COMPOUNDS USEFUL AS INHIBITORS OF ATR KINASE

BACKGROUND OF THE INVENTION

[0001] ATR ("ATM and Rad3 related") kinase is a protein kinase involved in cellular responses to DNA damage. ATR kinase acts with ATM ("ataxia telangiectasia mutated") kinase and many other proteins to regulate a cell's response to DNA damage, commonly referred to as the DNA Damage Response ("DDR"). The DDR stimulates DNA repair, promotes survival and stalls cell cycle progression by activating cell cycle checkpoints, which provide time for repair. Without the DDR, cells are much more sensitive to DNA damage and readily die from DNA lesions induced by endogenous cellular processes such as DNA replication or exogenous DNA damaging agents commonly used in cancer therapy.

[0002] Healthy cells can rely on a host of different proteins for DNA repair including the DDR kinase ATR. In some cases these proteins can compensate for one another by activating functionally redundant DNA repair processes. On the contrary, many cancer cells harbour defects in some of their DNA repair processes, such as ATM signaling, and therefore display a greater reliance on their remaining intact DNA repair proteins which include ATR.

[0003] In addition, many cancer cells express activated oncogenes or lack key tumour suppressors, and this can make these cancer cells prone to dysregulated phases of DNA replication which in turn cause DNA damage. ATR has been implicated as a critical component of the DDR in response to disrupted DNA replication. As a result, these cancer cells are more dependent on ATR activity for survival than healthy cells. Accordingly, ATR inhibitors may be useful for cancer treatment, either used alone or in combination with DNA damaging agents, because they shut down a DNA repair mechanism that is more important for cellular survival in many cancer cells than in healthy normal cells.

[0004] In fact, disruption of ATR function (e.g. by gene deletion) has been shown to promote cancer cell death both in the absence and presence of DNA damaging agents. This

suggests that ATR inhibitors may be effective both as single agents and as potent sensitizers to radiotherapy or genotoxic chemotherapy.

[0005] ATR peptide can be expressed and isolated using a variety of methods known in the literature (see e.g., Ünsal-Kaçmaz et al, *PNAS* 99: 10, pp6673-6678, May 14, 2002; see also Kumagai et al. Cell 124, pp943-955, March 10, 2006; Unsal-Kacmaz et al. Molecular and Cellular Biology, Feb 2004, p1292-1300; and Hall-Jackson et al. Oncogene 1999, 18, 6707-6713).

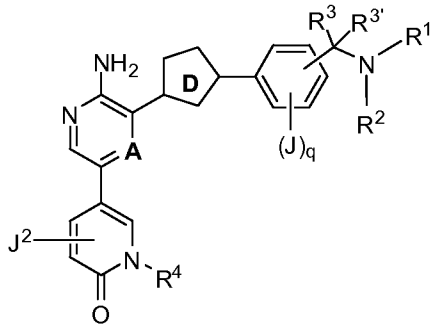
[0006] For all of these reasons, there is a need for the development of potent and selective ATR inhibitors for the treatment of cancer, either as single agents or as combination therapies with radiotherapy or genotoxic chemotherapy.

SUMMARY OF THE INVENTION

[0007] The present invention relates to pyrazine and pyridine compounds useful as inhibitors of ATR protein kinase. The invention also relates to pharmaceutically acceptable compositions comprising the compounds of this invention; methods of treating various diseases, disorders, and conditions using the compounds of this invention; processes for preparing the compounds of this invention; intermediates for the preparation of the compounds of this invention; and methods of using the compounds in *in vitro* applications, such as the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors. These compounds have an unexpected ability to treat cancer as single agents. These compounds also show surprising synergy with other cancer agents, such as cisplatin, in combination therapies.

DETAILED DESCRIPTION OF THE INVENTION

[0008] One aspect of the invention provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

A is C or N;

Ring D is isoxazolyl or oxadiazolyl;

J is -C_{1-3}alkyl, -O(C_{1-3}alkyl), halo, or CN;

q is 0 or 1;

R^1 is H, C_{1-6}aliphatic, phenyl, or tetrahydrofuranyl, wherein said C_{1-6}aliphatic is optionally substituted with one occurrence of OH and up to two occurrences of F;

R^2 is H or C_{1-3}alkyl;

or R^1 and R^2, together with the nitrogen atom to which they are attached, optionally form a 4-6 membered monocyclic heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

R^3 is H or C_{1-3}alkyl, wherein said alkyl is optionally substituted with up to three occurrences of F;

$R^{3'}$ is H or C_{1-3}alkyl;

or R^3 and $R^{3'}$, together with the carbon atom to which they are attached, form a 3-4 membered monocyclic saturated carbocyclic ring;

R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', S, or CO; and wherein one methylene unit of the C_{1-2}alkyl can optionally be replaced with C(=O);

R^4 is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 1 occurrence of CN and up to 4 occurrences of F;

Q is 3-6 membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; Q is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 4 occurrences of F;

R' is H or C_{1-4}alkyl;

R is H or C_{1-4}alkyl;

or R and R', together with the nitrogen to which they are attached, optionally form a 3-6 membered heterocyclic ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

J^2 is H, C_{1-6}aliphatic, halo, phenyl, or CN, wherein said C_{1-6}aliphatic is optionally substituted with 1-2 occurrences of halo, OH, CN, or OR .

[0009] In some embodiments,

R^1 is H, C_{1-6}aliphatic, or tetrahydrofuranyl, wherein said C_{1-6}aliphatic is optionally substituted with one occurrence of OH and up to two occurrences of F; $R^{3'}$ is H;

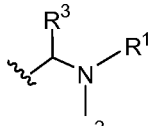
R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', S, or CO;

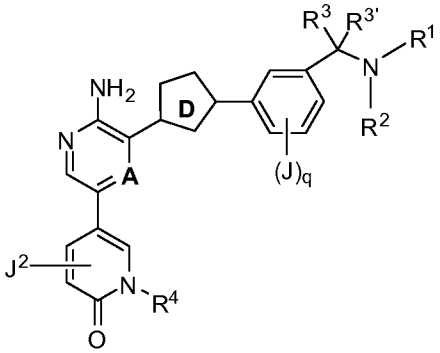
Q is 3-6 membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; Q is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 4 occurrences of F;

J^2 is H.

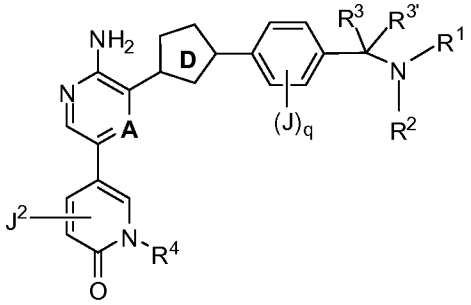
[0010] In some embodiments A is N. In other embodiments, R^2 is H.

[0011] In some embodiments, Ring D is isoxazolyl. In other embodiments, Ring D is oxadiazolyl.

[0012] Another embodiment provides compounds wherein  is bonded at the meta or para position of the phenyl ring as shown in Formula Ia and Ib below:



Ia



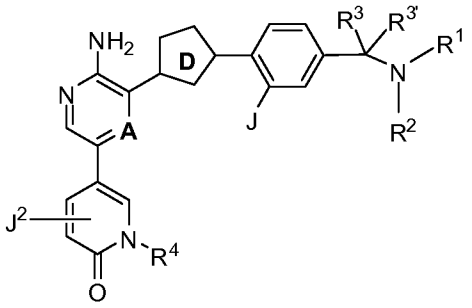
Ib.

[0013] In some embodiments, R^3 is H or methyl. In other embodiments, R^3 is H.

[0014] In some embodiments, R^1 is C_{1-6}aliphatic, phenyl, or tetrahydrofuranyl. In other embodiments, R^1 is C_{1-6}aliphatic or tetrahydrofuranyl. In yet other embodiments, R^1 is C_{1-4}alkyl or tetrahydrofuranyl. In some embodiments, R^1 is C_{1-4}alkyl. In other embodiments, R^1 is methyl, isopropyl, tert-butyl, or tetrahydrofuranyl.

[0015] Another embodiment provides compounds wherein the C_{1-6}alkyl of R^1 is optionally substituted with 1-2 occurrences of OH or fluoro. In some embodiments, q is 1.

[0016] Another embodiment provides compounds wherein J is bonded at the ortho position of the phenyl ring as shown in Formula Ic:

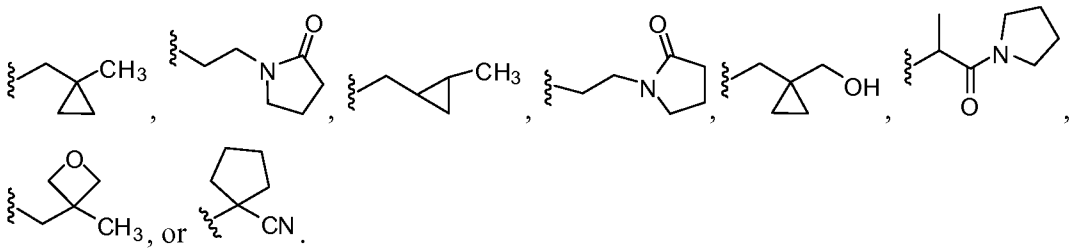


Ic.

[0017] In some embodiments, J is fluoro, C_{1-3}alkyl, $O(C_{1-3}$alkyl), or CN. In some embodiments, the C_{1-3}alkyl is methyl or isopropyl. In other embodiments, J is fluoro, CH_3, OCH_3, or CN.

[0018] Another aspect provides compounds wherein q is 0. In some embodiments, R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', or CO; and wherein one methylene unit of the C_{1-2}alkyl can optionally be replaced with C(=O). In some embodiments, Q is a 5 membered heteroaryl having 1-2 heteroatoms selected from O, N, or S; 4-6 membered heterocyclyl having 1 heteroatoms selected from O or N; or a 3-6 membered cycloalkyl. In other embodiments, Q is furanyl, thiazoyl, imidazolyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinonyl, or 3-6 membered cycloalkyl.

[0019] In some embodiments, R^4 is C_{1-10}aliphatic, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), -(C_{1-4}alkyl)-N(C_{1-3}alkyl)$_2$, -(C_{1-4}alkyl)-O(C_{1-3}alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted. In other embodiments, R^4 is C_{1-6}alkyl, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl. In yet other embodiments, R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, $CH(CH_3)COOH$, CH_2CONH_2, $CH(CH_3)CONH_2$, $CH(CH_3)CONHCH_3$, $CH(CH_3)CONCH_2CH_3)_2$, cyclobutyl, cyclopentyl, methylcyclopentyl, $CH(CH_3)$(cyclopropyl), CH_2(cyclopropyl), CH_2CH_2(cyclopropyl), CH_2CH_2(cyclopentyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $C(CH_3)_2CN$, $C(CH_2CH_3)_2CN$, $CH(CH_3)CN$, CH_2CN, $CH_2CH(CH_3)CH_2CH_3$, $CH(CH_2CH_3)_2$ $CH(CH_2OH)_2$ $CH(CH_3)CH_2OH$, $CH(CH_3)CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NH_2$, tetrahydrofuranyl, tetrohydropyranyl, CH_2(furanyl), CH_2(thiazolyl), CH_2(imidazolyl), CH_2CH_2CN, $CH_2CH(OCH_3)CH_2CH_3$, $CH_2CH_2CH(CH_3)CH_2CH_3$,



[0020] According to another embodiment, R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, $CH(CH_3)COOH$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, $CH(CH_3)CH_2OH$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NH_2$, $CH(CH_3)CH_2OCH_3$, or tetrahydrofuranyl.

[0021] According to yet another embodiment, R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, or tetrahydrofuranyl.

[0022] In some embodiments, J^2 is H, CN, F, Cl, Br, $CH{=}CH_2$, methyl, ethyl, isopropyl, CH_2OH, $CH(CH_2CH_3)CH_2CH_2CH_3$, $CH(CH_2CH_3)_2$, cyclopentyl, cyclohexyl, cyclohexenyl, or phenyl.

[0023] According to another embodiment,

A is N;

J^2 is H;

R^1 is methyl;

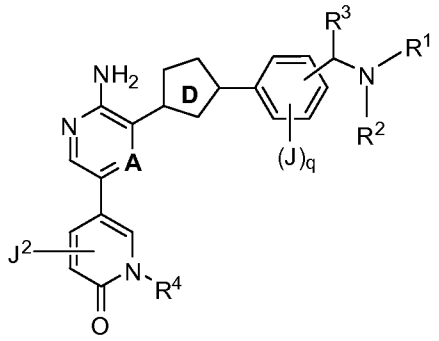
R^2 is H;

R^3 is H; and

R^4 is $C_{1\text{-}10}$aliphatic, -($C_{1\text{-}4}$alkyl)-CF_3, -($C_{1\text{-}4}$alkyl)-(C_3-C_6cycloaliphatic), -($C_{1\text{-}4}$alkyl)-N($C_{1\text{-}3}$alkyl)$_2$, -($C_{1\text{-}4}$alkyl)-O($C_{1\text{-}3}$alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted.

[0024] In some embodiments, R^4 is $C_{1\text{-}10}$aliphatic, -($C_{1\text{-}4}$alkyl)-CF_3, -($C_{1\text{-}4}$alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl. In other embodiments, said alkyl group is optionally substituted with CH_3, OH, OCH_3, NH_2, CN, or tetrahydrofuranyl.

[0025] Another aspect of this invention provides a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

A is C or N;

Ring D is isoxazolyl or oxadiazolyl;

J is -C_{1-3}alkyl, -O(C_{1-3}alkyl), halo, or CN;

q is 0 or 1;

R^1 is H, C_{1-6}aliphatic, or tetrahydrofuranyl, wherein said C_{1-6}aliphatic is optionally substituted with one occurrence of OH and up to two occurrences of F;

R^2 is H or C_{1-3}alkyl;

or R^1 and R^2, together with the nitrogen atom to which they are attached, optionally form a 4-6 membered monocyclic heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

R^3 is H or C_{1-3}alkyl, wherein said alkyl is optionally substituted with up to three occurrences of F;

R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', S, or CO; R^4 is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 1 occurrence of CN and up to 4 occurrences of F;

Q is 3-6 membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; Q is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 4 occurrences of F;

R' is H or C_{1-4}alkyl;

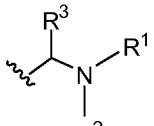
R is H or C_{1-4}alkyl;

or R and R', together with the nitrogen to which they are attached, optionally form a 3-6 membered heterocyclic ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

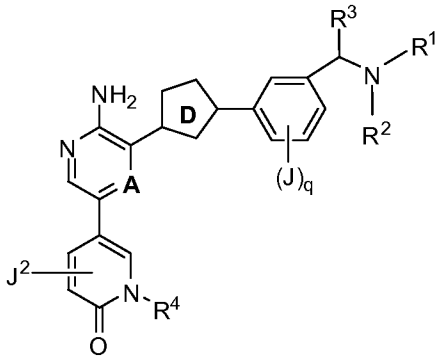
J^2 is H.

[0026] In some embodiments, A is N. In some embodiments, R^2 is H.

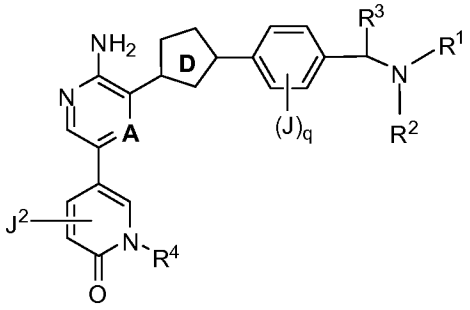
[0027] In some embodiments, Ring D is isoxazolyl. In other embodiments, Ring D is oxadiazolyl. In some embodiments, J^2 is H.



[0028] One embodiment provides compounds wherein is bonded at the meta or para position of the phenyl ring as shown in Formula Ia and Ib below:



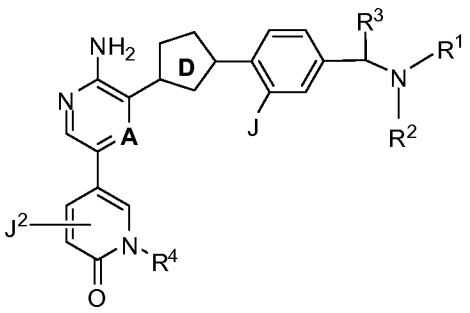
Ia



Ib.

[0029] In some embodiments, the compounds have formula Ib. In some embodiments, R^3 is H or methyl. In other embodiments, R^3 is H. In certain embodiments, R^1 is C_{1-6}aliphatic or tetrahydrofuranyl. In other embodiments, R^1 is C_{1-4}alkyl or tetrahydrofuranyl. In some embodiments, R^1 is C_{1-6}aliphatic. In other embodiments, R^1 is C_{1-4}alkyl. In yet other embodiments, R^1 is methyl, isopropyl, tert-butyl, or tetrahydrofuranyl.

[0030] Another embodiment provides compounds wherein q is 1. In some embodiments, J is bonded at the ortho position of the phenyl ring as shown in Formula Ic:



Ic.

[0031] In some embodiments, J is fluoro, CH_3, OCH_3, or CN.

[0032] Another embodiment provides compounds wherein q is 0.

[0033] In another embodiment, R^4 is C_{1-10}aliphatic, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), -(C_{1-4}alkyl)-N(C_{1-3}alkyl)$_2$, -(C_{1-4}alkyl)-O(C_{1-3}alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted. In some embodiments, R^4 is C_{1-6}alkyl, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl. In yet other embodiments, R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, $CH(CH_3)COOH$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, $CH(CH_3)CH_2OH$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NH_2$, $CH(CH_3)CH_2OCH_3$, or tetrahydrofuranyl. In yet other embodiments, R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, or tetrahydrofuranyl.

[0034] Another embodiment provides compounds wherein

A is N;

J^2 is H;

R^1 is methyl;

R^2 is H;

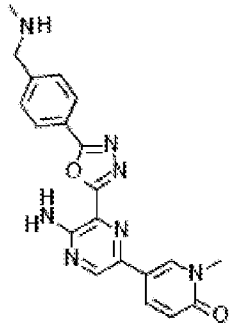
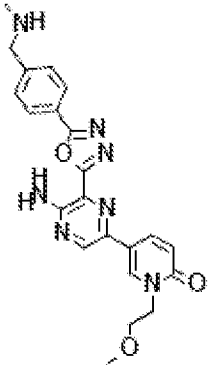
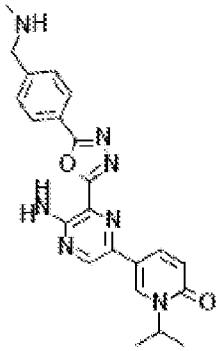
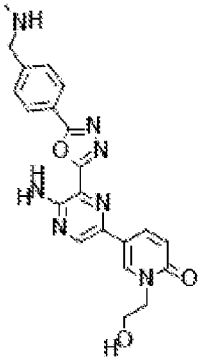
R^3 is H; and

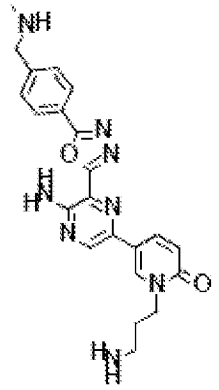
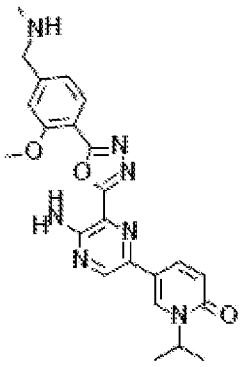
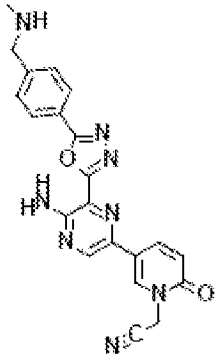
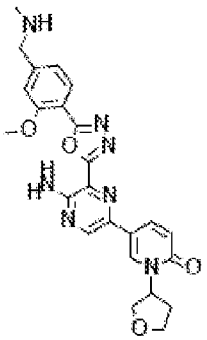
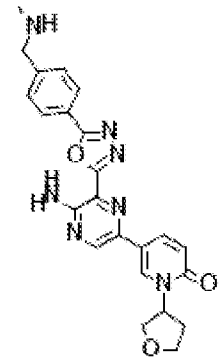
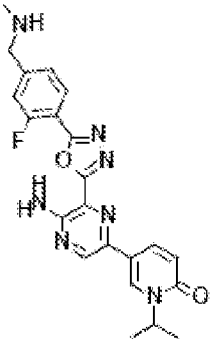
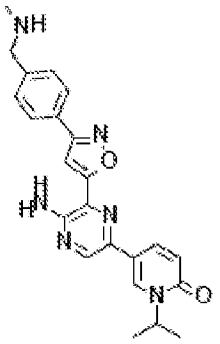
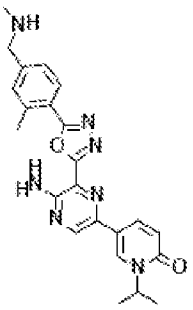
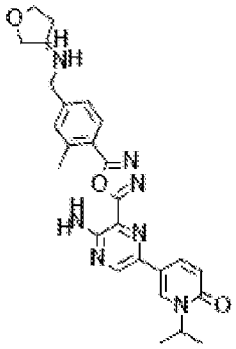
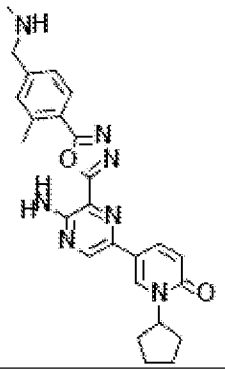
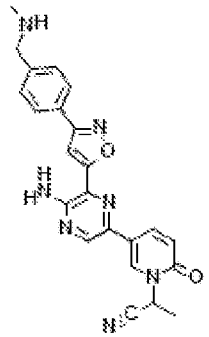
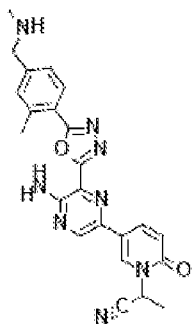
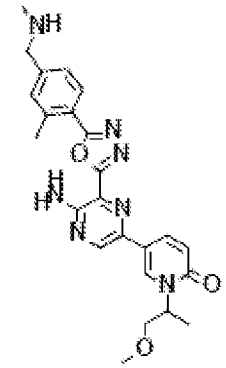
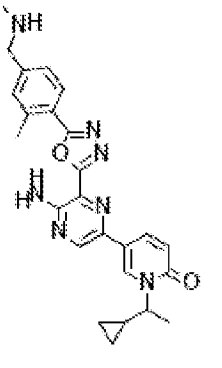
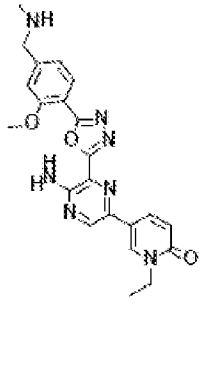
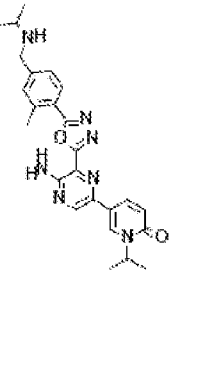
R^4 is C_{1-10}aliphatic, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), -(C_{1-4}alkyl)-N(C_{1-3}alkyl)$_2$, -(C_{1-4}alkyl)-O(C_{1-3}alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted.

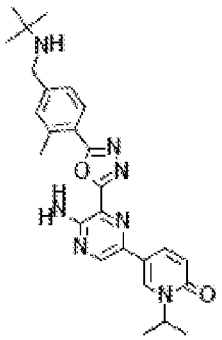
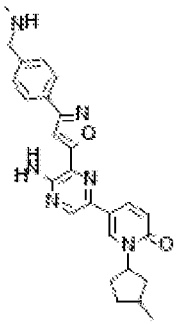
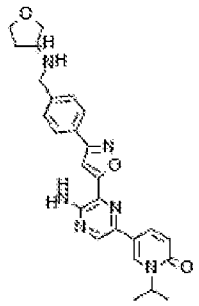
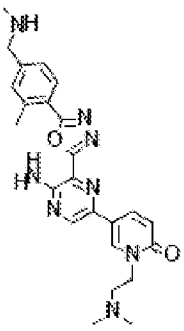
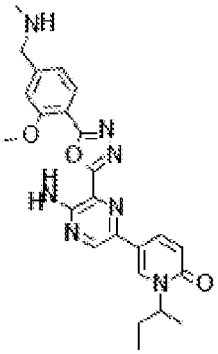
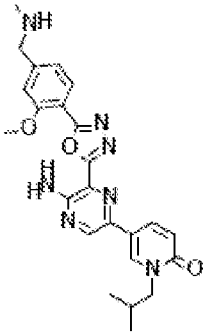
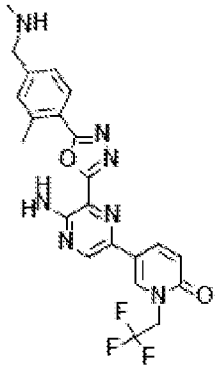
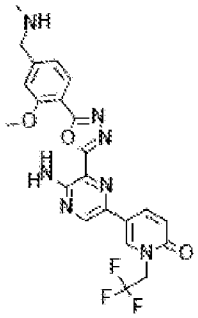
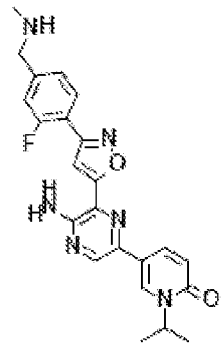
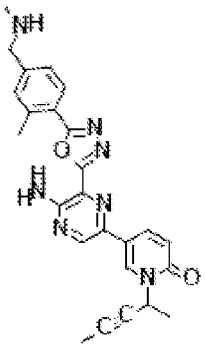
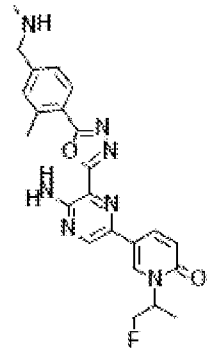
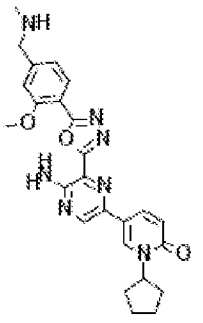
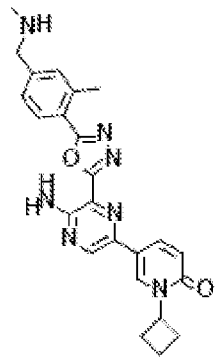
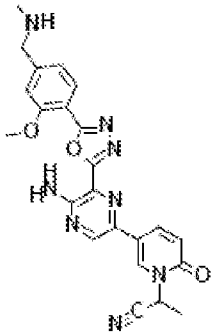
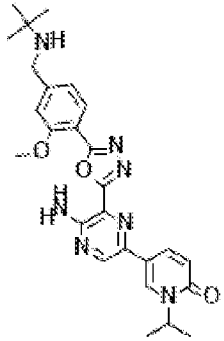
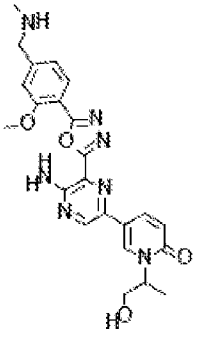
[0035] In some embodiments, R^4 is C_{1-10}aliphatic, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl.

