁺ : 629.63, found: 629.0, <i>t</i> _R = 5.26 min. [Method 4]	Atrop 2	-91.60
A-70	 N-[4-(6,7-dimethoxy-4-quinolyl)-3-fluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR δ 11.89 (s, 1 H) 8.73 (d, <i>J</i> =4.50 Hz, 1 H) 8.64 - 8.71 (m, 1 H) 7.92 - 8.06 (m, 1 H) 7.58 - 7.71 (m, 1 H) 7.49 - 7.55 (m, 1 H) 7.46 (s, 1 H) 7.36 (d, <i>J</i> =7.63 Hz, 1 H) 7.27 - 7.34 (m, 2 H) 7.01 (d, <i>J</i> =2.50 Hz, 1 H) 6.90 - 6.97 (m, 1 H) 6.86 (d, <i>J</i> =2.13 Hz, 1 H) 3.95 (s, 3 H) 3.82 (s, 3 H) 3.73 (s, 3 H) 2.02 (s, 3 H); MS (ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₅ F ₄ N ₃ O ₅ +H] ⁺ : 608.17, found: 608.2, <i>t</i> _R = 3.325 min. [Method 1]	Racemic	NA
A-71	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.84 (s, 1H), 11.60 (s, 1H), 8.76 (d, <i>J</i> = 2.8 Hz, 1H), 8.63 (d, <i>J</i> = 7.5 Hz, 1H), 8.01 (dd, <i>J</i> = 2.1, 13.1 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.42 (d, <i>J</i> = 8.5 Hz, 1H), 7.36 - 7.31 (m, 2H), 7.11 (t, <i>J</i> = 9.1 Hz, 1H), 6.37 (s, 1H), 3.97 - 3.88 (m, 6H), 1.88 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ F ₅ N ₄ O ₆ +H] ⁺ : 628.1, found: 629.3, <i>t</i> _R = 4.42 min. [Method 4]	Atrop 1	-15.01

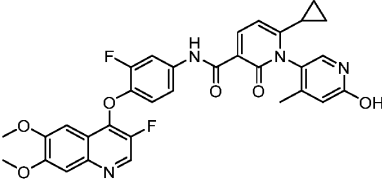
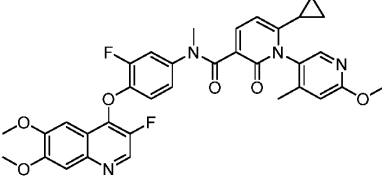
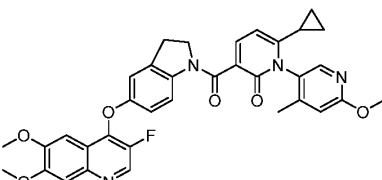
A-72	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-hydroxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.82(s, 1H), 11.60 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.63 (d, <i>J</i> = 7.5 Hz, 1H), 8.01 (dd, <i>J</i> = 2.4, 13.1 Hz, 1H), 7.71 (s, 1H), 7.47 (s, 1H), 7.42 (d, <i>J</i> = 9.5 Hz, 1H), 7.38 - 7.30 (m, 2H), 7.11 (t, <i>J</i> = 9.1 Hz, 1H), 6.37 (s, 1H), 3.99 - 3.87 (m, 6H), 1.88 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ F ₅ N ₄ O ₆ +H] ⁺ : 628.1, found: 629.3, <i>t_R</i> = 4.43 min. [Method 4]	Atrop 2	+22.97
A-73	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-acetyl-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.43 (s, 1H), 8.77 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.68 (d, <i>J</i> = 7.5 Hz, 1H), 8.09 (s, 1H), 7.98 (dd, <i>J</i> = 2.4, <i>J</i> = 13.1 Hz, 1H), 7.47 - 7.43 (m, 2H), 7.38 (br d, <i>J</i> = 8.9 Hz, 1H), 7.32 (s, 1H), 7.09 (t, <i>J</i> = 9.1 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.68 (s, 3H), 2.22 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ F ₅ N ₄ O ₆ +H] ⁺ : 655.15, found: 655.35, <i>t_R</i> = 5.14 min. [Method 4]	Atrop 1	+96.00
A-74	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-acetyl-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.43 (s, 1H), 8.77 (s, 1H), 8.75 (d, <i>J</i> = 2.8 Hz, 1H), 8.68 (d, <i>J</i> = 7.5 Hz, 1H), 8.09 (s, 1H), 7.98 (dd, <i>J</i> = 2.4, <i>J</i> = 13.2 Hz, 1H), 7.47 - 7.43 (m, 2H), 7.38 (br d, <i>J</i> = 8.1 Hz, 1H), 7.31 (s, 1H), 7.09 (t, <i>J</i> = 9.1 Hz, 1H), 3.95 (s, 3H), 3.91 - 3.86 (m, 3H), 2.68 (s, 3H), 2.22 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ F ₅ N ₄ O ₆ +H] ⁺ : 655.1, found: 655.35, <i>t_R</i> = 5.14 min. [Method 4]	Atrop 2	-105.6

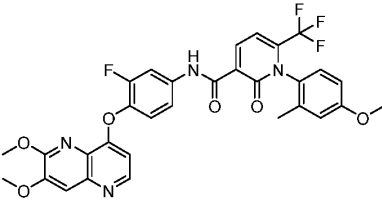
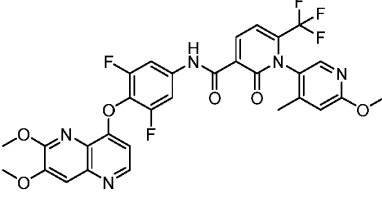
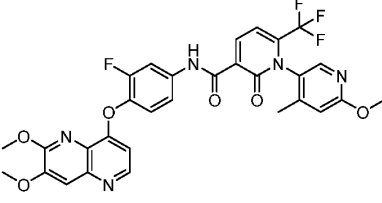
A-75	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ = 11.91 (s, 1H), 8.75 (d, <i>J</i> = 2.9 Hz, 1H), 8.48 (d, <i>J</i> = 7.9 Hz, 1H), 8.15 (s, 1H), 7.98 (dd, <i>J</i> = 2.4, 13.3 Hz, 1H), 7.46 (s, 1H), 7.35 - 7.28 (m, 2H), 7.07 (t, <i>J</i> = 9.1 Hz, 1H), 6.96 (s, 1H), 6.49 (d, <i>J</i> = 7.9 Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.40 - 1.32 (m, 1H), 0.95 - 0.84 (m, 4H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₃H₂₈F₂N₄O₆+H]⁺ : 615.6, found: 615.46, <i>t</i>_R=4.44 min. [Method 4]	Atrop 1	+12.24
A-76	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm): 11.56 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.66 - 8.63 (m, 1H), 8.16 (s, 1H), 7.99 (dd, <i>J</i> = 2.5, 13.1 Hz, 1H), 7.46 (s, 1H), 7.41 - 7.37 (m, 2H), 7.32 (s, 1H), 7.10 (t, <i>J</i> = 9.1 Hz, 1H), 6.90 (s, 1H), 4.35 (dq, <i>J</i> = 2.9, 6.9 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.03 (s, 3H), 1.36 - 1.32 (m, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₂H₂₅F₅N₄O₆+H]⁺: 657.17, found: 657.35, <i>t</i>_R=5.44 min. [Method 4]	Atrop 1	+12.48
A-77	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm): 11.57 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.68 - 8.64 (m, 1H), 8.16 (s, 1H), 7.99 (dd, <i>J</i> = 2.4, 13.2 Hz, 1H), 7.47 (s, 1H), 7.42 - 7.37 (m, 2H), 7.32 (s, 1H), 7.10 (t, <i>J</i> = 9.2 Hz, 1H), 6.91 (s, 1H), 4.35 (dq, <i>J</i> = 3.0, 6.8 Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 2.04 (s, 3H), 1.34 (t, <i>J</i> = 7.1 Hz, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₂H₂₅F₅N₄O₆+H]⁺: 657.17, found: 657.35, <i>t</i>_R=5.43 min. [Method 4]	Atrop 2	-12.63

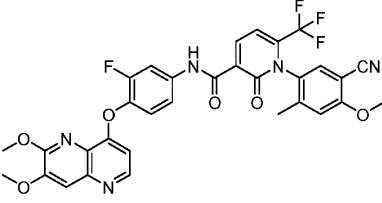
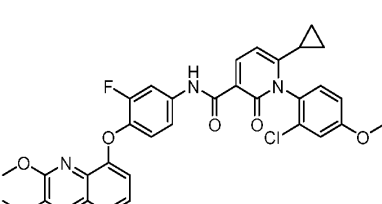
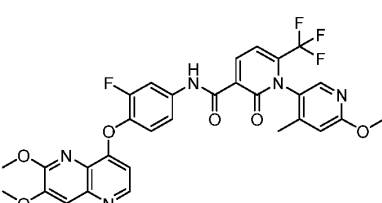
A-78	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-(1,1-difluoroethyl)-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.45 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.72 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.4, 13.3 Hz, 1H), 7.90 (s, 1H), 7.47 - 7.42 (m, 2H), 7.40 (br d, J = 9.0 Hz, 1H), 7.32 (s, 1H), 7.09 (t, J = 9.1 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.21 (s, 3H), 2.05 (t, J = 19.2 Hz, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ F ₇ N ₄ O ₅ +H] ⁺ : 677.16, found: 677.31, t _R = 5.30 min. [Method 4]	Atrop 1	+77.74
A-79	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-(1,1-difluoroethyl)-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.45 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.72 (s, 1H), 8.68 (d, J = 7.5 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.90 (s, 1H), 7.47 - 7.42 (m, 2H), 7.40 (br d, J = 9.0 Hz, 1H), 7.32 (s, 1H), 7.09 (t, J = 9.1 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.21 (s, 3H), 2.05 (t, J = 19.2 Hz, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₃ F ₇ N ₄ O ₅ +H] ⁺ : 677.16, found: 677.35, t _R = 5.31 min. [Method 4]	Atrop 2	-70.64
A-80	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.45 (s, 1H), 8.76 (d, J = 2.9 Hz, 1H), 8.67 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 6.5 Hz, 1H), 7.99 (dd, J = 2.4, 13.2 Hz, 1H), 7.76 (d, J = 10.0 Hz, 1H), 7.47 (s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.32 (s, 1H), 7.10 (t, J = 9.1 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.17 (s, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₀ F ₆ N ₄ O ₅ +H] ⁺ : 655.1, found: 655.41, t _R = 4.64 min. [Method 4]	Atrop 1	-104.6

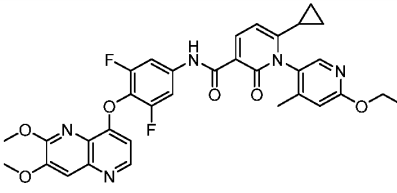
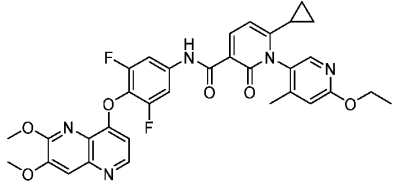
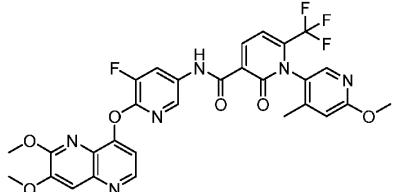
A-81	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-fluoro-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.45 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.67 (d, <i>J</i> = 7.5 Hz, 1H), 8.24 (d, <i>J</i> = 5.9 Hz, 1H), 7.99 (dd, <i>J</i> = 2.4, 13.2 Hz, 1H), 7.76 (d, <i>J</i> = 9.9 Hz, 1H), 7.47 (s, 1H), 7.42 (d, <i>J</i> = 7.8 Hz, 2H), 7.32 (s, 1H), 7.13 - 7.06 (m, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.17 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₀ F ₆ N ₄ O ₅ +H] ⁺ : 655.1, found: 655.41, <i>t_R</i> = 4.64 min. [Method 4]	Atrop 2	+97.28
A-82	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm = 12.04 - 11.82 (m, 1H), 8.88 - 8.74 (m, 1H), 8.57 - 8.41 (m, 2H), 8.24 - 8.08 (m, 2H), 7.51 - 7.36 (m, 1H), 7.27 - 7.19 (m, 1H), 7.01 - 6.88 (m, 1H), 6.57 - 6.39 (m, 1H), 4.46 - 4.26 (m, 2H), 4.02 - 3.78 (m, 7H), 2.07 - 1.98 (m, 3H), 1.39 - 1.30 (m, 4H), 0.99 - 0.86 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ F ₂ N ₅ O ₆ +H] ⁺ : 629.6, found: 630.48, <i>t_R</i> = 4.59 min. [Method 4]	Atrop 1	+10.4
A-83	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm = 11.48 (s, 1H), 8.76 (d, <i>J</i> = 2.9 Hz, 1H), 8.67 (d, <i>J</i> = 7.5 Hz, 1H), 8.36 (s, 1H), 8.04 - 7.58 (m, 2H), 7.47 (s, 1H), 7.44 - 7.37 (m, 2H), 7.32 (s, 1H), 7.28 (s, 1H), 7.10 (t, <i>J</i> = 9.2 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 2.14 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₁ F ₇ N ₄ O ₆ +H] ⁺ : 679.1, found: 679.0, <i>t_R</i> = 5.21 min. [Method 4]	Atrop 2	-48.8

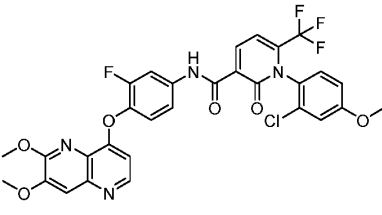
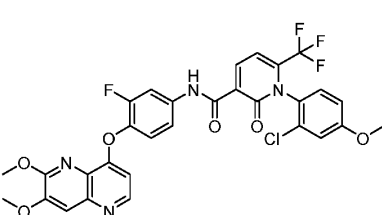
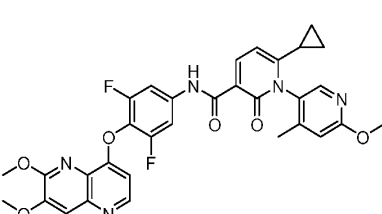
A-84	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.48 (s, 1H), 8.76 (d, J = 3.0 Hz, 1H), 8.66 (d, J = 7.8 Hz, 1H), 8.36 (s, 1H), 8.03 - 7.58 (m, 2H), 7.46 (s, 1H), 7.44 - 7.37 (m, 2H), 7.32 (s, 1H), 7.27 (s, 1H), 7.10 (t, J = 9.1 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 2.13 (s, 3H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₁ F ₇ N ₄ O ₆ +H] ⁺ : 679.1, found: 679.35, t _R = 4.74 min. [Method 4]	Atrop 1	+28.24
A-85	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.22 (s, 1 H) 8.79 (s, 1 H) 8.75 (d, J=2.75 Hz, 1 H) 7.96 (dd, J=13.20, 2.31 Hz, 1 H) 7.46 (s, 1 H) 7.30 - 7.40 (m, 3 H) 7.05 - 7.12 (m, 2 H) 6.99 (dd, J=8.63, 2.63 Hz, 1 H) 3.95 (s, 3 H) 3.88 (s, 3 H) 3.82 (s, 3 H) 2.06 (s, 3 H) 1.45 (td, J=8.00, 4.25 Hz, 1 H) 1.16 - 1.26 (m, 2 H) 1.00 - 1.12 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.6, found: 615.43, t _R = 4.65 min. [Method 4]	Atrop 1	-74.2
A-86	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.22 (s, 1 H) 8.79 (s, 1 H) 8.75 (d, J=2.75 Hz, 1 H) 7.96 (dd, J=13.26, 2.13 Hz, 1 H) 7.46 (s, 1 H) 7.29 - 7.40 (m, 3 H) 7.04 - 7.12 (m, 2 H) 6.99 (dd, J=8.75, 2.50 Hz, 1 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 3.82 (s, 3 H) 2.06 (s, 3 H) 1.41 - 1.49 (m, 1 H) 1.16 - 1.26 (m, 2 H) 0.99 - 1.10 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₂ N ₄ O ₆ +H] ⁺ : 615.6, found: 615.40, t _R = 5.33 min. [Method 4]	Atrop 2	+24.88

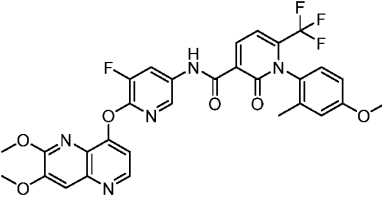
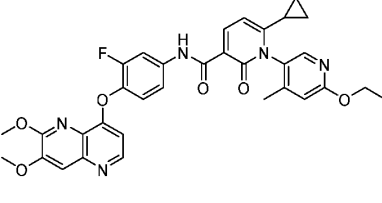
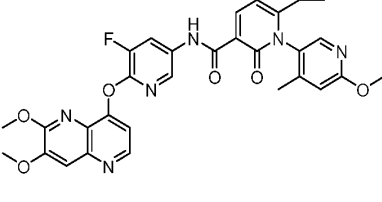
A-87	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-hydroxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm: 11.95 (s, 1 H) 11.79 (s, 1 H) 8.75 (d, J=2.75 Hz, 1 H) 8.45 (d, J=7.88 Hz, 1 H) 8.00 (dd, J=13.32, 2.31 Hz, 1 H) 7.65 (s, 1 H) 7.46 (s, 1 H) 7.30 - 7.36 (m, 2 H) 7.08 (t, J=9.07 Hz, 1 H) 6.44 (d, J=7.88 Hz, 1 H) 6.40 (s, 1 H) 3.95 (s, 3 H) 3.89 (s, 3 H) 1.85 (s, 3 H) 1.54 - 1.63 (m, 1 H) 0.88 - 1.00 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ F ₂ N ₄ O ₆ +H] ⁺ : 601.6, found: 601.32, t _R = 4.14 min. [Method 4]	Atrop 1	-40.32
A-88	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-N-methyl-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 8.76 (d, J=2.63 Hz, 1 H) 7.86 (br s, 1 H) 7.53 (br d, J=7.13 Hz, 1 H) 7.47 (s, 1 H) 7.37 - 7.42 (m, 1 H) 7.23 (s, 1 H) 6.89 - 7.02 (m, 2 H) 6.84 (s, 1 H) 6.06 (br d, J=6.75 Hz, 1 H) 3.94 - 3.96 (m, 3 H) 3.84 - 3.89 (m, 6 H) 3.26 (s, 3 H) 1.44 - 1.82 (m, 3 H) 1.11 (br s, 1 H) 0.67 (br d, J=7.63 Hz, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ F ₂ N ₄ O ₆ +H] ⁺ : 629.21, found: 629.4, t _R = 2.026 min. [Method 4]	Atrop 1 ^A	NA
A-89	 6-cyclopropyl-3-[5-[(3-fluoro-6,7-dimethoxy-4-quinolyloxy)indoline-1-carbonyl]-1-(6-methoxy-4-methyl-3-pyridyl)pyridin-2-one	¹ H NMR (400 MHz, DMSO-d ₆): δ 8.78 (d, J=2.63 Hz, 1 H) 8.09 (s, 1 H) 8.05 (d, J=8.76 Hz, 1 H) 7.69 (d, J=7.38 Hz, 1 H) 7.46 (s, 1 H) 7.23 (s, 1 H) 6.98 (s, 1 H) 6.92 (s, 2 H) 6.23 (d, J=7.38 Hz, 1 H) 3.95 - 4.00 (m, 2 H) 3.94 (s, 3 H) 3.88 (s, 3 H) 3.84 (s, 3 H) 3.05 (br t, J=8.19 Hz, 2 H) 2.02 (s, 3 H) 1.22 - 1.33 (m, 1 H) 0.81 (br d, J=3.25 Hz, 2 H) 0.74 (br d, J=8.38 Hz, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₅ H ₃₁ N ₄ O ₆ F +H] ⁺ : 623.22, found: 623.3, t _R = 2.927 min. [Method 4]	Atrop 1	NA

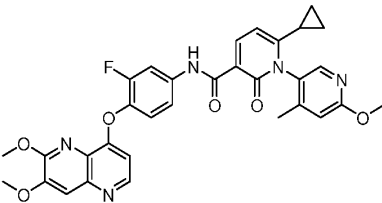
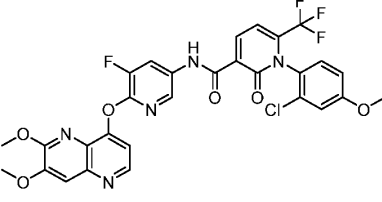
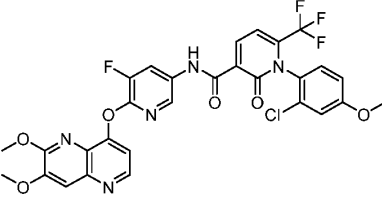
A-90	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.76 (s, 1H), δ 8.66 (d, <i>J</i> = 7.5 Hz, 1H), δ 8.55 (d, <i>J</i> = 5.3 Hz, 1H), δ 8.01 (dd, <i>J</i> = 2.4, 12.9 Hz, 1H), δ 7.65 (s, 1H), δ 7.52 (dd, <i>J</i> = 1.1, 9.0 Hz, 1H), δ 7.33 (dd, <i>J</i> = 8.3, 15.8 Hz, 3H), 7.01 (d, <i>J</i> = 2.6 Hz, 1H), 6.93 (dd, <i>J</i> = 2.8, 8.8 Hz, 1H), 6.84 (d, <i>J</i> = 5.1 Hz, 1H), δ 3.96 (s, 3H), δ 3.91 (s, 3H), δ 3.82 (s, 3H), δ 2.01 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ F ₄ N ₄ O ₆] ⁺ : 624.1, found: 625.42, <i>t_R</i> = 4.24 min. [Method 5]	Atrop 1	+89.5
A-91	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.75 (s, 1H), δ 8.67 (d, <i>J</i> = 7.6 Hz, 1H), δ 8.56 (d, <i>J</i> = 5.2 Hz, 1H), δ 8.20 (s, 1H), δ 7.81 (d, <i>J</i> = 10.4 Hz, 2H), δ 7.66 (s, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 6.94 (d, <i>J</i> = 6.4 Hz, 2H), δ 3.96 (s, 3H), δ 3.91 (s, 6H), δ 3.82 (s, 3H), δ 2.07 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₂ F ₅ N ₅ O ₆] ⁺ : 643.5, found: 644.36, <i>t_R</i> = 4.94 min. [Method 5]	Atrop 1	+23.5
A-92	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm = 11.62 (s, 1H), 8.66 (d, <i>J</i> = 7.6 Hz, 1H), 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 8.20 (s, 1H), 8.01 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1H), 7.65 (s, 1H), 7.52 (d, <i>J</i> = 8.8 Hz, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.32 (t, <i>J</i> = 9.2 Hz, 1H), 6.95 (s, 1H), 6.85 (d, <i>J</i> = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 6H), 2.05 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₃ F ₄ N ₅ O ₆] ⁺ : 625.1, find: 626.45, <i>t_R</i> = 4.15 min. [Method 5]	Atrop 2	-16.96