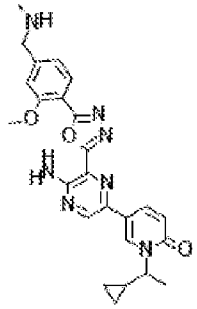
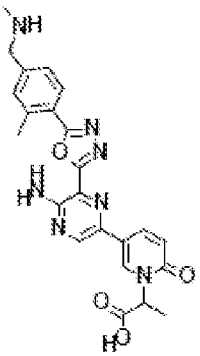
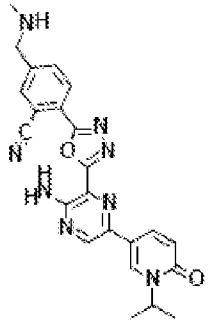
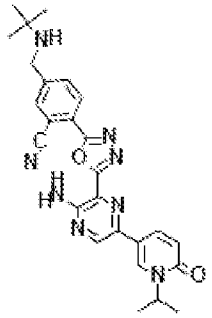
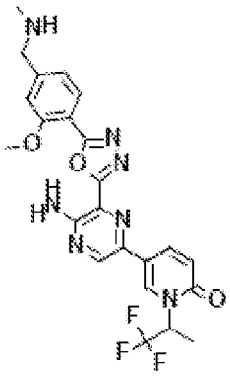
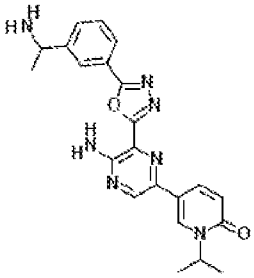
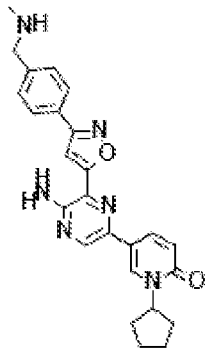
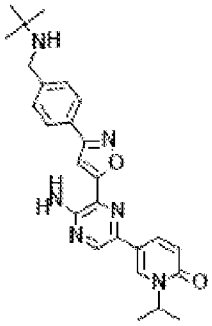
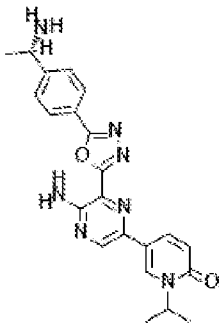
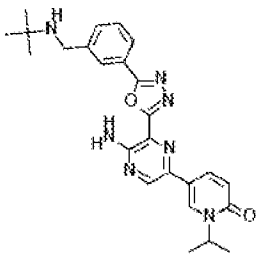
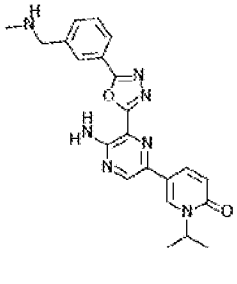
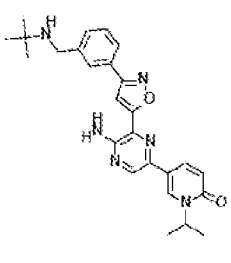
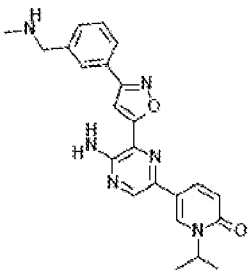
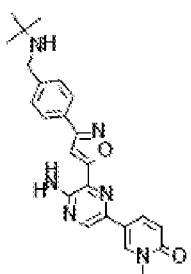
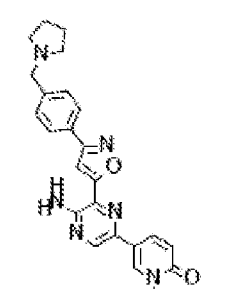
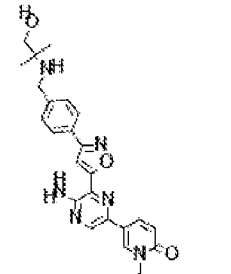
[0036] Another embodiment provides a compound selected from the following table:

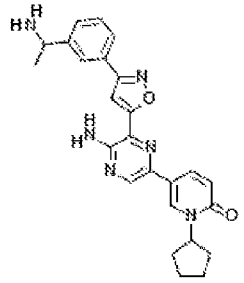
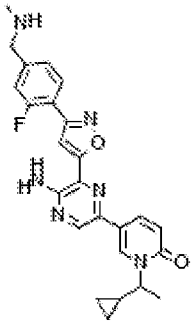
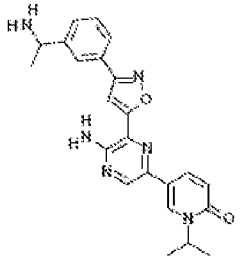
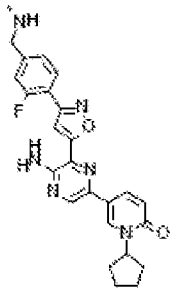
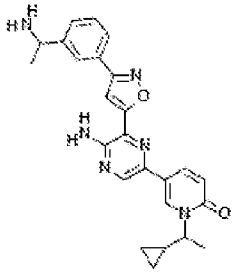
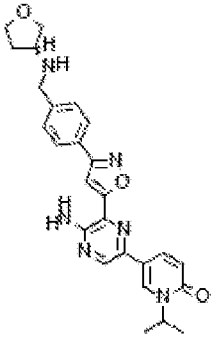
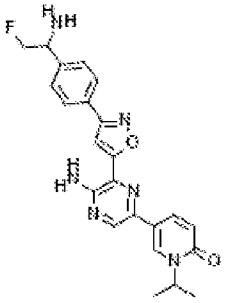
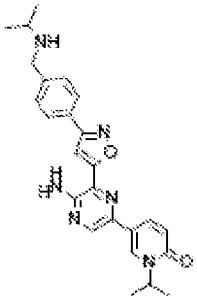
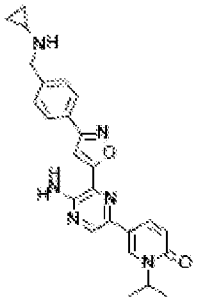
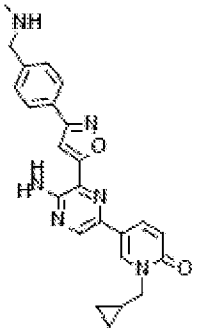
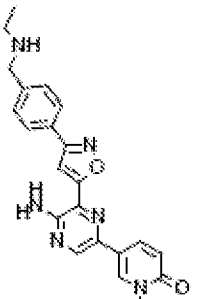
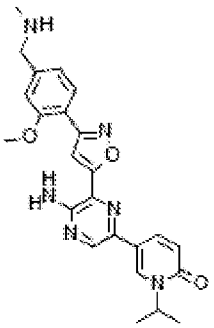
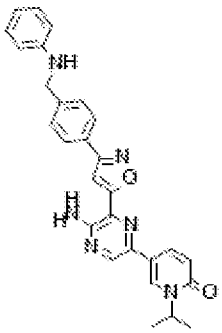
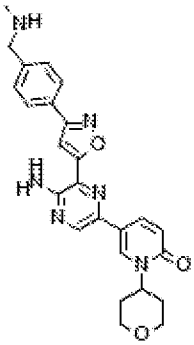
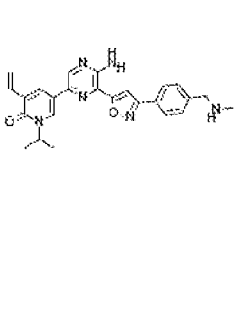
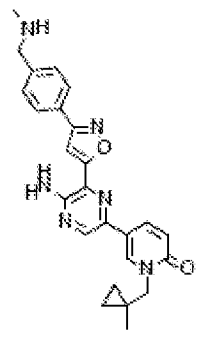
Table 1

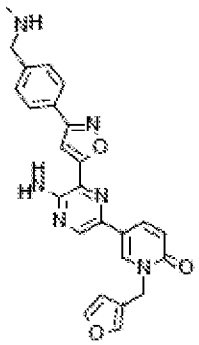
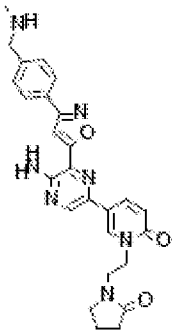
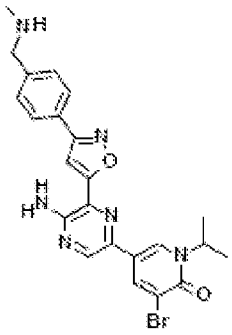
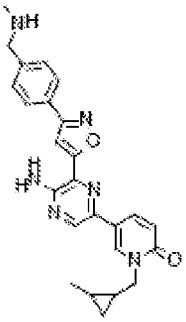
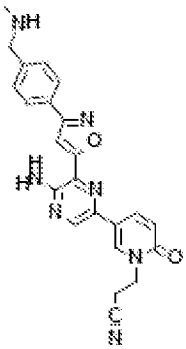
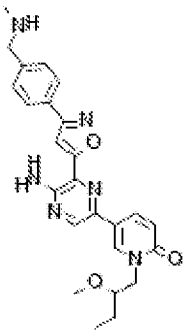
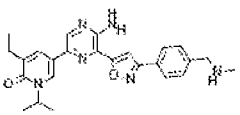
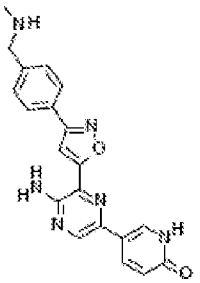
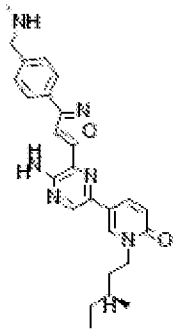
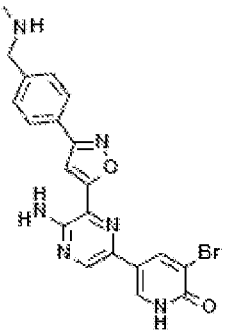
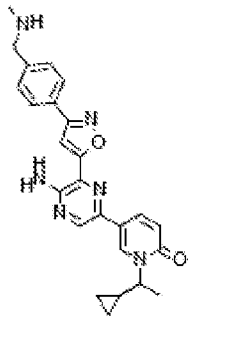
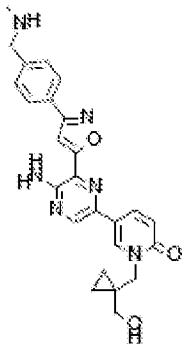
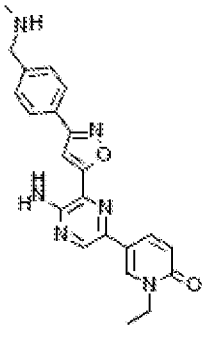
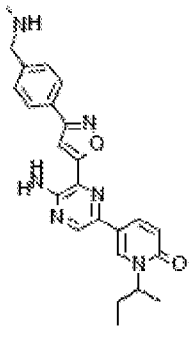
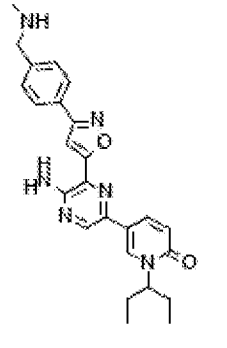
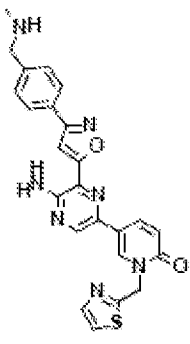
			
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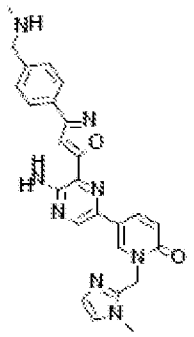
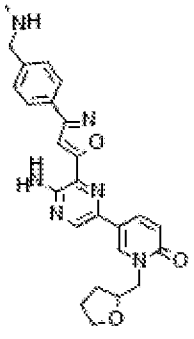
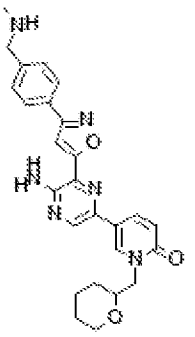
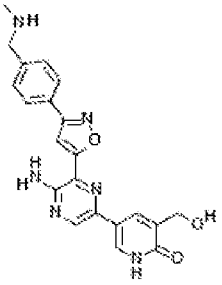
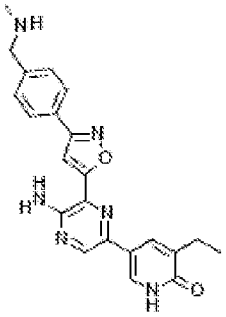
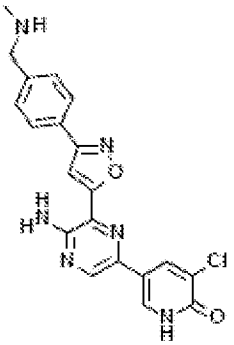
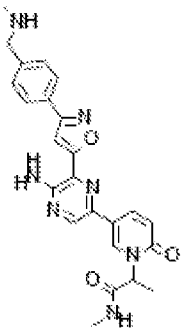
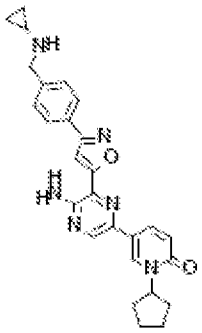
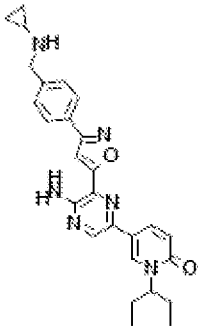
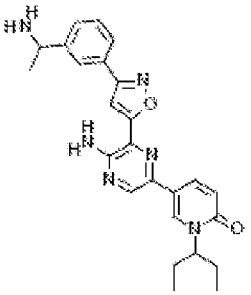
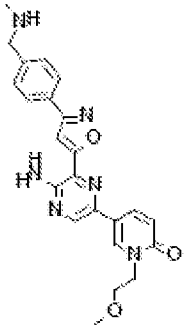
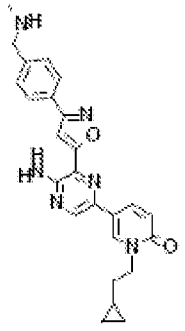
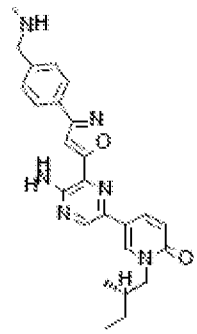
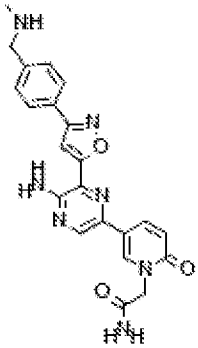
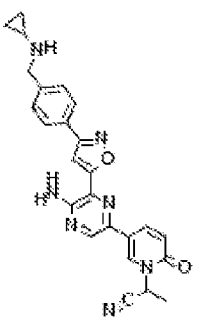
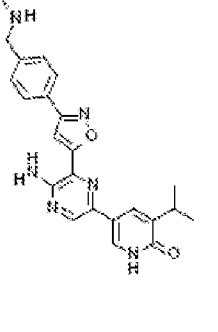
			
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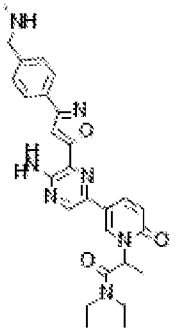
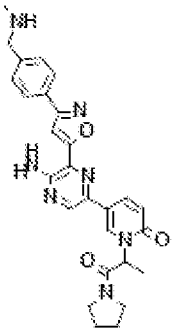
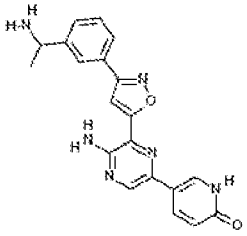
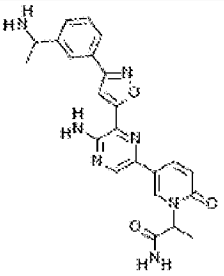
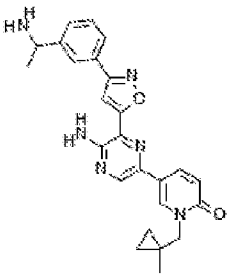
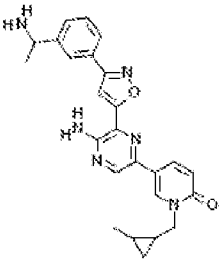
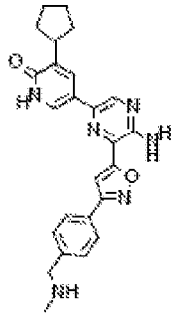
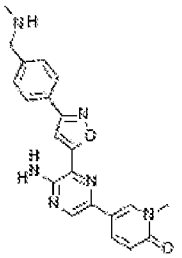
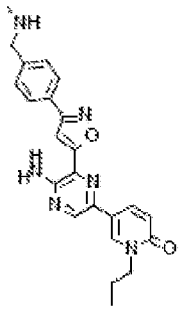
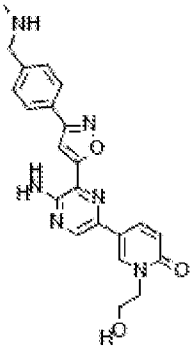
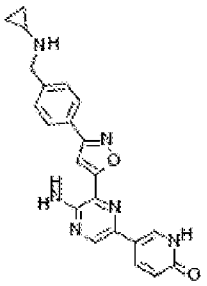
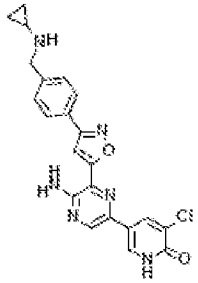
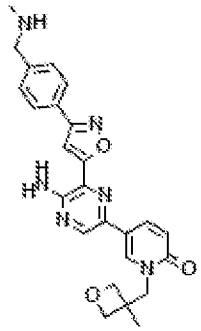
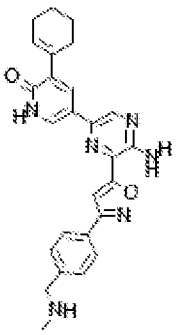
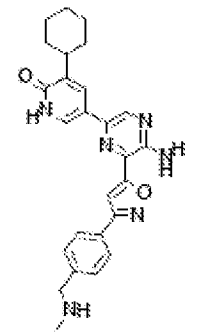
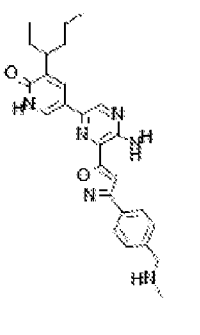
			
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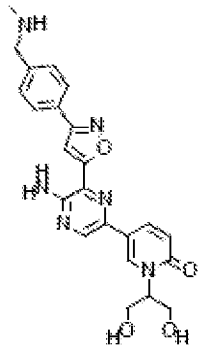
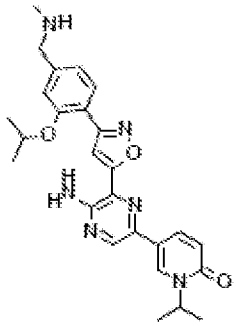
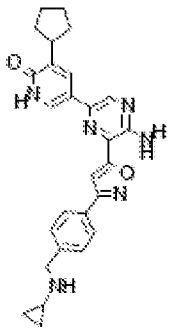
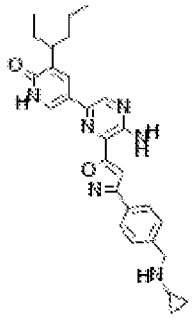
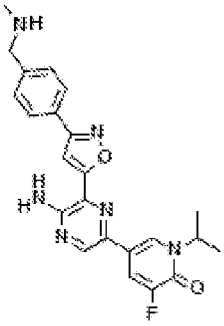
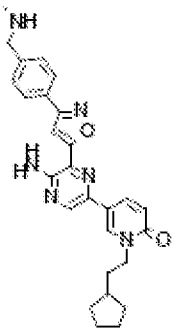
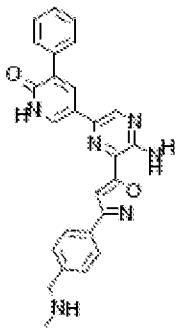
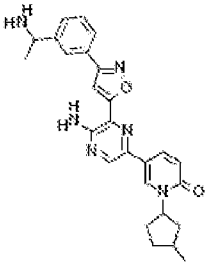
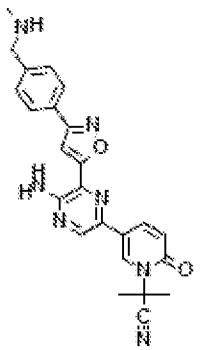
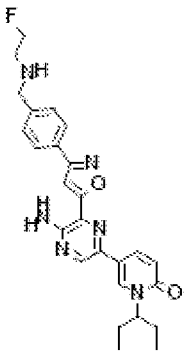
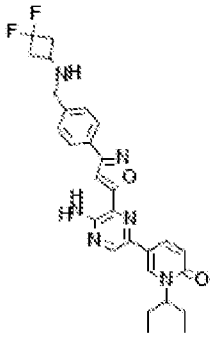
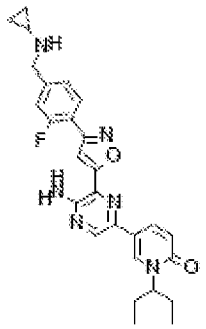
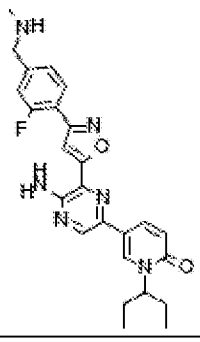
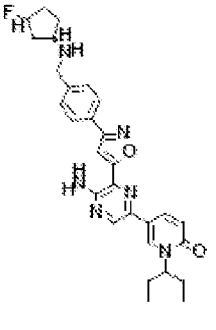
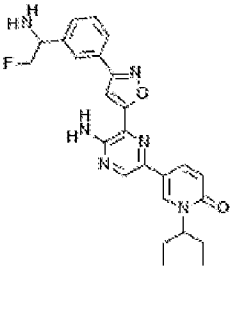
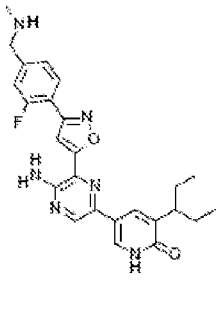
			