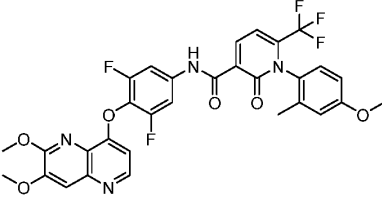
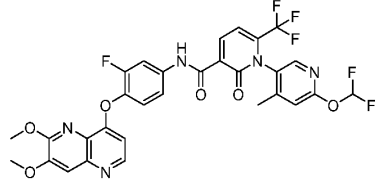
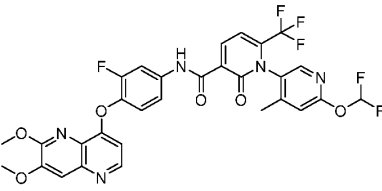
A-93	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.61 (s, 1H), 8.67 (d, <i>J</i> = 7.4 Hz, 1H), 8.56 (d, <i>J</i> = 5.3 Hz, 1H), 8.01 (dd, <i>J</i> = 2.3, <i>J</i> = 12.9 Hz, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 7.54 - 7.50 (m, 1H), 7.40 - 7.38 (m, 2H), 7.32 (t, <i>J</i> = 9.0 Hz, 1H), 6.85 (d, <i>J</i> = 4.9 Hz, 1H), 4.00 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₂H₂₃F₄N₅O₆+H]⁺: 649.16, found: 650.2, <i>t_R</i> = 4.50 min. [Method 5]	Atrop 2	-62.24
A-94	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-1-(2-chloro-4-methoxyphenyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹H NMR (400 MHz, DMSO-d₆): δ = 12.00 - 11.95 (m, 1H), 8.58 - 8.46 (m, 2H), 8.05 - 7.96 (m, 1H), 7.69 - 7.62 (m, 1H), 7.60 - 7.52 (m, 1H), 7.49 - 7.42 (m, 1H), 7.36 - 7.27 (m, 2H), 7.19 - 7.11 (m, 1H), 6.86 - 6.79 (m, 1H), 6.52 - 6.44 (m, 1H), 4.01 - 3.80 (m, 10H), 1.41 - 1.32 (m, 1H), 0.95 - 0.83 (m, 4H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₂H₂₆ClFN₄O₆+H]⁺: 616.15, found: 617.33, <i>t_R</i> = 4.990 min. [Method 5]	Atrop 1	+66.8
A-95	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ ppm = 11.62 (s, 1H), 8.66 (d, <i>J</i> = 7.6 Hz, 1H), 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 8.20 (s, 1H), 8.01 (dd, <i>J</i> = 2.0 Hz, <i>J</i> = 2.4 Hz, 1H), 7.65 (s, 1H), 7.52 (d, <i>J</i> = 8.8 Hz, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.32 (t, <i>J</i> = 9.2 Hz, 1H), 6.95 (s, 1H), 6.85 (d, <i>J</i> = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 6H), 2.05 (s, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₀H₂₃F₄N₅O₆+H]⁺: 625.1, find: 626.41, <i>t_R</i> = 4.15 min. [Method 5]	Atrop 1	+16.26

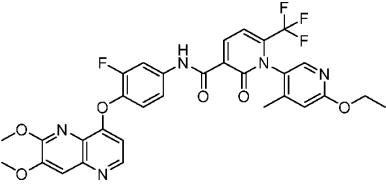
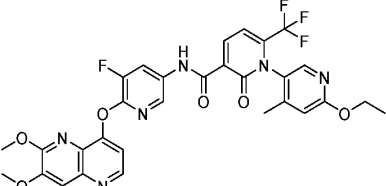
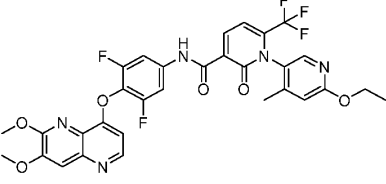
A-96	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.22 - 12.06 (m, 1H), 8.68 - 8.44 (m, 2H), 7.89 - 7.63 (m, 4H), 7.06 - 6.93 (m, 1H), 6.91 - 6.79 (m, 1H), 6.60 - 6.35 (m, 1H), 4.36 - 4.31 (m, 2H), 3.96 - 3.72 (m, 6H), 2.18 - 2.05 (m, 3H), 1.42 - 1.26 (m, 4H), 0.97 - 0.82 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ F ₂ N ₅ O ₆ +H] ⁺ : 629.6, found: 630.48, <i>t</i> _R = 4.41 min. [Method 5]	Atrop 1	+120.26
A-97	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 12.22 - 12.09 (m, 1H), 8.68 - 8.55 (m, 1H), 8.55 - 8.45 (m, 1H), 7.87 - 7.72 (m, 3H), 7.68 - 7.56 (m, 1H), 7.06 - 6.93 (m, 1H), 6.91 - 6.80 (m, 1H), 6.58 - 6.40 (m, 1H), 4.40 - 4.34 (m, 2H), 3.96 (d, <i>J</i> = 15.8 Hz, 7H), 2.14 (s, 3H), 1.48 - 1.33 (m, 4H), 0.98 - 0.82 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ F ₂ N ₅ O ₆ +H] ⁺ : 629.6, found: 630.48, <i>t</i> _R = 4.41 min. [Method 5]	Atrop 2	-93.4
A-98	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-5-fluoro-3-pyridyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ = 11.58 (s, 1H), 8.72 (d, <i>J</i> = 5.0 Hz, 1H), 8.66 (d, <i>J</i> = 7.5 Hz, 1H), 8.45 (dd, <i>J</i> = 2.1, 11.8 Hz, 1H), 8.20 - 8.16 (m, 2H), 7.66 (s, 1H), 7.44 (d, <i>J</i> = 5.0 Hz, 1H), 7.38 (d, <i>J</i> = 7.8 Hz, 1H), 6.93 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.54 (s, 3H), 2.04 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₂₉ H ₂₂ F ₂ N ₆ O ₆ +H] ⁺ : 627.5, found: 627.36, <i>t</i> _R = 4.74 min. [Method 5]	Atrop 1	+25.92

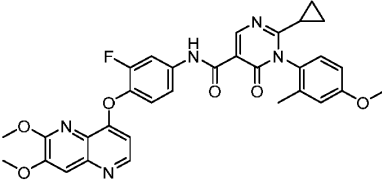
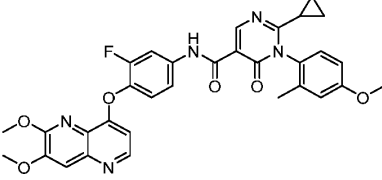
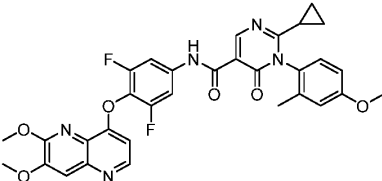
A-99	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.69 - 11.54 (m, 1H), 8.77 - 8.49 (m, 2H), 8.09 - 7.94 (m, 1H), 7.68 - 7.57 (m, 2H), 7.57 - 7.44 (m, 1H), 7.43 - 7.26 (m, 3H), 7.17 - 7.04 (m, 1H), 6.91 - 6.80 (m, 1H), 3.90 - 3.88 (m, 1H), 3.94 - 3.77 (m, 1H), 3.88 - 3.75 (m, 1H), 4.03 - 3.68 (m, 6H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ ClF ₄ N ₄ O ₆ +H] ⁺ : 644.1, found: 645.38, t _R = 4.37 min. [Method 5]	Atrop 1	+133.9 2
A-100	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.07 (s, 1H), 8.55 (d, J = 5.3 Hz, 1H), 8.50 (d, J = 7.9 Hz, 1H), 7.78 (d, J = 10.3 Hz, 2H), 7.66 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 2.6 Hz, 1H), 7.15 (dd, J = 2.7, 8.8 Hz, 1H), 6.92 (d, J = 5.3 Hz, 1H), 6.49 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 1.41 - 1.30 (m, 1H), 1.00 - 0.79 (m, 4H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ ClF ₄ N ₄ O ₆ +H] ⁺ : 644.1, found: 645.38, t _R = 4.35 min. [Method 5]	Atrop 2	-123.68
A-101	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ (ppm) = 12.7 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.50 (d, J = 8 Hz, 1H), 8.17 (s, 1H), 7.77 (dd, J = 10.4 Hz, 2H), 7.66 (s, 1H), 6.98 (s, 1H), 6.92 (d, J = 5.2 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 2.07 (s, 3H), 1.40-1.36 (m, 1H), 0.97-0.87 (m, 4H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₂ N ₅ O ₆] ⁺ : 615.19, found: 616.49, t _R = 4.14 min. [Method 5]	Atrop 1	+7.5

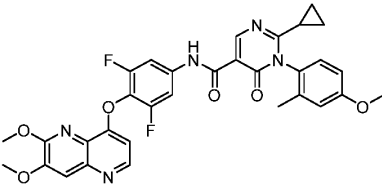
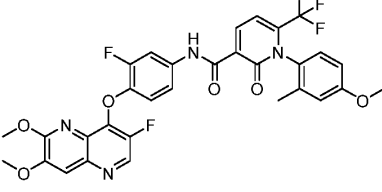
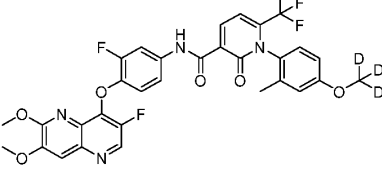
A-102	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-5-fluoro-3-pyridyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 11.74 (s, 1H), 8.74 (d, <i>J</i> = 5.0 Hz, 1H), 8.65 (d, <i>J</i> = 7.6 Hz, 1H), 8.47 (dd, <i>J</i> = 2.2, 11.8 Hz, 1H), 8.20 (d, <i>J</i> = 2.1 Hz, 1H), 7.66 (s, 1H), 7.46 (d, <i>J</i> = 5.1 Hz, 1H), 7.34 (d, <i>J</i> = 7.8 Hz, 1H), 7.29 (d, <i>J</i> = 8.8 Hz, 1H), 6.99 (d, <i>J</i> = 2.9 Hz, 1H), 6.91 (dd, <i>J</i> = 2.8, 8.7 Hz, 1H), 3.94 (s, 3H), 3.81 (s, 3H), 3.56 (s, 3H), 1.99 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₃ F ₄ N ₅ O ₆ +H] ⁺ : 626.1, found: 626.45, <i>t_R</i> = 4.34 min. [Method 5]	Atrop 1	+34.72
A-103	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm = 12.05 - 11.91 (m, 1H), 8.58 - 8.44 (m, 2H), 8.20 - 8.07 (m, 1H), 8.05 - 7.94 (m, 1H), 7.68 - 7.61 (m, 1H), 7.48 - 7.43 (m, 1H), 7.35 - 7.24 (m, 1H), 7.01 - 6.75 (m, 2H), 6.58 - 6.40 (m, 1H), 4.47 - 4.27 (m, 2H), 4.05 - 3.85 (m, 6H), 2.07 - 1.99 (m, 3H), 1.46 - 1.33 (m, 4H), 1.00 - 0.85 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₃₀ FN ₅ O ₆ +H] ⁺ : 611.6, found: 612.5, <i>t_R</i> = 4.07 min. [Method 5]	Atrop 1	+10.8
A-104	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm = 12.03 - 11.85 (m, 1H), 8.80 - 8.65 (m, 1H), 8.54 - 8.40 (m, 2H), 8.23 - 8.09 (m, 2H), 7.73 - 7.58 (m, 1H), 7.47 - 7.37 (m, 1H), 7.00 - 6.90 (m, 1H), 6.59 - 6.39 (m, 1H), 4.11 - 3.67 (m, 6H), 3.66 - 3.44 (m, 3H), 1.45 - 1.28 (m, 1H), 1.00 - 0.74 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₇ FN ₅ O ₆ +H] ⁺ : 598.2, found: 599.46, <i>t_R</i> = 3.96 min. [Method 5]	Atrop 1	+23.68

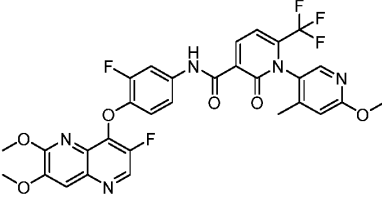
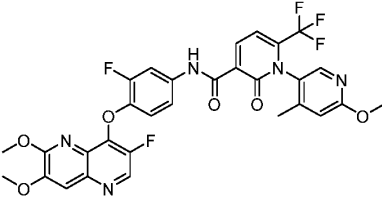
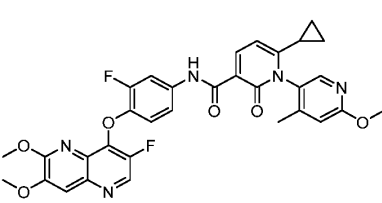
A-105	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyl-1-yl)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.98 (s, 1H), 8.55 (d, <i>J</i> = 5.1 Hz, 1H), 8.51 (d, <i>J</i> = 7.9 Hz, 1H), 8.17 (s, 1H), 8.01 (dd, <i>J</i> = 2.3, 13.1 Hz, 1H), 7.65 (s, 1H), 7.46 (br d, <i>J</i> = 8.6 Hz, 1H), 7.31 (t, <i>J</i> = 9.0 Hz, 1H), 6.98 (s, 1H), 6.82 (d, <i>J</i> = 5.3 Hz, 1H), 6.50 (d, <i>J</i> = 7.9 Hz, 1H), 3.97 (s, 3H), 3.92 (d, <i>J</i> = 6.8 Hz, 6H), 2.05 (s, 3H), 1.39 (br s, 1H), 1.01 - 0.86 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₇ N ₆ O ₆] ⁺ : 598.2, found: 599.4, <i>t_R</i> = 3.91 min. [Method 5]	Atrop 1	+7.6
A-106	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyl-1-yl)-5-fluoro-3-pyridyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.60 (s, 1H) 8.71 (d, <i>J</i> = 4.8 Hz, 1H) 8.66 (d, <i>J</i> = 7.8 Hz, 1H) 8.43 - 8.47 (m, 1H) 8.19 (d, <i>J</i> = 2.4 Hz, 1H) 7.66 (s, 1H) 7.59 (d, <i>J</i> = 8.8 Hz, 1H) 7.44 (d, <i>J</i> = 4.8 Hz, 1H) 7.37 (d, <i>J</i> = 7.6 Hz, 1H) 7.31 (d, <i>J</i> = 2.4 Hz, 1H) 7.10 - 7.13 (m, 1H) 3.94 (s, 3H), 3.86 (s, 3H), 3.54 (m, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₂₉ H ₂₀ ClF ₄ N ₅ O ₆ +H] ⁺ : 646.1, found: 646.2, <i>t_R</i> = 5.54 min. [Method 5]	Atrop 1	+173.3
A-107	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyl-1-yl)-5-fluoro-3-pyridyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.60 (s, 1H) 8.71 (d, <i>J</i> = 5.2 Hz, 1H) 8.66 (d, <i>J</i> = 7.6 Hz, 1H) 8.44 - 8.47 (m, 1H) 8.19 (d, <i>J</i> = 2.0 Hz, 1H) 7.66 (s, 1H) 7.59 (d, <i>J</i> = 8.8 Hz, 1H) 7.44 (d, <i>J</i> = 4.8 Hz, 1H) 7.37 (d, <i>J</i> = 7.6 Hz, 1H) 7.31 (d, <i>J</i> = 2.8 Hz, 1H) 7.10 - 7.13 (m, 1H) 3.94 (s, 3H), 3.86 (s, 3H), 3.54 (m, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₂₉ H ₂₀ ClF ₄ N ₅ O ₆ +H] ⁺ : 646.1, found: 646.2, <i>t_R</i> = 5.52 min. [Method 5]	Atrop 2	-149.0

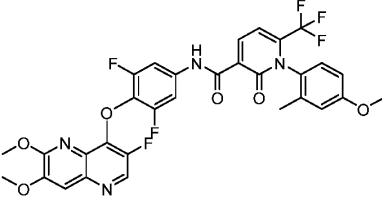
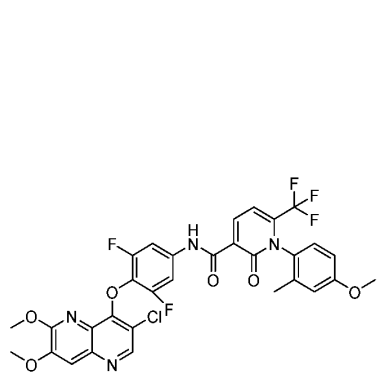
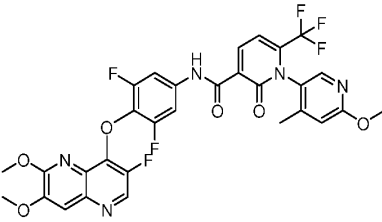
A-108	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.85 (s, 1H), δ 8.66 (d, <i>J</i> = 7.6 Hz, 1H), δ 8.56 (d, <i>J</i> = 5.2 Hz, 1H), δ 7.81 (d, <i>J</i> = 10 Hz, 1H) δ 7.66 (s, 1H), δ 7.35 (d, <i>J</i> = 5.6, Hz, 1H), δ 7.66 (s, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.31 (d, <i>J</i> = 8.8 Hz, 1H), 7.05 (d, <i>J</i> = 2.4 Hz, 1H), δ 6.93 (m, 2H) δ 3.96 (s, 3H), δ 3.91 (s, 3H), δ 3.82 (s, 3H), δ 2.01 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₃ F ₅ N ₄ O ₆ +H] ⁺ : 642.1, found: 643.44, <i>t_R</i> = 4.46 min. [Method 5]	Atrop 1	+54.3
A-109	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.55 (s, 1H), 8.68 (d, <i>J</i> = 7.6 Hz, 1H), 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 8.37 (s, 1H), 8.02-7.61 (m, 3H), 7.52 (d, <i>J</i> = 9.2 Hz, 1H), 7.42 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (t, <i>J</i> = 8.8 Hz, 1H), 7.28 (s, 1H), 6.85 (d, <i>J</i> = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.14 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ F ₆ N ₅ O ₆ +H] ⁺ : 661.1, found: 662.35, <i>t_R</i> = 5.06 min. [Method 5]	Atrop 1	+54.16
A-110	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.55 (s, 1H), 8.68 (d, <i>J</i> = 7.6 Hz, 1H), 8.56 (d, <i>J</i> = 5.2 Hz, 1H), 8.37 (s, 1H), 8.02-7.61 (m, 3H), 7.52 (d, <i>J</i> = 9.2 Hz, 1H), 7.42 (d, <i>J</i> = 8.0 Hz, 1H), 7.32 (t, <i>J</i> = 8.8 Hz, 1H), 7.28 (s, 1H), 6.85 (d, <i>J</i> = 5.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 2.14 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ F ₆ N ₅ O ₆ +H] ⁺ : 661.5, observed: 662.35, <i>t_R</i> = 5.06 min. [Method 5]	Atrop 2	-56.40

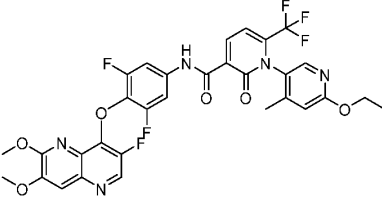
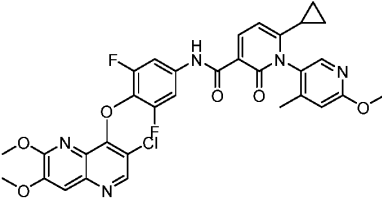
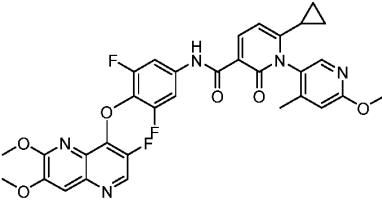
A-111	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.62 (s, 1H), 8.67 (d, J = 7.6 Hz, 1H), 8.56 (d, J = 5.3 Hz, 1H), 8.18 (s, 1H), 8.01 (dd, J = 2.3, 13.0 Hz, 1H), 7.66 (s, 1H), 7.55 - 7.51 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 9.0 Hz, 1H), 6.92 (s, 1H), 6.85 (d, J = 5.1 Hz, 1H), 4.40 - 4.32 (m, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 2.05 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₅ F ₄ N ₅ O ₆ +H] ⁺ : 640.1, found: 640.35, t _R = 5.07 min. [Method 5]	Atrop 1	+8.88
A-112	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-5-fluoro-3-pyridyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.58 (s, 1H), 8.72 (d, J = 5.0 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.46 (dd, J = 2.1, 11.8 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.16 (s, 1H), 7.66 (s, 1H), 7.44 (d, J = 5.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 6.90 (s, 1H), 4.34 (br dd, J = 2.3, 7.1 Hz, 2H), 3.94 (s, 3H), 3.55 (s, 3H), 2.04 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₄ F ₄ N ₆ O ₆ +H] ⁺ : 641.1, found: 641.34, t _R = 4.98 min. [Method 5]	Atrop 1	+21.68
A-113	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.70 (s, 1H), 8.67 (d, J = 7.5 Hz, 1H), 8.56 (d, J = 5.1 Hz, 1H), 8.18 (s, 1H), 7.81 (d, J = 10.3 Hz, 2H), 7.66 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 6.94 (d, J = 5.0 Hz, 1H), 6.92 (s, 1H), 4.35 (dq, J = 2.8, 6.9 Hz, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 2.05 (s, 3H), 1.37 - 1.32 (t, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ F ₅ N ₅ O ₆ +H] ⁺ : 658.1, found: 658.37, t _R = 4.52 min. [Method 5]	Atrop 1	+22.00