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I-49	I-50	I-51	I-52

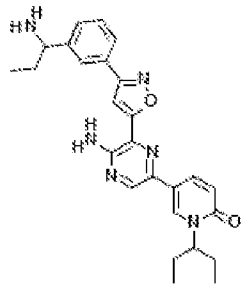
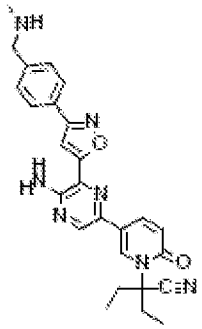
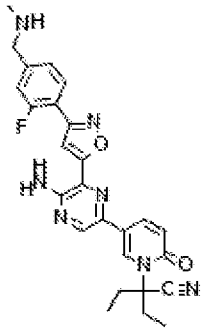
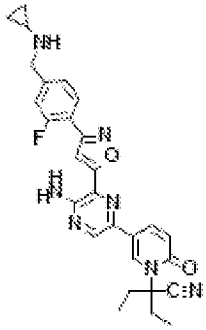
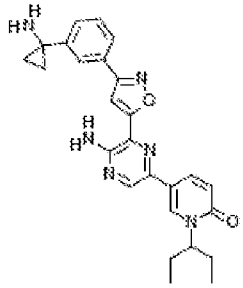
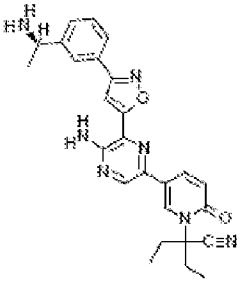
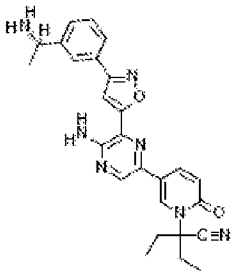
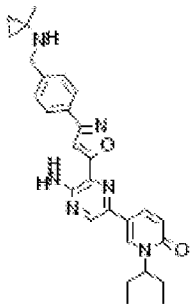
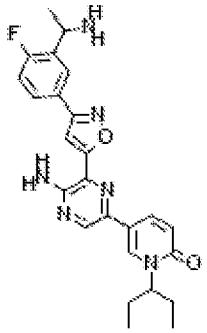
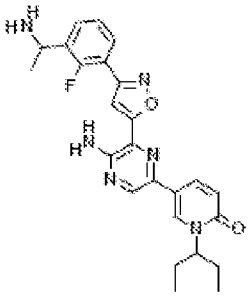
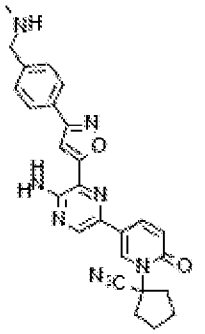
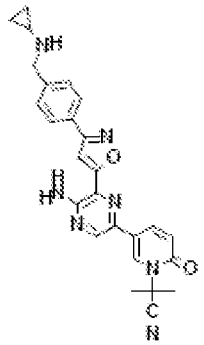
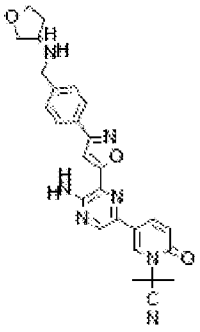
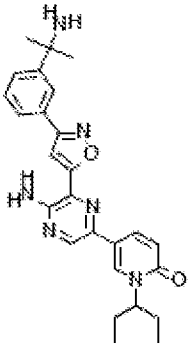
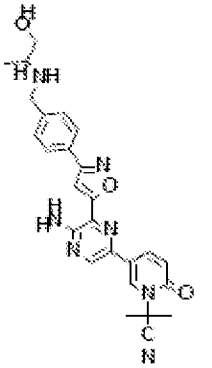
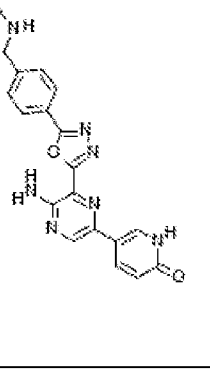
			
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I-61	I-62	I-63	I-64
			
I-65	I-66	I-67	I-68

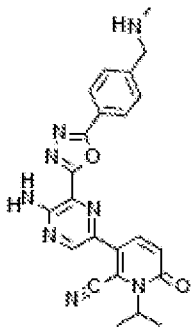
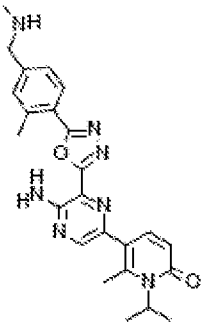
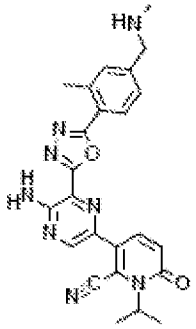
			
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I-81	I-82	I-83	I-84

			
I-85	I-86	I-87	I-88
			
I-89	I-90	I-91	I-92
			
I-93	I-94	I-95	I-96
			
I-97	I-98	I-99	I-100

			
I-101	I-102	I-103	I-104
			
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I-113	I-114	I-115	I-116

			
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I-125	I-126	I-127	I-128
			
I-129	I-130	I-131	I-132

			
I-133	I-134	I-135	I-136
			
I-137	I-138	I-139	I-140
			
I-141	I-142	I-143	I-144
			
I-145	I-146	I-147	I-148

			
I-149	I-150	I-151	

[0037] In some embodiments, the variables are as depicted in the compounds of the disclosure including compounds in the tables above.

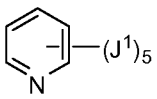
[0038] Compounds of this invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0039] As described herein, a specified number range of atoms includes any integer therein. For example, a group having from 1-4 atoms could have 1, 2, 3, or 4 atoms.

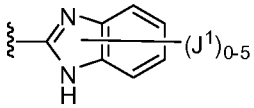
[0040] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally herein, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a

specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

[0041] Unless otherwise indicated, a substituent connected by a bond drawn from the center of a ring means that the substituent can be bonded to any position in the ring. In example **i** below, for instance, J^1 can be bonded to any position on the pyridyl ring. For bicyclic rings, a bond drawn through both rings indicates that the substituent can be bonded from any position of the bicyclic ring. In example **ii** below, for instance, J^1 can be bonded to the 5-membered ring (on the nitrogen atom, for instance), and to the 6-membered ring.



i



ii

[0042] The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, recovery, purification, and use for one or more of the purposes disclosed herein. In some embodiments, a stable compound or chemically feasible compound is one that is not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0043] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched), branched, or cyclic, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation that has a single point of attachment to the rest of the molecule.

[0044] Unless otherwise specified, aliphatic groups contain 1-20 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-10 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-8 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-6 aliphatic carbon atoms, and in yet other embodiments aliphatic groups contain 1-4 aliphatic carbon atoms. Aliphatic groups may be linear or branched, substituted or unsubstituted alkyl, alkenyl, or alkynyl groups. Specific examples include, but are not limited to, methyl, ethyl, isopropyl, n-propyl, sec-butyl, vinyl, n-butenyl, ethynyl, and tert-butyl. Aliphatic groups may also be cyclic, or have a combination of linear or branched and cyclic groups. Examples of such types of aliphatic groups include, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, $-CH_2$-cyclopropyl, $CH_2CH_2CH(CH_3)$-cyclohexyl.

[0045] The term "cycloaliphatic" (or "carbocycle" or "carbocyclyl") refers to a monocyclic C_3-C_8 hydrocarbon or bicyclic C_8-C_{12} hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. Examples of cycloaliphatic groups include, but are not limited to, cycloalkyl and cycloalkenyl groups. Specific examples include, but are not limited to, cyclohexyl, cyclopropenyl, and cyclobutyl.

[0046] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic, or tricyclic ring systems in which one or more ring members are an independently selected heteroatom. In some embodiments, the "heterocycle", "heterocyclyl", or "heterocyclic" group has three to fourteen ring members in which one or more ring members is a heteroatom independently selected from oxygen, sulfur, nitrogen, or phosphorus, and each ring in the system contains 3 to 7 ring members.

[0047] Examples of heterocycles include, but are not limited to, 3-1H-benzimidazol-2-one, 3-(1-alkyl)-benzimidazol-2-one, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholino, 3-morpholino, 4-morpholino, 2-thiomorpholino, 3-thiomorpholino, 4-thiomorpholino, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-tetrahydropiperazinyl, 2-tetrahydropiperazinyl, 3-tetrahydropiperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 1-pyrazolinyl, 3-pyrazolinyl, 4-pyrazolinyl, 5-pyrazolinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2-thiazolidinyl, 3-thiazolidinyl, 4-thiazolidinyl, 1-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, indolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, benzothiolane, benzodithiane, and 1,3-dihydro-imidazol-2-one.

[0048] Cyclic groups, (e.g. cycloaliphatic and heterocycles), can be linearly fused, bridged, or spirocyclic.

[0049] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0050] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation. As would be known by one of skill in the art, unsaturated groups can be partially unsaturated or fully unsaturated. Examples of partially unsaturated groups include, but are not limited to, butene, cyclohexene, and tetrahydropyridine. Fully unsaturated groups

can be aromatic, anti-aromatic, or non-aromatic. Examples of fully unsaturated groups include, but are not limited to, phenyl, cyclooctatetraene, pyridyl, thienyl, and 1-methylpyridin-2(1H)-one.

[0051] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

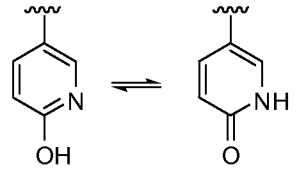
[0052] The terms "haloalkyl", "haloalkenyl", "haloaliphatic", and "haloalkoxy" mean alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. This term includes perfluorinated alkyl groups, such as $-CF_3$ and $-CF_2CF_3$.

[0053] The terms "halogen", "halo", and "hal" mean F, Cl, Br, or I.

[0054] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring".

[0055] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". Examples of heteroaryl rings include, but are not limited to, 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, benzimidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, pyridazinyl (e.g., 3-pyridazinyl), 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, tetrazolyl (e.g., 5-tetrazolyl), triazolyl (e.g., 2-triazolyl and 5-triazolyl), 2-thienyl, 3-thienyl, benzofuryl, benzothiophenyl, indolyl (e.g., 2-indolyl), pyrazolyl (e.g., 2-pyrazolyl), isothiazolyl, 1,2,3-oxadiazolyl, 1,2,5-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,3-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, purinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl (e.g., 2-quinolinyl, 3-quinolinyl, 4-quinolinyl), and isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, or 4-isoquinolinyl).

[0056] It shall be understood that the term "heteroaryl" includes certain types of heteroaryl rings that exist in equilibrium between two different forms. More specifically, for example, species such hydropyridine and pyridinone (and likewise hydroxypyrimidine and pyrimidinone) are meant to be encompassed within the definition of "heteroaryl."



[0057] The term "protecting group" and "protective group" as used herein, are interchangeable and refer to an agent used to temporarily block one or more desired functional groups in a compound with multiple reactive sites. In certain embodiments, a protecting group has one or more, or preferably all, of the following characteristics: a) is added selectively to a functional group in good yield to give a protected substrate that is b) stable to reactions occurring at one or more of the other reactive sites; and c) is selectively removable in good yield by reagents that do not attack the regenerated, deprotected functional group. As would be understood by one skilled in the art, in some cases, the reagents do not attack other reactive groups in the compound. In other cases, the reagents may also react with other reactive groups in the compound. Examples of protecting groups are detailed in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999 (and other editions of the book), the entire contents of which are hereby incorporated by reference. The term "nitrogen protecting group", as used herein, refers to an agent used to temporarily block one or more desired nitrogen reactive sites in a multifunctional compound. Preferred nitrogen protecting groups also possess the characteristics exemplified for a protecting group above, and certain exemplary nitrogen protecting groups are also detailed in Chapter 7 in Greene, T.W., Wuts, P. G in "Protective Groups in Organic Synthesis", Third Edition, John Wiley & Sons, New York: 1999, the entire contents of which are hereby incorporated by reference.

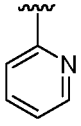
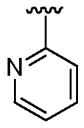
[0058] In some embodiments, a methylene unit of an alkyl or aliphatic chain is optionally replaced with another atom or group. Examples of such atoms or groups include, but are not limited to, nitrogen, oxygen, sulfur, -C(O)-, -C(=N-CN)-, -C(=NR)-, -C(=NOR)-, -SO-, and $-SO_2-$. These atoms or groups can be combined to form larger groups. Examples of such larger groups include, but are not limited to, -OC(O)-, -C(O)CO-, $-CO_2-$, -C(O)NR-, -C(=N-CN), -NRCO-, -NRC(O)O-, $-SO_2NR-$, $-NRSO_2-$, -NRC(O)NR-, -OC(O)NR-, and $-NRSO_2NR-$, wherein R is, for example, H or C_{1-6}aliphatic. It should be understood that these groups can be bonded to the methylene units of the aliphatic chain via single, double, or triple bonds. An example of an optional replacement (nitrogen atom in this case) that is bonded to the aliphatic chain via a double bond would be $-CH_2CH=N-CH_3$. In some cases, especially on the terminal end, an optional replacement can be bonded to the aliphatic group

via a triple bond. One example of this would be $CH_2CH_2CH_2C{\equiv}N$. It should be understood that in this situation, the terminal nitrogen is not bonded to another atom.

[0059] It should also be understood that, the term "methylene unit" can also refer to branched or substituted methylene units. For example, in an isopropyl moiety [$-CH(CH_3)_2$], a nitrogen atom (e.g. NR) replacing the first recited "methylene unit" would result in dimethylamine [$-N(CH_3)_2$]. In instances such as these, one of skill in the art would understand that the nitrogen atom will not have any additional atoms bonded to it, and the "R" from "NR" would be absent in this case.

[0060] Unless otherwise indicated, the optional replacements form a chemically stable compound. Optional replacements can occur both within the chain and/or at either end of the chain; i.e. both at the point of attachment and/or also at the terminal end. Two optional replacements can also be adjacent to each other within a chain so long as it results in a chemically stable compound. For example, a C_3 aliphatic can be optionally replaced by 2 nitrogen atoms to form $-C-N{\equiv}N$. The optional replacements can also completely replace all of the carbon atoms in a chain. For example, a C_3 aliphatic can be optionally replaced by -NR-, -C(O)-, and -NR- to form -NRC(O)NR- (a urea).

[0061] Unless otherwise indicated, if the replacement occurs at the terminal end, the replacement atom is bound to a hydrogen atom on the terminal end. For example, if a methylene unit of $-CH_2CH_2CH_3$ were optionally replaced with -O-, the resulting compound could be $-OCH_2CH_3$, $-CH_2OCH_3$, or $-CH_2CH_2OH$. It should be understood that if the terminal atom does not contain any free valence electrons, then a hydrogen atom is not required at the terminal end (e.g., $-CH_2CH_2CH{=}O$ or $-CH_2CH_2C{\equiv}N$).

[0062] Unless otherwise indicated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, geometric, conformational, and rotational) forms of the structure. For example, the R and S configurations for each asymmetric center, (Z) and (E) double bond isomers, and (Z) and (E) conformational isomers are included in this invention. As would be understood to one skilled in the art, a substituent can freely rotate around any rotatable bonds. For example, a substituent drawn as  also represents .

[0063] Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, geometric, conformational, and rotational mixtures of the present compounds are within the scope of the invention.

[0064] Unless otherwise indicated, all tautomeric forms of the compounds of the invention are within the scope of the invention.

[0065] Additionally, unless otherwise indicated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools or probes in biological assays.

Pharmaceutically Acceptable Salts

[0066] The compounds of this invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable salt.

[0067] A "pharmaceutically acceptable salt" means any non-toxic salt of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of the ATR protein kinase.

[0068] Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.,* describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, **1977**, *66*, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. These salts can be prepared *in situ* during the final isolation and purification of the compounds. Acid addition salts can be prepared by 1) reacting the purified compound in its free-based form with a suitable organic or inorganic acid and 2) isolating the salt thus formed.

[0069] Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate,

dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, glycolate, gluconate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0070] Base addition salts can be prepared by 1) reacting the purified compound in its acid form with a suitable organic or inorganic base and 2) isolating the salt thus formed. Salts derived from appropriate bases include alkali metal (e.g., sodium, lithium, and potassium), alkaline earth metal (e.g., magnesium and calcium), ammonium and $N^+(C_{1-4}alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0071] Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate. Other acids and bases, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid or base addition salts.

Abbreviations

[0072] The following abbreviations are used:

DMSO	dimethyl sulfoxide
ATP	adenosine triphosphate
^{1}HNMR	proton nuclear magnetic resonance
HPLC	high performance liquid chromatography
LCMS	liquid chromatography-mass spectrometry
TLC	thin layer chromatography
Rt	retention time

Compound Uses

[0073] One aspect of this invention provides compounds that are inhibitors of ATR kinase, and thus are useful for treating or lessening the severity of a disease, condition, or disorder where ATR is implicated in the disease, condition, or disorder.

[0074] Another aspect of this invention provides compounds that are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abnormal cell proliferation. Such diseases include, a proliferative or hyperproliferative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer and myeloproliferative disorders.

[0075] In some embodiments, said compounds are selected from the group consisting of a compound of formula I. Te term "cancer" includes, but is not limited to the following cancers. Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial

carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma] hairy cell; lymphoid disorders; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma, undifferentiated thyroid cancer, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

[0076] Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions. In some embodiments, the cancer is selected from colorectal, thyroid, or breast cancer.

[0077] The term “myeloproliferative disorders”, includes disorders such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, systemic mast cell disease, and hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia (APL), and acute lymphocytic leukemia (ALL).

Pharmaceutically Acceptable Derivatives or Prodrugs

[0078] In addition to the compounds of this invention, pharmaceutically acceptable derivatives or prodrugs of the compounds of this invention may also be employed in compositions to treat or prevent the herein identified disorders.

[0079] The compounds of this invention can also exist as pharmaceutically acceptable derivatives.

[0080] A “pharmaceutically acceptable derivative” is an adduct or derivative which, upon administration to a patient in need, is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof. Examples of

pharmaceutically acceptable derivatives include, but are not limited to, esters and salts of such esters.

[0081] A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable ester, salt of an ester or other derivative or salt thereof of a compound, of this invention which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. Particularly favoured derivatives or prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

[0082] Pharmaceutically acceptable prodrugs of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

Pharmaceutical Compositions

[0083] The present invention also provides compounds and compositions that are useful as inhibitors of ATR kinase.

[0084] One aspect of this invention provides pharmaceutically acceptable compositions that comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle.

[0085] The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention.

[0086] Some examples of materials which can serve as pharmaceutically acceptable carriers 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, or 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, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

Combination Therapies

[0087] Another aspect of this invention is directed towards a method of treating cancer in a subject in need thereof, comprising administration of a compound of this invention or a pharmaceutically acceptable salt thereof, and an additional therapeutic agent. In some embodiments, said method comprises the sequential or co-administration of the compound or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent.

[0088] In some embodiments, said additional therapeutic agent is an anti-cancer agent. In other embodiments, said additional therapeutic agent is a DNA-damaging agent. In yet other embodiments, said additional therapeutic agent is selected from radiation therapy, chemotherapy, or other agents typically used in combination with radiation therapy or chemotherapy, such as radiosensitizers and chemosensitizers.

[0089] As would be known by one of skill in the art, radiosensitizers are agents that can be used in combination with radiation therapy. Radiosensitizers work in various different ways, including, but not limited to, making cancer cells more sensitive to radiation therapy, working in synergy with radiation therapy to provide an improved synergistic effect, acting additively with radiation therapy, or protecting surrounding healthy cells from damage caused

by radiation therapy. Likewise chemosensitizers are agents that can be used in combination with chemotherapy. Similarly, chemosensitizers work in various different ways, including, but not limited to, making cancer cells more sensitive to chemotherapy, working in synergy with chemotherapy to provide an improved synergistic effect, acting additively to chemotherapy, or protecting surrounding healthy cells from damage caused by chemotherapy.

[0090] Examples of DNA-damaging agents that may be used in combination with compounds of this invention include, but are not limited to Platinating agents, such as Carboplatin, Nedaplatin, Satraplatin and other derivatives; Topo I inhibitors, such as Topotecan, irinotecan/SN38, rubitecan and other derivatives; Antimetabolites, such as Folic family (Methotrexate, Pemetrexed and relatives); Purine antagonists and Pyrimidine antagonists (Thioguanine, Fludarabine, Cladribine, Cytarabine, Gemcitabine, 6-Mercaptopurine, 5-Fluorouracil (5FU) and relatives); Alkylating agents, such as Nitrogen mustards (Cyclophosphamide, Melphalan, Chlorambucil, mechlorethamine, Ifosfamide and relatives); nitrosoureas (eg Carmustine); Triazenes (Dacarbazine, temozolomide); Alkyl sulphonates (eg Busulfan); Procarbazine and Aziridines; Antibiotics, such as Hydroxyurea, Anthracyclines (doxorubicin, daunorubicin, epirubicin and other derivatives); Anthracenediones (Mitoxantrone and relatives); Streptomyces family (Bleomycin, Mitomycin C, actinomycin); and Ultraviolet light.

[0091] Other therapies or anticancer agents that may be used in combination with the inventive agents of the present invention include surgery, radiotherapy (in but a few examples, gamma-radiation, neutron beam radiotherapy, electron beam radiotherapy, proton therapy, brachytherapy, and systemic radioactive isotopes, to name a few), endocrine therapy, biologic response modifiers (interferons, interleukins, and tumor necrosis factor (TNF) to name a few), hyperthermia and cryotherapy, agents to attenuate any adverse effects (e.g., antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, the DNA damaging agents listed herein, spindle poisons (Vinblastine, Vincristine, Vinorelbine, Paclitaxel), podophyllotoxins (Etoposide, Irinotecan, Topotecan), nitrosoureas (Carmustine, Lomustine), inorganic ions (Cisplatin, Carboplatin), enzymes (Asparaginase), and hormones (Tamoxifen, Leuprolide, Flutamide, and Megestrol), Gleevec™, adriamycin, dexamethasone, and cyclophosphamide.

[0092] A compound of the instant invention may also be useful for treating cancer in combination with any of the following therapeutic agents: abarelix (Plenaxis depot®); aldesleukin (Prokine®); Aldesleukin (Proleukin®); Alemtuzumabb (Campath®); alitretinoin

(Panretin®); allopurinol (Zyloprim®); altretamine (Hexalen®); amifostine (Ethyol®); anastrozole (Arimidex®); arsenic trioxide (Trisenox®); asparaginase (Elspar®); azacitidine (Vidaza®); bevacuzimab (Avastin®); bexarotene capsules (Targretin®); bexarotene gel (Targretin®); bleomycin (Blenoxane®); bortezomib (Velcade®); busulfan intravenous (Busulfex®); busulfan oral (Myleran®); calusterone (Methosarb®); capecitabine (Xeloda®); carboplatin (Paraplatin®); carmustine (BCNU®, BiCNU®); carmustine (Gliadel®); carmustine with Polifeprosan 20 Implant (Gliadel Wafer®); celecoxib (Celebrex®); cetuximab (Erbitux®); chlorambucil (Leukeran®); cisplatin (Platinol®); cladribine (Leustatin®, 2-CdA®); clofarabine (Clolar®); cyclophosphamide (Cytoxan®, Neosar®); cyclophosphamide (Cytoxan Injection®); cyclophosphamide (Cytoxan Tablet®); cytarabine (Cytosar-U®); cytarabine liposomal (DepoCyt®); dacarbazine (DTIC-Dome®); dactinomycin, actinomycin D (Cosmegen®); Darbepoetin alfa (Aranesp®); daunorubicin liposomal (DanuoXome®); daunorubicin, daunomycin (Daunorubicin®); daunorubicin, daunomycin (Cerubidine®); Denileukin diftitox (Ontak®); dexrazoxane (Zinecard®); docetaxel (Taxotere®); doxorubicin (Adriamycin PFS®); doxorubicin (Adriamycin®, Rubex®); doxorubicin (Adriamycin PFS Injection®); doxorubicin liposomal (Doxil®); dromostanolone propionate (dromostanolone®); dromostanolone propionate (masterone injection®); Elliott's B Solution (Elliott's B Solution®); epirubicin (Ellence®); Epoetin alfa (epogen®); erlotinib (Tarceva®); estramustine (Emcyt®); etoposide phosphate (Etopophos®); etoposide, VP-16 (Vepesid®); exemestane (Aromasin®); Filgrastim (Neupogen®); floxuridine (intraarterial) (FUDR®); fludarabine (Fludara®); fluorouracil, 5-FU (Adrucil®); fulvestrant (Faslodex®); gefitinib (Iressa®); gemcitabine (Gemzar®); gemtuzumab ozogamicin (Mylotarg®); goserelin acetate (Zoladex Implant®); goserelin acetate (Zoladex®); histrelin acetate (Histrelin implant®); hydroxyurea (Hydrea®); Ibritumomab Tiuxetan (Zevalin®); idarubicin (Idamycin®); ifosfamide (IFEX®); imatinib mesylate (Gleevec®); interferon alfa 2a (Roferon A®); Interferon alfa-2b (Intron A®); irinotecan (Camptosar®); lenalidomide (Revlimid®); letrozole (Femara®); leucovorin (Wellcovorin®, Leucovorin®); Leuprolide Acetate (Eligard®); levamisole (Ergamisol®); lomustine, CCNU (CeeBU®); meclorethamine, nitrogen mustard (Mustargen®); megestrol acetate (Megace®); melphalan, L-PAM (Alkeran®); mercaptopurine, 6-MP (Purinethol®); mesna (Mesnex®); mesna (Mesnex tabs®); methotrexate (Methotrexate®); methoxsalen

(Uvadex®); mitomycin C (Mutamycin®); mitotane (Lysodren®); mitoxantrone (Novantrone®); nandrolone phenpropionate (Durabolin-50®); nelarabine (Arranon®); Nofetumomab (Verluma®); Oprelvekin (Neumega®); oxaliplatin (Eloxatin®); paclitaxel (Paxene®); paclitaxel (Taxol®); paclitaxel protein-bound particles (Abraxane®); palifermin (Kepivance®); pamidronate (Aredia®); pegademase (Adagen (Pegademase Bovine)®); pegaspargase (Oncaspar®); Pegfilgrastim (Neulasta®); pemetrexed disodium (Alimta®); pentostatin (Nipent®); pipobroman (Vercyte®); plicamycin, mithramycin (Mithracin®); porfimer sodium (Photofrin®); procarbazine (Matulane®); quinacrine (Atabrine®); Rasburicase (Elitek®); Rituximab (Rituxan®); sargramostim (Leukine®); Sargramostim (Prokine®); sorafenib (Nexavar®); streptozocin (Zanosar®); sunitinib maleate (Sutent®); talc (Sclerosol®); tamoxifen (Nolvadex®); temozolomide (Temodar®); teniposide, VM-26 (Vumon®); testolactone (Teslac®); thioguanine, 6-TG (Thioguanine®); thiotepa (Thioplex®); topotecan (Hycamtin®); toremifene (Fareston®); Tositumomab (Bexxar®); Tositumomab/I-131 tositumomab (Bexxar®); Trastuzumab (Herceptin®); tretinoin, ATRA (Vesanoid®); Uracil Mustard (Uracil Mustard Capsules®); valrubicin (Valstar®); vinblastine (Velban®); vincristine (Oncovin®); vinorelbine (Navelbine®); zoledronate (Zometa®) and vorinostat (Zolinza®).