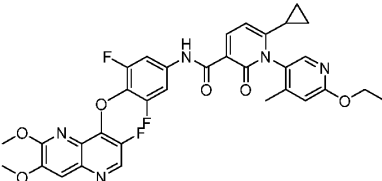
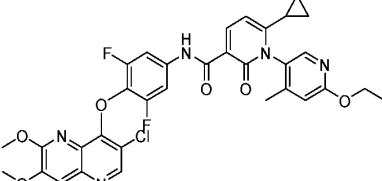
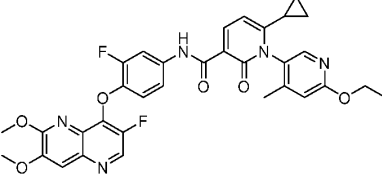
A-114	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 11.29 (s, 1 H) 8.81 (s, 1 H) 8.55 (d, J=5.13 Hz, 1 H) 7.99 (dd, J=13.01, 2.25 Hz, 1 H) 7.65 (s, 1 H) 7.47 (dd, J=8.88, 1.13 Hz, 1 H) 7.38 (d, J=8.63 Hz, 1 H) 7.32 (t, J=9.01 Hz, 1 H) 7.08 (d, J=2.63 Hz, 1 H) 7.00 (dd, J=8.63, 2.75 Hz, 1 H) 6.83 (d, J=5.25 Hz, 1 H) 3.96 (s, 3 H) 3.92 (s, 3 H) 3.83 (s, 3 H) 2.07 (s, 3 H) 1.46 (td, J=8.10, 3.94 Hz, 1 H) 1.17 - 1.28 (m, 2 H) 1.02 - 1.11 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₂₉ H ₂₀ ClF ₄ N ₅ O ₆ +H] ⁺ : 598.1, found: 598.2, tR= 4.75 min. [Method 5]	Atrop 1	+34.4
A-115	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.29 (s, 1 H) 8.81 (s, 1 H) 8.55 (d, J=5.13 Hz, 1 H) 7.99 (dd, J=13.07, 2.31 Hz, 1 H) 7.65 (s, 1 H) 7.44 - 7.49 (m, 1 H) 7.35 - 7.42 (m, 1 H) 7.29 - 7.34 (m, 1 H) 7.08 (d, J=2.63 Hz, 1 H) 7.00 (dd, J=8.63, 2.75 Hz, 1 H) 6.83 (d, J=5.13 Hz, 1 H) 3.96 (s, 3 H) 3.92 (s, 3 H) 3.83 (s, 3 H) 2.07 (s, 3 H) 1.43 - 1.49 (m, 1 H) 1.19 - 1.27 (m, 2 H) 1.03 - 1.10 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₂₉ H ₂₀ ClF ₄ N ₅ O ₆ +H] ⁺ : 598.1, found: 598.2, tR= 4.75 min. [Method 5]	Atrop 2	-38.1
A-116	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 11.37 (s, 1 H) 8.81 (s, 1 H) 8.56 (d, J=5.13 Hz, 1 H) 7.78 (br d, J=10.26 Hz, 2 H) 7.66 (s, 1 H) 7.39 (d, J=8.63 Hz, 1 H) 7.09 (d, J=2.38 Hz, 1 H) 7.01 (dd, J=8.63, 2.50 Hz, 1 H) 6.93 (d, J=5.25 Hz, 1 H) 3.97 (s, 3 H) 3.92 (s, 3 H) 3.83 (s, 3 H) 2.08 (s, 3 H) 1.44 - 1.54 (m, 1 H) 1.18 - 1.28 (m, 2 H) 1.00 - 1.13 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₂ N ₅ O ₆ +H] ⁺ : 616.4, find: 616.4, tR= 6.15 min. [Method 5]	Atrop 1	+28.0

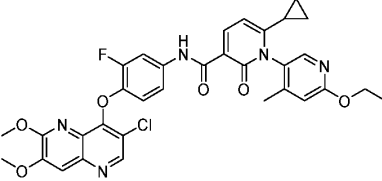
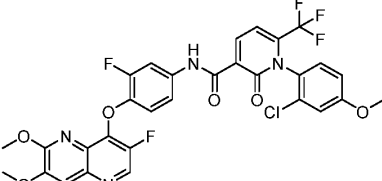
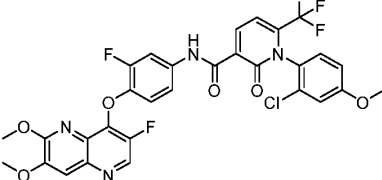
A-117	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-2-cyclopropyl-1-(4-methoxy-2-tolyl)-6-oxo-1,6-dihydro-5-pyrimidinecarboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 11.25 - 11.49 (m, 1 H) 8.81 (s, 1 H) 8.55 (d, J=5.25 Hz, 1 H) 7.77 (br d, J=10.26 Hz, 2 H) 7.66 (s, 1 H) 7.39 (d, J=8.75 Hz, 1 H) 7.08 (d, J=2.50 Hz, 1 H) 7.00 (dd, J=8.76, 2.63 Hz, 1 H) 6.92 (d, J=5.13 Hz, 1 H) 3.96 (s, 3 H) 3.92 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₂ N ₅ O ₆ +H] ⁺ : find: 616.41, tR= 5.30 min. [Method 5]	Atrop 2	-24.8
A-118	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.65 (s, 1H), 8.90 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 7.6 Hz, 1H), 7.93 (dd, J = 2.4 Hz, J = 13.2 Hz, 1H), 7.68 (s, 1H), 7.35-7.28 (m, 3H), 7.09 (t, J = 9.2 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 6.91 (dd, J = 2.8 Hz, J = 8.8 Hz 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 1.99 (s, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₃ F ₅ N ₄ O ₆] ⁺ : 643.15, found: 643.40, tR= 4.83 min. [Method 5]	Atrop 1	25.6
A-119	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-1-[4-(²H₃)methoxy-2-tolyl]-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.7 (s, 1 H), 8.90 (d, J=2 Hz, 1 H), 8.63 (d, J=7.6 Hz, 1 H), 7.93 (dd, J=13.2, 2.4 Hz, 1 H), 7.68 (s, 1 H), 7.34-7.33 (m, 2 H), 7.28 (d, J=8.8 Hz, 1 H), 7.09 (t, J = 9.2, 1 H), 6.99-6.98 (m 1 H), 6.92=6.89 (m, 1 H), 3.93 (s, 3 H), 3.60 (s, 3 H), 1.99 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ D ₃ H ₂₀ F ₅ N ₄ O ₆ +H] ⁺ : 646.1, found: 646.37, tR= 5.63 min. [Method 5]	Atrop 1	+87.7

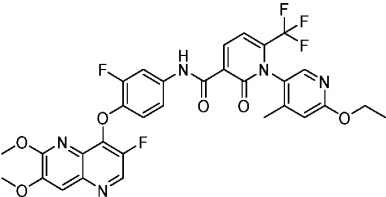
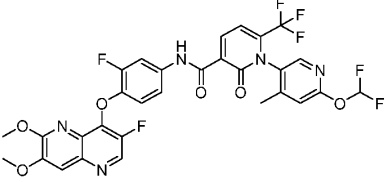
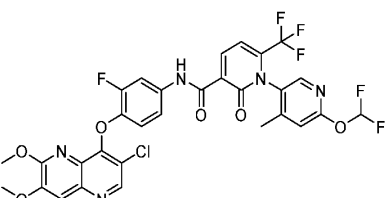
A-120	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): 11.55 (s, 1H), 8.90 (d, <i>J</i> = 1.6 Hz, 1H), 8.64 (d, <i>J</i> = 7.6 Hz, 1H), 8.17 (s, 1H), 7.92 (dd, <i>J</i> = 2.4 Hz, <i>J</i> = 13.2 Hz, 1H), 7.68 (s, 1H), 7.36 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 15.6 Hz, 2H), 7.09 (t, <i>J</i> = Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.60 (s, 3H), 2.04 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₂ F ₅ N ₅ O ₆ +H] ⁺ : 644.10, found: 644.43, <i>t</i> _R = 4.70 min. [Method 5]	Atrop 1	+9.7
A-121	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): 11.54 (s, 1H), 8.90 (d, <i>J</i> = 1.6 Hz, 1H), 8.64 (d, <i>J</i> = 7.6 Hz, 1H), 8.17 (s, 1H), 7.92 (dd, <i>J</i> = 2.4 Hz, <i>J</i> = 13.2 Hz, 1H), 7.68 (s, 1H), 7.36 (dd, <i>J</i> = 7.6 Hz, <i>J</i> = 15.6 Hz, 2H), 7.09 (t, <i>J</i> = Hz, 1H), 6.93 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.60 (s, 3H), 2.04 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₂ F ₅ N ₅ O ₆ +H] ⁺ : 644.10, found: 644.43, <i>t</i> _R = 4.70 min. [Method 5]	Atrop 2	-15.0
A-122	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (401 MHz, DMSO-d ₆) δ 11.88 (s, 1H), 8.90 (d, <i>J</i> = 2.0 Hz, 1H), 8.48 (d, <i>J</i> = 7.8 Hz, 1H), 8.16 (s, 1H), 7.94 (dd, <i>J</i> = 2.4, 13.3 Hz, 1H), 7.68 (s, 1H), 7.27 (td, <i>J</i> = 1.2, 8.9 Hz, 1H), 7.07 (t, <i>J</i> = 9.1 Hz, 1H), 6.97 (s, 1H), 6.49 (d, <i>J</i> = 7.9 Hz, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.61 (s, 3H), 2.03 (s, 3H), 1.39 - 1.32 (m, 1H), 0.94 - 0.85 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₅ N ₅ O ₆] ⁺ : 615.1, found: 616.0, <i>t</i> _R = 4.50 min. [Method 5]	Atrop 1	+62.0

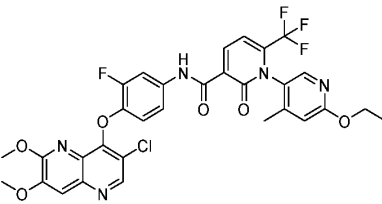
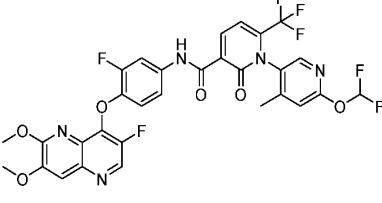
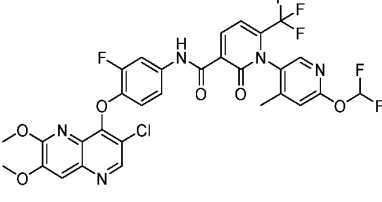
A-123	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.78 (s, 1H), 8.89 (s, 1H), 8.63 (d, <i>J</i> = 7.6 Hz, 1H), 7.67-7.71 (m, 3H), 7.34 (d, <i>J</i> = 7.6 Hz, 1H), 7.29 (d, <i>J</i> = 9.2 Hz, 1H), 6.99 (s, 1H), 6.93-6.90 (m, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.57 (s, 3H), 1.20 (s, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₁H₂₂F₆N₄O₆+H]⁺ : 660.1, found: 661.2, t_R = 5.16 min. [Method 5]	Atrop 1	+64.32
A-124	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹H NMR (400 MHz, DMSO-d₆): δ ppm 11.78 (s, 1H), 8.83 (s, 1H), 8.63 (d, <i>J</i> = 7.6 Hz, 1H), 7.70-7.67 (m, 3H), 7.34 (d, <i>J</i> = 7.6 Hz, 1H), 7.29 (d, <i>J</i> = 8.4 Hz, 1H), 6.99 (s, 1H), 6.93-6.90 (m, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H), 2.00 (s, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₁H₂₂ClF₅N₄O₆+H]⁺ : 677.0, found: 677.34, t_R = 5.09 min. [Method 5]	Atrop 2	+88.48
A-125	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆): δ 11.62 (s, 1H), 8.90 (d, <i>J</i> = 2.0 Hz, 1H), 8.65 (d, <i>J</i> = 7.6 Hz, 1H), 8.19 (s, 1H), 7.73-7.68 (m, 3H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 6.95 (s, 1H), 3.925 (s, 3H), 3.907 (s, 3H), 3.57 (s, 3H), 2.05 (s, 3H); MS(ES⁺) <i>m/z</i> calc'd for [M+H]⁺ [C₃₀H₂₁F₆N₅O₆+H]⁺ : 661.5, found: 662.40, LCMS: t_R = 4.82 min. [Method 5]	Atrop 1	+25.36

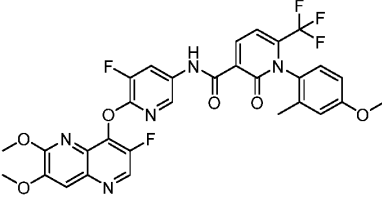
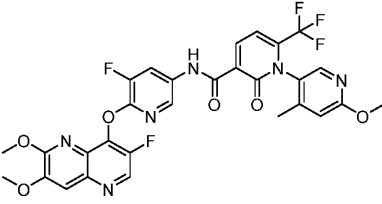
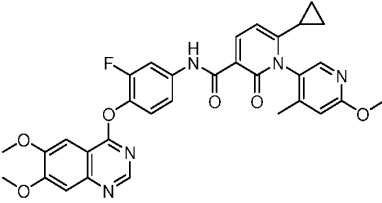
A-126	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.62 (s, 1H), 8.89 (d, <i>J</i> = 2.0 Hz, 1H), 8.64 (d, <i>J</i> = 7.6 Hz, 1H), 8.16 (s, 1H), 7.72 - 7.70 (m, 1H), 7.69 - 7.66 (m, 2H), 7.38 (d, <i>J</i> = 7.8 Hz, 1H), 6.91 (s, 1H), 4.39 - 4.30 (m, 2H), 3.92 (s, 3H), 3.57 (s, 3H), 2.04 (s, 3H), 1.34 (t, <i>J</i> = 7.1 Hz, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₃ F ₆ N ₅ O ₆ +H] ⁺ : 676.1, found: 676.47, <i>t_R</i> = 5.01 min. [Method 5]	Atrop 1	+19.92
A-127	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.96 (s, 1H), 8.82 (s, 1H), 8.47 (d, <i>J</i> = 7.6 Hz, 1H), 8.15 (s, 1H), 7.67-7.63 (m, 3H), 6.96 (s, 1H), 6.49 (d, <i>J</i> = 7.6 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.50 (s, 3H), 2.03 (s, 3H), 1.38-1.33 (m, 1H), 0.94-0.87 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ ClF ₂ N ₅ O ₆ +H] ⁺ : 650.0, observed: 650.35, <i>t_R</i> = 5.71 min. [Method 5]	Racemic	NA
A-128	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.96 (s, 1H), 8.88 (d, <i>J</i> = 2.0 Hz, 1H), 8.47 (d, <i>J</i> = 8.0 Hz, 1H), 8.15 (s, 1H), 7.66-7.64 (m, 3H), 7.96 (s, 1H), 7.49 (d, <i>J</i> = 8.0 Hz, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.57 (s, 3H), 2.03 (s, 3H), 1.40-1.33 (m, 1H), 0.96-0.86 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ F ₃ N ₅ O ₆ +H] ⁺ : 633.6, observed: 634.43, <i>t_R</i> = 4.71 min. [Method 5]	Atrop 1	+55.80

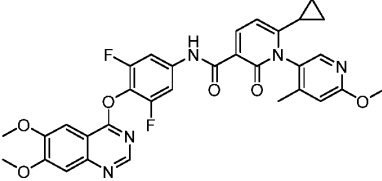
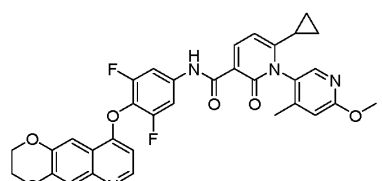
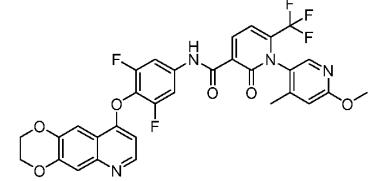
A-129	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm 11.99 (s, 1H), 8.88 (d, <i>J</i> = 2.0 Hz, 1H), 8.47 (d, <i>J</i> = 7.6 Hz, 1H), 8.13 (s, 1H), 7.67-7.64 (m, 3H), 6.93 (s, 1H), 6.48 (d, <i>J</i> = 8.0 Hz, 1H), 4.38-4.32 (m, 2H), 3.92 (s, 3H), 3.58 (s, 3H), 2.02 (s, 3H), 1.39-1.33 (m, 4H), 0.93-0.85 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ F ₃ N ₅ O ₆ +H] ⁺ : 647.1, found: 648.38, <i>t_R</i> = 1.78 min. [Method 5]	Atrop 1	-6.40
A-130	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.99 (s, 1H), 8.82 (s, 1H), 8.47 (d, <i>J</i> = 7.6 Hz, 1H), 8.13 (s, 1H), 7.67-7.63 (m, 3H), 6.93 (s, 1H), 6.49 (d, <i>J</i> = 8.0 Hz, 1H), 4.37-4.33 (m, 2H), 3.93 (s, 3H), 3.50 (s, 3H), 2.03 (s, 3H), 1.37-1.33 (m, 4H), 1.24 (s, 1H), 0.93-0.88 (m, 4H); M (ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ ClF ₂ N ₅ O ₆ +H] ⁺ : 664.1, found: 664.42, <i>t_R</i> = 5.07 min. [Method 5]	Atrop 1	ND
A-131	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ ppm = 11.88 (s, 1H), 8.90 (d, <i>J</i> = 2.0 Hz, 1H), 8.45 (d, <i>J</i> = 7.6 Hz, 1H), 8.12 (s, 1H), 7.92 (dd, <i>J</i> = 2.4, <i>J</i> = 13.2 Hz, 1H), 7.68 (s, 1H), 7.26 (d, <i>J</i> = 9.2, 1H), 7.07 (t, <i>J</i> = 9.2 Hz, 1H), 6.92 (s, 1H), 6.48 (d, <i>J</i> = 8.0 Hz, 1H), 4.36-4.33 (m, 2H), 3.93 (s, 3H), 3.61 (s, 3H), 2.02 (s, 3H), 1.34 (t, <i>J</i> = 6.8, 4H), 0.92-0.86 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ F ₂ N ₅ O ₆ +H] ⁺ : 630.21, found: 630.44, <i>t_R</i> = 4.70 min. [Method 5]	Atrop 1	+45.0

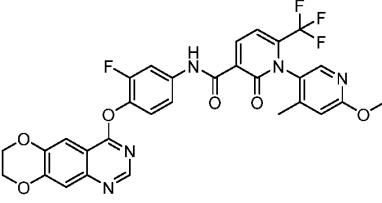
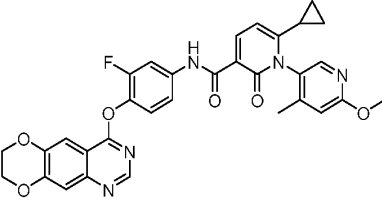
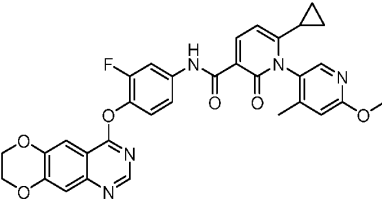
A-132	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.88 (s, 1H), 8.90 (d, <i>J</i> = 2.0 Hz, 1H), 8.45 (d, <i>J</i> = 7.6 Hz, 1H), 8.84 (s, 1H), 8.46 (d, <i>J</i> = 8.0 Hz, 1H), 8.11 (s, 1H), 7.91 (dd, <i>J</i> = 2.4 Hz, <i>J</i> = 13.2, 1H), 7.67 (s, 1H), 7.23 (d, <i>J</i> = 8.8 Hz, 1H), 6.97-6.92 (m, 2H), 6.47 (d, <i>J</i> = 8.0 Hz, 1H), 4.37-4.31 (m, 2H), 3.93 (s, 3H), 3.53 (s, 3H), 2.01 (s, 3H), 1.34 (t, <i>J</i> = 6.8, 4H), 0.92-0.85 (m, 4H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ ClFN ₅ O ₆ +H] ⁺ : 646.18.15, found: 646.36, <i>t_R</i> = 5.86 min. [Method 5]	Atrop 1 ^B	ND
A-133	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.53 (s, 1H), 8.91 (d, <i>J</i> = 1.9 Hz, 1H), 8.66 (d, <i>J</i> = 7.5 Hz, 1H), 7.93 (dd, <i>J</i> = 2.5, 13.1 Hz, 1H), 7.69 (s, 1H), 7.60 (d, <i>J</i> = 9.0 Hz, 1H), 7.39 - 7.31 (m, 3H), 7.15 - 7.06 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.61 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ ClF ₅ N ₄ O ₆ +H] ⁺ : 662.10, found: 663.30, <i>t_R</i> = 5.75 min. [Method 5]	Atrop 1	+201.68
A-134	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-1-(2-chloro-4-methoxyphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹ H NMR (401 MHz, DMSO-d ₆) δ = 11.54 (s, 1H), 8.91 (d, <i>J</i> = 1.8 Hz, 1H), 8.66 (d, <i>J</i> = 7.5 Hz, 1H), 7.94 (dd, <i>J</i> = 2.4, 13.2 Hz, 1H), 7.69 (s, 1H), 7.61 (d, <i>J</i> = 8.9 Hz, 1H), 7.42 - 7.31 (m, 4H), 7.21 - 7.01 (m, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 3.60 (s, 3H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ ClF ₅ N ₄ O ₆ +H] ⁺ : 662.10, found: 663.30, <i>t_R</i> = 5.72 min. [Method 5]	Atrop 2	-140.64