[0093] For a comprehensive discussion of updated cancer therapies see, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

Compositions for Administration into a Subject

[0094] The ATR kinase inhibitors or pharmaceutical salts thereof may be formulated into pharmaceutical compositions for administration to animals or humans. These pharmaceutical compositions, which comprise an amount of the ATR inhibitor effective to treat or prevent the diseases or conditions described herein and a pharmaceutically acceptable carrier, are another embodiment of the present invention.

[0095] The exact amount of compound required for treatment will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and

uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0096] In some embodiments, these compositions optionally further comprise one or more additional therapeutic agents. For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known agents with which these compositions can be combined are listed above under the "Combination Therapies" section and also throughout the specification. Some embodiments provide a simultaneous, separate or sequential use of a combined preparation.

Modes of Administration and Dosage Forms

[0097] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[0098] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate,

benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[0099] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00100] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00101] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00102] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00103] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00104] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00105] The active compounds can also be in microencapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as

sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00106] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, eardrops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00107] The compositions of the present invention 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, but is not limited to, subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[00108] Sterile injectable forms of the compositions of this invention 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. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as

oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00109] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include, but are not limited to, lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00110] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

[00111] The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00112] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00113] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively,

the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00114] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[00115] The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00116] The amount of protein kinase inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00117] It should also be understood that 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 inhibitor will also depend upon the particular compound in the composition.

Administering with another Agent

[00118] Depending upon the particular protein kinase-mediated conditions to be treated or prevented, additional drugs, which are normally administered to treat or prevent that condition, may be administered together with the compounds of this invention.

[00119] Those additional agents may be administered separately, as part of a multiple dosage regimen, from the protein kinase inhibitor-containing compound or composition.

Alternatively, those agents may be part of a single dosage form, mixed together with the protein kinase inhibitor in a single composition.

[00120] Another aspect of this invention is directed towards a method of treating cancer in a subject in need thereof, comprising the sequential or co-administration of a compound of this invention or a pharmaceutically acceptable salt thereof, and an anti-cancer agent. In some embodiments, said anti-cancer agent is selected from Platinating agents, such as Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin and other derivatives; Topo I inhibitors, such as Camptothecin, Topotecan, irinotecan/SN38, rubitecan and other derivatives; Antimetabolites, such as Folic family (Methotrexate, Pemetrexed and relatives); Purine family (Thioguanine, Fludarabine, Cladribine, 6-Mercaptopurine and relatives); Pyrimidine family (Cytarabine, Gemcitabine, 5-Fluorouracil and relatives); Alkylating agents, such as Nitrogen mustards (Cyclophosphamide, Melphalan, Chlorambucil, mechlorethamine, Ifosfamide, and relatives); nitrosoureas (e.g. Carmustine); Triazenes (Dacarbazine, temozolomide); Alkyl sulphonates (e.g. Busulfan); Procarbazine and Aziridines; Antibiotics, such as Hydroxyurea; Anthracyclines (doxorubicin, daunorubicin, epirubicin and other derivatives); Anthracenediones (Mitoxantrone and relatives); Streptomyces family (Bleomycin, Mitomycin C, actinomycin) and Ultraviolet light.

Biological Samples

[00121] As inhibitors of ATR kinase, the compounds and compositions of this invention are also useful in biological samples. One aspect of the invention relates to inhibiting ATR kinase activity in a biological sample, which method comprises contacting said biological sample with a compound described herein or a composition comprising said compound. The term "biological sample", as used herein, means an in vitro or an ex vivo sample, including, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. The term "compounds described herein" includes compounds of formula I.

[00122] Inhibition of ATR kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, and biological specimen storage.

Study of Protein Kinases

[00123] Another aspect of this invention relates to the study of protein kinases in biological and pathological phenomena; the study of intracellular signal transduction

pathways mediated by such protein kinases; and the comparative evaluation of new protein kinase inhibitors. Examples of such uses include, but are not limited to, biological assays such as enzyme assays and cell-based assays.

[00124] The activity of the compounds as protein kinase inhibitors may be assayed *in vitro, in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of the activated kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/kinase complex and determining the amount of radiolabel bound, or by running a competition experiment where new inhibitors are incubated with the kinase bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of ATR is set forth in the Examples below.

[00125] Another aspect of the invention provides a method for modulating enzyme activity by contacting a compound described herein with ATR kinase.

Methods of Treatment

[00126] In one aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where ATR kinase is implicated in the disease state. In another aspect, the present invention provides a method for treating or lessening the severity of an ATR kinase disease, condition, or disorder where inhibition of enzymatic activity is implicated in the treatment of the disease. In another aspect, this invention provides a method for treating or lessening the severity of a disease, condition, or disorder with compounds that inhibit enzymatic activity by binding to the ATR kinase. Another aspect provides a method for treating or lessening the severity of a kinase disease, condition, or disorder by inhibiting enzymatic activity of ATR kinase with an ATR kinase inhibitor.

[00127] One aspect of the invention relates to a method of inhibiting ATR kinase activity in a patient, which method comprises administering to the patient a compound described herein, or a composition comprising said compound. In some embodiments, said method is used to treat or prevent a condition selected from proliferative and hyperproliferative diseases, such as cancer.

[00128] Another aspect of this invention provides a method for treating, preventing, or lessening the severity of proliferative or hyperproliferative diseases comprising administering an effective amount of a compound, or a pharmaceutically acceptable composition

comprising a compound, to a subject in need thereof. In some embodiments, said subject is a patient. The term "patient", as used herein, means an animal, preferably a human.

[00129] In some embodiments, said method is used to treat or prevent cancer. In some embodiments, said method is used to treat or prevent a type of cancer with solid tumors. In yet another embodiment, said cancer is selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-

thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma, undifferentiated thyroid cancer, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

[00130] In some embodiments, the cancer is selected from the cancers described herein. In some embodiments, said cancer is lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, or brain cancer.

[00131] In certain embodiments, an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective in order to treat said disease. The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of said disease.

[00132] One aspect provides a method for inhibiting ATR in a patient comprising administering a compound described herein as described herein. Another embodiment provides a method of treating cancer comprising administering to a patient a compound described herein, wherein the variables are as defined herein.

[00133] Some embodiments comprising administering to said patient an additional therapeutic agent selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said compound as a single dosage form or separately from said compound as part of a multiple dosage form.

[00134] In some embodiments, said DNA-damaging agent is selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonates, an antimetabolite, or an antibiotic. In other embodiments, said DNA-damaging agent is selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.

[00135] Examples of Platinating agents include Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Satraplatin and other derivatives. Other platinating agents include Lobaplatin,

and Triplatin. Other platinating agents include Tetranitrate, Picoplatin, Satraplatin, ProLindac and Aroplatin.

[00136] Examples of Topo I inhibitor include Camptothecin, Topotecan, irinotecan/SN38, rubitecan and other derivatives. Other Topo I inhibitors include Belotecan.

[00137] Examples of Topo II inhibitors include Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin and Teniposide.

[00138] Examples of Antimetabolites include members of the Folic family, Purine family (purine antagonists), or Pyrimidine family (pyrimidine antagonists). Examples of the Folic family include methotrexate, pemetrexed and relatives; examples of the Purine family include Thioguanine, Fludarabine, Cladribine, 6-Mercaptopurine, and relatives; examples of the Pyrimidine family include Cytarabine, gemcitabine, 5-Fluorouracil (5FU) and relatives.

[00139] Some other specific examples of antimetabolites include Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine and Hydroxyurea.

[00140] Examples of alkylating agents include Nitrogen mustards, Triazenes, alkyl sulphonates, Procarbazine and Aziridines. Examples of Nitrogen mustards include Cyclophosphamide, Melphalan, Chlorambucil and relatives; examples of nitrosoureas include Carmustine; examples of triazenes include Dacarbazine and temozolomide; examples of alkyl sulphonates include Busulfan.

[00141] Other specific examples of alkylating agents include Mechlorethamine, Cyclophosphamide, Ifosfamide, Trofosfamide, Chlorambucil, Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin and Plicamycin.

[00142] Examples of antibiotics include Mitomycin, Hydroxyurea; Anthracyclines, Anthracenediones, Streptomyces family. Examples of Anthracyclines include doxorubicin, daunorubicin, epirubicin and other derivatives; examples of Anthracenediones include Mitoxantrone and relatives; examples of Streptomyces family inclue Bleomycin, Mitomycin C, and actinomycin.

[00143] In certain embodiments, said platinating agent is Cisplatin or Oxaliplatin; said Topo I inhibitor is Camptothecin; said Topo II inhibitor is Etoposide; and said antibiotic is

Mitomycin. In other embodiments, said platinating agent is selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from a member of the Folic Family, the Purine Family, or the Pyrimidine Family; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, or Streptomyces family.

[00144] Another embodiment provides a method of promoting cell death in cancer cells comprising administering to a patient a compound described herein, , or a composition comprising said compound.

[00145] Yet another embodiment provides a method of preventing cell repair of DNA damage in cancer cells comprising administering to a patient a compound described herein, or a composition comprising said compound. Yet another embodiment provides a method of preventing cell repair caused by of DNA damage in cancer cells comprising administering to a patient a compound of formula I, or composition comprising said compound.

[00146] Another embodiment provides a method of sensitizing cells to DNA damaging agents comprising administering to a patient a compound described herein, or a composition comprising said compound.

[00147] In some embodiments, the method is used on a cancer cell having defects in the ATM signaling cascade. In some embodiments, said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX. In another embodiment, the cell is a cancer cell expressing DNA damaging oncogenes. In some embodiments, said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.

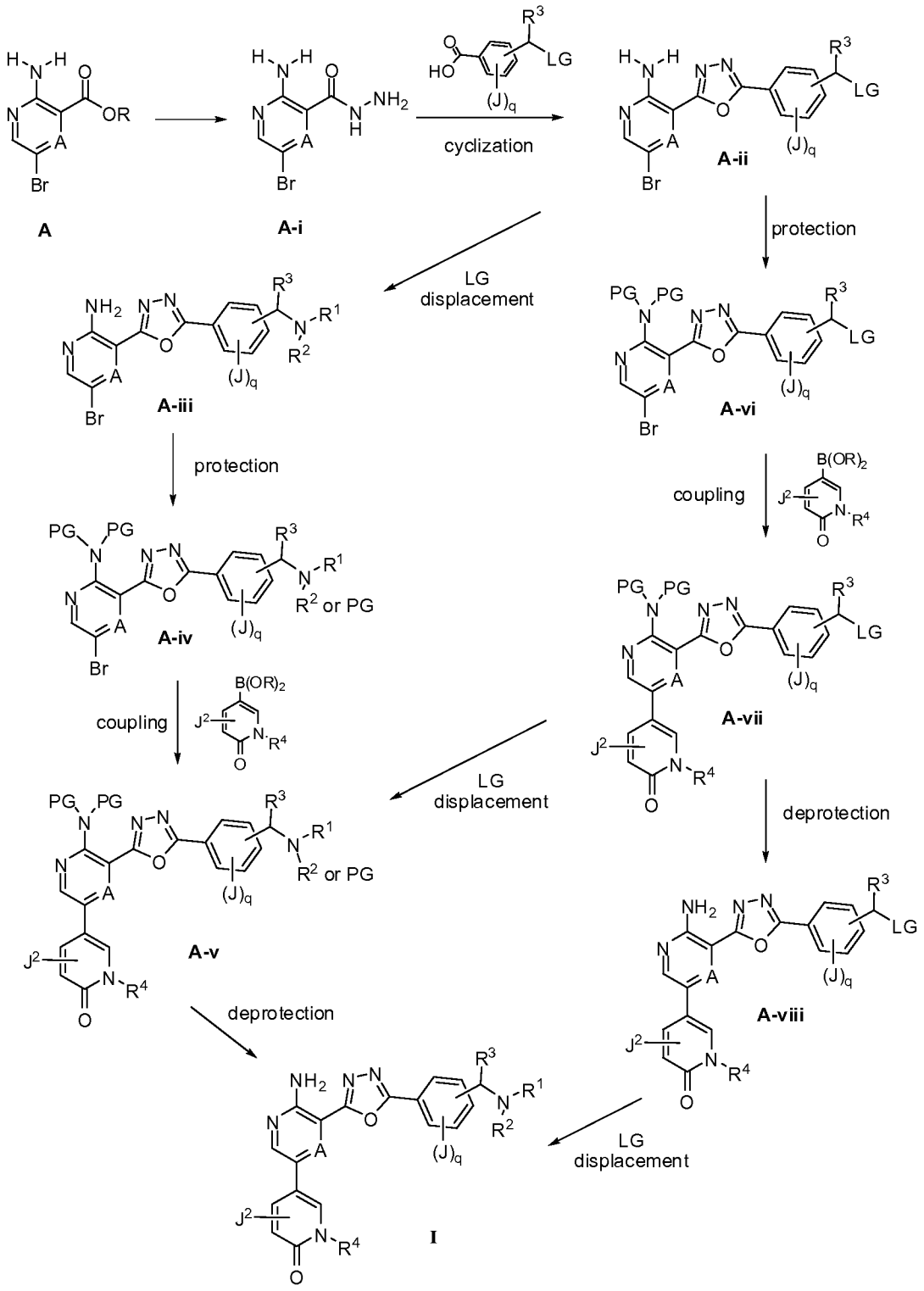
[00148] Yet another embodiment provides use of a compound described herein as a radio-sensitizer or a chemo-sensitizer.

[00149] Yet other embodiment provides use of a compound of formula I as a single agent (monotherapy) for treating cancer. In some embodiments, the compounds of formula I are used for treating patients having cancer with a DNA-damage response (DDR) defect. In other embodiments, said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, or H2AX.

SCHEMES AND EXAMPLES

[00150] The compounds of the disclosure may be prepared in light of the specification using steps generally known to those of ordinary skill in the art. Those compounds may be analyzed by known methods, including but not limited to LCMS (liquid chromatography mass spectrometry) and NMR (nuclear magnetic resonance). The following generic schemes and examples illustrate how to prepare the compounds of the present disclosure. The examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way. ^{1}H-NMR spectra were recorded at 400 MHz using a Bruker DPX 400 instrument. Mass spec. samples were analyzed on a MicroMass Quattro Micro mass spectrometer operated in single MS mode with electrospray ionization.

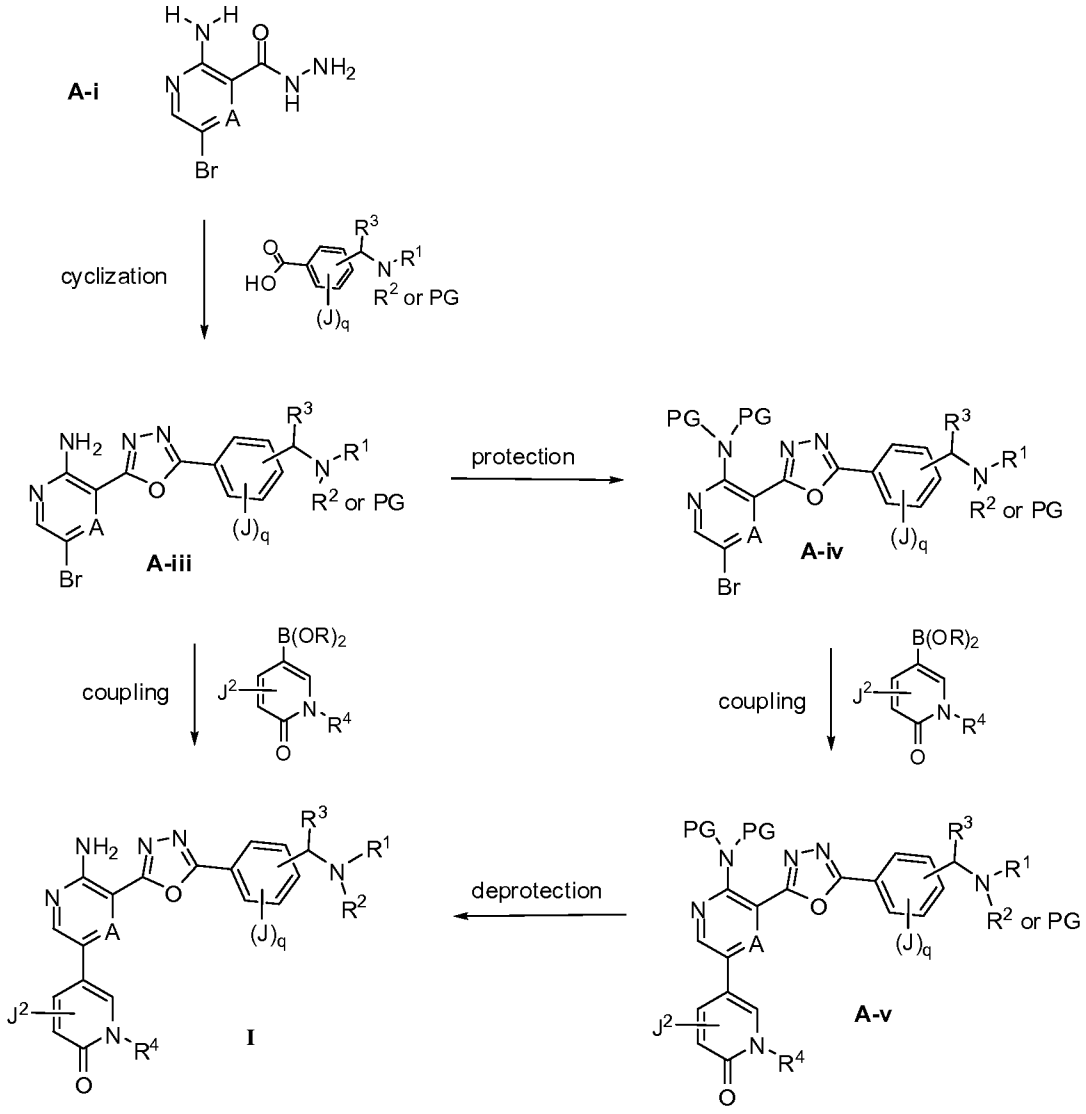
Scheme A-1


A
A-i
cyclization
A-ii
protection
LG displacement
A-iii
A-vi
protection
coupling
A-iv
A-vii
coupling
LG displacement
deprotection
A-v
A-viii
deprotection
LG displacement
I

[00151] Scheme A-1 depicts a general method for making compounds of Formula **I** in which Ring D is oxadiazole. Compound **A**, preferably the methyl ester, is reacted with hydrazine to form the acyl hydrazide **A-i**. From compounds of Formula **A-i** and an appropriately substituted benzoic acid, the corresponding 1,3,4-oxadiazole **A-ii** can be obtained using reagents such as, but not limited to, PPh_3Br_2 and a base. Alternatively, compounds of Formula **A-ii** can be obtained from the step-wise condensation of the acyl hydrazide **A-i** with the appropriate acid, followed by cyclodehydration using but not limited to reagents such as PPh_3Br_2, $POCl_3$, or T3P®. The leaving group LG of compound **A-ii** consists of a group which may be displaced by an amine of formula NHR^1R^2 resulting in compounds of Formula **A-iii**, and includes but is not limited to chlorine and bromine. Compounds of Formula **A-iii** are then protected with a suitable amine protecting group PG such as, but not limited to BOC (^{t}Butyl Carbamate), to give compounds of Formula **A-iv** (if R^2 = H in **A-iii**, then R^2 is protected as PG).

[00152] The pyridone ring system is introduced under metal-mediated coupling conditions, including but not limited to Suzuki coupling with an appropriate boronic ester or boronic acid to provide compounds of Formula **A-v**. Removal of the nitrogen protecting groups PG from compounds of Formula **A-v** takes place under standard conditions known to those skilled in the art such as, but not limited to, treatment with HCl or TFA to provide compounds of Formula **I** in which Ring D is oxadiazole. Protection, coupling, leaving group displacement, and deprotection reactions for the generation of compounds of Formula **A-vi** through **A-viii** are analogous to those described above. In addition, substituents R^4 on Formula **I** can undergo further functionalization by reactions known to those skilled in the art such as, but not limited to hydrolysis, nucleophilic displacement reactions, acylation reactions, amide bond formation reactions, or further deprotection to reveal additional functionality.

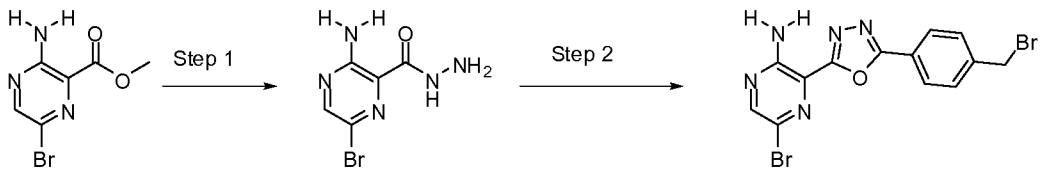
Scheme A-2



[00153] Scheme A-2 depicts a general method for making compounds of Formula **I** which Ring D is oxadiazole. From compounds of formula **A-i** and the appropriate benzoic acid substituted by an amine of formula $-NR^1R^2$ (protected as PG if R^2=H), the corresponding 1,3,4-oxadiazole **A-iii** can be obtained using reagents such as, but not limited to, PPh_3Br_2 and a base. Alternatively, compounds of Formula **A-iii** can be obtained from the step-wise condensation of the acyl hydrazide **A-i** with the substituted benzoic acid, followed by cyclodehydration using but not limited to reagents such as PPh_3Br_2, $POCl_3$, or T3P®. Compounds of Formula **A-iii** may be protected with a suitable amine protecting group PG such as, but not limited to BOC (^{t}Butyl Carbamate), to give compounds of Formula **A-iv**. The pyridone ring system is introduced under metal-mediated coupling conditions, including

but not limited to Suzuki coupling of **A-iv** with an appropriate boronic ester or boronic acid to provide compounds of Formula **A-v**. Removal of the nitrogen protecting groups PG from compounds of Formula **A-v** takes place under standard conditions known to those skilled in the art such as, but not limited to, treatment with HCl or TFA to provide compounds of Formula **I** in which Ring D is oxadiazole. Alternatively, compounds of Formula **I** in which Ring D is oxadiazole may be accessed directly from **A-iii** utilizing the metal-mediated coupling conditions described above. In addition, substituents R^4 on Formula **I** can undergo further functionalization by reactions known to those skilled in the art such as, but not limited to, hydrolysis, nucleophilic displacement reactions, acylation reactions, amide bond formation reactions, or further deprotection to reveal additional functionality.
Preparations 1-7 relate to Scheme A1 and A2.

Preparation 1: Synthesis of 5-bromo-3-(5-(4-(bromomethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine

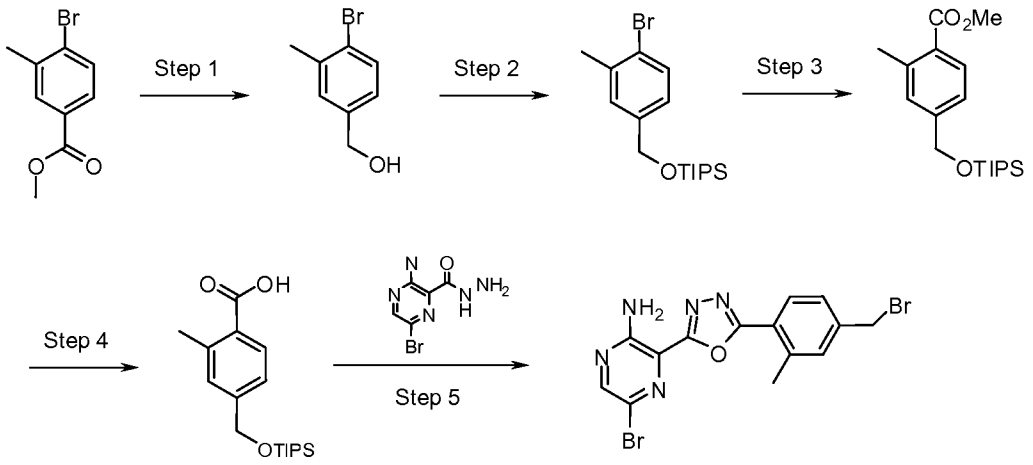


[00154] Step 1: To a suspension of methyl 3-amino-6-bromo-pyrazine-2-carboxylate (2.5 g, 10.8 mmol) in ethanol (50 mL) was added hydrazine hydrate (3.2 g, 3 mL, 64.6 mmol) and the reaction mixture heated at 70 °C for 1.5 h forming a thick yellow solid. The reaction mixture was filtered and the solid washed with water (20 mL) and ethanol (40 mL). The solid was dried *in vacuo* to yield 3-amino-6-bromo-pyrazine-2-carbohydrazide (2.7 g, 94% yield) as a light yellow solid. LC/MS m/z 233.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.31 (s, 1H), 7.62 (s, 2H), 4.53 (d, J = 3.5 Hz, 2H).

[00155] Step 2: Dibromo(triphenyl)phosphorane (1.746 g, 4.137 mmol) was added to a suspension of 3-amino-6-bromo-pyrazine-2-carbohydrazide (200 mg, 0.862 mmol) and 4-(bromomethyl)benzoic acid (185 mg, 0.862 mmol) in acetonitrile (4 mL) at room temperature and the resulting suspension stirred for 1 h. The reaction mixture was diluted with acetonitrile (2 mL), treated dropwise with DIEA (900 µL, 5.171 mmol) and stirred for 16 h. The suspension was filtered, washed with acetonitrile and hexane, and dried to provide 5-bromo-3-(5-(4-(bromomethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine (354 mg, 68%

yield) as a yellow solid. LC/MS m/z 412.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.80 (s, 2H), 7.72 (d, J = 8.2 Hz, 2H), 4.82 (s, 2H).

Preparation 2: Synthesis of 5-bromo-3-(5-(4-(bromomethyl)-2-methylphenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine



[00156] Step 1: To a solution of methyl 4-bromo-3-methylbenzoate (50 g, 219 mmol) in THF (500 mL) at 0 °C was added lithium aluminum hydride (262 mL of 1 M solution in THF, 262 mmol) over 15 min. After stirring for 20 min, water (50 mL) was added dropwise, followed by 1 M NaOH (50 mL), and water (50 mL). The reaction mixture was filtered through Celite and concentrated *in vacuo*. The resulting residue was azeotroped once with toluene, then dissolved in DCM, dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to provide (4-bromo-3-methylphenyl)methanol as a colorless solid (42 g, 96% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 8.1 Hz, 1H), 7.29 (s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 5.23 (t, J = 5.7 Hz, 1H), 4.44 (d, J = 5.7 Hz, 2H), 2.33 (s, 3H).

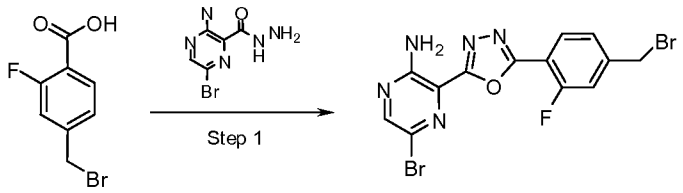
[00157] Step 2: A solution of (4-bromo-3-methylphenyl)methanol (5.0 g, 24.87 mmol) and imidazole (5.1 g, 74.61 mmol) in THF (50 mL) was cooled to 0 °C and treated with chloro(triisopropyl)silane (7. 2 g, 7.9 mL, 37.30 mmol), then allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with water and DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield (4-bromo-3-methylbenzyloxy)triisopropylsilane as a colorless oil, (8.8 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.04 (d, J = 8.1 Hz, 1H), 4.75 (s, 2H), 2.39 (s, 3H), 1.22 – 1.14 (m, 3H), 1.09 (d, J = 6.5 Hz, 18H).

[00158] Step 3: A solution of (4-bromo-3-methylbenzyloxy)triisopropylsilane (6.8 g, 19.03 mmol), $Pd(OAc)_2$ (427 mg, 1.90 mmol), 3-diphenylphosphanylpropyl(diphenyl) phosphane (785 mg, 1.90 mmol), and triethylamine (8.5 mL, 60.90 mmol) in DMF (38 mL) and MeOH (23 mL) was treated with CO gas at 40 psi and heated at 80 °C for 14 h. The reaction mixture was cooled to room temperature and depressurized. The reaction was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (0-50% ethyl acetate/hexanes) to provide methyl 2-methyl-4-((triisopropylsilyloxy)methyl)benzoate as a colorless oil (6.0 g, 94% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 9.0 Hz, 2H), 4.84 (s, 2H), 3.88 (s, 3H), 2.60 (s, 3H), 1.22 – 1.12 (m, 3H), 1.09 (d, J = 6.6 Hz, 18H).

[00159] Step 4: Methyl 2-methyl-4-(triisopropylsilyloxymethyl)benzoate (6.0 g, 17.83 mmol) in THF (35 mL) was treated with lithium hydroxide (2.6 g, 107.0 mmol) in water (18 mL) followed by MeOH (18 mL) and the reaction mixture was heated to 60 °C for 2 h. The solvent was removed *in vacuo*, and the resulting residue was diluted with ethyl acetate and quenched with 1N HCl to pH 2. The resulting layers were separated and the organic phase was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield 2-methyl-4-(triisopropylsilyloxymethyl)benzoic acid as a colorless solid (5.4 g, 94% yield). LC/MS m/z 321.5 [M]-. ^1H NMR (400 MHz, DMSO-d_6) δ 12.70 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.25 (m, 2H), 4.82 (s, 2H), 2.52 (s, 3H), 1.22 – 1.11 (m, 3H), 1.05 (d, J = 7.0 Hz, 18H).

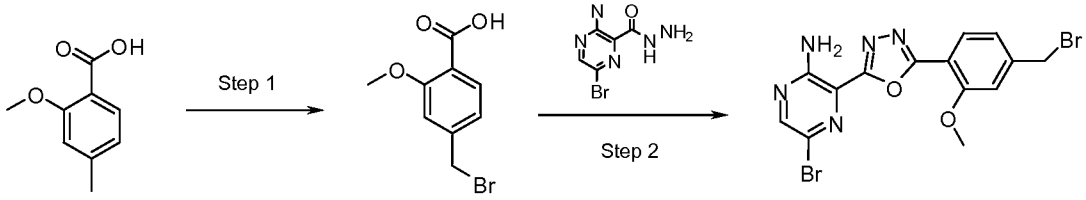
[00160] Step 5: Dibromo(triphenyl)phosphorane (25.0 g, 56.9 mmol) was added to a suspension of 3-amino-6-bromo-pyrazine-2-carbohydrazide (3.0 g, 12.9 mmol) and 2-methyl-4-(triisopropylsilyloxymethyl)benzoic acid (4.2 g, 12.9 mmol) in anhydrous acetonitrile (100 mL). The reaction mixture was stirred for 2 h at room temperature and then cooled to 0 °C. DIEA (10.0 g, 14 mL, 77.6 mmol) was added dropwise and the reaction stirred for 1.5 h. Water (50 mL) was added dropwise to the stirring solution and the resulting suspension stirred for 20 min. The precipitate was collected by filtration and the solid was washed with a 10% aqueous acetonitrile until the dark color disappeared. The solid was then dried to yield 5-bromo-3-(5-(4-(bromomethyl)-2-methylphenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine as a yellow solid (3.4 g, 62% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 67.6 Hz, 2H), 7.69 – 7.45 (m, 2H), 4.77 (s, 2H), 2.70 (s, 3H).

Preparation 3: Synthesis of 5-bromo-3-(5-(4-(bromomethyl)-2-fluorophenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine



[00161] Step 1: 4-(Bromomethyl)-2-fluorobenzoic acid was prepared as described in the *Journal of Fluorine Chemistry*, **2002**, *116*, 173-179. Dibromo(triphenyl)phosphorane (18.40 g, 43.60 mmol) was added to a suspension of 4-(bromomethyl)-2-fluorobenzoic acid (2.54 g, 10.90 mmol) and 3-amino-6-bromo-pyrazine-2-carbohydrazide (2.53 g, 10.90 mmol) in acetonitrile (75 mL). The reaction mixture was stirred for 30 min at room temperature, then cooled to 0 °C and treated with DIEA (11.0 mL, 65.4 mmol). The reaction mixture was then stirred at room temperature for 3 h and filtered. The resulting solid was washed with 20% water/CH_3CN and dried to give 5-bromo-3-(5-(4-(bromomethyl)-2-fluorophenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine as a yellow solid (1.69 g, 36% yield). LC/MS m/z 429.8 $[M+H]^+$.

Preparation 4: Synthesis of 5-bromo-3-(5-(4-(bromomethyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine

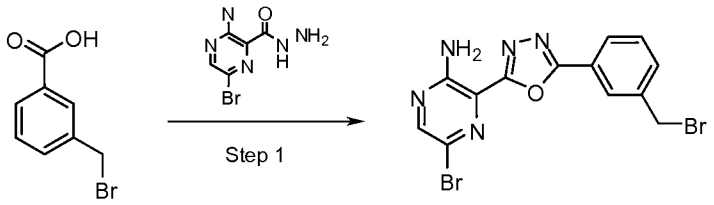


[00162] Step 1: 2-Methoxy-4-methylbenzoic acid (8.0 g, 48.1 mmol) in CCl_4 (80 mL) was treated with *N*-bromosuccinimide (9.1 g, 51.0 mmol) followed by AIBN (791 mg, 4.81 mmol) and heated at reflux for 3 h. The reaction mixture was allowed to cool to room temperature. The resulting precipitate was removed by filtration and washed with water to remove the excess succinamide and unreacted starting material. The solid was then washed with acetonitrile, dissolved in DCM, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 4-(bromomethyl)-2-methoxybenzoic acid (5.15 g, 44% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.16 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.10 (s, 1H), 4.48 (s, 2H), 4.11 (s, 3H).

[00163] Step 2: Dibromo(triphenyl)phosphorane (19.17 g, 43.61 mmol) was added to a suspension of 3-amino-6-bromo-pyrazine-2-carbohydrazide (2.3 g, 9.91 mmol) and 4-

(bromomethyl)-2-methoxybenzoic acid (2.43 g, 9.91 mmol) in acetonitrile (70 mL). The reaction mixture was stirred at room temperature for 2 h and then cooled in an ice water bath upon which DIEA (7.69 g, 10.4 mL, 59.47 mmol) was added dropwise. The ice water bath was removed after the addition of DIEA and the reaction mixture was stirred overnight. Water (20 mL) was added dropwise to the stirring solution and was allowed to stir for an additional 20 min after the water addition. The resulting precipitate was filtered and then washed with a 1:1 water/acetonitrile mixture until the dark color disappeared. The solid was then washed with water and hexane and dried to yield 5-bromo-3-[5-[4-(bromomethyl)-2-methoxy-phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-amine (1.88 g, 43% yield) as a mustard yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.42 (s, 1H), 7.27 (d, J = 7.9 Hz, 1H), 4.79 (s, 2H), 3.95 (s, 3H).

Preparation 5: Synthesis of 5-bromo-3-(5-(3-(bromomethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine

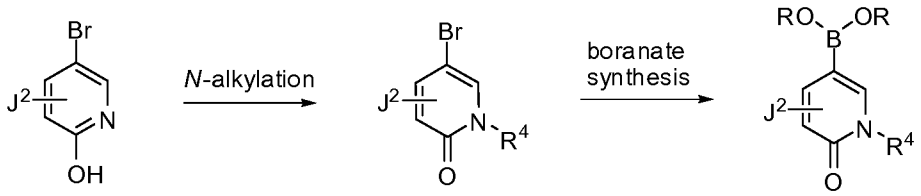


[00164] Step 1: Dibromo(triphenyl)phosphorane (9.0 g, 20.46 mmol) was added to a suspension of 3-(bromomethyl)benzoic acid (1.0 g, 4.65 mmol) in anhydrous acetonitrile (31 mL). The reaction mixture was stirred for 1 h at room temperature and then cooled at 0 °C upon which DIEA (8.0 mL, 45.9 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. Water (50 mL) was added dropwise to the stirring solution and was allowed to stir for an additional 20 min. The reaction mixture was filtered and the resulting solid was washed with a 10% water/acetonitrile mixture until the dark color disappeared. The solid was dried to yield 5-bromo-3-(5-(3-(bromomethyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine as a yellow solid (1.9 g, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.20 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.64 (dd, J = 19.0, 11.0 Hz, 1H), 4.90 (s, 2H).

Preparation 6: (*R*)-4-(1-(*tert*-butoxycarbonylamino)ethyl)benzoic acid was prepare as described in the *Journal of Ocular Pharmacology and Therapeutics*, **2009**, *25*, 187-194.

Preparation 7: 3-(1-(*tert*-butoxycarbonylamino)ethyl)benzoic acid was prepared as described in WO2009/036996.

Scheme B.

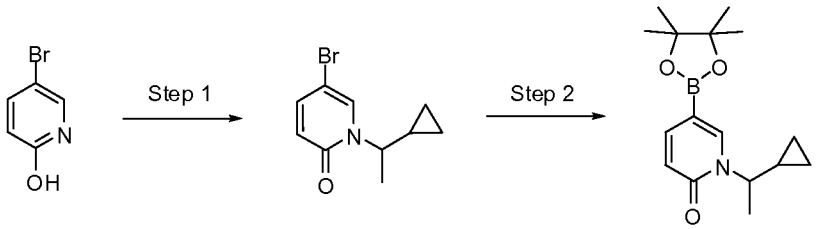


B **B-i** **B-ii**

[00165] Scheme B depicts a general method for the preparation of intermediates of Formula **B-ii**. Compound **B** is reacted with an alcohol R^4OH under Mitsunobu conditions to give rise to compounds of the Formula **B-i**. Suitable Mitsunobu conditions include but are not limited to Bu_3P / DEAD in an appropriate solvent such as $CHCl_3$ or THF.

[00166] Alternatively, compounds of formula **B-i** may be obtained from **B** using alkylation conditions known to those skilled in the art such as, but not limited to, treatment of **B** with R^4-LG and base, wherein LG is an appropriate leaving group such as halogen, mesylate, or triflate. Compounds of Formula **B-i** are converted to the corresponding boronic acid or ester **B-ii** utilizing standard conditions known to those skilled in the art such as, but not limited to, treatment with bis(pinacolato)diboron, Pd-catalyst, and base.

[00167] Preparation 8. Synthesis of 1-(1-cyclopropylethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one



[00168] Step 1: To a solution of 2-hydroxy-5-bromopyridine (6.0 g, 34.5 mmol) in THF (60 mL) at 0 °C was added a solution of DEAD (30 mL of 40 %w/v, 68.96 mmol) in THF (50 mL) over 20 min. The resulting mixture was then treated dropwise with tributylphosphine (14.0 g, 17 mL, 68.7 mmol) over 10 min. The reaction mixture was stirred for 30 min at 0 °C and then treated with 1-cyclopropylethanol (4.5 g, 51.7 mmol) and stirred at room

temperature for 16 h. The reaction mixture was poured onto ice and quenched with HCl. The layers were separated and the organic layer was washed with 1 M HCl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel chromatography (0-60% ethyl acetate/hexanes) provided 5-bromo-1-(1-cyclopropylethyl)pyridin-2-one (2.0 g, 24% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 2.6 Hz, 1H), 7.33 (dd, J = 9.6, 2.7 Hz, 1H), 6.50 (d, J = 9.6 Hz, 1H), 4.38 – 4.26 (m, 1H), 1.40 (d, J = 6.7 Hz, 3H), 1.10 – 0.99 (m, 1H), 0.80 – 0.68 (m, 1H), 0.59 – 0.42 (m, 2H), 0.38 – 0.26 (m, 1H).

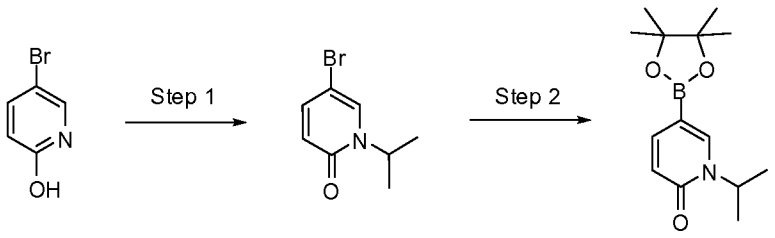
[00169] Step 2: 5-Bromo-1-(1-cyclopropylethyl)pyridin-2-one (3.5 g, 14.5 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (5.5 g, 21.7 mmol), $Pd(dppf)Cl_2$ (1.1 g, 1.5 mmol) and potassium acetate (4.3 g, 43.4 mmol) were dissolved in dioxane (37 mL) and heated at 90 °C for 2 h. The reaction mixture was filtered through Celite and washed with dichloromethane. The filtrate was concentrated *in vacuo*, and purification by silica gel chromatography (0-60% ethyl acetate/hexanes) provided 1-(1-cyclopropylethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (1.9 g, 45% yield). LC/MS m/z 290.3 $[M+H]^+$.

[00170] The following boron pinacol esters were prepared using procedures analogous to that described above:

1-*sec*-butyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 278.1 $[M+H]^+$.

1-(1-methoxypropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 294.5 $[M+H]^+$.

Preparation 9. Synthesis of 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one



[00171] Step 1: Potassium *tert*-butoxide (16.8 g, 142.2 mmol) was added to a suspension of 5-bromo-1*H*-pyridin-2-one (25.0 g, 142.2 mmol) in DME (248 mL) and the reaction mixture was stirred for 30 min. To the mixture were added potassium carbonate (13.8 g, 99.5 mmol) and 2-bromopropane (35.0 g, 26.7 mL, 284.4 mmol) and the mixture refluxed for 65 h. The reaction mixture was filtered and concentrated *in vacuo*. The resulting solid was recrystallized from dichloromethane / hexane to provide 5-bromo-1-isopropyl-pyridin-2-one (19.1 g, 88.40 mmol, 62% yield) as off-white crystals. LC/MS m/z 217.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.7 Hz, 1H), 7.31 (dd, J = 9.7, 2.7 Hz, 1H), 6.49 (d, J = 9.6 Hz, 1H), 5.22 (dt, J = 13.6, 6.8 Hz, 1H), 1.36 (d, J = 6.8 Hz, 6H).

[00172] Step 2: 5-Bromo-1-isopropyl-pyridin-2-one (9.0 g, 41.7 mmol), bis(dipinacolato)diboron (15.9 g, 62.5 mmol) , potassium acetate (10.2 g, 104.2 mmol) and Pd(dppf)Cl_2 (915 mg, 1.25 mmol) were suspended in dioxane (30 mL). The reaction mixture was degassed then heated at 100 °C under an atmosphere of nitrogen for 16 h. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography (5-60% ethyl acetate/dichloromethane) provided 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (7.9 g, 72% yield). LC/MS m/z 264.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.56 (dd, *J* = 9.0, 1.7 Hz, 1H), 6.52 (d, *J* = 9.1 Hz, 1H), 5.26 (hept, *J* = 6.9 Hz, 1H), 1.39 (d, *J* = 6.9 Hz, 6H), 1.31 (s, 12H).

[00173] The following boron pinacol esters were prepared from corresponding R-X (X = halide or other leaving group) using procedures analogous to that described above:

1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 236.2 $[M+H]^+$.

1-isobutyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 278.1 $[M+H]^+$.

2-(2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-1(2*H*)-yl)acetonitrile. LC/MS m/z 261.2 $[M+H]^+$.

1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 250.1 $[M+H]^+$.

1-(2-methoxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 280.4 $[M+H]^+$.

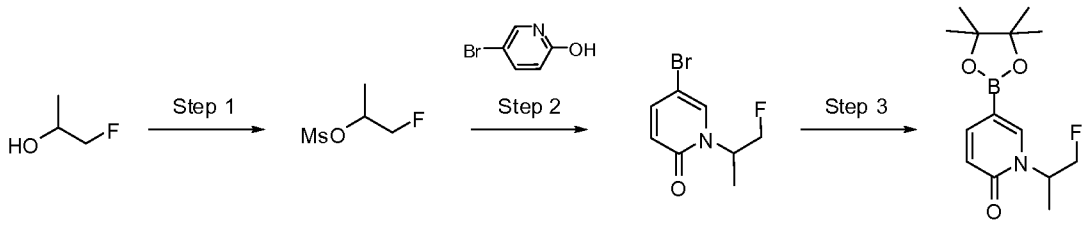
1-(tetrahydrofuran-3-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 292.2 $[M+H]^+$.

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(1,1,1-trifluoropropan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 318.3 $[M+H]^+$.

2-(2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-1(2*H*)-yl)propanenitrile. LC/MS m/z 275.3 $[M+H]^+$.

1-(2-hydroxyethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 266.0 $[M+H]^+$.

[00174] Preparation 10. Synthesis of 1-(1-fluoropropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one.



Step 1: 1-Fluoropropan-2-ol (1.2 g, 15.4 mmol) and DMAP (188 mg, 1.54 mmol) in DCM (30 mL) were cooled to 0 °C and treated with TEA (1.7 g, 2.4 mL, 16.9 mmol) followed by MsCl (1.8 g, 1.3 mL, 16.1 mmol). The reaction mixture was warmed gradually to room temperature and stirred for 1 h. The reaction mixture was then washed with saturated NH_4Cl solution and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* to provide (2-fluoro-1-methyl-ethyl) methanesulfonate which was carried immediately into the next step.

[00175] Step 2: 5-Bromo-1*H*-pyridin-2-one (2.7 g, 15.4 mmol) in DME (30 mL) was treated with KO^{t}Bu (1.7 g, 15.4 mmol) and the reaction was stirred for 30 min. The reaction was then treated with K_2CO_3 (1.5 g, 10.7 mmol) and a solution of (2-fluoro-1-methyl-ethyl) methanesulfonate (2.4 g, 15.4 mmol) in DME (10 mL). The reaction was stirred at room temperature for 20 min, and then heated at reflux for 16 h. The reaction was cooled, diluted with ethyl acetate and washed with saturated NH_4Cl solution, water, and brine. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (0-

90% ethyl acetate/hexanes) to provide 5-bromo-1-(2-fluoro-1-methyl-ethyl)pyridin-2-one as a colorless solid (1.2 g, 33% yield). LC/MS m/z 235.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 2.5 Hz, 1H), 7.36 (dd, J = 9.7, 2.5 Hz, 1H), 6.51 (d, J = 9.6 Hz, 1H), 5.38 – 5.14 (m, 1H), 4.67 (d, J = 3.2 Hz, 1H), 4.55 (d, J = 3.2 Hz, 1H), 1.51 (d, J = 7.2 Hz, 3H).

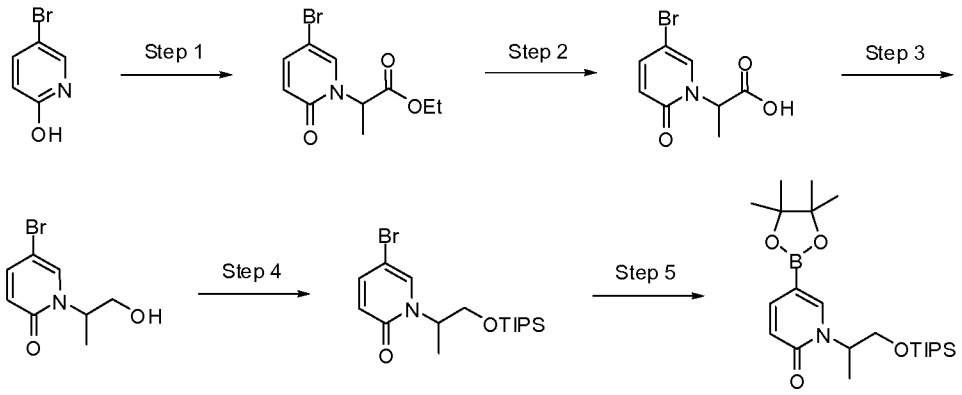
[00176] Step 3: 5-Bromo-1-(2-fluoro-1-methyl-ethyl)pyridin-2-one (550 mg, 2.35 mmol) , potassium acetate (692 mg, 7.05 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (895 mg, 3.53 mmol), and $Pd(dppf)Cl_2$ (172 mg, 0.24 mmol) were combined in dioxane (12 mL) and heated to 90 °C for 2.5 h. The reaction mixture was cooled to room temperature and filtered. The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (0-80% ethyl acetate/hexanes) to provide 1-(1-fluoropropan-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (455 mg, 69% yield). LC/MS m/z 235.1 $[M+H]^+$.

[00177] The following boron pinacol esters were prepared from corresponding R^4-OMs using procedures analogous to that described above:

5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(1,1,1-trifluoropropan-2-yl)pyridin-2(1*H*)-one. LC/MS m/z 318.3 $[M+H]^+$.

1-(pent-3-yn-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one LC/MS m/z 288.5 $[M+H]^+$.

Preparation 11. Synthesis of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(1-(triisopropylsilyloxy)propan-2-yl)pyridin-2(1*H*)-one



[00178] Step 1: Ethyl 2-bromopropanoate (5.0 mL, 38.4 mmol) was dissolved in acetone (60 mL) and sodium iodide (12.67 g, 84.54 mmol) was added. The mixture was stirred for 2 h and the solvents removed under reduced pressure. In a separate flask 5-bromo-1*H*-pyridin-2-one (3.34 g, 19.21 mmol) was suspended in DME (40 mL) and KO^{t}Bu (2.16 g, 19.21 mmol) added, followed by stirring for 15 min. K_2CO_3 (1.86 g, 13.45 mmol) and the prepared ethyl 2-iodopropanoate were then added and the mixture heated to 85 °C for 1 h. The reaction was poured into water and extracted with ethyl acetate. The combined organic fractions were dried over Na_2SO_4, filtered, concentrated to provide ethyl 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)propanoate (3.68 g, 70% yield). LC/MS m/z 275.9 $[M+H]^+$.

[00179] Step 2: To a solution of ethyl 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)propanoate (3.68 g, 13.43 mmol) in methanol (15 mL) and THF (15 mL) was added aqueous sodium hydroxide (18.8 mL of 1 M, 18.8 mmol) and the solution stirred for 18 h at room temperature. 3 M HCl was then added until the pH reached ~1 and the mixture was extracted with ethyl acetate. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated to provide 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)propanoic acid (2.61 g, 79% yield). LC/MS m/z 246.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.09-7.93 (m, 1H), 7.60-7.49 (m, 1H), 6.39 (dd, J = 9.7, 4.2 Hz, 1H), 5.13 (tt, J = 11.4, 5.6 Hz, 1H), 1.56 (dd, J = 7.2, 4.1 Hz, 3H).