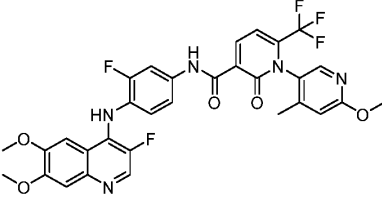
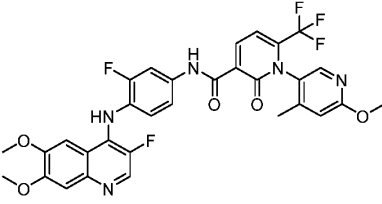
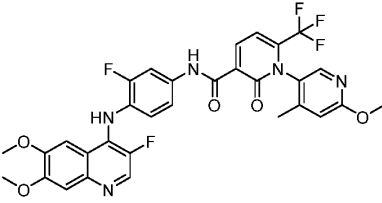
A-135	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.54 - 11.52 (m, 1H), 8.90 (d, J = 1.9 Hz, 1H), 8.64 (d, J = 7.5 Hz, 1H), 8.15 (s, 1H), 7.93 (dd, J = 2.4, 13.2 Hz, 1H), 7.68 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.34 (br d, J = 9.0 Hz, 1H), 7.10 (t, J = 9.1 Hz, 1H), 6.90 (s, 1H), 4.38 - 4.32 (m, 2H), 3.93 (s, 3H), 3.60 (s, 3H), 2.03 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); MS(ES+) m/z for [M+H] ⁺ : [C ₃₁ H ₂₄ F ₅ N ₅ O ₆ +H] ⁺ : 658.16, found: 658.37, t _R = 5.70 min. [Method 5]	Atrop 1	+48.32
A-136	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.45 (s, 1H), 8.91 (d, J = 1.9 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.98 - 7.59 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.37 - 7.31 (m, 1H), 7.27 (s, 1H), 7.10 (t, J = 9.1 Hz, 1H), 3.93 (s, 3H), 3.61 (s, 3H), 2.14 (s, 3H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ F ₇ N ₅ O ₆ +H] ⁺ : 680.5, found: 680.31, t _R = 5.62 min. [Method 5]	Atrop 1	-36.56
A-137	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.44 (s, 1H), 8.85 (s, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.97 - 7.61 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.34 - 7.29 (m, 1H), 7.27 (s, 1H), 6.99 (t, J = 9.1 Hz, 1H), 3.94 (s, 3H), 3.54 (s, 3H), 2.13 (s, 3H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ ClF ₆ N ₅ O ₆ +H] ⁺ : 697.0, found: 696.25, t _R = 5.79 min. [Method 5]	Atrop 1	ND

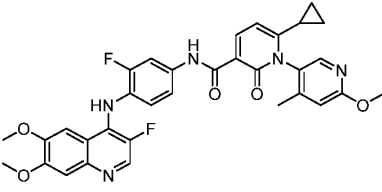
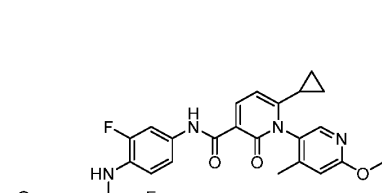
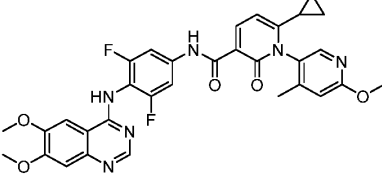
A-138	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) : δ 11.52 (s, 1H), 8.85 (s, 1H), 8.65 - 8.62 (m, 1H), 8.15 (s, 1H), 7.92 (dd, J = 2.4, 13.2 Hz, 1H), 7.68 (s, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.31 (br d, J = 8.4 Hz, 1H), 6.98 (t, J = 9.3 Hz, 1H), 6.90 (s, 1H), 4.37 - 4.32 (m, 2H), 3.93 (s, 3H), 3.53 (s, 3H), 2.03 (s, 3H), 1.36 - 1.32 (m, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ ClF ₄ N ₅ O ₆ +H] ⁺ : 674.14, found: 674.32, t _R = 5.87 min. [Method 5]	Atrop 1	ND
A-139	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)phenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.45 (s, 1H), 8.91 (d, J = 1.9 Hz, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.98 - 7.59 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.37 - 7.31 (m, 1H), 7.27 (s, 1H), 7.10 (t, J = 9.1 Hz, 1H), 3.93 (s, 3H), 3.61 (s, 3H), 2.14 (s, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ F ₇ N ₅ O ₆ +H] ⁺ : 680.5, found: 680.31, t _R = 5.62 min. [Method 5]	Atrop 2	+48.0
A-140	 N-[4-(3-chloro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-fluorophenyl]-6'-difluoromethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.44 (s, 1H), 8.85 (s, 1H), 8.66 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.97 - 7.61 (m, 3H), 7.41 (d, J = 7.8 Hz, 1H), 7.34 - 7.29 (m, 1H), 7.27 (s, 1H), 6.99 (t, J = 9.1 Hz, 1H), 3.94 (s, 3H), 3.54 (s, 3H), 2.13 (s, 3H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₀ ClF ₆ N ₅ O ₆ +H] ⁺ : 697.0, found: 696.25, t _R = 5.79 min. [Method 5]	Atrop 2	ND

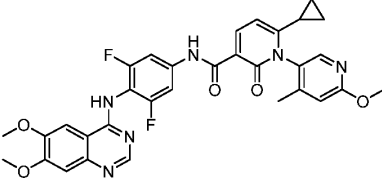
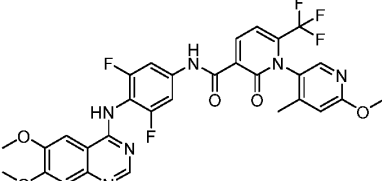
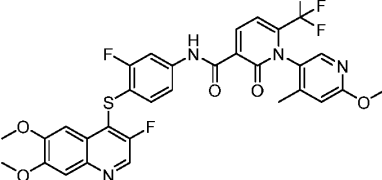
A-141	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-pyridyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	¹H NMR (400 MHz, DMSO-d₆) δ 11.78 (s, 1H), 8.94 (d, J = 1.2 Hz, 1H), 8.64 (d, J = 7.6 Hz, 1H), 8.49 (dd, J = 2.4, J = 12 Hz, 1H), 8.16 (d, J = 2.0, 1H), 7.69 (s, 1H), 7.30 (dd, J = 7.6, J = 21.6 Hz, 2H), 6.98 (d, J = 2.4 Hz, 1H), 6.90 (dd, J = 2.8, J = 8.8 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 1.99 (s, 3H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₀H₂₂F₅N₅O₆+H]⁺: 644.15, found: 644.43, t_R=4.71 min. [Method 5]	Atrop 1	+27.52
A-142	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3-pyridyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆) δ ppm 11.58 (s, 1 H) 8.95 (d, J=1.38 Hz, 1 H) 8.66 (d, J=7.63 Hz, 1 H) 8.49 (dd, J=11.82, 2.19 Hz, 1 H) 8.16 - 8.20 (m, 2 H) 7.70 (s, 1 H) 7.39 (d, J=7.63 Hz, 1 H) 6.94 (s, 1 H) 3.94 (s, 3 H) 3.90 (s, 3 H) 3.59 (s, 3 H) 2.04 (s, 3 H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₂₉H₂₁F₅N₆O₆+H]⁺: 645.1, found: 643.40, t_R=4.83 min. [Method 5]	Atrop 1	+12.48
A-143	 N-[4-(6,7-dimethoxy-4-quinazolinyl)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-d₆) δ ppm= 12.09 - 11.91 (m, 1H), 8.62 - 8.45 (m, 2H), 8.25 - 8.14 (m, 1H), 8.05 - 7.90 (m, 1H), 7.65 - 7.54 (m, 1H), 7.52 - 7.37 (m, 3H), 7.04 - 6.91 (m, 1H), 6.60 - 6.42 (m, 1H), 4.07 - 3.86 (m, 9H), 2.08 - 1.92 (m, 3H), 1.48 - 1.33 (m, 1H), 1.02 - 0.80 (m, 4H); MS(ES⁺) m/z calc'd for [M+H]⁺ [C₃₂H₂₈FN₅O₆+H]⁺: 597.2, found: 598.4, t_R= 4.25 min. [Method 6]	Atrop 1	+6.0

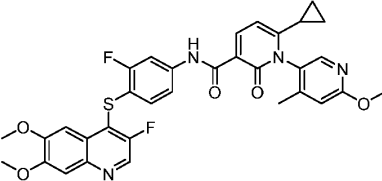
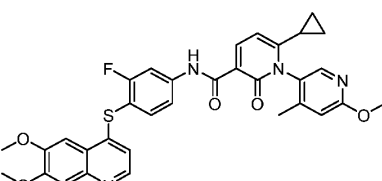
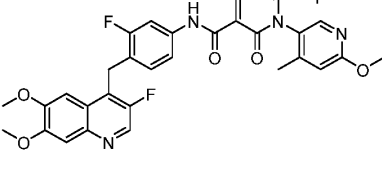
A-144	 N-[4-(6,7-dimethoxy-4-quinazolinyl)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 12.1 (s, 1H), 8.60 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H), 8.18 (s, 1H), 7.85 - 7.73 (m, 2H), 7.59 (s, 1H), 7.45 (s, 1H), 6.98 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 3.99 (s, 6H), 3.92 (s, 3H), 2.06 (s, 3H), 1.43 - 1.33 (m, 1H), 0.99 - 0.87 (m, 4H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₇ F ₂ N ₅ O ₆ +H] ⁺ : 616.1, found: 616.49, t _R =4.43 min. [Method 6]	Racemic	NA
A-145	 6-cyclopropyl-N-[4-(2,3-dihydro[1,4]dioxino[2,3-g]quinolin-9-yloxy)-3,5-difluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 12.11 (s, 1 H) 8.45 - 8.54 (m, 2 H) 8.18 (s, 1 H) 7.82 (d, J=10.13 Hz, 2 H) 7.62 (s, 1 H) 7.43 (s, 1 H) 6.98 (s, 1 H) 6.45 - 6.59 (m, 2 H) 4.41 (s, 4 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.33 - 1.43 (m, 1 H) 0.84 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₄ F ₅ N ₃ O ₆ +H] ⁺ : 613.282, found: 613.2, t _R =3.239 min. [Method 4]	Atrop 1 ^A	NA
A-146	 N-[4-(2,3-dihydro[1,4]dioxino[2,3-g]quinolin-9-yloxy)-3,5-difluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.73 (s, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.49 (d, J=5.13 Hz, 1 H) 8.21 (s, 1 H) 7.86 (d, J=10.01 Hz, 2 H) 7.62 (s, 1 H) 7.44 (s, 1 H) 7.40 (d, J=7.75 Hz, 1 H) 6.95 (s, 1 H) 6.55 (d, J=5.13 Hz, 1 H) 4.42 (s, 4 H) 3.91 (s, 3 H) 2.06 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₁ F ₅ N ₄ O ₆ +H] ⁺ : 641.14, found: 641.3, t _R =2.201 min. [Method 4]	Atrop 1	NA

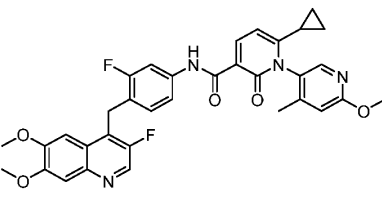
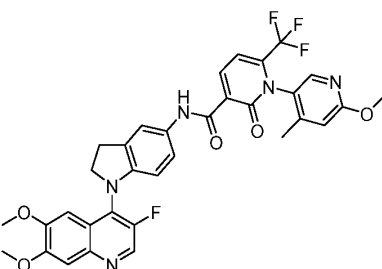
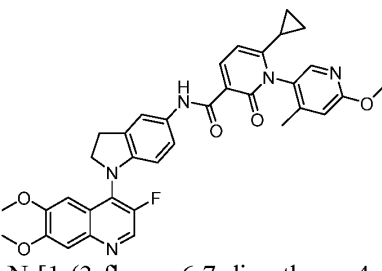
A-147	 N-[4-(5,8-dioxa-1,3-diaza-6,7-dihydro-4-anthryloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.64 (s, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.52 (s, 1 H) 8.21 (s, 1 H) 7.92 - 8.03 (m, 1 H) 7.68 (s, 1 H) 7.51 - 7.58 (m, 1 H) 7.42 - 7.49 (m, 1 H) 7.36 - 7.42 (m, 2 H) 6.95 (s, 1 H) 4.45 (br d, J=8.63 Hz, 4 H) 3.91 (s, 3 H) 2.06 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ F ₄ N ₅ O ₆ +H] ⁺ : 624.1, found: 624.3, t _R =2.481 min. [Method 4]	Atrop 1	ND
A-148	 N-[4-(5,8-dioxa-1,3-diaza-6,7-dihydro-4-anthryloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.99 (s, 1 H) 8.48 - 8.54 (m, 2 H) 8.18 (s, 1 H) 7.94 - 8.00 (m, 1 H) 7.68 (s, 1 H) 7.37 - 7.50 (m, 3 H) 6.98 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 4.45 (br dd, J=12.82, 4.44 Hz, 4 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.33 - 1.41 (m, 1 H) 0.84 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ FN ₅ O ₆ +H] ⁺ : 596.19, found: 596.3, t _R =1.981 min. [Method 4]	Atrop 1 ^A	ND
A-149	 N-[4-(5,8-dioxa-1,3-diaza-6,7-dihydro-4-anthryloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.99 (s, 1 H) 8.48 - 8.54 (m, 2 H) 8.18 (s, 1 H) 7.94 - 8.00 (m, 1 H) 7.68 (s, 1 H) 7.37 - 7.50 (m, 3 H) 6.98 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 4.45 (br dd, J=12.82, 4.44 Hz, 4 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.33 - 1.41 (m, 1 H) 0.84 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ FN ₅ O ₆ +H] ⁺ : 596.19, found: 596.3, t _R =2.185 min. [Method 4]	Atrop 2	ND

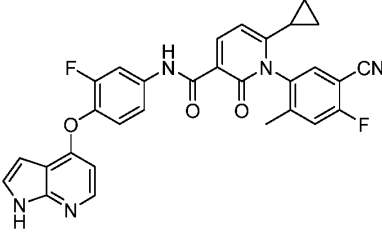
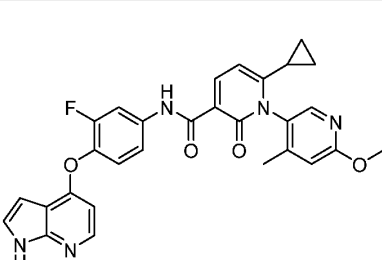
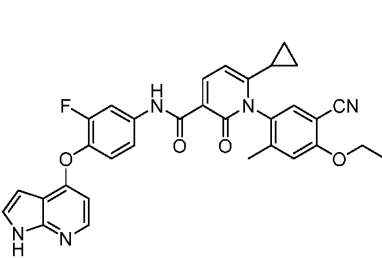
A-150	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylamino)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.50 Hz, 1 H) 8.53 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.38, 2.25 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.10 (s, 1 H) 6.95 (s, 1 H) 3.90 - 3.93 (m, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 642.54, found: 642.2, t _R = 3.177 min. [Method 7]	Racemic	NA
A-151	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylamino)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 8.55 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.45, 2.19 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.11 (t, J=9.19 Hz, 1 H) 6.95 (s, 1 H) 3.91 (s, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 642.54, found: 642.2, t _R = 0.762 min. [Method 7]	Atrop 1	+5.96
A-152	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylamino)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.53 (s, 1 H) 8.65 (d, J=7.63 Hz, 1 H) 8.55 (s, 1 H) 8.45 (d, J=4.13 Hz, 1 H) 8.19 (s, 1 H) 7.84 (dd, J=13.45, 2.19 Hz, 1 H) 7.60 (s, 1 H) 7.34 - 7.40 (m, 2 H) 7.31 (s, 1 H) 7.11 (t, J=9.19 Hz, 1 H) 6.95 (s, 1 H) 3.91 (s, 6 H) 3.89 (s, 3 H) 2.05 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₄ N ₅ F ₅ O ₅ +H] ⁺ : 642.54, found: 642.2, t _R = 1.389 min. [Method 7]	Atrop 2	ND

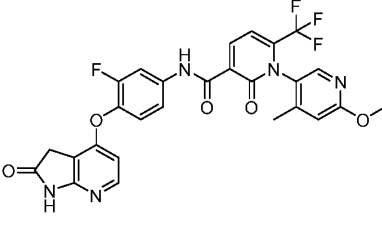
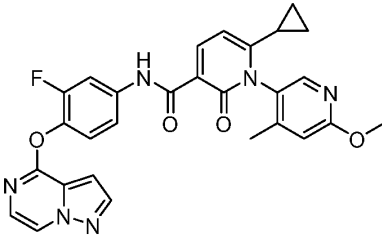
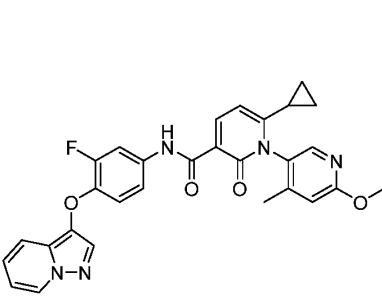
A-153	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylamino)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.87 (s, 1 H) 8.49 (br d, J=7.75 Hz, 2 H) 8.44 (d, J=4.25 Hz, 1 H) 8.16 (s, 1 H) 7.84 (dd, J=13.51, 2.38 Hz, 1 H) 7.60 (s, 1 H) 7.30 (s, 2 H) 7.05 - 7.14 (m, 1 H) 6.97 (s, 1 H) 6.49 (d, J=7.88 Hz, 1 H) 3.90 (d, J=1.75 Hz, 6 H) 3.89 (s, 3 H) 2.03 (s, 3 H) 1.32 - 1.41 (m, 1 H) 0.84 - 0.95 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ N ₅ F ₂ O ₅ +H] ⁺ : 614.21, found: 614.2, t _R = 3.033 min. [Method 7]	Atrop 1	ND
A-154	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylamino)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.87 (s, 1 H) 8.46 - 8.53 (m, 2 H) 8.44 (d, J=4.13 Hz, 1 H) 8.16 (s, 1 H) 7.84 (dd, J=13.51, 1.88 Hz, 1 H) 7.60 (s, 1 H) 7.25 - 7.32 (m, 2 H) 7.04 - 7.15 (m, 1 H) 6.97 (s, 1 H) 6.49 (d, J=7.88 Hz, 1 H) 3.91 (d, J=1.38 Hz, 6 H) 3.89 (s, 3 H) 2.03 (s, 3 H) 1.36 (s, 1 H) 0.93 (br d, J=3.13 Hz, 2 H) 0.87 (br dd, J=8.07, 3.19 Hz, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ F ₂ N ₅ O ₅ +H] ⁺ : 614.21, found: 614.2, t _R = 3.030 min. [Method 7]	Atrop 2	ND
A-155	 N-[4-(6,7-dimethoxy-4-quinazolinylamino)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.05 (s, 1 H) 9.38 (s, 1 H) 8.51 (d, J=7.75 Hz, 1 H) 8.33 (s, 1 H) 8.18 (s, 1 H) 7.81 (s, 1 H) 7.66 (d, J=10.01 Hz, 2 H) 7.20 (s, 1 H) 6.98 (s, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.93 (d, J=0.63 Hz, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.34 - 1.42 (m, 1 H) 0.86 - 0.99 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ F ₂ N ₆ O ₅ +H] ⁺ : 615.21, found: 615.4, t _R = 1.913 min. [Method 7]	Atrop 2	ND

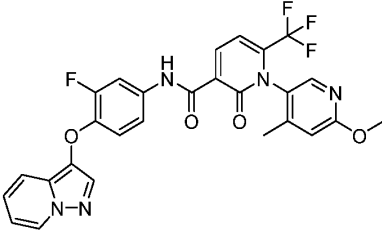
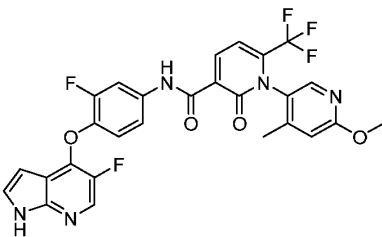
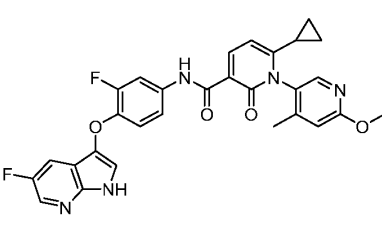
A-156	 N-[4-(6,7-dimethoxy-4-quinazolinylamino)-3,5-difluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 12.05 (s, 1 H) 9.37 (s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.32 (s, 1 H) 8.29 - 8.36 (m, 1 H) 8.18 (s, 1 H) 7.81 (s, 1 H) 7.66 (s, 1 H) 7.64 (s, 1 H) 7.59 - 7.71 (m, 1 H) 7.20 (s, 1 H) 6.98 (s, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.93 (s, 6 H) 3.91 (s, 3 H) 2.05 (s, 3 H) 1.34 - 1.42 (m, 1 H) 0.86 - 0.96 (m, 4 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₈ F ₂ N ₆ O ₅ +H] ⁺ : 615.21, found: 615.2, t _R = 2.886 min. [Method 3]	Atrop 1	ND
A-157	 N-[4-(6,7-dimethoxy-4-quinazolinylamino)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 11.69 (s, 1 H) 9.41 (s, 1 H) 8.68 (d, J=7.63 Hz, 1 H) 8.33 (s, 1 H) 8.21 (s, 1 H) 7.81 (s, 1 H) 7.71 (s, 1 H) 7.69 (s, 1 H) 7.40 (d, J=7.63 Hz, 1 H) 7.20 (s, 1 H) 6.96 (s, 1 H) 3.93 (s, 6 H) 3.91 (s, 3 H) 2.06 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₃ F ₅ N ₆ O ₅ +H] ⁺ : 643.17, found: 643.3, t _R = 2.007 min. [Method 7]	Atrop 1	ND
A-158	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylthio)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.62 (s, 1 H) 8.75 (s, 1 H) 8.62 (d, J=7.63 Hz, 1 H) 8.17 (s, 1 H) 7.86 (dd, J=11.94, 1.69 Hz, 1 H) 7.52 (s, 1 H) 7.46 (s, 1 H) 7.35 - 7.43 (m, 3 H) 6.93 (s, 1 H) 3.93 (s, 3 H) 3.89 (s, 3 H) 3.87 (s, 3 H) 2.02 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₁ H ₂₃ F ₅ N ₄ O ₅ S+H] ⁺ : 659.13, found: 659.1, t _R = 2.755 min [Method 4]	Racemic	NA