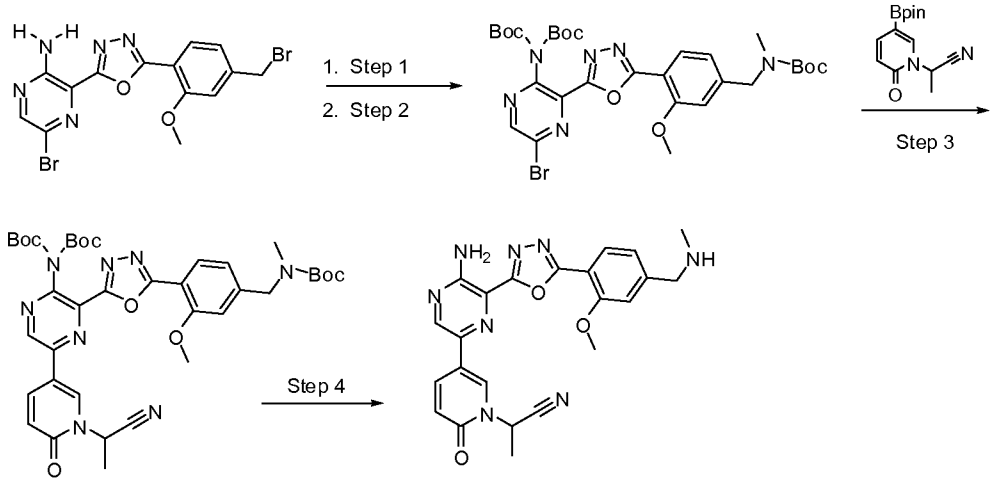
[00180] Step 3: To a solution of 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)propanoic acid (1.33 g, 5.41 mmol) in anhydrous THF (25 mL) was added borane-dimethylsulfide (1.23 g, 1.44 mL, 16.22 mmol) and the mixture heated to 55 °C. After 3 h, additional borane-dimethylsulfide (1.23 g, 1.44 mL, 16.22 mmol) was added and the reaction heated at reflux for 2 h. The reaction was quenched with 3 M HCl (30 mL) then diluted with water and extracted with ethyl acetate. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated to provide 5-bromo-1-(1-hydroxypropan-2-yl)pyridin-2(1*H*)-one (0.82 g, 65% yield). LC/MS m/z 232.9 $[M+H]^+$.

[00181] Step 4: To a solution of 5-bromo-1-(1-hydroxypropan-2-yl)pyridin-2(1*H*)-one (819 mg, 3.53 mmol) and imidazole (529 mg, 7.76 mmol) in THF (8 mL) was added chloro(triisopropyl)silane (638 mg, 788 µL, 4.24 mmol) and the reaction stirred at room temperature for 1 h. The reaction was poured into water and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to provide 5-bromo-1-(1-(triisopropylsilyloxy)propan-2-yl)pyridin-2(1*H*)-one as a clear oil. LC/MS m/z 247.0 $[M+H]^+$.

Step 5: 5-Bromo-1-(1-(triisopropylsilyloxy)propan-2-yl)pyridin-2(1*H*)-one (431 mg, 1.24 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (474 mg, 1.87 mmol), $Pd(dppf)Cl_2$ (91 mg, 0.12 mmol), and potassium acetate (366 mg, 3.73 mmol) were dissolved in dioxane (8 mL) and heated at 90 °C. The mixture was filtered through Celite and washed with methylene chloride. The filtrate was concentrated and purified by silica gel chromatography (0-100% ethyl acetate/hexanes) to provide 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(1-(triisopropylsilyloxy) propan-2-yl)pyridin-2(1*H*)-one (335 mg, 46% yield) as a pale yellow oil. LC/MS m/z 394.1 $[M+H]^+$.

Example 1. Synthesis of 2-[5-[5-amino-6-[5-[2-methoxy-4-(methylaminomethyl) phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanenitrile

Compound I-34



[00182] Step 1: To a solution of 5-bromo-3-(5-(4-(bromomethyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine (5.0 g, 11.3 mmol) in THF (125 mL) was added sodium carbonate (3.6 g, 34.0 mmol) in one portion. Methylamine (28.3 ml, 2 M in methanol, 56.7 mmol) was then added dropwise over 10 min. The suspension was stirred for 30 min and then heated at 60 °C for 1 h. After cooling, the reaction mixture was diluted with water and extracted with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The solid was then triturated with ether to provide 5-bromo-3-(5-(2-methoxy-4-((methylamino)methyl) phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine (4.1 g, 92% yield) as a light yellow solid. LC/MS m/z 392.3 $[M+H]^+$.

[00183] Step 2: A solution of 5-bromo-3-(5-(2-methoxy-4-((methylamino)methyl)phenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-amine (1.7 g, 4.35 mmol) in THF (20 mL) was treated with $(Boc)_2O$ (4.7 g, 5.0 mL, 21.72 mmol) and DMAP (53 mg, 0.43 mmol). The reaction mixture was stirred for 30 min at room temperature followed by 16 h at 45 °C. The solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (10-50% ethyl acetate/hexanes) to provide *tert*-butyl *N*-[[4-[5-[3-[bis(*tert*-butoxycarbonyl) amino]-6-bromo-pyrazin-2-yl]-1,3,4-oxadiazol-2-yl]-3-methoxy-phenyl]methyl]-*N*-methyl-carbamate as an off-white foam (1.9 g, 63% yield). LC/MS m/z 692.5 $[M+H^+$.

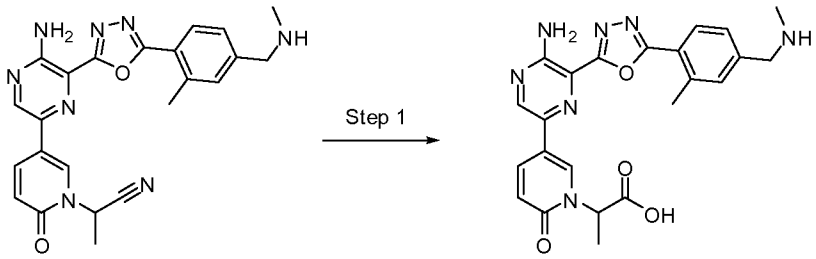
[00184] Step 3: *tert*-Butyl *N*-[[4-[5-[3-[bis(*tert*-butoxycarbonyl)amino]-6-bromo-pyrazin-2-yl]-1,3,4-oxadiazol-2-yl]-3-methoxy-phenyl]methyl]-*N*-methyl-carbamate (200 mg, 0.28 mmol), 2-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1pyridyl]propanenitrile (101 mg, 0.37 mmol) , and $Pd(dppf)Cl_2$ (23 mg, 0.03 mmol) were dissolved in acetonitrile (5 mL) and Na_2CO_3 (2.8 mL of 2 M solution in water, 5.6 mmol). The reaction mixture was heated at 85 °C for 1 h, then cooled and partitioned between ethyl acetate and water. The organic layer washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (20-100% ethyl acetate/DCM) to provide di-*tert*-butyl 3-(5-(4-((tert-butoxycarbonyl (methyl)amino)methyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-5-(1-(1-cyanoethyl)-6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yliminodicarbonate as a yellow foam (178 mg, 83% yield). LC/MS m/z 759.9 $[M+H]^+$

[00185] Step 4: Di-*tert*-butyl 3-(5-(4-((tert-butoxycarbonyl(methyl)amino)methyl)-2-methoxyphenyl)-1,3,4-oxadiazol-2-yl)-5-(1-(1-cyanoethyl)-6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yliminodicarbonate (178 mg, 0.24 mmol) was dissolved in DCM (3 mL) and TFA (1 mL) and stirred for 30 min. The reaction was diluted with DCM and washed with 50% saturated sodium carbonate and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by HPLC (10-99% CH_3CN/5mM HCl) and the resulting hydrochloride salt partitioned between DCM and 50% saturated sodium bicarbonate. The organic phase was separated, dried over Na_2SO_4, and concentrated *in vacuo* to provide 2-[5-[5-amino-6-[5-[2-methoxy-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanenitrile **Compound I-34** (55 mg, 42% yield). LC/MS m/z 459.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.21 (dd, J = 9.6, 2.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.68 (s, 2H), 7.29 (s, 1H), 7.13 (d, J = 8.1 Hz, 1H), 6.67 (d,

J = 9.6 Hz, 1H), 5.90 (q, J = 7.1 Hz, 1H), 3.96 (s, 3H), 3.76 (s, 2H), 2.32 (s, 3H), 1.79 (d, J = 7.1 Hz, 3H).

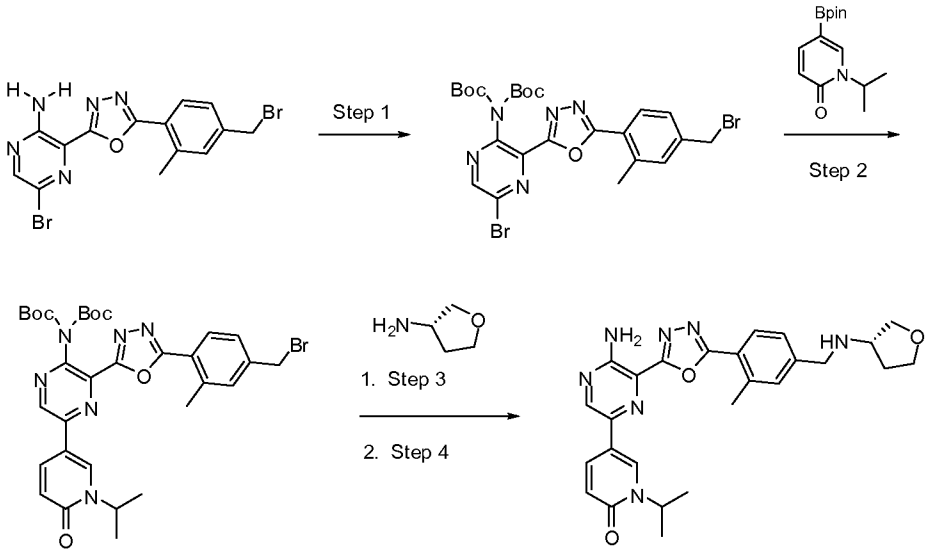
Example 2. Synthesis of 2-[5-[5-amino-6-[5-[2-methyl-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanoic acid

Compound I-38



[00186] Step 1: 2-[5-[5-amino-6-[5-[2-methyl-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanenitrile (25 mg, 0.05 mmol) was suspended in 1 N HCl and heated to 50 °C for 1.5 h, resulting in clean conversion to the acid. The reaction was concentrated *in vacuo* to provide 2-[5-[5-amino-6-[5-[2-methyl-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-2-oxo-1-pyridyl] propanoic acid **Compound I-38**. LC/MS m/z 461.5 $[M+H]^+$.

Example 3. Synthesis of 5-[5-amino-6-[5-[2-methyl-4-[[[(3*S*)-tetrahydrofuran-3-yl]amino]methyl]phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one **Compound I-13.**



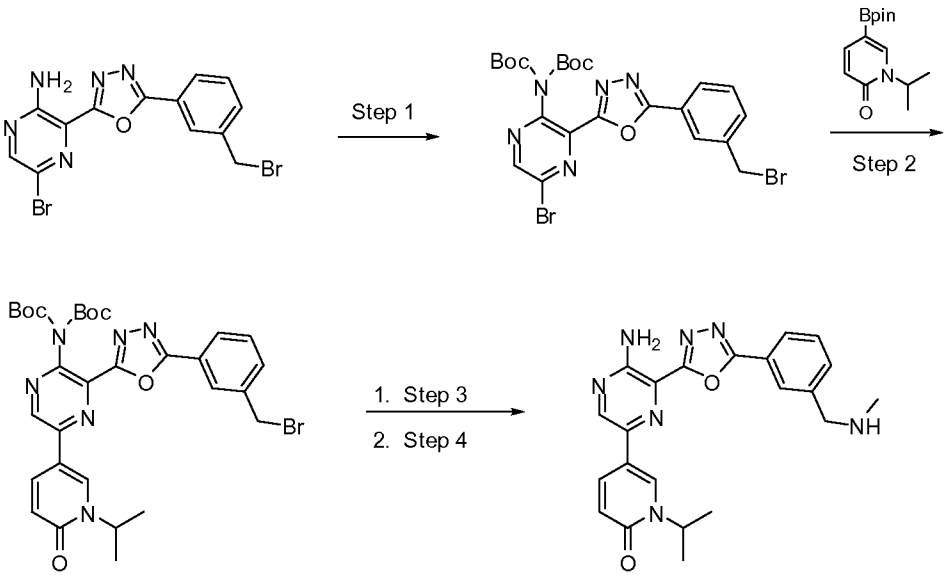
[00187] Step 1: To a mixture of 5-bromo-3-[5-[4-(bromomethyl)-2-methyl-phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-amine (3.1 g, 7.29 mmol) and DMAP (89 mg, 0.73 mmol) in THF (96 mL) was added $(Boc)_2O$ (6.7 g, 29.2 mmol) at room temperature. The reaction mixture was heated at 50 °C for 2 h, then allowed to cool to room temperature and partitioned between ethyl acetate and 1 M HCl. The organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (0-15% ethyl acetate/hexanes) to provide *tert*-butyl *N*-[5-bromo-3-[5-[4-(bromomethyl)-2-methyl-phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (3.3 g, 72% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.64 - 7.45 (m, 2H), 4.77 (s, 2H), 2.70 (s, J = 15.7 Hz, 3H), 1.28 (s, 18H).

[00188] Step 2: An aqueous solution of Na_2CO_3 (1.4 mL of 2 M, 2.88 mmol) was added to a mixture of *tert*-butyl *N*-[5-bromo-3-[5-[4-(bromomethyl)-2-methyl-phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (600 mg, 0.96 mmol), 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (253 mg, 0.96 mmol) and $Pd(PPh_3)_2$ (67 mg, 0.10 mmol) in DME (9 mL). The reaction mixture was degassed with argon, sealed and heated at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature and was partitioned between ethyl acetate and water. The aqueous layer was extracted once with ethyl acetate and the combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography (0-70% ethyl acetate/hexanes) provided *tert*-butyl *N*-[3-[5-[4-(bromomethyl)-2-methyl-phenyl]-1,3,4-oxadiazol-2-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]-*N*-tert-butoxycarbonyl-carbamate (300 mg, 46%) as

a yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.72 (d, J = 2.3 Hz, 1H), 8.29 (dd, J = 9.5, 2.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 6.64 (d, J = 9.5 Hz, 1H), 5.26 - 5.04 (m, 1H), 4.81 (s, 2H), 2.72 (s, 3H), 1.44 (d, J = 6.9 Hz, 6H), 1.29 (s, 18H).

[00189] Step 3 and 4: To *tert*-butyl *N*-[3-[5-[4-(bromomethyl)-2-methyl-phenyl]-1,3,4-oxadiazol-2-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]-*N*-tert-butoxycarbonyl-carbamate (200 mg, 0.29 mmol) and (3*S*)-tetrahydrofuran-3-amine (77 mg, 0.8799 mmol) in DMF (5 mL) was added DIEA (190 mg, 255 µL, 1.47 mmol) and the reaction mixture was heated at 85 °C for 45 min. The reaction was cooled and solvent was removed *in vacuo*. The residue was treated with 50% TFA/DCM (1 mL) and stirred at room temperature for 20 min. The reaction was concentrated and purified by HPLC (CH_3CN/5 mM HCl) to provide 5-[5-amino-6-[5-[2-methyl-4-[[[(3*S*)-tetrahydrofuran-3-yl]amino]methyl] phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one **Compound I-13**. LC/MS m/z 488.2 $[M+H]^+$.

Example 4. Synthesis of 5-[5-amino-6-[5-[3-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one **Compound I-47**



[00190] Step 1: To a mixture of 5-bromo-3-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-amine (1.0 g, 2.43 mmol) and DMAP (30 mg, 0.24 mmol) in THF (31 mL) was added $(Boc)_2O$ (2.2 g, 2.3 mL, 9.73 mmol). The reaction mixture was heated at 50 °C for 3 h, then allowed to cool to room temperature and partitioned between ethyl acetate and 1 M HCl. The organic layer was washed with saturated $NaHCO_3$ solution and brine,

dried over $MgSO_4$, filtered and concentrated to dryness under reduced pressure. The residue was purified by silica gel column chromatography (0-10% ethyl acetate/hexanes) to provide *tert*-butyl *N*-[5-bromo-3-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (0.7 g, 45%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ9.7 (d, J = 5.3 Hz, 1H), 8.22 (s, 1H), 8.07 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 4.88 (s, 2H), 1.29 (s, 18H).

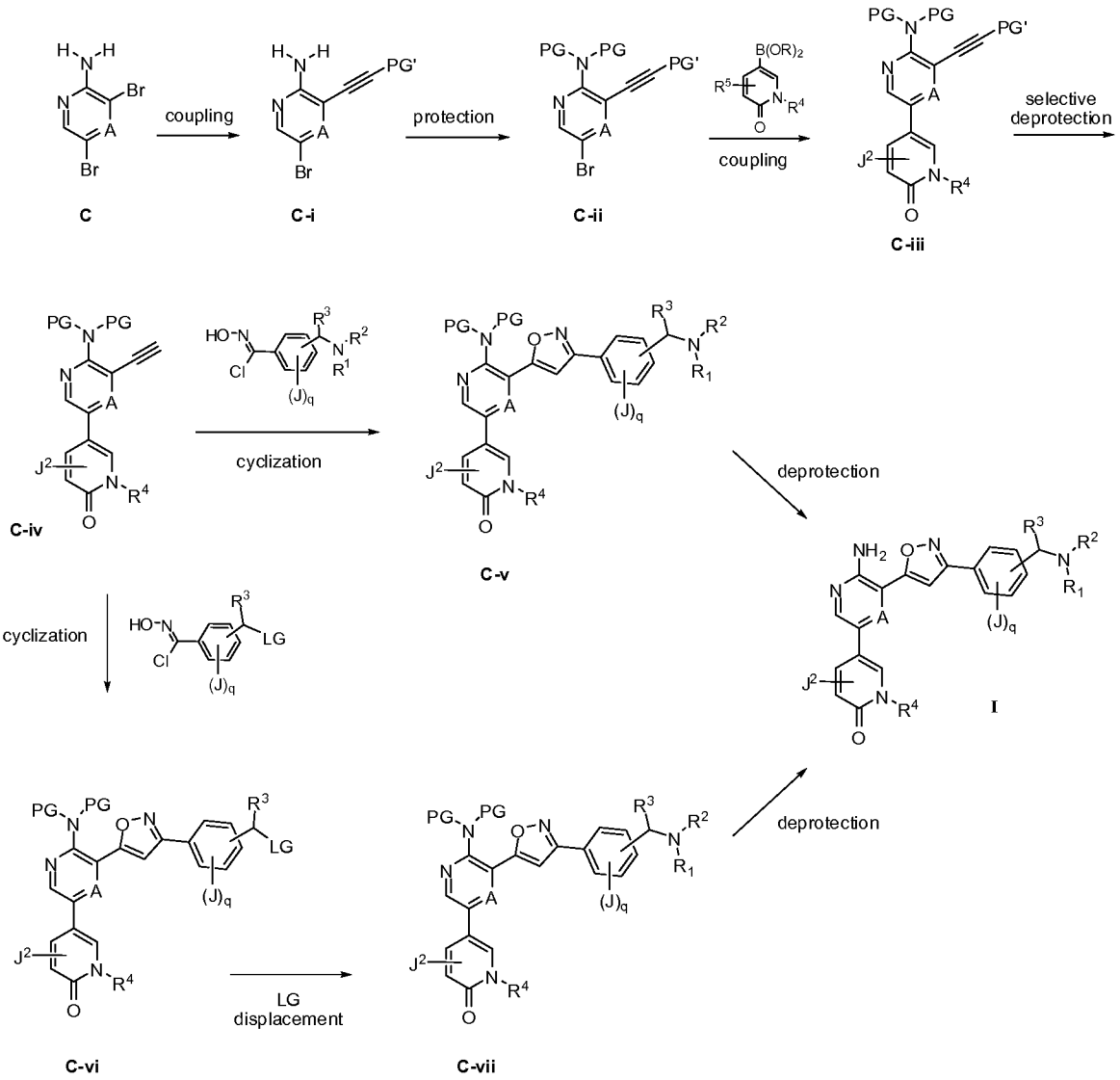
[00191] Step 2: A solution of aqueous Na_2CO_3 (1.2 mL of 2 M, 2.45 mmol) was added to a mixture of 1-isopropyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (215 mg, 0.82 mmol), *tert*-butyl *N*-[5-bromo-3-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (500 mg, 0.82 mmol) and $Pd(dppf)Cl_2$ (60 mg, 0.082 mmol) in acetonitrile (7 mL). The reaction mixture was degassed with argon, sealed and heated at 80 °C for 30 min. The reaction mixture was allowed to cool to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted once with ethyl acetate and the combined organics dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography (0-60% ethyl acetate/hexanes) provided *tert*-butyl *N*-[3-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (267 mg, 49%) as an orange oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.73 (s, 1H), 8.32 (dd, J = 9.5, 2.6 Hz, 1H), 8.25 (s, 1H), 8.16-8.06 (m, 1H), 7.80 (d, J = 1.0 Hz, 1H), 7.73-7.66 (m, 1H), 6.64 (d, J = 9.5 Hz, 1H), 5.17-5.08 (m, 1H), 4.87 (s, 2H), 1.45 (d, J = 7.2 Hz, 6H), 1.29 (s, 18H).

[00192] Step 3: *tert*-Butyl *N*-[3-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (265 mg, 0.40 mmol) was dissolved in dichloromethane (3 mL) followed by the addition of HCl (4.0 mL of 4 M solution in dioxane, 15.88 mmol). The reaction mixture was stirred at room temperature for 2 h. The solvent and excess HCl were removed under reduced pressure to provide 5-[5-amino-6-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one as a yellow solid which was taken directly to the next step. LC/MS m/z 468.3 $[M+H]^+$.

[00193] Step 4: A mixture of 5-[5-amino-6-[5-[3-(bromomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one (70 mg, 0.14 mmol), methylamine (3.0 mL of 2 M solution in THF, 6.0 mmol) and Na_2CO_3 (44 mg, 0.42 mmol) was stirred for 1 h at 70 °C. The reaction mixture was cooled to room temperature, diluted with DMF (1 mL) and purified by HPLC (10-99% CH_3CN/ 5mM HCl) to provide 5-[5-amino-6-[5-[3-(methylamino -methyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one **Compound I-**

47. ^{1}H NMR (400 MHz, DMSO-d_6) 9.26 (s, 2H), 8.95 (s, 1H), 8.44 - 8.29 (m, 2H), 8.24 - 8.13 (m, 2H), 7.84 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.66 (s, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.21 - 5.06 (m, 1H), 4.29 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 5.2 Hz, 3H), 1.42 (d, J = 6.8 Hz, 6H).

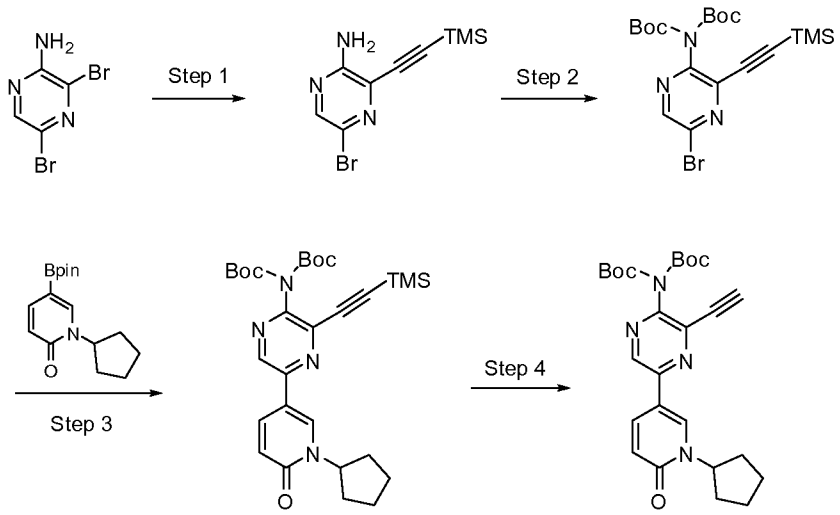
Scheme C



[00194] Scheme C depicts a general method for making compounds of Formula **I** in which Ring D is isoxazole. Compound **C** is selectively reacted with a suitably protected alkyne under Sonogashira coupling conditions to provide compounds of Formula **C-i**. Suitable alkyne protecting groups PG' include, but are not limited to, TMS, TES or TIPS. Compounds of Formula **C-i** are then protected with a suitable amine protecting group PG

orthogonal to PG' such as, but not limited to BOC (^{t}Butyl Carbamate), to give compounds of Formula **C-ii**. The pyridone ring system is introduced under metal-mediated coupling conditions, including but not limited to Suzuki coupling of **C-ii** with an appropriate boronic ester or boronic acid to provide compounds of Formula **C-iii**. Compounds of Formula **C-iii** are then selectively deprotected under standard conditions known to those skilled in the art such as, but not limited to, treatment with base such as K_2CO_3 or fluoride to remove the alkyne protecting group PG' to yield compounds of Formula **C-iv**. The assembly of the 3,5-disubstituted isoxazole can be achieved through the 1,3-dipolar cycloaddition of the terminal acetylene of compound **C-iv** with an appropriate chloro oxime to provide the desired isoxazole. Compounds of Formula **C-v** are constructed via a route wherein the amine functionality $-NR^1R^2$ (protected as PG if R^2=H) is installed on the chloro oxime building block prior to cyclization, while compounds of Formula **C-vi** are constructed via the cyclization wherein the chloro oxime building block is functionalizaed with the appropriate leaving group (LG). Isoxazole intermediate **C-vi** is further functionalized through the nucleophilic displacement of the leaving group (LG) with the amine NHR^1R^2 to form compounds of Formula **C-vii**. Suitable leaving groups include but are not limited to halogens, mesylates, or triflates. Removal of the nitrogen protecting group PG from compounds of Formula **C-v** and **C-vii** takes place under standard conditions known to those skilled in the art such as, but not limited to, treatment with HCl or TFA to provide compounds of Formula **I** in which Ring D is isoxazole. In addition, substituents R^4 on Formula **I** can undergo further functionalization by reactions known to those skilled in the art such as, but not limited to, hydrolysis, nucleophilic displacement reactions, acylation reactions, amide bond formation reactions, or further deprotection to reveal additional functionality.

Preparation 12. Synthesis of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[5-(1-cyclopentyl-6-oxo-3-pyridyl)-3-ethynyl-pyrazin-2-yl]carbamate



[00195] Step 1: (Trimethylsilyl)acetylene (1.9 g, 2.7 mL, 18.8 mmol) was added dropwise to a solution of 3,5-dibromopyrazin-2-amine (5.0 g, 19.8 mmol), triethylamine (10.0 g, 13.8 mL, 98.9 mmol), copper (I) iodide (452 mg, 2.37 mmol) and $Pd(PPh_3)_4$ (1.14 g, 0.99 mmol) in DMF (25 mL) and the resulting solution stirred at room temperature for 30 min. The reaction was diluted with ethyl acetate and water and the layers separated. The aqueous layer was extracted further with ethyl acetate and the combined organics washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The mixture was purified via silica gel chromatography (0-15% ethyl acetate/hexanes) to afford 5-bromo-3-((trimethylsilyl) ethynyl)pyrazin-2-amine as a yellow solid (3.99g, 75% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 0.30 (s, 9H), 8.06 (s, 1H); MS (ES^+) 271.82

[00196] Step 2: 5-Bromo-3-(2-trimethylsilylethynyl)pyrazin-2-amine (480 mg, 1.78 mmol) was dissolved in DCM (15 mL) and treated with Boc-anhydride (1.16 g, 1.22 mL, 5.33 mmol), followed by DMAP (22 mg, 0.18 mmol). The mixture was allowed to stir at room temperature overnight. The reaction was washed with $NaHCO_3$, extracted with DCM, dried over $MgSO_4$, filtered and concentrated. The resulting brown oil was purified by silica gel chromatography (0-10% ethyl acetate/hexanes) to afford the product as a colorless oil (641 mg, 77% yield). ^1H NMR (400 MHz, DMSO-d_6) δ 0.00 (s, 9H), 1.11 (s, 18H) and 8.63 (s, 1H).

[00197] Step 3: 1-Cyclopentyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-one (4.71 g, 16.29 mmol), *tert*-butyl *N*-[5-bromo-3-(2-trimethylsilylethynyl)pyrazin-2-yl]-*N*-*tert*-butoxycarbonyl-carbamate (5.11 g, 10.86 mmol), and $Pd(PPh_3)_2Cl_2$ (762 mg, 1.09 mmol) were combined in acetonitrile (50 mL) and treated with aqueous sodium carbonate (16 mL of 2 M, 32 mmol) and heated at 50 °C for 2 h. The reaction was diluted with water and ethyl

acetate, passed through a pad of Celite and the layers separated. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel chromatography (10-100% ethyl acetate/hexane) provided *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[5-(1-cyclopentyl-6-oxo-3-pyridyl)-3-(2-trimethylsilylethynyl) pyrazin-2-yl]carbamate as a brown foam (4.36 g, 73% yield). LC/MS m/z 553.5$[M+H]^+$.

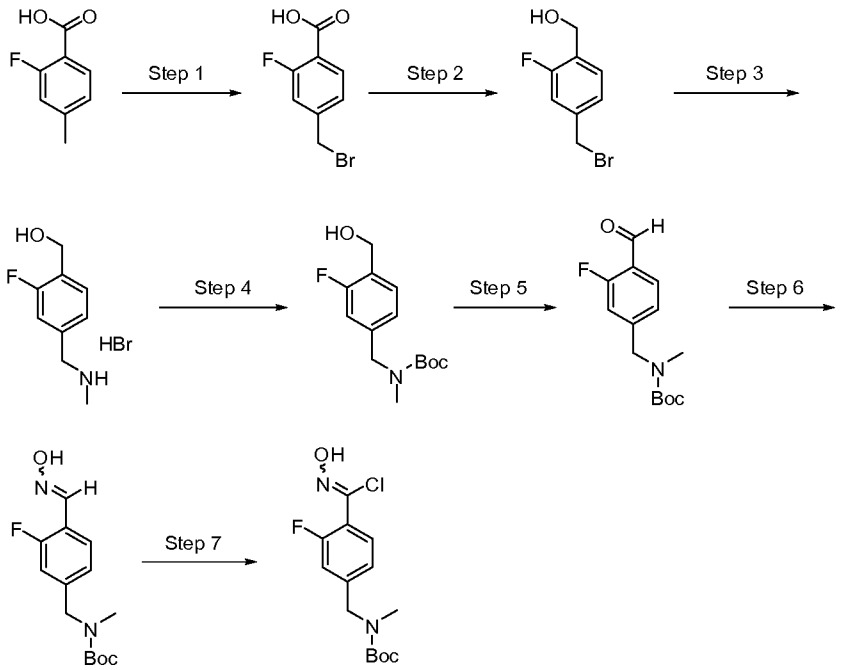
[00198] Step 4: *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-[5-(1-cyclopentyl-6-oxo-3-pyridyl)-3-(2-trimethylsilylethynyl)pyrazin-2-yl]carbamate (4.36 g, 7.89 mmol) in DMF (20 mL) was treated with sodium carbonate (4.7 mL of 2 M, 9.4 mmol) and heated at 75 °C for 1 h. The reaction was cooled to room temperature, treated with water (60 mL) and sonicated for 1 h. The solution was decanted from the insoluble material, taken up in ethyl acetate and washed with 0.5 N HCl and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[5-(1-cyclopentyl-6-oxo-3-pyridyl)-3-ethynyl-pyrazin-2-yl]carbamate as a brown foam (3.1 g, 82% yield). LC/MS m/z 481 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.52 (d, J = 2.5 Hz, 1H), 8.14 (dd, J = 9.6, 2.6 Hz, 1H), 6.55 (d, J = 9.5 Hz, 1H), 5.16 – 5.05 (m, 1H), 4.89 (s, 1H), 2.08 – 2.00 (m, 2H), 1.94 – 1.81 (m, 4H), 1.73 – 1.60 (m, 2H), 1.38 (s, 18H).

[00199] The following acetylene intermediates if Formula **C-iv** were prepared in an analogous manner:

[00200] *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-[5-[1-(1-cyclopropylethyl)-6-oxo-3-pyridyl]-3-ethynyl-pyrazin-2-yl]carbamate. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 (t, J = 4.9 Hz, 1H), 8.83 – 8.67 (m, 1H), 8.15 (dd, J = 12.3, 5.3 Hz, 1H), 6.56 (dd, J = 9.4, 5.4 Hz, 1H), 4.21 (d, J = 6.5 Hz, 1H), 1.56 – 1.43 (m, 5H), 1.42 – 1.30 (m, 21H), 0.68 (s, 1H), 0.46 (d, J = 5.8 Hz, 2H), 0.20 (d, J = 5.1 Hz, 1H).

[00201] *tert*-Butyl *N*-tert-butoxycarbonyl-*N*-[3-ethynyl-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]carbamate. LC/MS m/z 455.5 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.28 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 9.5, 2.6 Hz, 1H), 6.68 (d, J = 9.5 Hz, 1H), 5.32 (dt, J = 13.6, 6.7 Hz, 1H), 3.46 (s, 1H), 1.46 (d, J = 6.8 Hz, 6H), 1.42 (s, 18H).

Preparation 13. Synthesis of *tert*-butyl 4-(chloro(hydroxyimino)methyl)-3-fluorobenzyl (methyl)carbamate



[00202] Step 1: AIBN (533 mg, 3.24 mmol) and *N*-bromosuccinimide (6.35 g, 35.68 mmol) were added to 2-fluoro-4-methyl-benzoic acid (5.0 g, 32.4 mmol) in CCl_4 (50 mL) and the reaction mixture heated for 3 h at 90 °C. The reaction mixture was cooled, filtered, and the filter cake was washed once with CCl_4, then three times with water. The filter cake was then dissolved in a 1:1 mixture of acetonitrile/MeOH, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-(bromomethyl)-2-fluoro-benzoic acid (4.7 g, 62% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ13.30 (s, 1H), 7.89 – 7.81 (m, 1H), 7.42 (dd, J = 8.9, 4.0 Hz, 1H), 7.38 (dd, J = 8.0, 1.5 Hz, 1H), 4.73 (s, 2H).

[00203] Step 2: 4-(Bromomethyl)-2-fluoro-benzoic acid (4.65 g, 19.95 mmol) was dissolved in anhydrous THF (70 mL) under a nitrogen atmosphere and cooled in an ice bath. A solution of borane-THF complex (32 mL of 1 M, 32 mmol) in THF was added dropwise and the reaction mixture was allowed to warm to room temperature over 5 h. The reaction mixture was quenched with methanol and concentrated *in vacuo*. The resulting residue was partitioned between ethyl acetate and 1 M HCl and the aqueous layer was extracted once with ethyl acetate. The combined organics were dried over Na_2SO_4, filtered and concentrated to provide (4-(bromomethyl)-2-fluorophenyl)methanol as a white solid (4.12 g, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 (t, J = 7.8 Hz, 1H), 7.33 – 7.22 (m, 2H), 5.29 (s, 1H), 4.70 (s, 2H), 4.53 (s, 2H).

[00204] Step 3: [4-(Bromomethyl)-2-fluoro-phenyl]methanol (5.14 g, 23.46 mmol) was dissolved in methylamine (235 mL of 2 M in methanol, 470 mmol) and heated at 45 °C for 1

h. The reaction mixture was allowed to cool to room temperature, and the solvent and excess methyamine removed under reduced pressure. The residue was triturated with Et_2O to provide [2-fluoro-4-(methylaminomethyl)phenyl]methanol (4.84 g, 82% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.53 (t, J = 7.7 Hz, 1H), 7.35 – 7.25 (m, 2H), 5.35 (t, J = 5.2 Hz, 1H), 4.56 (d, J = 4.8 Hz, 2H), 4.12 (s, 2H), 3.33 (s, 1H), 2.55 (s, 2H), 2.37 (s, 1H).

[00205] Step 4: To a mixture of [2-fluoro-4-(methylaminomethyl)phenyl]methanol (4.58 g, 18.31 mmol) and triethylamine (17.9 mL, 128 mmol) in THF (137 mL) was added $(Boc)_2O$ (4.80 g, 22.0 mmol) in one portion. Water (7 mL) was added to form a homogeneous solution and the reaction was stirred for 4 h. The reaction mixture was partitioned between ethyl acetate and 1 M HCl. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated to an oil under reduced pressure. Silica gel chromatography (0-30% ethyl acetate/hexanes) provided *tert*-butyl *N*-[[3-fluoro-4-(hydroxymethyl)phenyl]methyl]-*N*-methyl-carbamate (3.53 g, 72% yield) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 11.1 Hz, 1H), 5.23 (t, J = 5.7 Hz, 1H), 4.52 (d, J = 5.7 Hz, 2H), 4.33 (s, 2H), 2.76 (s, 3H), 1.41 (d, J = 16.7 Hz, 9H).

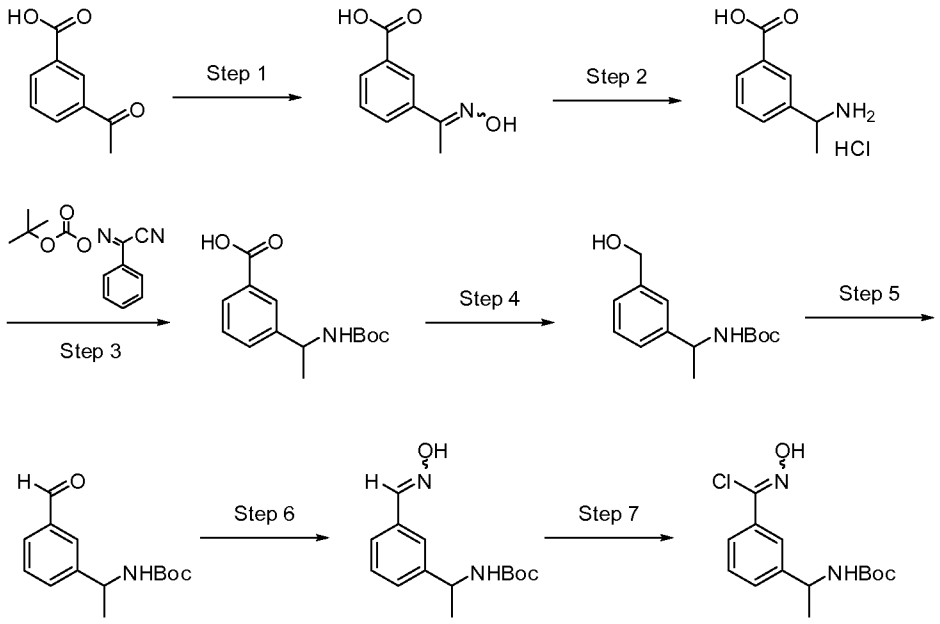
[00206] Step 5: To a solution of *tert*-butyl *N*-[[3-fluoro-4-(hydroxymethyl)phenyl]methyl]-*N*-methyl-carbamate (3.51 g, 13.03 mmol) in DCM (30 mL) was added MnO_2 (9.06 g, 104.2 mmol) and the reaction stirred at room temperature for 48 h. An additional 9 g of MnO_2 was added and the reaction stirred for an additional 24 h. The reaction mixture was filtered through Celite and concentrated *in vacuo* to provide *tert*-butyl *N*-[(3-fluoro-4-formyl-phenyl)methyl]-*N*-methyl-carbamate (2.56 g, 74% yield) as a clear yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.85 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 10.1 Hz, 2H), 4.46 (s, 2H), 2.82 (s, 3H), 1.39 (d, J = 36.5 Hz, 9H).

[00207] Step 6: To a solution of *tert*-butyl *N*-[(3-fluoro-4-formyl-phenyl)methyl]-*N*-methyl-carbamate (2.5 g, 9.4 mmol) in THF (43 mL) was added sodium acetate (1.92 g, 23.38 mmol). The solution was cooled to 0 °C (ice bath) and hydroxylamine hydrochloride (845 mg, 12.16 mmol) added. The reaction was allowed to warm to room temperature over 2 h. The solvents were removed *in vacuo* and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide *tert*-butyl 3-fluoro-4-((hydroxyimino) methyl)benzyl(methyl)carbamate (2.62 g, 99% yield) as a white solid. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 11.56 (s, 1H), 8.19 (s, 1H), 7.72 (t, J = 7.8 Hz, 1H), 7.16 – 7.01 (m, 2H), 4.38 (s, 2H), 2.79 (s, 3H), 1.40 (d, J = 23.7 Hz, 9H).

[00208] Step 7: To a solution of *tert*-butyl 3-fluoro-4-((hydroxyimino)methyl)benzyl(methyl) carbamate (2.6 g, 9.2 mmol) in DMF (30 mL) at 0 °C was added *N*-chlorosuccinimide (1.35 g, 10.1 mmol). The reaction was stirred at 0 °C for 1 h then allowed to warm to room temperature and stirred for 3 h. The reaction was concentrated under reduced pressure, diluted with ethyl acetate and washed with 0.5 HCl, water, brine, and dried over Na_2SO_4. The organics were concentrated *in vacuo* to provide *tert*-butyl 4-(chloro(hydroxyimino)methyl)-3-fluorobenzyl (methyl)carbamate as a colorless oil, which was carried forward without purification.

Preparation 14. Synthesis of *tert*-butyl 1-(3-(chloro(hydroxyimino)methyl)phenyl) ethylcarbamate



[00209] Step 1: 3-Acetylbenzoic acid (10.0 g, 60.9 mmol), hydroxylamine hydrochloride (33.9 g, 487.4 mmol) and sodium acetate (45.0 g, 548.3 mmol) were suspended in ethanol (115 mL) and water (115 mL) and the mixture refluxed for 30 min. The solvents were removed under reduced pressure, and the resulting residue was triturated with water. The resulting solid was filtered and dried to provide 3-(1-(hydroxyimino)ethyl)benzoic acid (10.34 g, 95% yield) a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.86 (s, 1H), 11.36 (s,

1H), 8.22 (s, 1H), 7.95 - 7.91 (m, 1H), 7.88 (dd, J = 4.7, 3.1 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 2.18 (s, 3H).

[00210] Step 2: 3-(1-(Hydroxyimino)ethyl)benzoic acid (2.28 g, 12.73 mmol) and palladium on carbon (10 wt.%, 1.355 g, 12.73 mmol) in ethanol (170 mL) and aq. HCl (2.1 mL of 12 M, 24.2 mmol) were stirred under an atmosphere of H_2 at 40 psi for 6 h. The reaction mixture was sparged with nitrogen for 30 min then filtered through a pad of Celite eluting with methanol. The filtrate was concentrated under reduced pressure and triturated with Et_2O to provide 3-(1-aminoethyl)benzoic acid hydrochloride (2.4 g, 94% yield) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 4.55 (q, J = 6.7 Hz, 1H), 1.66 (d, J = 6.9 Hz, 3H).

[00211] Step 3: To a solution of 3-(1-aminoethyl)benzoic acid (10.2 g, 50.6 mmol) in water (283 mL) and was added a solution of *tert*-butyl [(cyano-phenyl-methylene)amino] carbonate (13.1 g, 53. 1 mmol) in acetone (283 mL) followed by triethylamine (21 mL, 151 mmol). After stirring for 16 h at room temperature, the reaction mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate and water and the layers separated. The organic layer was extracted with saturated sodium bicarbonate solution. The combined aqueous layers were acidified to pH 2 with 1 N HCl and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield an off-white solid. The solid was triturated with ethyl acetate/hexanes to provide 3-[1-(*tert*-butoxycarbonylamino)ethyl]benzoic acid (8.3 g, 62% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 8.02 – 7.94 (m, 1H), 7.60 – 7.51 (m, 1H), 7.43 (t, J = 7.7 Hz, 1H), 4.88 (s, 1H), 1.48 (d, J = 6.7 Hz, 3H), 1.37 (s, 9H).

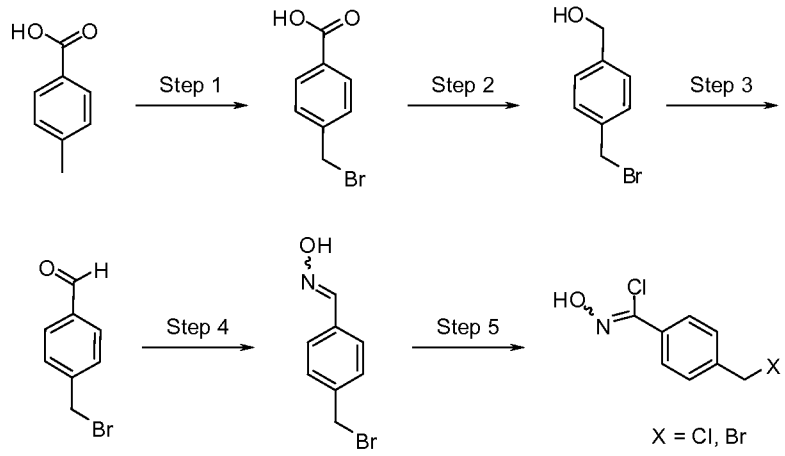
[00212] Step 4: 3-[1-(*tert*-butoxycarbonylamino)ethyl]benzoic acid (7.57 g, 28.53 mmol) was dissolved in anhydrous THF (45 mL) followed by the dropwise addition of borane-dimethylsulfide (42.8 mL of 2 M in THF, 85.6 mmol). The reaction was stirred for 3 h at room temperature then cooled to 0 °C and quenched with MeOH. The solvents were removed under reduced pressure and the resulting residue partitioned between 1M HCl and ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography (30% ethyl acetate/hexanes) provided *tert*-butyl *N*-[1-[3-(hydroxymethyl)phenyl] ethyl]carbamate (4.91 g, 68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.38 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 4.3 Hz, 2H), 7.14 (d, J = 7.7 Hz, 2H), 5.17 (t, J = 5.7 Hz, 1H), 4.64 – 4.54 (m, 1H), 4.47 (d, J = 5.6 Hz, 2H), 1.36 (s, 9H), 1.28 (d, J = 7.0 Hz, 3H).

[00213] Step 5: To a solution of *tert*-butyl *N*-[1-[3-(hydroxymethyl)phenyl]ethyl]carbamate (4.91 g, 19.54 mmol) in DCM (40 mL) was added MnO_2 (13.59 g, 156.3 mmol) and the reaction mixture was stirred at room temperature for 48 h at room temperature. An additional 3 g of MnO_2 was added and the reaction mixture was stirred for an additional 12 h. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to provide *tert*-butyl *N*-[1-(3-formylphenyl)ethyl]carbamate (4.0 g, 82% yield) as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ10.00 (s, 1H), 7.83 (s, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 15.4, 7.8 Hz, 2H), 4.75 – 4.64 (m, 1H), 1.41 – 1.30 (m, 12H).

[00214] Step 6: To a solution of *tert*-butyl *N*-[1-(3-formylphenyl)ethyl]carbamate (4.0 g, 16.0 mmol) and sodium acetate (3.3 g, 40.1 mmol) in THF (69 mL) at 0 °C was added hydroxylamine hydrochloride (1.4 g, 20.9 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was concentrated and the resulting residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide *tert*-butyl 1-(3-((hydroxyimino)methyl)phenyl)ethylcarbamate as a colorless gel (4.24 g, quantitative yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.11 (s, 1H), 7.53 (s, 1H), 7.41 (q, J = 8.3 Hz, 2H), 7.38 – 7.24 (m, 2H), 4.61 (dd, J = 14.0, 6.7 Hz, 1H), 1.33 (d, J = 21.1 Hz, 9H), 1.30 (d, J = 7.0 Hz, 3H).

[00215] Step 7: To a solution of *tert*-butyl 1-(3-((hydroxyimino)methyl)phenyl)ethylcarbamate (4.2 g, 16.0 mmol) in DMF (69 mL) at 0 °C was added *N*-chlorosuccinimide (2.4 g, 17.6 mmol) and the reaction stirred for 2 h while allowing to warm to room temperature. The reaction mixture was diluted with ethyl acetate (300 mL) and then washed with saturated brine solution. The organic layer was dried over Na_2SO_4, filtered and concentrated to a thick colorless gel. The residue was then triturated with Et_2O/hexanes and filtered to provide *tert*-butyl 1-(3-(chloro(hydroxyimino)methyl) phenyl) ethylcarbamate (4.3 g, 90% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.72 (s, 1H), 7.69 - 7.60 (m, 1H), 7.45 (dd, J = 36.5, 6.2 Hz, 3H), 4.64 (dt, J = 12.6, 6.4 Hz, 1H), 1.45 - 1.25 (m, 12H).

Preparation 15. Synthesis of 4-(chloromethyl)-*N*-hydroxybenzimidoyl chloride



[00216] Step 1: A solution of 4-methylbenzoic acid (10.0 g, 73.5 mmol) in ethyl acetate (142 mL) was treated with a solution of BrO_3Na (28.2 g, 220.4 mmol) in water (110 mL). A solution of $NaHSO_3$ (22.9 g, 220.4 mmol) in water (220 mL) was then added dropwise over 20 min to the reaction mixture [Caution: exotherm] and the reaction mixture stirred for 4 h. The aqueous layer was extracted with Et_2O. The combined organics were washed with 1 M $Na_2S_2O_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting solid was recrystallized from methanol to provide 4-(bromomethyl)benzoic acid (12.2 g, 77% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.93 (d, J = 8.2 Hz, 2H), 7.58 (t, J = 9.2 Hz, 2H), 4.76 (s, 2H).

[00217] Step 2: A solution of 4-(bromomethyl)benzoic acid (5.5 g, 25.6 mmol) in THF (30 mL) was cooled to 0 °C and treated with borane-THF solution (38.4 mL of 1 M, 38.4 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 2 h. The reaction was quenched with methanol followed by water and then concentrated under reduced pressure. The residue was partitioned between 1N HCl and ethyl acetate, and the organic layer washed with $NaHCO_3$, water, and brine. The solution was dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide [4-(bromomethyl)phenyl] methanol as a colorless solid (5.1 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.69 (s, 2H), 4.50 (s, 2H), 1.73 – 1.62 (m, 1H).

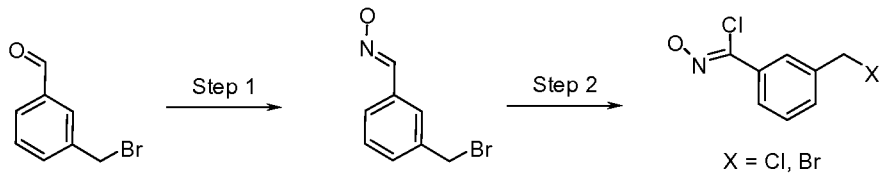
[00218] Step 3: A solution of [4-(bromomethyl)phenyl]methanol (5.1 g, 25.4 mmol) in DCM (56 mL) was treated with MnO_2 (17.7 g, 203.0 mmol) and stirred for 16 h. Additional MnO_2 was added (17.7 g, 203.0 mmol) and stirring continued for 48 h. The reaction was filtered through Celite and washed with DCM. The filtrate was concentrated *in vacuo* and

purified by silica gel chromatography (0-50% ethyl acetate/hexanes) to provide 4-(bromomethyl) benzaldehyde as a white solid (3.2 g, 63% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 8.1 Hz, 2H), 4.79 (s, 2H).