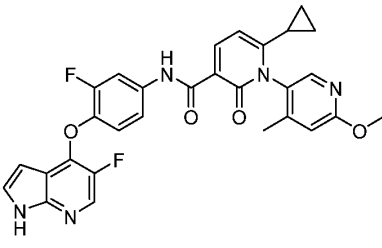
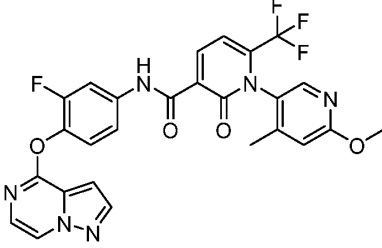
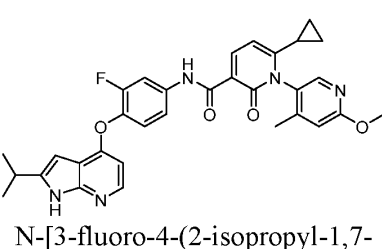
A-159	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)sulfanyl]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.99 (s, 1 H) 8.74 (s, 1 H) 8.46 (d, J=7.88 Hz, 1 H) 8.14 (s, 1 H) 7.86 (dd, J=12.01, 1.75 Hz, 1 H) 7.52 (s, 1 H) 7.45 (s, 1 H) 7.31 - 7.40 (m, 2 H) 6.95 (s, 1 H) 6.48 (d, J=7.88 Hz, 1 H) 3.92 (s, 3 H) 3.89 (s, 3 H) 3.87 (s, 3 H) 2.01 (s, 3 H) 1.30 - 1.39 (m, 1 H) 0.90 - 0.97 (m, 2 H) 0.83 - 0.89 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₈ N ₄ SF ₂ O ₅ +H] ⁺ : 631.17, found: 631.2, t _R = 3.370 min. [Method 4]	Atrop 1 ^A	ND
A-160	 6-cyclopropyl-N-[4-[(6,7-dimethoxy-4-quinolyl)sulfanyl]-3-fluoro-phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 12.16 (s, 1 H) 8.51 (d, J=7.75 Hz, 1 H) 8.43 (d, J=4.88 Hz, 1 H) 8.17 (s, 1 H) 8.03 (dd, J=11.44, 1.94 Hz, 1 H) 7.64 (t, J=8.25 Hz, 1 H) 7.57 (dd, J=8.63, 2.00 Hz, 1 H) 7.40 (s, 1 H) 7.33 (s, 1 H) 6.98 (s, 1 H) 6.66 (d, J=4.75 Hz, 1 H) 6.51 (d, J=7.88 Hz, 1 H) 3.94 (d, J=1.88 Hz, 6 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.34 - 1.41 (m, 1 H) 0.93 - 0.98 (m, 2 H) 0.86 - 0.92 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₉ N ₄ SFO ₅ +H] ⁺ : 613.18, found: 613.2, t _R = 3.285 min. [Method 4]	Atrop 1 ^A	ND
A-161	 N-{3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl}-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.53 (s, 1 H) 8.69 (s, 1 H) 8.62 (d, J=7.50 Hz, 1 H) 8.17 (s, 1 H) 7.79 (dd, J=12.51, 1.88 Hz, 1 H) 7.33 - 7.41 (m, 3 H) 7.27 (dd, J=8.50, 1.88 Hz, 1 H) 7.13 (t, J=8.50 Hz, 1 H) 6.92 (s, 1 H) 4.41 (s, 2 H) 3.90 (d, J=4.00 Hz, 6 H) 3.86 (s, 3 H) 2.02 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₅ F ₅ N ₄ O ₅ +H] ⁺ : 641.17, found: 641.2, t _R = 3.374 min. [Method 8]	Atrop 1	ND

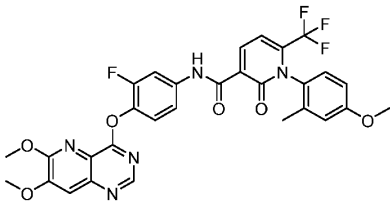
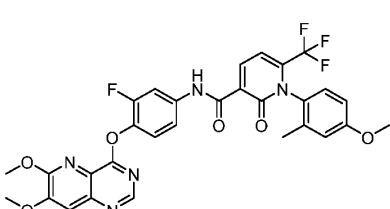
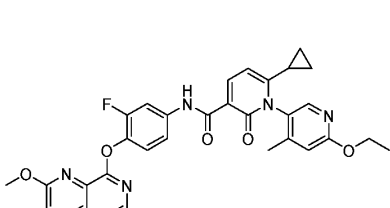
A-162	 6-cyclopropyl-N-[3-fluoro-4-[(3-fluoro-6,7-dimethoxy-4-quinolyl)methyl]phenyl]-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.87 (s, 1 H) 8.68 (s, 1 H) 8.45 (d, J=7.88 Hz, 1 H) 8.13 (s, 1 H) 7.80 (dd, J=12.63, 1.88 Hz, 1 H) 7.39 (s, 1 H) 7.34 (s, 1 H) 7.19 (dd, J=8.38, 1.88 Hz, 1 H) 7.06 - 7.13 (m, 1 H) 6.95 (s, 1 H) 6.46 (d, J=7.88 Hz, 1 H) 4.39 (s, 2 H) 3.90 (d, J=2.50 Hz, 6 H) 3.86 (s, 3 H) 2.00 (s, 3 H) 1.29 - 1.38 (m, 1 H) 0.88 - 0.94 (m, 2 H) 0.82 - 0.88 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₄ H ₃₀ F ₂ N ₄ O ₅ +H] ⁺ : 613.22, found: 613.2, t _R = 3.240 min. [Method 8]	Atrop 1	ND
A-163	 N-[1-(3-fluoro-6,7-dimethoxy-4-quinolyl)-5-indolyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.38 (d, J=1.75 Hz, 1 H) 8.72 (d, J=3.00 Hz, 1 H) 8.64 (d, J=7.50 Hz, 1 H) 8.19 (s, 1 H) 7.71 (br d, J=6.38 Hz, 1 H) 7.44 (s, 1 H) 7.38 (d, J=7.75 Hz, 1 H) 7.23 - 7.29 (m, 1 H) 7.16 (d, J=4.25 Hz, 1 H) 6.95 (s, 1 H) 6.17 (dd, J=8.44, 1.69 Hz, 1 H) 4.22 (br dd, J=4.13, 2.00 Hz, 1 H) 3.96 - 4.04 (m, 1 H) 3.94 (s, 3 H) 3.91 (s, 3 H) 3.78 (d, J=3.50 Hz, 3 H) 3.22 - 3.32 (m, 2 H) 2.05 (s, 3 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₃ H ₂₇ N ₅ O ₅ F ₄ +H] ⁺ : 650.20, found: 650.2, t _R = 3.349 min. [Method 9]	Atrop 1	ND
A-164	 N-[1-(3-fluoro-6,7-dimethoxy-4-quinolyl)-5-indolyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ 11.64 (s, 1 H) 8.70 (d, J=3.13 Hz, 1 H) 8.46 (d, J=7.88 Hz, 1 H) 8.14 (s, 1 H) 7.68 (br d, J=5.25 Hz, 1 H) 7.43 (s, 1 H) 7.18 - 7.24 (m, 1 H) 7.16 (d, J=3.38 Hz, 1 H) 6.96 (s, 1 H) 6.47 (d, J=7.75 Hz, 1 H) 6.14 (d, J=8.66 Hz, 1 H) 4.15 - 4.24 (m, 1 H) 3.98 (br s, 1 H) 3.93 (s, 3 H) 3.91 (s, 3 H) 3.77 (d, J=2.75 Hz, 3 H) 3.21 - 3.28 (m, 2 H) 2.03 (s, 3 H) 1.28 - 1.41 (m, 1 H) 0.89 - 0.95 (m, 2 H) 0.82 - 0.88 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₅ H ₃₂ N ₅ O ₅ F+H] ⁺ : 622.24, found: 622.2, t _R = 3.195 min. [Method 9]	Racemic	NA

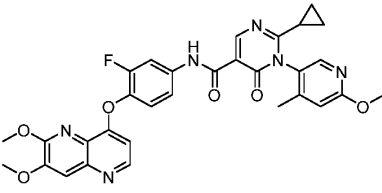
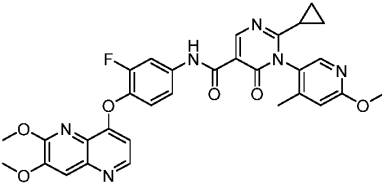
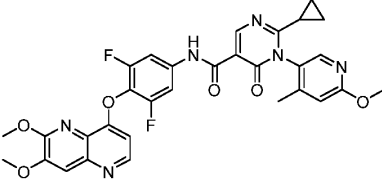
A-165	 N-[4-(1,7-diaza-1H-inden-4-yloxy)-3-fluorophenyl]-1-(5-cyano-4-fluoro-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR δ 12.10 (br s, 1 H) 11.90 (s, 1 H) 8.52 (d, J=7.76 Hz, 1 H) 8.18 (t, J=5.75 Hz, 2 H) 8.03 (br d, J=13.01 Hz, 1 H) 7.77 (d, J=10.13 Hz, 1 H) 7.51 (dd, J=8.88, 1.50 Hz, 1 H) 7.46 (br s, 1 H) 7.40 (s, 1 H) 6.53 (d, J=7.63 Hz, 2 H) 6.33 (br s, 1 H) 2.15 (s, 3 H) 1.36 (br d, J=13.51 Hz, 1 H) 0.84 - 0.96 (m, 4 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₀ H ₂₁ O ₃ N ₅ F ₂ +H] ⁺ : 538.52, found: 538.2, t _R = 2.973 min. [Method 10]	Racemic	NA
A-166	 N-[4-(1,7-diaza-1H-inden-4-yloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.99 (s, 1 H) 11.76 (br s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.16 (s, 1 H) 8.07 (d, J=5.50 Hz, 1 H) 8.00 (dd, J=13.01, 2.38 Hz, 1 H) 7.46 (dd, J=8.94, 1.56 Hz, 1 H) 7.30 - 7.40 (m, 2 H) 6.97 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.38 (d, J=5.38 Hz, 1 H) 6.22 (dd, J=3.38, 1.88 Hz, 1 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.30 - 1.42 (m, 1 H) 0.90 - 0.97 (m, 2 H) 0.82 - 0.90 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₂₉ H ₂₄ FN ₅ O ₄ +H] ⁺ : 526.18, found: 526.2, t _R = 2.986 min. [Method 10]	Racemic	NA
A-167	 N-[4-(1,7-diaza-1H-inden-4-yloxy)-3-fluorophenyl]-1-(5-cyano-4-ethoxy-2-tolyl)-6-cyclopropyl-2-oxo-1,2-dihydronicotinamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.99 (s, 1 H) 11.77 (br s, 1 H) 8.50 (d, J=7.88 Hz, 1 H) 8.07 (d, J=5.38 Hz, 1 H) 8.00 (dd, J=13.07, 2.31 Hz, 1 H) 7.90 (s, 1 H) 7.44 - 7.51 (m, 1 H) 7.31 - 7.41 (m, 3 H) 6.48 (d, J=7.88 Hz, 1 H) 6.38 (d, J=5.38 Hz, 1 H) 6.23 (dd, J=3.31, 1.69 Hz, 1 H) 4.20 - 4.34 (m, 2 H) 2.10 (s, 3 H) 1.42 (t, J=6.94 Hz, 3 H) 1.29 - 1.37 (m, 1 H) 0.90 - 0.97 (m, 2 H) 0.82 - 0.90 (m, 2 H); MS(ES ⁺) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₂₆ FN ₅ O ₄ +H] ⁺ : 564.19, found: 564.2, t _R = 3.079 min. [Method 10]	Racemic	NA

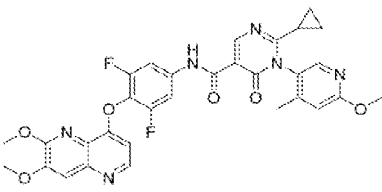
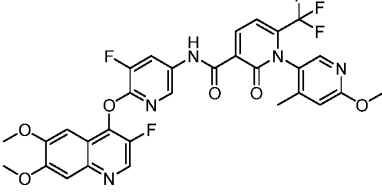
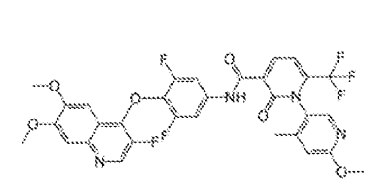
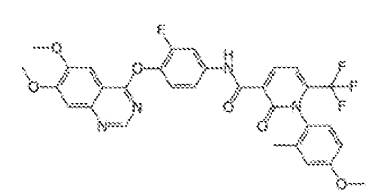
A-168	 N-[3-fluoro-4-(2-oxo-1,7-diaza-4-indanyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ = 11.63 (s, 1 H) 11.06 (s, 1 H) 8.66 (d, J=7.63 Hz, 1 H) 8.19 (s, 1 H) 7.95 - 8.03 (m, 2 H) 7.54 (dd, J=8.88, 1.13 Hz, 1 H) 7.28 - 7.43 (m, 2 H) 6.95 (s, 1 H) 6.38 (d, J=6.13 Hz, 1 H) 3.91 (s, 3 H) 3.39 (s, 2 H) 2.05 (s, 3 H); MS(ES+) m/z calc'd for [M+H]⁺ [C₂₇H₁₉F₄N₅O₅+H]⁺: 570.13, found: 570.2, <i>t</i>_R= 2.985 min. [Method 10]	Racemic	NA
A-169	 N-[4-(1,5,7a-triaza-4-indenyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 11.98 (s, 1 H) 8.55 (dd, J=4.82, 0.69 Hz, 1 H) 8.48 - 8.53 (m, 1 H) 8.21 (d, J=2.38 Hz, 1 H) 8.17 (s, 1 H) 7.94 - 8.00 (m, 1 H) 7.40 - 7.48 (m, 2 H) 7.35 - 7.39 (m, 1 H) 7.11 - 7.17 (m, 1 H) 6.97 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.28 - 1.45 (m, 1 H) 0.91 - 0.96 (m, 2 H) 0.84 - 0.90 (m, 2 H); MS(ES+) m/z calc'd for [M+H]⁺ [C₂₈H₂₃O₄FN₆+H]⁺: 526.5, found: 527.2, <i>t</i>_R= 3.156 min. [Method 10]	Racemic	NA
A-170	 N-[4-(1,7a-diaza-3-indenyloxy)-3-fluorophenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹H NMR (400 MHz, DMSO-<i>d</i>₆): δ 11.85 (s, 1 H) 8.62 (d, J=7.00 Hz, 1 H) 8.47 (d, J=7.88 Hz, 1 H) 8.15 (s, 1 H) 8.05 (s, 1 H) 7.95 (dd, J=13.38, 2.38 Hz, 1 H) 7.46 (d, J=8.88 Hz, 1 H) 7.24 (dt, J=8.97, 1.20 Hz, 1 H) 7.18 (ddd, J=8.91, 6.72, 0.75 Hz, 1 H) 6.96 (s, 1 H) 6.90 - 6.95 (m, 1 H) 6.86 - 6.90 (m, 1 H) 6.48 (d, J=7.88 Hz, 1 H) 3.90 (s, 3 H) 2.02 (s, 3 H) 1.31 - 1.40 (m, 1 H) 0.89 - 0.95 (m, 2 H) 0.86 (dt, J=8.10, 2.58 Hz, 2 H); MS(ES+) m/z calc'd for [M+H]⁺ [C₂₉H₂₄FN₅O₄+H]⁺: 526.18, found: 526.2, <i>t</i>_R= 3.191 min. [Method 10]	Racemic	NA

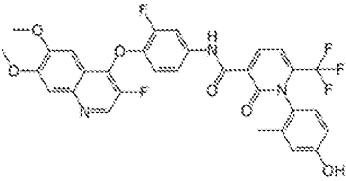
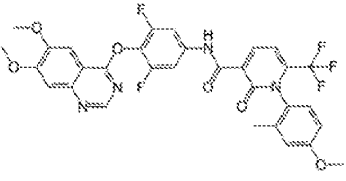
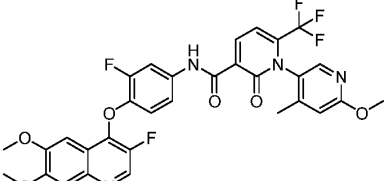
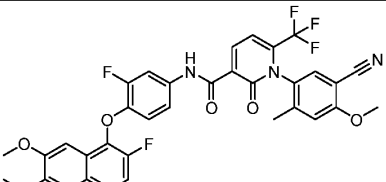
A-171	 N-[4-(1,7a-diaza-3-indenyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.51 (s, 1 H) 8.64 (dd, J=7.32, 4.32 Hz, 2 H) 8.18 (s, 1 H) 8.06 (s, 1 H) 7.95 (dd, J=13.26, 2.50 Hz, 1 H) 7.46 (d, J=9.01 Hz, 1 H) 7.38 (d, J=7.63 Hz, 1 H) 7.29 - 7.34 (m, 1 H) 7.15 - 7.22 (m, 1 H) 6.86 - 7.00 (m, 3 H) 3.90 (s, 3 H) 2.03 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₂₇ H ₁₉ F ₄ N ₅ O ₄ +H] ⁺ : 554.14, found: 554.2, t _R =3.326 min. [Method 10]	Atrop 1	ND
A-172	 N-[3-fluoro-4-(5-fluoro-1,7-diaza-1H-inden-4-yloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆) δ = 11.93 (br s, 1 H) 11.62 (s, 1 H) 8.66 (d, J=7.50 Hz, 1 H) 8.29 (d, J=3.75 Hz, 1 H) 8.19 (s, 1 H) 7.99 (dd, J=13.01, 2.38 Hz, 1 H) 7.48 (dd, J=8.88, 1.13 Hz, 1 H) 7.39 (d, J=7.63 Hz, 2 H) 7.30 (t, J=9.07 Hz, 1 H) 6.95 (s, 1 H) 5.61 (d, J=3.38 Hz, 1 H) 3.90 (s, 3 H) 2.05 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₂₇ H ₁₈ F ₅ N ₅ O ₄ +H] ⁺ : 572.13, found: 572.1, t _R =3.249 min. [Method 10]	Atrop 1	ND
A-173	 N-[3-fluoro-4-(5-fluoro-1,7-diaza-1H-inden-3-yloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO-d ₆): δ = 11.85 (s, 1 H) 11.72 - 11.80 (m, 1 H) 8.47 (d, J=7.88 Hz, 1 H) 8.22 - 8.31 (m, 1 H) 8.15 (s, 1 H) 7.94 (dd, J=13.32, 2.44 Hz, 1 H) 7.60 (dd, J=9.01, 2.75 Hz, 1 H) 7.55 (s, 1 H) 7.22 (br d, J=9.01 Hz, 1 H) 6.90 - 6.98 (m, 2 H) 6.48 (d, J=7.88 Hz, 1 H) 3.90 (s, 3 H) 2.02 (s, 3 H) 1.31 - 1.41 (m, 1 H) 0.83 - 0.94 (m, 4 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₂₉ H ₂₃ F ₂ N ₅ O ₄ +H] ⁺ : 544.17, found: 544.2, t _R =3.163 min. [Method 10]	Racemic	NA

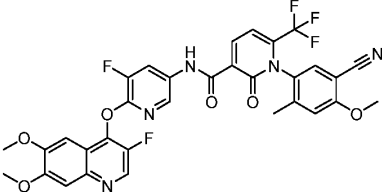
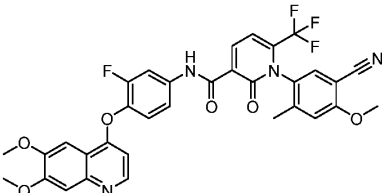
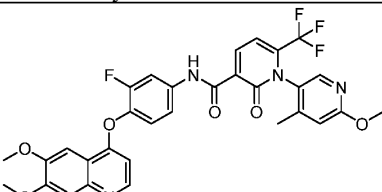
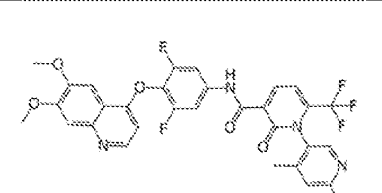
A-174	 N-[3-fluoro-4-(5-fluoro-1,7-diaza-1H-inden-4-yloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ = 11.98 (s, 1 H) 11.91 (br s, 1 H) 8.50 (d, J=7.88 Hz, 1 H) 8.29 (d, J=3.75 Hz, 1 H) 8.17 (s, 1 H) 7.99 (dd, J=13.13, 2.38 Hz, 1 H) 7.39 - 7.44 (m, 1 H) 7.35 - 7.39 (m, 1 H) 7.25 - 7.32 (m, 1 H) 6.97 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 5.60 (dd, J=3.44, 1.81 Hz, 1 H) 3.91 (s, 3 H) 2.04 (s, 3 H) 1.31 - 1.44 (m, 1 H) 0.91 - 0.97 (m, 2 H) 0.85 - 0.91 (m, 2 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₂₉ H ₂₃ F ₂ N ₅ O ₄ +H] ⁺ : 544.17, found: 544.3, t _R = 2.323 min. [Method 10]	Racemic	NA
A-175	 N-(3-fluoro-4-pyrazolo[1,5-a]pyrazin-4-yloxy-phenyl)-1-(6-methoxy-4-methyl-3-pyridyl)-2-oxo-6-(trifluoromethyl)pyridine-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.63 (s, 1 H) 8.68 (d, J=7.50 Hz, 1 H) 8.56 (d, J=4.75 Hz, 1 H) 8.17 - 8.26 (m, 2 H) 7.96 (br d, J=1.75 Hz, 1 H) 7.54 (br d, J=9.51 Hz, 1 H) 7.47 (t, J=8.69 Hz, 1 H) 7.35 - 7.41 (m, 2 H) 7.09 - 7.17 (m, 1 H) 6.95 (s, 1 H) 3.91 (s, 3 H) 2.06 (s, 3 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₂₆ H ₁₈ O ₄ F ₄ N ₆ +H] ⁺ : 555.13, found: 555.2, t _R = 3.289 min. [Method 10]	Atrop 1	ND
A-176	 N-[3-fluoro-4-(2-isopropyl-1,7-diaza-1H-inden-4-yloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆): δ 11.98 (s, 1 H) 11.64 (s, 1 H) 8.51 (d, J=7.88 Hz, 1 H) 8.17 (s, 1 H) 7.93 - 8.03 (m, 2 H) 7.45 (br d, J=8.75 Hz, 1 H) 7.30 (t, J=8.94 Hz, 1 H) 6.97 (s, 1 H) 6.50 (d, J=7.88 Hz, 1 H) 6.30 (d, J=5.38 Hz, 1 H) 6.00 (d, J=1.50 Hz, 1 H) 3.91 (s, 3 H) 2.96 - 3.04 (m, 1 H) 2.04 (s, 3 H) 1.34 - 1.41 (m, 1 H) 1.27 (d, J=6.88 Hz, 6 H) 0.85 - 0.97 (m, 4 H); MS(ES+) m/z calc'd for [M+H] ⁺ [C ₃₂ H ₃₀ O ₄ N ₅ F+H] ⁺ : 568.23, found: 568.3, t _R = 3.320 min. [Method 11]	Racemic	NA

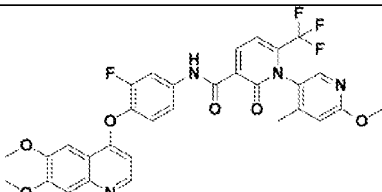
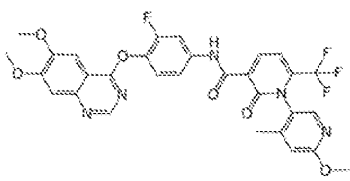
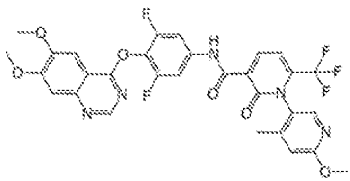
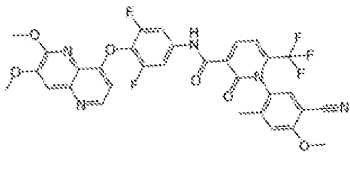
A-177	 N-(4-(((6,7-dimethoxy-2,3-dihydro-4H-pyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-1-(4-methoxy-2-methylphenyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.78 (s, 1 H) 8.67 (d, <i>J</i> =7.50 Hz, 1 H) 8.60 (s, 1 H) 7.98 (dd, <i>J</i> =12.57, 2.19 Hz, 1 H) 7.66 (s, 1 H) 7.52 - 7.58 (m, 1 H) 7.40 - 7.50 (m, 1 H) 7.34 (dd, <i>J</i> =14.38, 8.25 Hz, 2 H) 7.01 (d, <i>J</i> =2.50 Hz, 1 H) 6.90 - 6.97 (m, 1 H) 4.09 (s, 3 H) 3.99 - 4.06 (m, 3 H) 3.82 (s, 3 H) 2.02 (s, 3 H); MS(ES+) <i>m/z</i> calc'd for [C ₃₀ H ₂₃ F ₄ N ₅ O ₆ +H] ⁺ : 625, found: 626, <i>t</i> _R = 5.198 min. [Method 5]	Atrop 1	+83.36
A-178	 6-cyclopropyl-N-(4-(((6,7-dimethoxy-2,3-dihydro-4H-pyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-6'-methoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.99 (s, 1H), 8.60 (s, 1H), 8.52-8.510 (d, <i>J</i> = 7.6 Hz, 1H), 8.18 (s, 1H), 7.98 (dd, <i>J</i> = 2.0, 14.8 Hz, 1H), 7.66 (s, 1H), 7.49-7.40 (m, 2H), 6.98 (s, 1H), 6.51 (d, <i>J</i> = 7.6 Hz, 1H), 4.09 (s, 3H), 4.02 (s, 3H), 3.92 (s, 3H), 2.05 (s, 3H), 1.38-1.36 (m, 1H), 0.94 - 0.88 (m, 4H); MS(ES+) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₇ FN ₆ O ₆ +H] ⁺ : 599.1, found: 599.42, <i>t</i> _R =5.14 min. [Method 5]	Atrop 2	-19.44
A-179	 6-cyclopropyl-N-(4-(((6,7-dimethoxy-2,3-dihydro-4H-pyrido[3,2-d]pyrimidin-4-yl)oxy)-3-fluorophenyl)-6'-ethoxy-4'-methyl-2-oxo-2H-[1,3'-bipyridine]-3-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.99 (s, 1 H) 8.60 (s, 1 H) 8.52 (d, <i>J</i> =7.88 Hz, 1 H) 8.15 (s, 1 H) 7.98 (dd, <i>J</i> =12.82, 2.31 Hz, 1 H) 7.66 (s, 1 H) 7.47 - 7.50 (m, 1 H) 7.40 - 7.45 (m, 1 H) 6.95 (s, 1 H) 6.51 (d, <i>J</i> =7.88 Hz, 1 H) 4.37 (td, <i>J</i> =7.04, 2.44 Hz, 2 H) 4.09 (s, 3 H) 4.03 (s, 3 H) 2.05 (s, 3 H) 1.36 (t, <i>J</i> =7.00 Hz, 4 H) 0.87 - 0.95 (m, 4 H); MS(ES+) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₂ H ₂₉ FN ₆ O ₆ +H] ⁺ : 613.21, found: 613.39, <i>t</i> _R = 5.03 min. [Method 5]	Atrop 1 ^B	ND

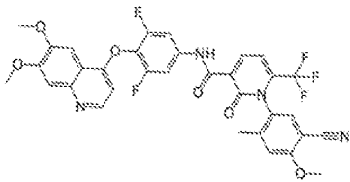
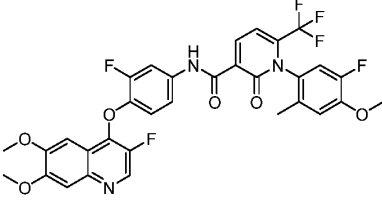
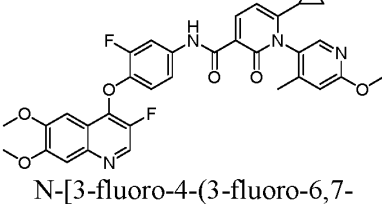
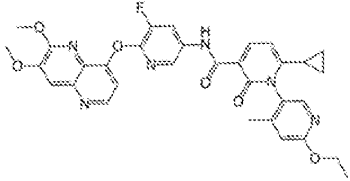
A-180	 2-cyclopropyl-N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-1-(6-methoxy-4-methylpyridin-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.17 (s, 1 H) 8.82 (s, 1 H) 8.55 (d, <i>J</i> =5.13 Hz, 1 H) 8.28 (s, 1 H) 7.99 (dd, <i>J</i> =13.01, 2.38 Hz, 1 H) 7.65 (s, 1 H) 7.47 (dd, <i>J</i> =8.94, 1.19 Hz, 1 H) 7.32 (t, <i>J</i> =9.01 Hz, 1 H) 7.01 (s, 1 H) 6.84 (d, <i>J</i> =5.25 Hz, 1 H) 3.97 (s, 3 H) 3.92 (s, 6 H) 2.11 (s, 3 H) 1.52 (dq, <i>J</i> =8.21, 4.02 Hz, 1 H) 1.22 - 1.29 (m, 2 H) 1.09 (br dd, <i>J</i> =8.07, 3.44 Hz, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₇ FN ₆ O ₆ +H] ⁺ : 598.5, found: 599.5, <i>t</i> _R = 4.77 min. [Method 5]	Atrop 1	-42.56
A-181	 2-cyclopropyl-N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3-fluorophenyl)-1-(6-methoxy-4-methylpyridin-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.17 (s, 1 H) 8.82 (s, 1 H) 8.55 (d, <i>J</i> =5.13 Hz, 1 H) 8.28 (s, 1 H) 7.99 (dd, <i>J</i> =13.01, 2.38 Hz, 1 H) 7.65 (s, 1 H) 7.47 (dd, <i>J</i> =8.94, 1.19 Hz, 1 H) 7.32 (t, <i>J</i> =9.01 Hz, 1 H) 7.01 (s, 1 H) 6.84 (d, <i>J</i> =5.25 Hz, 1 H) 3.97 (s, 3 H) 3.92 (s, 6 H) 2.11 (s, 3 H) 1.49 - 1.56 (m, 1 H) 1.22 - 1.28 (m, 2 H) 1.09 (br dd, <i>J</i> =8.07, 3.44 Hz, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₇ FN ₆ O ₆ +H] ⁺ : 598.5, found: 599.5, <i>t</i> _R = 4.77 min. [Method 5]	Atrop 2	+53.2
A-182	 2-cyclopropyl-N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3,5-difluorophenyl)-1-(6-methoxy-4-methylpyridin-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.25 (s, 1 H) 8.82 (s, 1 H) 8.56 (d, <i>J</i> =5.13 Hz, 1 H) 8.29 (s, 1 H) 7.78 (br d, <i>J</i> =10.26 Hz, 2 H) 7.66 (s, 1 H) 7.01 (s, 1 H) 6.94 (d, <i>J</i> =5.13 Hz, 1 H) 3.97 (s, 3 H) 3.92 (s, 6 H) 2.11 (s, 3 H) 1.51 - 1.58 (m, 1 H) 1.25 (br dd, <i>J</i> =8.25, 4.25 Hz, 2 H) 1.07 - 1.14 (m, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₆ F ₂ N ₆ O ₆ +H] ⁺ : 616.19, found: 617.44, <i>t</i> _R = 4.64 min. [Method 5]	Atrop 1	-55.92

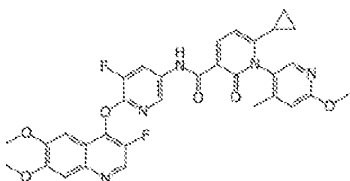
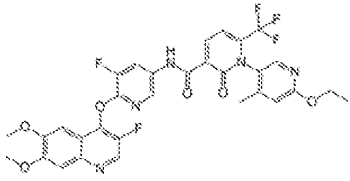
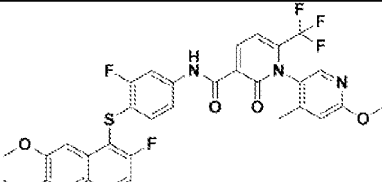
A-183	 2-cyclopropyl-N-(4-((6,7-dimethoxy-1,5-naphthyridin-4-yl)oxy)-3,5-difluorophenyl)-1-(6-methoxy-4-methylpyridin-3-yl)-6-oxo-1,6-dihydropyrimidine-5-carboxamide	¹ HNMR (400 MHz, DMSO- <i>d</i> ₆) δ ppm 11.25 (s, 1 H) 8.82 (s, 1 H) 8.56 (d, <i>J</i> =5.25 Hz, 1 H) 8.28 (s, 1 H) 7.78 (d, <i>J</i> =10.26 Hz, 2 H) 7.66 (s, 1 H) 7.01 (s, 1 H) 6.93 (d, <i>J</i> =5.25 Hz, 1 H) 3.97 (s, 3 H) 3.92 (d, <i>J</i> =0.75 Hz, 6 H) 2.11 (s, 3 H) 1.50 - 1.58 (m, 1 H) 1.21 - 1.30 (m, 2 H) 1.06 - 1.14 (m, 2 H); MS(ES ⁺) <i>m/z</i> calc'd for [M+H] ⁺ [C ₃₁ H ₂₆ F ₂ N ₆ O ₆] ⁺ : 616.19, found: 617.44, <i>t</i> _R =4.643 min. [Method 5]	Atrop 2	+14.8
A-184	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES ⁺) calc. for [C ₃₀ H ₂₂ F ₅ N ₅ O ₆ +H] ⁺ 644.16, found 644.56 HPLC: CHIRALPAK-1K (250 x 4.6mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN COLUMN ID: M-ARD-CAL-028 <i>t</i> _R = 5.2 min	Atrop 1	+21
A-185	 N-[3,5-difluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES ⁺) calc. for [C ₃₁ H ₂₂ F ₆ N ₄ O ₆ +H] ⁺ 661.15, found 661.53 HPLC: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028 <i>t</i> _R = 5.9 min	Atrop 1	+68
A-186	 N-[4-(6,7-dimethoxy-4-quinazolinylloxy)-3-fluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES ⁺) calc. for [C ₃₁ H ₂₄ F ₄ N ₄ O ₆ +H] ⁺ 625.17, found 625.10 HPLC: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028. <i>t</i> _R = 7.3 min	Atrop 1	+28.8

A-187	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(4-hydroxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C₃₁H₂₂F₅N₃O₆+H]⁺ 628.15, found 628.46. HPLC: CHIRALCEL OX-H (150*4.6mm,5μm), Mobile Phase A: CO₂, Mobile Phase B: MeOH, A/B: 70:30, Flow: 2g-30%, COLUMN ID: M-ARD-CAL-051. t_R = 6.7 min	Atrop 1	+93.6
A-188	 N-[4-(6,7-dimethoxy-4-quinazolinylloxy)-3,5-difluorophenyl]-1-(4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C₃₁H₂₃F₅N₄O₆+H]⁺ 643.16, found 643.28 HPLC: CHIRALPAK-IK (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 14.6 min	Atrop 1	+57.8
A-189	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C₃₁H₂₃F₅N₄O₆+H]⁺ 643.16, found 643.31 HPLC: CHIRALPAK-IK (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 6.9 min	Atrop 2	-34.6
A-190	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C₃₃H₂₃F₅N₄O₆+H]⁺ 667.16, found 667.2 HPLC: CHIRALPAK IK (250 x 4.6mm, 5μm) Mobile Phase A: EtOH / MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 5.9 min	Atrop 1	+19

A-191	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C32H22F5N5O6+H]⁺ 668.16, found 667.9 HPLC: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028. t_R = 5.5 min	Atrop 1	+50.8
A-192	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C33H24F4N4O6+H]⁺ 649.17, found 649.30 HPLC: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 7.1 min	Atrop 1	+185.2
A-193	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C31H24F4N4O6+H]⁺ 625.17, found 625.38 HPLC: CHIRALPAK-1K (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 20/80 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028. t_R = 6.4 min	Atrop 2	+37.4
A-194	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C31H23F5N4O6+H]⁺ 643.16, found 643.48 HPLC: CHIRALPAK-1K (150X4.6mm,5μm), Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 80/20 Flow: 1.0 ml/MIN, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 4.1 min	Atrop 1	+49.4

A-195	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C₃₁H₂₄F₄N₄O₆+H]⁺ 625.17, found 625.32 HPLC: CHIRALPAK-IK (250 x 4.6 mm, 5μm) Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN A/B: 20/80 Flow: 1.5 ml/MIN, COLUMN ID: M-ARD-CAL-028. t_R = 5.1 min	Atrop 1	+110.2
A-196	 N-[4-(6,7-dimethoxy-4-quinazolinyloxy)-3-fluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C₃₀H₂₃F₄N₅O₆+H]⁺ 626.17, found 626.45 HPLC: CHIRALPAK IK (250X4.6mm, 5μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL-028 t_R = 5.5 min	Atrop 1	+247.6
A-197	 N-[4-(6,7-dimethoxy-4-quinazolinyloxy)-3,5-difluorophenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C₃₀H₂₂F₅N₅O₆+H]⁺ 644.16, found 644.43 HPLC: CHIRALPAK IK (250*4.6mm, 5μm) Mobile Phase A : EtOH/MeOH (50/50) Mobile Phase B : ACN A B : 80:20 Flow: 1.5 ml/MIN Column ID : M-ARD\CAL-028. t_R = 5.7 min	Atrop 1	+45.4
A-198	 N-[4-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-3,5-difluorophenyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C₃₂H₂₂F₅N₅O₆+H]⁺ 668.16, found 668.45 HPLC: CHIRALPAK IK (250X4.6mm, 5μm), Mobile Phase A: EtOH/MeOH (50/50) Mobile Phase B: ACN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL/OLD-028. t_R = 3.5 min	Atrop 1	-53.4

A-199	 N-[4-(6,7-dimethoxy-4-quinolyloxy)-3,5-difluorophenyl]-1-(5-cyano-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C33H23F5N4O6+H]⁺ 667.16, found 667.46 HPLC: CHIRALPAK IK (250X4.6mm, 5μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A B: 80:20, Flow rate: 1.50mL/min, Column ID: M-ARD-CAL/OLD-028. t_R = 3.5 min	Atrop 1	-29.6
A-200	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-1-(5-fluoro-4-methoxy-2-tolyl)-2-oxo-6-(trifluoromethyl)-1,2-dihydronicotinamide	MS (ES+) calc. for [C32H23F6N3O6+H]⁺ 660.16, found 660.43 HPLC: CHIRALPAK IK (250X4.6 mm, 5μm), Mobile Phase A : EtOH/MeOH (50/50), Mobile Phase B : ACN, A/B : 80:20, Flow: Flow rate : 1.50 ml/min, COLUMN ID: M-ARD-CAL/OLD-028. t_R = 3.7 min	Atrop 1	+89.8
A-201	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)phenyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C33H28F2N4O6+H]⁺ 615.21, found 615.36 HPLC: CHIRALPAK IK (250*4.6mm, 5μm) Mobile Phase A : EtOH/MeOH (50/50) Mobile Phase B : ACN A B : 80:20 Flow: 1.5 ml/MIN Column ID : M-ARD-CAL-028. t_R = 7.2 min	Atrop 2	-11.2
A-202	 N-[6-(6,7-dimethoxy-1,5-diaza-4-naphthyloxy)-5-fluoro-3-pyridyl]-6-cyclopropyl-6'-ethoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C32H29FN6O6+H]⁺ 613.22, found 613.49 HPLC: CHIRALPAK IK (250X4.6mm, 5μm), Mobile Phase A: EtOH/MeOH (50/50), Mobile Phase B: ACN, A B: 80:20, Flow rate: 1.50mL/Min, Column ID: M-ARD-CAL-028. t_R = 5.4 min	Atrop 1	-9.84

A-203	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-6-cyclopropyl-6'-methoxy-4'-methyl-2-oxo-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C ₃₂ H ₂₇ F ₂ N ₅ O ₆ +H] ⁺ 616.20, found 616.20	Racemic	NA
A-204	 N-[5-fluoro-6-(3-fluoro-6,7-dimethoxy-4-quinolyloxy)-3-pyridyl]-6'-ethoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C ₃₁ H ₂₄ F ₅ N ₅ O ₆ +H] ⁺ 658.17, found 658.30	Racemic	NA
A-205	 N-[3-fluoro-4-(3-fluoro-6,7-dimethoxy-4-quinolylthio)phenyl]-6'-methoxy-4'-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydro[1,3'-bipyridyl]-3-carboxamide	MS (ES+) calc. for [C ₃₁ H ₂₃ F ₅ N ₄ O ₅ S+H] ⁺ 659.14, found 659.10 HPLC: Chiralpak AD-3, (50×4.6mm I.D., 3μm) Mobile phase: A: CO ₂ B:EtOH[0.2%NH ₃ (7M in MeOH)] Gradient: A:B=50:50 Flow rate: 4mL/min t _R = 1.56 min	Atrop 1	+16.2

^APrepared using Intermediate 59 atropisomer 1.

^BPrepared using Intermediate 64 atropisomer 1.

^CSOR: Specific optical rotation; ND: Not determined; NA: Not applicable.

Biochemical Assays

BRET Assay

[1266] The following experiments were conducted using the Nano BRET™ TE from Promega. Specific components and conditions were used to obtain the PLK4 IC₅₀ results are summarized below.

NanoBRET Construct	NanoLuc©-PLK4 Fusion Vector (Promega, Catalog NV1881)
Cell Line	HEK-293 Cell Line (ATCC, Catalog CRL-1573)
Tracer Used	K-10 Tracer [NanoBRET TE Intracellular Kinase Detection Reagent, K-10 (Promega, Catalog N2840)
[Tracer] Km	282.6
[Tracer] for assay	200
Compound “Pre-incubation Time”	4 h
Tracer Incubation Time	2 h

GENERAL PROTOCOL:

Bacterial Transformation:

[1267] Frozen Competent Cells (Promega; Cat #L2005) were thawed on ice. 25 ng of DNA was added per 50 µl tube of Competent Cells. The tubes were quickly flicked several times and were immediately returned to ice for 30 minutes. The competent cells were subjected to Heat-shock for 15–20 seconds in a water bath at exactly 42 °C. The tubes were immediately returned to ice for 2 minutes. 450 µl of room temperature SOC medium was then added to each transformation reaction. The tubes were incubated for 60 minutes at 37 °C with shaking. 100 µl of the undiluted SOC was then spread onto agar plates containing 50 µg/ml Kanamycin. The plates were Incubated at 37°C for 12–14 hours.

Plasmid Amplification and Purification

[1268] Single colony was picked and inoculated to 2 ml LB broth containing antibiotic 50 ug/ml kanamycin. After 4-6 hours of incubation in bacterial shaker, 1 ml of bacterial culture was inoculated to 100 ml LB broth for plasmid amplification. After 12-16 hours of incubation at 37

°C on bacterial shaker, bacterial cells were collected and lysed for plasmid purification using HiSpeed® Plasmid Midi Kit (Qiagen; Cat#12643) as per the manufacturer's instructions. Purified plasmids were quantified using NanoDrop and aliquoted for storage in -20 °C. The remaining 1 ml of bacterial culture from Step-2 was used for glycerol stock preparation. 1 part of Glycerol was added to 4 parts of Bacterial culture, mixed well, and stored in -80 °C.

Transient Transfection of HEK293: (As per Promega)

[1269] HEK293 cells were trypsinized and adjusted the cell density to 2×10^5 cells/ml using complete medium. DNA-lipid complexes were prepared for transfection as per the Promega: 1 µg Nano Luc Fusion DNA mixed with 4 µg Carrier DNA in 500 µl Opti-MEM. 15 µl of FuGENE® HD Transfection Reagent (Promega; Cat#E2312) was added and mixed well. The resulting media was incubated at ambient temperature for 20 minutes to allow complexes to form. 1 part of lipid: DNA complex (e.g., 1ml) was mixed with 10 parts of HEK293 cells (e.g., 10 ml) in suspension at 2×10^5 cells/ml. This was mixed gently by inversion 5 times. 10,000 cells (25 µl) were seeded/well in Poly-D-Lysine coated 384-well plate (PerkinElmer; Cat#6007680). The next day, cells were treated with different concentrations of staurosporine and Kinase specific tool compound. 1 hr later, K10 Tracer was added for tracer titration. After 2 hours of incubation, plates were equilibrated to room temperature for 15 minutes. 20 µl of 3X Complete Substrate plus Inhibitor Solution (freshly prepared as per the instruction from the Promega; Cat#N2161) was added per well. After 2-3 mins, measured donor emission wavelength (e.g., 450 nm) and acceptor emission wavelength (e.g., 610 nm). BRET ratios were determined, and a background correction was performed with no tracer controls. The % displacement and % binding were calculated using milli BRET ratios and plotted to obtain the PLK4 NanoBRET IC₅₀ values summarized in **TABLE 3**.

[1270] NanoBRET™ ratio equation:

$$BRET\ Ratio = \frac{Acceptor_{sample}}{Donor_{sample}} \times 1000$$

[1271] NanoBRET™ ratio equation, including optional background correction:

$$BRET\ Ratio = \left[\left(\frac{Acceptor_{sample}}{Donor_{sample}} \right) - \left(\frac{Acceptor_{no-tracer\ control}}{Donor_{no-tracer\ control}} \right) \right] \times 1000$$

[1272] The results from this assay are shown in in **TABLE 3**, where A: ≤ 100 nM; B: >100 nM to 1 µM; C: ≥ 1 µM.

TABLE 3.

Ex. No.	Nano BRET PLK4
2	C
4	A
5	B
6	B
7	B
8	B
9	B
10	B
11	B
12	B
13	B
14	C
15	A
16	B
17	B
18	B
19	A
20	C
21	B
22	A
23	C
24	A
25	B
26	C
27	A
28	B
29	B
30	B
31	B
32	A
33	B
34	B
35	A
36	B
40	B
44	C
45	A

Ex. No.	Nano BRET PLK4
46	B
47	B
48	C
49	B
50	A
51	B
52	B
53	A
54	B
55	A
56	C
57	A
58	C
59	A
60	B
61	B
62	A
63	C
64	A
65	C
66	A
67	B
68	C
69	B
70	B
71	C
72	B
73	C
74	A
75	B
76	A
77	C
78	B
79	C
80	C
81	A
82	C

Ex. No.	Nano BRET PLK4
83	A
84	B
85	B
86	A
87	C
88	B
89	C
90	C
91	C
92	A
93	C
94	A
95	B
96	A
97	C
98	A
99	C
100	B
101	B
102	C
103	B
104	A
105	B
106	C
107	A
108	A
109	A
110	B
111	C
112	A
113	C
114	B
115	B
116	B
117	C
118	C
119	C

WO 2025/096463

Ex. No.	Nano BRET PLK4
120	A
121	A
122	A
123	A
124	B
125	C
126	A
127	B
128	A
129	A
130	A
131	B
132	A
133	A
134	A
135	A
136	A
137	C
138	A
139	A
140	B
141	C
142	C
143	A
144	A
145	C
146	A
147	A
148	B
149	A
150	B
151	A
152	B
153	A
154	A
155	B
156	A
157	C

PCT/US2024/053448

Ex. No.	Nano BRET PLK4
A-17	B
A-18	A
A-19	C
A-21	A
A-22	A
A-23	A
A-24	A
A-25	A
A-26	A
A-27	A
A-28	A
A-29	A
A-33	C
A-34	A
A-35	A
A-36	A
A-37	A
A-38	C
A-39	A
A-40	B
A-41	B
A-42	B
A-43	B
A-44	A
A-45	B
A-46	A
A-47	A
A-48	A
A-49	A
A-50	B
A-51	B
A-53	A
A-54	A
A-55	A
A-56	A
A-57	C
A-58	A
A-59	C

WO 2025/096463

Ex. No.	Nano BRET PLK4
A-60	A
A-61	A
A-62	B
A-65	A
A-66	C
A-67	A
A-68	A
A-69	B
A-70	C
A-71	A
A-72	C
A-73	A
A-74	C
A-75	A
A-76	A
A-77	C
A-78	A
A-79	C
A-80	A
A-81	C
A-82	A
A-83	C
A-84	A
A-85	B
A-86	A
A-87	B
A-90	A
A-91	A
A-92	B
A-93	B
A-94	A
A-95	A
A-96	B
A-98	B
A-99	A
A-100	C
A-101	A
A-102	B

PCT/US2024/053448

Ex. No.	Nano BRET PLK4
A-149	C
A-150	A
A-151	A
A-152	C
A-153	A
A-154	C
A-155	C
A-156	B
A-157	B
A-158	A
A-161	B
A-163	C
A-164	C
A-167	C
A-168	C
A-169	C
A-170	C
A-171	C
A-172	B
A-175	C
A-184	A
A-185	A
A-186	A
A-187	A
A-188	A
A-189	C
A-190	C
A-191	C
A-193	C
A-194	A
A-195	A
A-196	A
A-197	A
A-198	C
A-199	C
A-200	B
A-201	B
A-202	A

Ex. No.	Nano BRET PLK4
A-203	A
A-204	A

Ex. No.	Nano BRET PLK4
A-205	A

PLK4 ADP Kinase Assay

[1273] Test compounds (4.5 mM stock in DMSO) were diluted 3 fold in series in DMSO and 1.2 µl per well were added into 384-well polypropylene black plates (NUNC). Thirty µl per well of 6.9 nM recombinant GST-tag human PLK4 (amino acids #1-836) (SignalChem, Cat # P44-11G) in ice-cold Assay Buffer (50 mM HEPES, pH 7.5, 10 mM MgCl₂, 1mM EGTA, 0.01% Brij35, 1 mM DTT, 0.2 mg/mL BSA) was added into “Sample” wells. Thirty µl of Assay Buffer was also added into “Blank” wells. The samples were spun by centrifuge at 1,200 rpm (Eppendorf 5810R Plate centrifuge) for 1 minute and incubated at room temperature (22 °C) for 15 min. Ten µl per well of 8.2 µM swine myelin basic protein (MBP, SignalChem, Cat # M42-51 N) and 41.2 µM ATP in Assay Buffer was added. The samples were spun by centrifuge at 1,200 rpm for 1 minute and incubated at room temperature (22 °C) for 4 hours. Five µl per well was transferred to white 384-well OptiPlate (Perkin Elmer) and 5 µl per well of ADP-Glo reagent (Promega) was added. The plate was incubated at room temperature for 40 min. Ten µl per well of Kinase Detection reagent was added and the plate incubated at room temperature for another 50 min. Assay signals were monitored by reading luminescence on Victor X5 reader (Perkin Elmer).

[1274] In order to rule out that compound inhibition is due to inhibiting detection enzymes in ADP-Glo reagents, all the compounds were also tested in Deconvolution assay. Test compounds (4.5 mM stock in DMSO) were diluted 3 folds in series in DMSO and 1.2 µl per well were added into 384-well polypropylene black plates (NUNC). Forty µl per well of 2.06 µM ADP in Assay Buffer (50 mM HEPES, pH 7.5, 10 mM MgCl₂, 1 mM EGTA, 0.01% Brij35, 1 mM DTT, 0.2 mg/mL BSA) was added into “Sample” wells. Forty µl of Assay Buffer was also added into “Blank” wells. The samples were spun by centrifuge at 1,200 rpm (Eppendorf 5810R Plate centrifuge) for 1 minute. Five µl per well was transferred to white 384-well OptiPlate (Perkin Elmer) and 5 µl per well of ADP-Glo reagent (Promega) was added. The plate was incubated at room temperature for 40 min. Ten µl per well of Kinase Detection reagent was added and the plate incubated at room temperature for another 50 min. Assay signals were monitored by reading luminescence on Victor X5 reader (Perkin Elmer).

[1275] IC₅₀ values were calculated using either Prism (GraphPad) or XLfit software (IDBS), and are shown in in **TABLE 4**, where A: ≤ 8 nM; B: >8 nM to 15 nM; C: >15 nM to 30 nM, D >30 nM.

TABLE 4.

Ex. No.	PLK4 ADP Kinase	Ex. No.	PLK4 ADP Kinase	Ex. No.	PLK4 ADP Kinase
188	A	A-44	B	A-150	B
A-2	A	A-45	C	A-151	A
A-5	A	A-46	C	A-152	D
A-6	C	A-47	C	A-153	A
A-7	B	A-48	C	A-154	C
A-8	A	A-49	B	A-155	C
A-9	A	A-50	C	A-156	A
A-10	B	A-51	C	A-157	A
A-11	C	A-52	B	A-158	B
A-12	C	A-53	A	A-159	B
A-13	B	A-54	B	A-160	A
A-14	B	A-55	B	A-161	B
A-15	C	A-56	B	A-163	D
A-16	A	A-57	D	A-164	D
A-23	B	A-58	B	A-168	C
A-24	B	A-59	D	A-169	D
A-25	B	A-60	A	A-170	D
A-26	B	A-61	A	A-171	D
A-27	B	A-62	D	A-172	B
A-28	B	A-63	A	A-173	D
A-29	B	A-64	A	A-174	C
A-31	C	A-65	A	A-175	D
A-32	B	A-66	D	A-176	D
A-33	C	A-88	D	A-178	A
A-34	A	A-89	D	A-189	D
A-35	A	A-145	B	A-203	A
A-36	B	A-146	B	A-204	B
A-41	C	A-147	C	A-205	A
A-42	C	A-148	B		
A-43	B	A-149	D		

[1276] While we have described a number of embodiments, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods

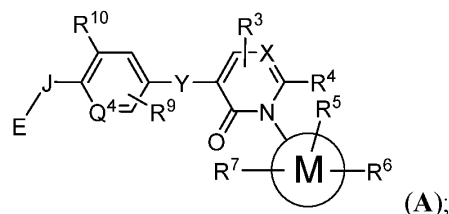
of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

[1277] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

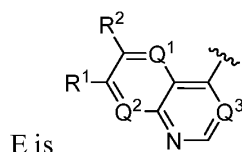
CLAIMS

What is claimed is:

1. A compound of the Formula A:



or a pharmaceutically acceptable salt thereof, wherein



or a bicyclic heterocyclic ring system comprising a 5-membered ring ortho-fused to a 6-membered ring, wherein the bicyclic heterocyclic ring system is optionally substituted by 1 to 3 groups independently selected from halo, oxo, and (C₁-C₄)alkyl;

R¹ and R² are each independently -OR^a or -NR^bR^c; or R¹ and R², together with the carbon atoms to which R¹ and R² are bound, form a 5- to 7-membered heterocyclyl;

R^a is selected from (C₁-C₄)alkyl, 4- to 6-membered heterocyclyl, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), and -(C₁-C₄)alkyl[4- to 6-membered heterocyclyl], wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 2 groups independently selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy;

R^b and R^c are each independently selected from hydrogen and (C₁-C₄)alkyl, or R^b and R^c taken together with the nitrogen atom to which R^b and R^c are attached form a 4- to 6-membered heterocyclyl;

R³ is hydrogen or (C₁-C₄)alkoxy;

R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and said 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups independently selected from halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, cyano, and -NH(C₁-C₄)alkyl;

Ring M is a 6-membered aryl or 6-membered heteroaryl;

R⁵ and R⁷ are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, hydroxy, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R^6 is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy;

R^8 and R^9 are each independently hydrogen or halo;

J is O, NR¹¹, S, or CH₂;

R^{10} is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₃-C₆)cycloalkyl, or deuterated(C₁-C₄)alkyl, and R^{11} is hydrogen; or R^{10} and R^{11} , together with the atoms to which R^{10} and R^{11} are bound, form a 5-membered heterocyclyl;

each of Q¹ and Q² is independently CH or N;

Q³ is CR⁸ or N;

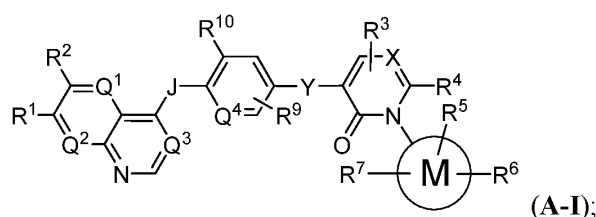
Q⁴ is N, CH, or a carbon atom attached to R⁹;

X is N, CH, or a carbon atom attached to R³; and

Y is -NHC(O)- or -C(O)NH-;

provided that: (i) if R⁴ is CH₃, then: (a) R⁵ is not hydrogen or (b) Q³ is CR⁸ wherein R⁸ is halo; and (ii) if Q¹ is N, Q² is CH, Q³ is CR⁸, and R⁴ is CH₃ or CH₂OH, then R⁸ is halo.

2. The compound of Claim 1, wherein the compound is of the Formula **A-I**:

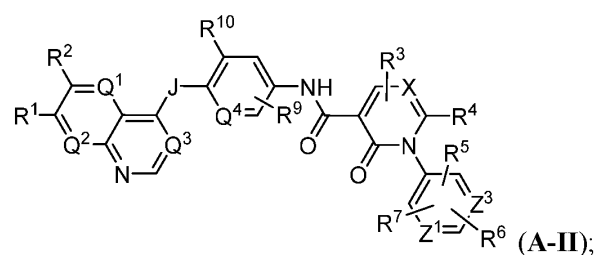


or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1 or Claim 2, or a pharmaceutically-acceptable salt thereof,

wherein is , wherein Z¹, Z², and Z³ are each independently N, CH, or a carbon atom bound to one of R⁵, R⁶, and R⁷.

4. The compound of Claim 3, wherein the compound is of the Formula **A-II**:



or a pharmaceutically acceptable salt thereof.

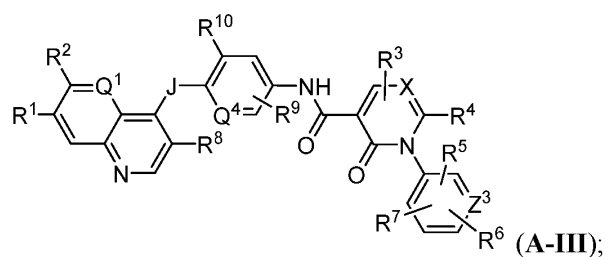
5. The compound of Claim 3 or Claim 4, or a pharmaceutically acceptable salt thereof, wherein Z^1 and Z^3 are each independently CH or a carbon atom bound to one of R^5 and R^7 .

6. The compound of Claim 3 or Claim 4, or a pharmaceutically acceptable salt thereof, wherein Z^1 and Z^3 are each N.

7. The compound of Claim 3 or Claim 4, or a pharmaceutically acceptable salt thereof, wherein Z^1 is CH or a carbon atom bound to R^7 , and Z^3 is N.

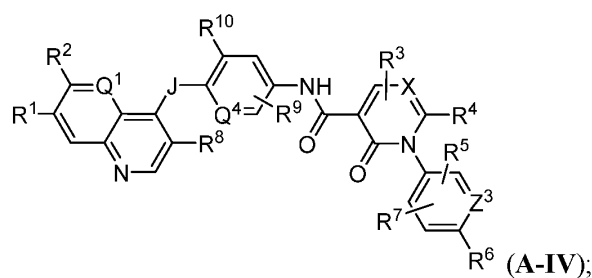
8. The compound of Claim 3 or Claim 4, or a pharmaceutically acceptable salt thereof, wherein Z^1 is N and Z^3 is CH or a carbon atom bound to R^5 .

9. The compound of Claim 3, wherein the compound is of the Formula **A-III**:



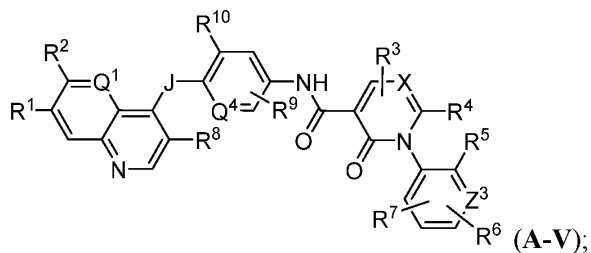
or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 3, wherein the compound is of the Formula **A-IV**:



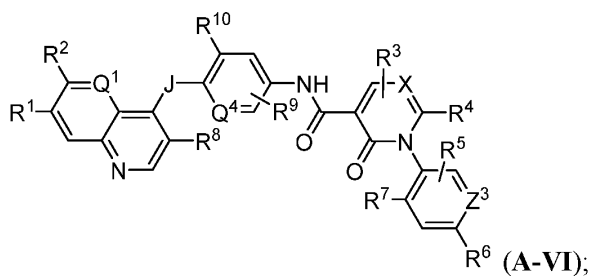
or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 3, wherein the compound is of the Formula **A-V**:



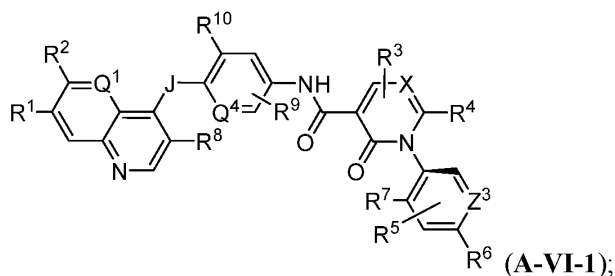
or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 3, wherein the compound is of the Formula **A-VI**:



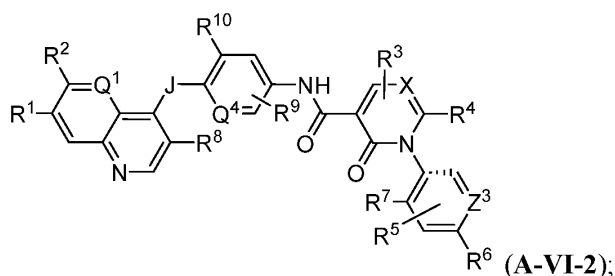
or a pharmaceutically acceptable salt thereof.

13. The compound of Claim 3, wherein the compound is of the Formula **A-VI-1**:



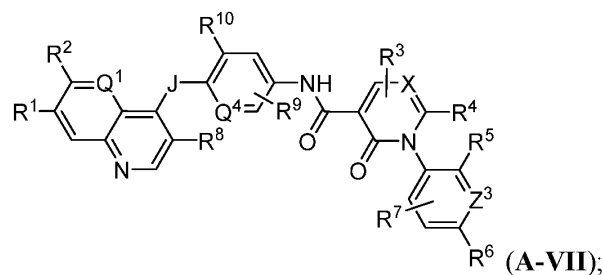
or a pharmaceutically acceptable salt thereof.

14. The compound of Claim 3, wherein the compound is of the Formula **A-VI-2**:



or a pharmaceutically acceptable salt thereof.

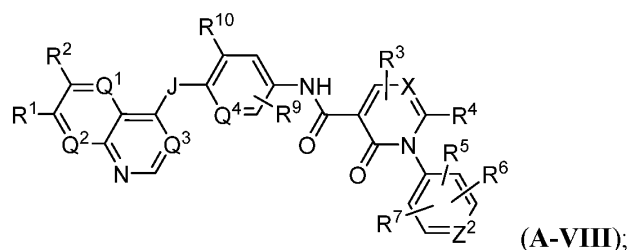
15. The compound of Claim 3, wherein the compound is of the Formula **A-VII**:



or a pharmaceutically acceptable salt thereof.

16. The compound of any one of Claims 3 and 9 to 15, or a pharmaceutically acceptable salt thereof, wherein Z³ is N.

17. The compound of Claim 3, wherein the compound is of the Formula A-VIII:



or a pharmaceutically acceptable salt thereof.

18. The compound of any one of Claims 3 and 17, or a pharmaceutically acceptable salt thereof, wherein Z² is N.

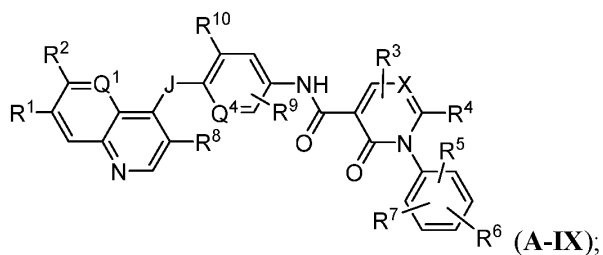
19. The compound of any one of Claims 1 to 8, 17, and 18, or a pharmaceutically acceptable salt thereof, wherein Q¹ and Q² each are CH, and Q³ is CR⁸.

20. The compound of any one of Claims 1 to 8, 17, and 18, or a pharmaceutically acceptable salt thereof, wherein Q¹ and Q² each are CH, and Q³ is N.

21. The compound of any one of Claims 1 to 8, 17, and 18, or a pharmaceutically acceptable salt thereof, wherein Q¹ is N, Q² is CH, and Q³ is CR⁸.

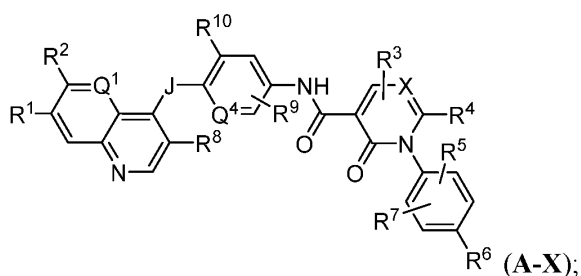
22. The compound of any one of Claims 1 to 8, 17, and 18, or a pharmaceutically acceptable salt thereof, wherein Q¹ is CH, Q² is N, and Q³ is CR⁸.

23. The compound of Claim 1, wherein the compound is of the Formula A-IX:



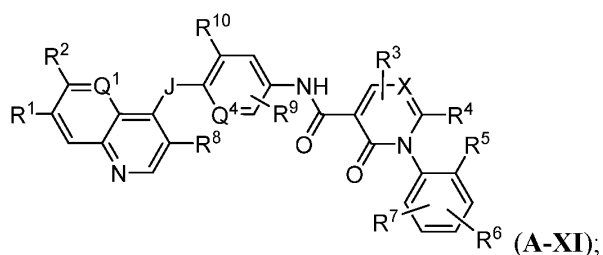
or a pharmaceutically acceptable salt thereof.

24. The compound of Claim 1, wherein the compound is of the Formula **A-X**:



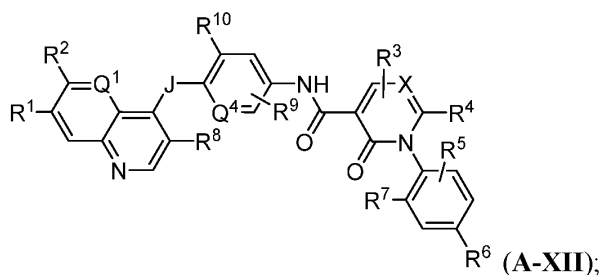
or a pharmaceutically acceptable salt thereof.

25. The compound of Claim 1, wherein the compound is of the Formula **A-XI**:



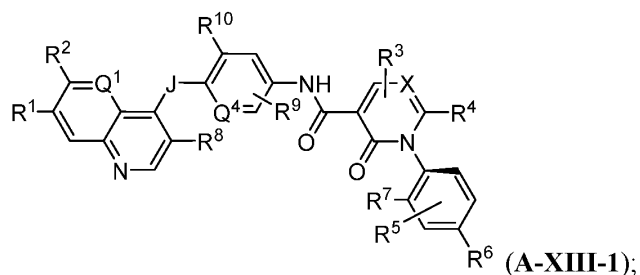
or a pharmaceutically acceptable salt thereof.

26. The compound of Claim 1, wherein the compound is of the Formula **A-XII**:



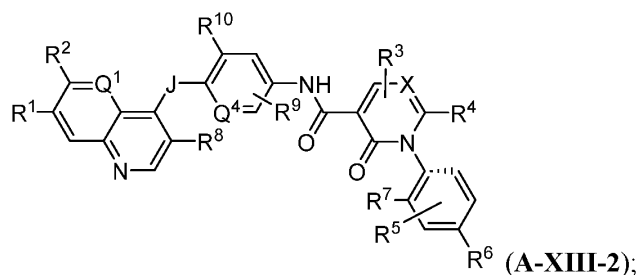
or a pharmaceutically acceptable salt thereof.

27. The compound of Claim 1, wherein the compound is of the Formula **A-XIII-1**:



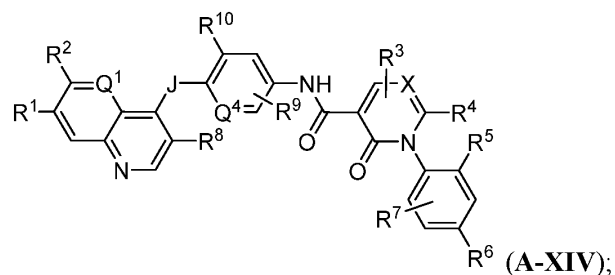
or a pharmaceutically acceptable salt thereof.

28. The compound of Claim 1, wherein the compound is of the Formula A-XIII-2:



or a pharmaceutically acceptable salt thereof.

29. The compound of Claim 1, wherein the compound is of the Formula A-XIV:



or a pharmaceutically acceptable salt thereof.

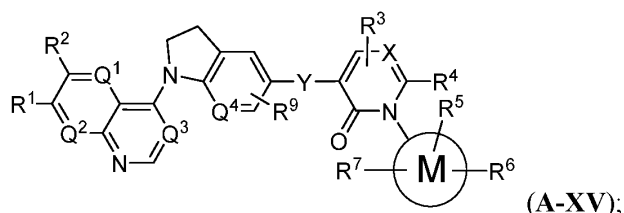
30. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein J is O.

31. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein J is S.

32. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein J is CH₂.

33. The compound of any one of Claims 1 to 29, or a pharmaceutically acceptable salt thereof, wherein J is NR¹¹.

34. The compound of any one of Claims 1 to 3, wherein the compound is of the Formula **A-XV**:



or a pharmaceutically acceptable salt thereof.

35. The compound of any one of Claims 1-33, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is halo.

36. The compound of any one of Claims 1-33, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is fluoro.

37. The compound of any one of Claims 1 to 18, 23 to 29, and 34, or a pharmaceutically acceptable salt thereof, wherein Q¹ is N.

38. The compound of any one of Claims 1 to 18, 23 to 29, and 34, or a pharmaceutically acceptable salt thereof, wherein Q¹ is CH.

39. The compound of any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Q⁴ is N.

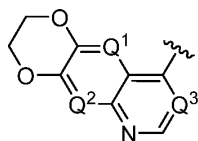
40. The compound of any one of Claims 1 to 38, or a pharmaceutically acceptable salt thereof, wherein Q⁴ is a carbon atom bound to R⁹.

41. The compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R⁹ is hydrogen.

42. The compound of any one of Claims 1 to 40, or a pharmaceutically acceptable salt thereof, wherein R⁹ is fluoro.

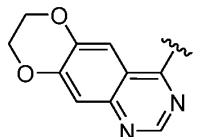
43. The compound of any one of Claims 1 to 42, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.
44. The compound of any one of Claims 1 to 43, or a pharmaceutically acceptable salt thereof, wherein R⁵ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, cyano, hydroxy, or halo.
45. The compound of any one of Claims 1 to 44, or a pharmaceutically acceptable salt thereof, wherein R⁵ is CH₃, CF₃, cyano, hydroxy, fluoro, chloro, or bromo.
46. The compound of any one of Claims 1 to 45, or a pharmaceutically acceptable salt thereof, wherein X is CH.
47. The compound of any one of Claims 1 to 45, or a pharmaceutically acceptable salt thereof, wherein X is N.
48. The compound of any one of Claims 1 to 47, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.
49. The compound of any one of Claims 1 to 19, 21 to 29, 34, 37, and 38, or a pharmaceutically acceptable salt thereof, wherein R⁸ is fluoro.
50. The compound of any one of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, wherein each R^a is independently selected from (C₁-C₄)alkyl, oxetanyl, cyclopropyl, cyclobutyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), -(C₁-C₄)alkyl[pyrrolidinyl], -(C₁-C₄)alkyl[piperizinyl], and -(C₁-C₄)alkyl[morpholinyl], wherein said cyclopropyl, cyclobutyl, piperazinyl, pyrrolidinyl, and oxetanyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy.
51. The compound of any one of Claims 1 to 49, or a pharmaceutically acceptable salt thereof, wherein R¹ and R² are each independently selected from OCH₃,
- OCH₃,
and
wherein R¹ and R² are each independently selected from OCH₃,
and
wherein R¹ and R² are each independently selected from OCH₃,
and
wherein R¹ and R² are each independently selected from OCH₃,
and
wherein R¹ and R² are each independently selected from OCH₃,

52. The compound of any one of Claims 1 to 49, or a pharmaceutically-acceptable salt



thereof, wherein E is

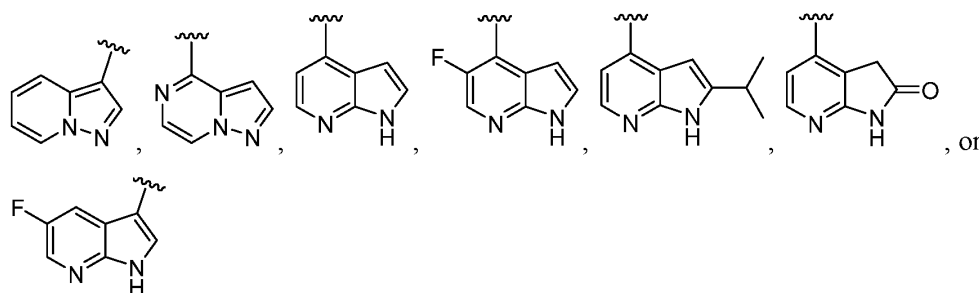
53. The compound of any one of Claims 1 to 49, or a pharmaceutically-acceptable salt



thereof, wherein E is

54. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein E is pyrazolo[1,5-a]pyridyl, pyrazolo[1,5-a]pyrazolyl, 1H-pyrrolo[2,3-b]pyridyl, 1,3-dihydro-2H-pyrrolo[2,3-b]pyridin-2-one, each of which is optionally substituted with 1 to 3 groups independently selected from halo and (C₁-C₄)alkyl.

55. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein E is

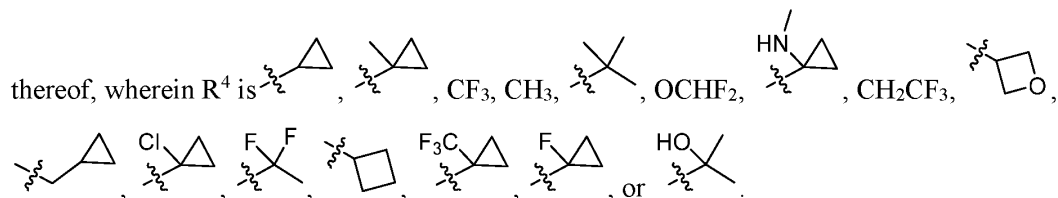


56. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

57. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said (C₃-C₆)cycloalkyl is

optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

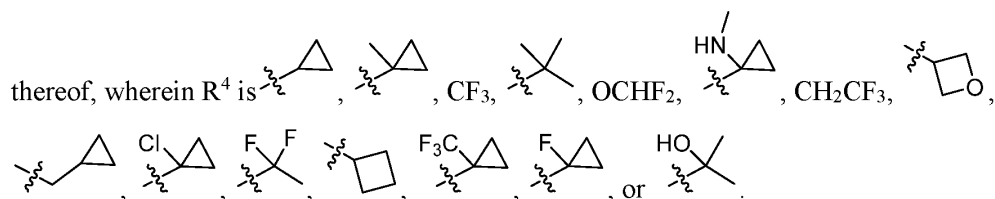
58. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt



59. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₂-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

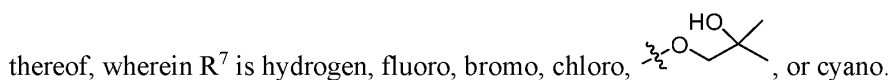
60. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt thereof, wherein R⁴ is (C₂-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₂-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said cyclopropyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

61. The compound of any one of Claims 1 to 55, or a pharmaceutically acceptable salt



62. The compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, halo, -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl], or cyano.

63. The compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt



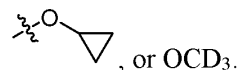
64. The compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, wherein R⁷ is hydrogen, cyano, hydroxy, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.

65. The compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, wherein R^7 is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, cyano, hydroxy, or halo.

66. The compound of any one of Claims 1 to 61, or a pharmaceutically acceptable salt thereof, wherein R^7 is CH₃, CF₃, cyano, hydroxy, fluoro, chloro, or bromo.

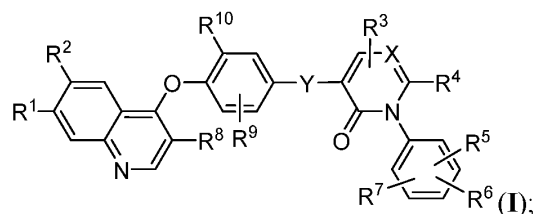
67. The compound of any one of Claims 1 to 66, or a pharmaceutically acceptable salt thereof, wherein R^6 is halo, hydroxy, cyano, (C₂-C₄)acyl, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy.

68. The compound of any one of Claims 1 to 66, or a pharmaceutically acceptable salt thereof, wherein R^6 is cyano, CHF₂, hydroxy, acetyl, OCH₃, OEt, fluoro, OCHF₂, OCF₃,



69. The compound of any one of Claims 1 to 66, or a pharmaceutically acceptable salt thereof, wherein R^6 is fluoro.

70. The compound of claim 1, wherein the compound is of the Formula I:



or a pharmaceutically acceptable salt thereof, wherein

R^1 and R^2 are each independently -OR^a or -NR^bR^c;

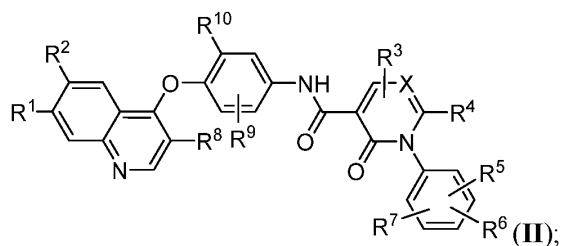
R^5 and R^7 are each independently hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, halo, cyano, -(C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, -O(C₃-C₆)cycloalkyl, deuterated(C₁-C₄)alkoxy, or -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl];

R^6 is halo, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, (C₁-C₄)alkoxy, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -O(C₃-C₆)cycloalkyl, or deuterated (C₁-C₄)alkoxy;

R^8 and R^9 are each independently hydrogen or fluoro;

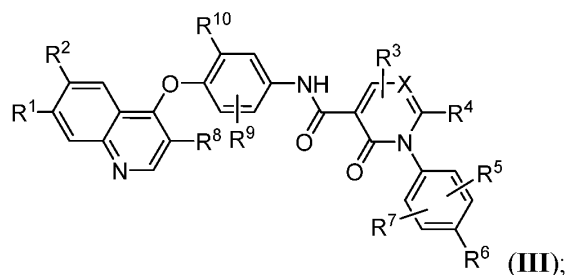
provided that if R^4 is CH₃, then R^5 is not hydrogen.

71. The compound of Claim 70, wherein the compound is of the Formula II:



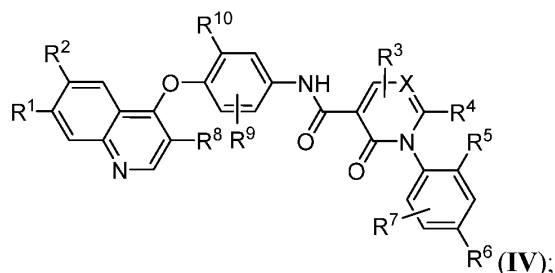
or a pharmaceutically acceptable salt thereof.

72. The compound of Claim 70 or Claim 71, wherein the compound is of the Formula **III**:



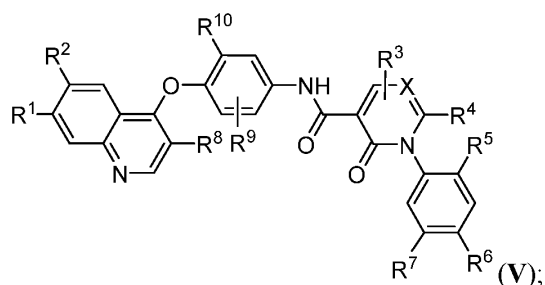
or a pharmaceutically acceptable salt thereof.

73. The compound of any one of Claims 70 to 72, wherein the compound is of Formula **IV**:



or a pharmaceutically acceptable salt thereof.

74. The compound of any one of Claims 70 to 73, wherein the compound is of Formula **V**:



or a pharmaceutically acceptable salt thereof.

75. The compound of any one of Claims 70 to 74, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is halo.

76. The compound of any one of Claims 70 to 75, or a pharmaceutically acceptable salt thereof, wherein R¹⁰ is fluoro.

77. The compound of any one of Claims 70 to 76, or a pharmaceutically acceptable salt thereof, wherein R⁵ is hydrogen, (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.

78. The compound of any one of Claims 70 to 77, or a pharmaceutically acceptable salt thereof, wherein R⁵ is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, or halo.

79. The compound of any one of Claims 70 to 78, or a pharmaceutically acceptable salt thereof, wherein R⁵ is CH₃, CF₃, or chloro.

80. The compound of any one of Claims 70 to 79, or a pharmaceutically acceptable salt thereof, wherein X is CH.

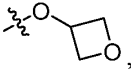
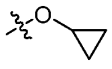
81. The compound of any one of Claims 70 to 80, or a pharmaceutically acceptable salt thereof, wherein R³ is hydrogen.

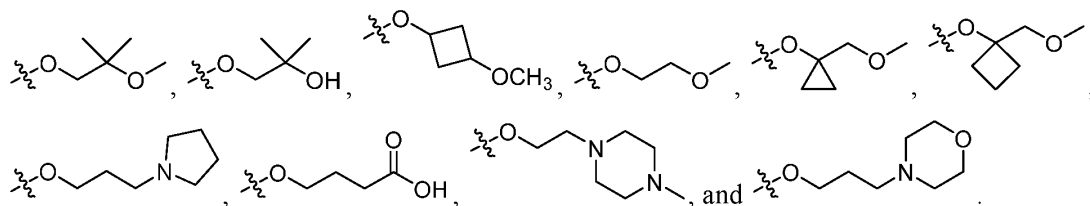
82. The compound of any one of Claims 70 to 81, or a pharmaceutically acceptable salt thereof, wherein R⁹ is hydrogen.

83. The compound of any one of Claims 70 to 82, or a pharmaceutically acceptable salt thereof, wherein R⁸ is fluoro.

84. The compound of any one of Claims 70 to 83, or a pharmaceutically acceptable salt thereof, wherein each R^a is independently selected from (C₁-C₄)alkyl, oxetanyl, cyclopropyl, cyclobutyl, -(C₁-C₄)alkyl(C₁-C₄)alkoxy, hydroxy(C₁-C₄)alkyl, -(C₁-C₄)alkyl(COOH), -(C₁-C₄)alkyl[pyrrolidinyl], -(C₁-C₄)alkyl[piperizinyl], and -(C₁-C₄)alkyl[morpholinyl], wherein said cyclopropyl, cyclobutyl, piperazinyl, pyrrolidinyl, and oxetanyl are each optionally substituted by 1 to 2 groups selected from (C₁-C₄)alkyl, (C₁-C₄)alkoxy, and -(C₁-C₄)alkyl(C₁-C₄)alkoxy.

85. The compound of any one of Claims 70 to 84, or a pharmaceutically acceptable salt

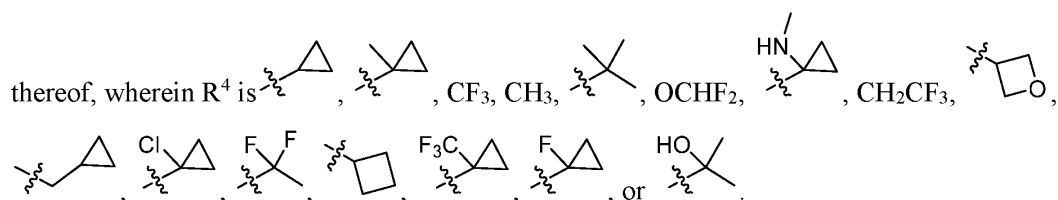
thereof, wherein R¹ and R² are each independently selected from OCH₃, , ,



86. The compound of any one of Claims 70 to 85, or a pharmaceutically acceptable salt thereof, wherein R^4 is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, (C₃-C₆)cycloalkyl, -(C₁-C₄)alkyl(C₃-C₆)cycloalkyl, or 4- to 6-membered heterocyclyl, wherein said (C₃-C₆)cycloalkyl and 4- to 6-membered heterocyclyl are each optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

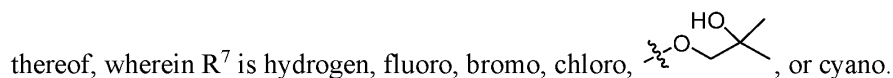
87. The compound of any one of Claims 70 to 86, or a pharmaceutically acceptable salt thereof, wherein R^4 is (C₁-C₄)alkyl, halo(C₁-C₄)alkyl, hydroxy(C₁-C₄)alkyl, halo(C₁-C₄)alkoxy, cyclopropyl, -(C₁-C₄)alkyl[cyclopropyl], or oxetanyl, wherein said cyclopropyl is optionally substituted by 1 to 3 groups selected from halo, NH(C₁-C₄)alkyl, and halo(C₁-C₄)alkyl.

88. The compound of any one of Claims 70 to 87, or a pharmaceutically acceptable salt

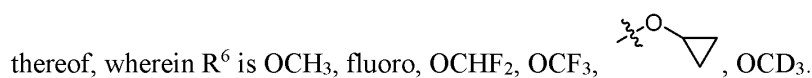


89. The compound of any one of Claims 70 to 88, or a pharmaceutically acceptable salt thereof, wherein R^7 is hydrogen, halo, -(C₁-C₄)alkoxy[hydroxy(C₁-C₄)alkyl], or cyano.

90. The compound of any one of Claims 70 to 89, or a pharmaceutically acceptable salt



91. The compound of any one of Claims 70 to 90, or a pharmaceutically acceptable salt



92. The compound of any one of Claims 70 to 91, or a pharmaceutically acceptable salt thereof, wherein R⁶ is fluoro.
93. The compound of Claim 1, wherein the compound is selected from any of those in Table 1; or a pharmaceutically acceptable salt thereof.
94. The compound of Claim 1, wherein the compound is selected from any of those in Table 2; or a pharmaceutically acceptable salt thereof.
95. The compound of any one of Claims 1 to 92, or a pharmaceutically acceptable salt thereof, wherein the compound is a single atropisomer.
96. The compound of Claim 95, or a pharmaceutically acceptable salt thereof, wherein the single atropisomer has a negative specific optical rotation.
97. The compound of Claim 95, or a pharmaceutically acceptable salt thereof, wherein the single atropisomer has a positive specific optical rotation.
98. A pharmaceutical composition comprising a compound of any one of Claims 1 to 97, or a pharmaceutically acceptable salt thereof.
99. A pharmaceutical composition, the pharmaceutical composition comprising a population of molecules with a structure according to a compound of any one of Claims 1 to 94, wherein at least about 97% of the molecules of the population have the same atropisomeric configuration.
100. The pharmaceutical composition of Claim 99, further comprising a pharmaceutically acceptable carrier.
101. A method of treating a condition, comprising administering to a subject in need a therapeutically effective amount of a compound of any one of Claims 1 to 97, or a pharmaceutically acceptable salt thereof; or the pharmaceutical composition of any one of Claims 98 to 100.
102. The method of claim 101, wherein the condition is responsive to the modulation of PLK4.

103. The method of Claim 101, wherein the condition is cancer.