[00219] Step 4: A solution of 4-(bromomethyl)benzaldehyde (5.0 g, 25.1 mmol) in THF (50 mL) at 0 °C was treated with sodium acetate (4.5 g, 55.3 mmol) followed by hydroxylamine hydrochloride (1.9 g, 27.6 mmol). The reaction was allowed to warm to room temperature and then stirred for 16 h. The reaction was concentrated and the resulting residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide 4-(bromomethyl) benzaldehyde oxime as a colorless solid (5.3 g, 98% yield). LC/MS m/z 215.3 $[M+H]^+$.

[00220] Step 5: A solution of 4-(bromomethyl)benzaldehyde oxime (521 mg, 2.43 mmol) in DMF (10 mL) at 0 °C was treated with *N*-chlorosuccinimide (358 mg, 2.68 mmol). The reaction mixture was allowed to warm to room temperature and then stirred for 16 h. The reaction mixture was concentrated and partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to provide a mixture of 4-(chloromethyl)-*N*-hydroxybenzimidoyl chloride and 4-(bromomethyl)-*N*-hydroxybenzimidoyl chloride as a light yellow oil in quantitative yield. The crude material was taken forward without further purification.

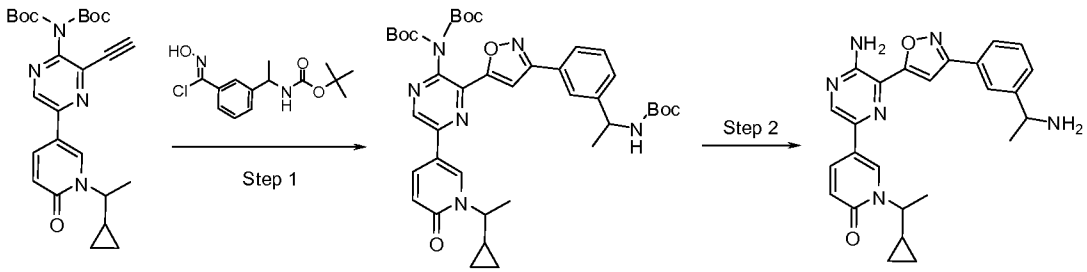
Preparation 16. Synthesis of 3-(chloromethyl)-*N*-hydroxybenzimidoyl chloride



[00221] Step 1: To a solution of 3-(bromomethyl)benzaldehyde (2.5 g, 12.6 mmol) in ethanol (13 mL) was added hydroxylamine (830 µL of 50 %w/v, 12.6 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was removed under reduced pressure and the resulting residue partitioned between ethyl acetate and water. The organic layer was washed with saturated aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Silica gel column chromatography (0-5% ethyl acetate/hexanes) provided 3-(bromomethyl)benzaldehyde oxime (2.7 g, 58%). LC/MS m/z 215.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.31 (s, 1H), 8.14 (s, 1H), 7.68 (s, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 4.72 (s, 2H).

[00222] Step 2: To a solution of 3-(bromomethyl)benzaldehyde oxime (500 mg, 2.34 mmol) in DMF (1.5 mL) was added *N*-chlorosuccinimide (312 mg, 2.34 mmol) and the reaction mixture stirred at 50 °C for 2 h. Additional *N*-chlorosuccinimide (150 mg) was added after 2 h and the reaction mixture stirred for another 2 h, after which the reaction was poured onto ice and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Silica gel chromatography (0-10% ethyl acetate/hexanes) provided a mixture of 3-(chloromethyl)-*N*-hydroxybenzimidoyl chloride and 3-(bromomethyl)-*N*-hydroxybenzimidoyl chloride (348 mg, 60%). The crude material was taken forward without further purification.

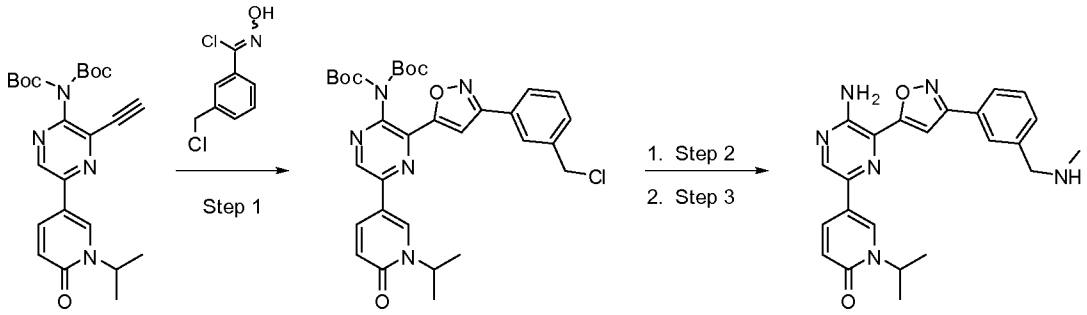
Example 5. Synthesis of 5-(5-amino-6-(3-(3-(1-aminoethyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)-1-(1-cyclopropylethyl)pyridin-2(1*H*)-one **Compound I-57**



[00223] Step 1: To a solution of *tert*-butyl 1-(3-(chloro(hydroxyimino)methyl)phenyl) ethylcarbamate (942 mg, 3.15 mmol) and *tert*-butyl *N*-tert-butoxycarbonyl-*N*-[5-[1-(1-cyclopropylethyl)-6-oxo-3-pyridyl]-3-ethynyl-pyrazin-2-yl]carbamate (505 mg, 1.05 mmol) in THF (5 mL) was added triethylamine (440 µL, 3.15 mmol) dropwise at room temperature. The reaction was heated at 65 °C for 1 h, then cooled and poured onto ice. The aqueous solution was extracted with ethyl acetate, and the combined organics layers dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography (10-30% ethyl acetate/DCM) provided *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[3-[3-[3-[1-(*tert*-butoxycarbonylamino) ethyl]phenyl]isoxazol-5-yl]-5-[1-(1-cyclopropylethyl)-6-oxo-3-pyridyl]pyrazin-2-yl]carbamate (273 mg, 35%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.87 (d, J = 2.3 Hz, 1H), 8.42 (d, J = 12.0 Hz, 1H), 7.94 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 8.3 Hz, 1H), 7.61 - 7.42 (m, 3H), 6.62 (d, J = 9.6 Hz, 1H), 4.80 - 4.67 (m, 1H), 4.25 (dd, J = 15.7, 8.2 Hz, 1H), 1.62 - 1.55 (m, 1H), 1.52 - 1.48 (m, 3H), 1.42 - 1.29 (m, 30H), 0.78 - 0.65 (m, 1H), 0.49 (dd, J = 11.7, 5.7 Hz, 2H), 0.23 (dd, J = 9.3, 3.9 Hz, 1H).

[00224] Step 2: To a solution of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[3-[3-[3-[1-(*tert*-butoxycarbonylamino)ethyl]phenyl]isoxazol-5-yl]-5-[1-(1-cyclopropylethyl)-6-oxo-3-pyridyl]pyrazin-2-yl]carbamate (273 mg, 0.37 mmol) in anhydrous DCM (3 mL) was added HCl (3.7 mL of 4 M in dioxane, 14.7 mmol) and the reaction stirred for 4 h at room temperature. The solvents and excess HCl were removed under reduced pressure. The resulting solid was triturated with MeOH/Et_2O, filtered and dried to provide 5-[5-amino-6-[3-[3-(1-aminoethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-1-(1-cyclopropylethyl)pyridin-2-one (140 mg, 78%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.57 – 8.47 (m, 4H), 8.22 (s, 1H), 8.17 (dd, J = 9.5, 2.6 Hz, 1H), 8.02 (t, J = 5.1 Hz, 1H), 7.77 (s, 1H), 7.72 – 7.60 (m, 2H), 6.54 (d, J = 9.5 Hz, 1H), 4.59 – 4.49 (m, 1H), 4.24 (tt, J = 13.6, 6.8 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.56 – 1.51 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H), 0.68 (dd, J = 14.3, 7.8 Hz, 1H), 0.52 – 0.41 (m, 2H), 0.26 – 0.15 (m, 1H).

Example 6. Synthesis of 5-(5-amino-6-(3-(3-((methylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)-1-isopropylpyridin-2(1*H*)-one (**Compound I-49**)



[00225] Step 1: To a solution of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[3-ethynyl-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]carbamate (300 mg, 0.66 mmol) and 3-(chloromethyl)-*N*-hydroxybenzimidoyl chloride (135 mg, 0.66 mmol) in THF (1.5 mL) was added triethylamine (110 µL, 0.79 mmol) dropwise. The reaction was heated at 65 °C for 1 h, then cooled and poured onto ice. The aqueous solution was extracted with ethyl acetate, and the combined organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel chromatography (0-60% ethyl acetate/hexanes) provided *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[3-[3-[3-(chloromethyl)phenyl]isoxazol-5-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]carbamate (300 mg, 73%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.73 (s, 1H), 8.30 (dd, J = 17.5, 14.8 Hz, 2H), 8.17 – 8.02 (m, 1H), 7.79 (d, J = 7.9 Hz,

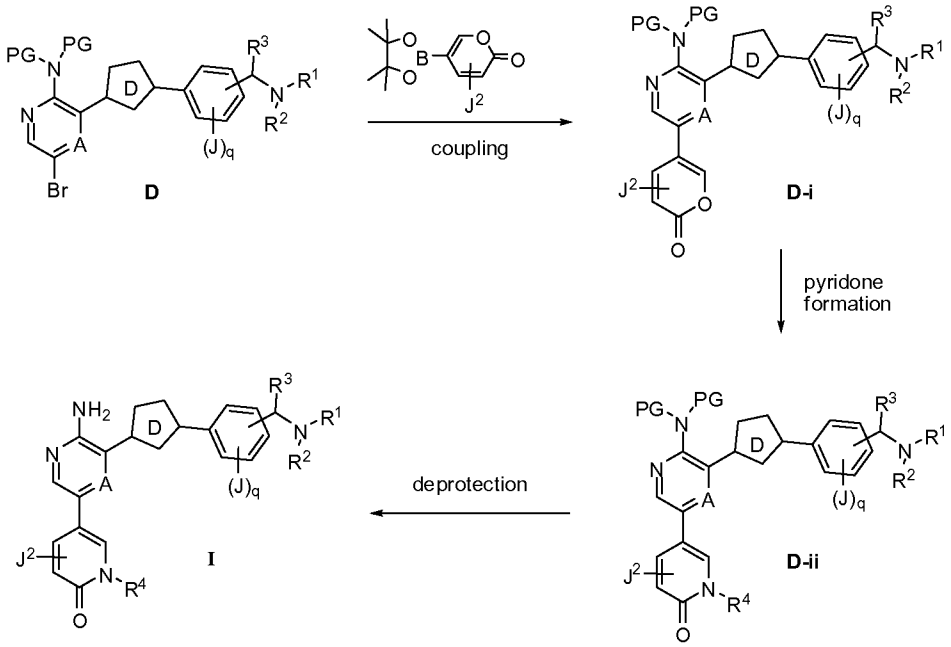
1H), 7.74 – 7.64 (m, 1H), 6.64 (d, J = 9.5 Hz, 1H), 5.76 (s, 2H), 4.87 (s, 1H), 1.45 (d, J = 7.2 Hz, 6H), 1.29 (s, 18H).

[00226] Step 2: To a solution of *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-[3-[3-[3-(chloromethyl)phenyl] isoxazol-5-yl]-5-(1-isopropyl-6-oxo-3-pyridyl)pyrazin-2-yl]carbamate (295 mg, 0.47 mmol) in DCM (3 mL) was added HCl (4.7 mL of 4 M in dioxane, 19.0 mmol). The reaction was stirred at room temperature for 3 h, and then heated at 40 °C for 1 h. The solvent and excess HCl were removed under reduced pressure to provide 5-[5-amino-6-[3-[3-(chloromethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one in quantitative yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.34 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 9.5, 2.4 Hz, 1H), 8.10 (s, 1H), 7.99 (d, J = 7.0 Hz, 1H), 7.75 (s, 1H), 7.64 – 7.57 (m, 2H), 6.54 (d, J = 9.5 Hz, 1H), 5.12 (m, 1H), 4.88 (s, 2H), 1.41 (d, J = 6.8 Hz, 6H).

[00227] Step 3: A mixture of 5-[5-amino-6-[3-[3-(chloromethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one (90 mg, 0.20 mmol), methylamine (5.0 mL of 2 M in THF, 10.0 mmol) and Na_2CO_3 (62 mg, 0.59 mmol) was stirred for 16 h at 70 °C. HPLC purification (10-99% CH_3CN/ 5mM HCl) provided 5-[5-amino-6-[3-[3-(methylaminomethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-1-isopropyl-pyridin-2-one

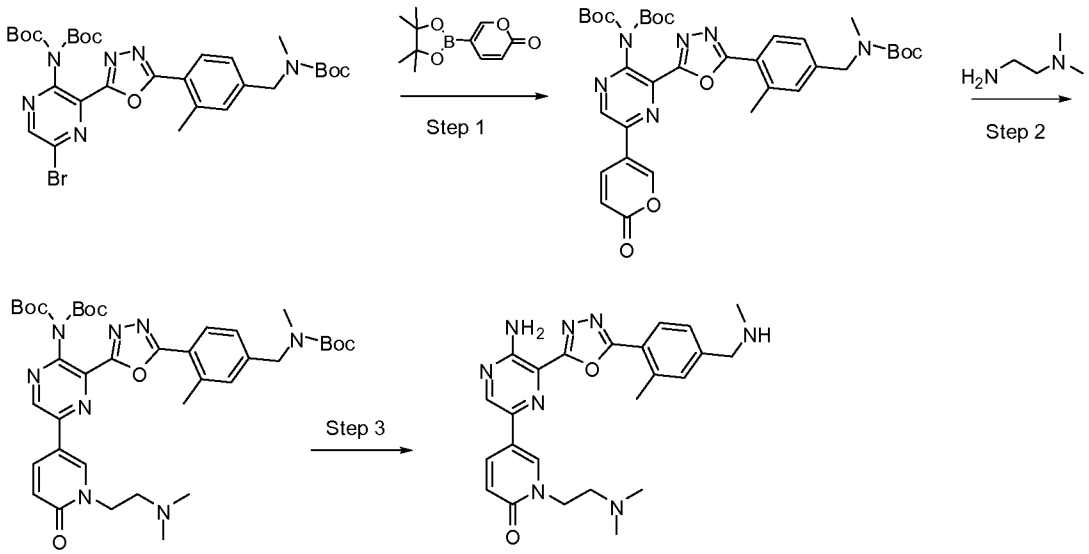
[00228] (**Compound I-49**). LC/MS m/z 417.5 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.37 (s, 2H), 8.81 (s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.25 (s, 1H), 8.16 (dd, J = 9.5, 2.5 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 9.5 Hz, 1H), 5.13 (dt, J = 13.7, 6.9 Hz, 1H), 4.23 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.3 Hz, 3H), 1.42 (t, J = 9.3 Hz, 6H).

Scheme D



[00229] Scheme D depicts a general method for making compounds of Formula **I**. Compounds of Formula **D** are protected with a suitable amine protecting group PG such as, but not limited to BOC (^{t}Butyl Carbamate), and if R^2 = H in $-NR^1R^2$, then R^2 is protected as PG. The pyrone ring system is introduced under metal-mediated coupling conditions, including but not limited to Suzuki coupling with an appropriate pyrone boronic ester or boronic acid to provide compounds of Formula **D-i**. The pyrone **D-i** is converted to the corresponding pyridone **D-ii** by treatment with either neat amine NHR^1R^2 or NHR^1R^2 in an appropriate solvent such as, but not limited to, methanol (See *Bull. Korean Chem. Soc.* **2001**, *22*, 234-236). Removal of the nitrogen protecting group PG from compounds of Formula **D-ii** takes place under standard conditions known to those skilled in the art such as, but not limited to, treatment with HCl or TFA to provide compounds of Formula **I**. In addition, substituents R^4 on Formula **I** can undergo further functionalization by reactions known to those skilled in the art such as, but not limited to, hydrolysis, nucleophilic displacement reactions, acylation reactions, amide bond formation reactions, or further deprotection to reveal additional functionality. The intermediate 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one was synthesized as described in *Synlett,* **2003**, *2*, 253-255.

Example 7. Synthesis of 5-[5-amino-6-[5-[2-methyl-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-(2-dimethylaminoethyl)pyridin-2-one (**Compound I-24**)



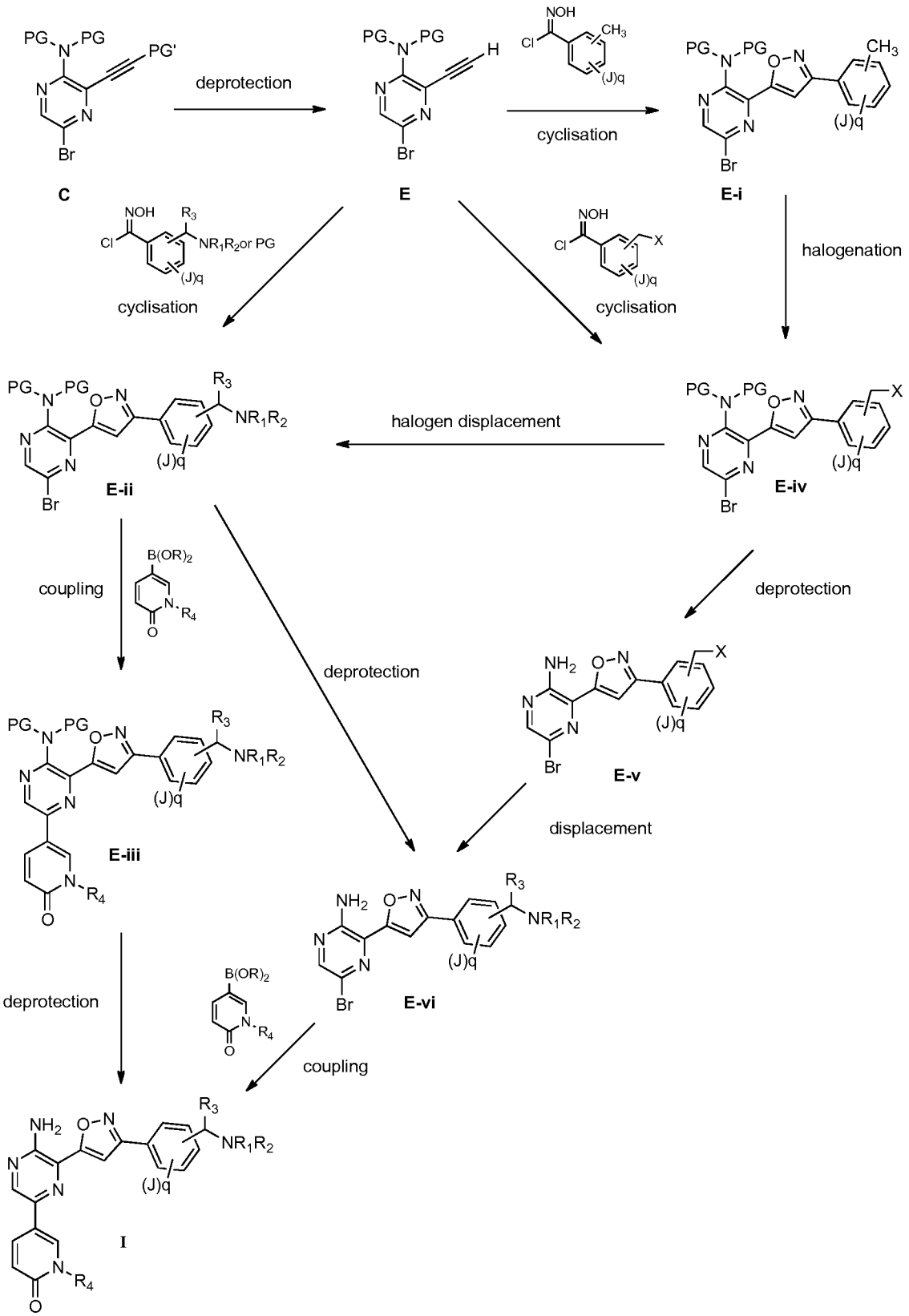
[00230] Step 1: Di-*tert*-butyl 5-bromo-3-(5-(4-((*tert*-butoxycarbonyl(methyl)amino) methyl)-2-methylphenyl)-1,3,4-oxadiazol-2-yl)pyrazin-2-yliminodicarbonate (545 mg, 0.807 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2H-pyran-2-one (197 mg, 0.887 mmol), and $Pd(PPh_3)_2$ (57 mg, 0.08 mmol) were dissolved in DME (4 mL) and aqueous Na_2CO_3 (800 µL of 2 M, 1.60 mmol). The mixture was heated at 80 °C for 1 h under nitrogen atmosphere. The mixture was filtered through Celite and washed with ethyl acetate. The filtrate was concentrated and the crude material was partially purified by silica gel chromatography (0-50% ethyl acetate/hexanes) to give an off-white solid (423 mg, 76% yield). LC/MS m/z 691.3 $[M+H]^+$.

[00231] Step 2: Di-*tert*-butyl 3-(5-(4-((*tert*-butoxycarbonyl(methyl)amino)methyl)-2-methylphenyl)-1,3,4-oxadiazol-2-yl)-5-(2-oxo-2*H*-pyran-5-yl)pyrazin-2-yliminodicarbonate (85 mg, 0.1231 mmol) was dissolved in methanol (1 mL) and the mixture cooled to 0 °C. *N*,*N*-dimethylethane-1,2-diamine (24 mg, 30 µL, 0.28 mmol) was added and the mixture stirred for 30 min, then allowed to warm to room temperature and stirred for 3 h. The mixture was concentrated in vacuo and silica gel chromatography (0-10% methanol/DCM) provided the desired product. LC/MS m/z 761.4 $[M+H]^+$.

[00232] Step 3: Di-*tert*-butyl 3-(5-(4-((*tert*-butoxycarbonyl(methyl)amino)methyl)-2-methylphenyl)-1,3,4-oxadiazol-2-yl)-5-(1-(2-(dimethylamino)ethyl)-6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yliminodicarbonate from Step 2 was dissolved in 4 M HCl in dioxane (1 mL) and stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the resulting solid triturated with Et_2O and filtered to provide 5-[5-amino-6-[5-[2-methyl-4-(methylaminomethyl)phenyl]-1,3,4-oxadiazol-2-yl]pyrazin-2-yl]-1-

(2-dimethylaminoethyl)pyridin-2-one (8 mg, 12% yield from Step 1). LC/MS m/z 461.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.38 – 10.23 (m, 1H), 9.38 – 9.28 (m, 2H), 8.84 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.27 – 8.10 (m, 2H), 7.65 (d, J = 9.8 Hz, 4H), 6.65 (d, J = 9.5 Hz, 1H), 4.41 (t, J = 6.3 Hz, 2H), 4.20 (t, J = 5.8 Hz, 3H), 3.57 – 3.45 (m, 4H), 2.87 (d, J = 4.7 Hz, 7H), 2.75 (s, 3H), 2.58 (t, J = 5.3 Hz, 4H).

Scheme E-1


deprotection
cyclisation
halogenation
cyclisation
cyclisation
halogen displacement
coupling
deprotection
deprotection
displacement
deprotection
coupling
C
E
E-i
E-ii
E-iii
E-iv
E-v
E-vi
I

[00233] Scheme E-1 depicts a general method for making compounds of Formula **I** in which Ring **D** is isoxazole. Compound **C** contains amino protecting groups PG, and a alkyne protecting group PG'. Suitable PG include, but are not limited to Boc (tert-butoxycarbonyl); Suitable PG' include, but are not limited to, TMS, TES or TIPS. Compounds of Formula **C** are selectively deprotected using conditions such as but not limited to K_2CO_3 or fluoride to remove the alkyne protecting group PG' to yield compounds of Formula **E**. The assembly of the 3,5-disubstituted isoxazole can be achieved through 1,3-dipolar cycloaddition of the terminal acetylene of compound **E** with an appropriate chloro oxime, under basic conditions, to provide the desired isoxazole in compounds of Formula **Ei**, **Eii** or **Eiv**. Suitable conditions include, but are not limited to use of triethylamine.

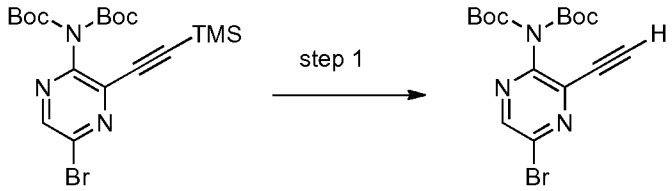
[00234] Compounds of Formula **E-i** are subjected to halogenation of the benzylic methyl with reagents such as, but not limited to NBS to give compounds of Formula **E-iv,** where X is a halogen. Compounds of Formula **E-iv** can also be made directly with the halogen already in place on the chloro oxime prior to cyclisation. The leaving group X on compounds of Formula **E-iv** may be displaced by an amine of Formula NHR_1R_2, leading to compounds of Formula **E-ii**. Compounds of Formula **E-ii** can be made directly from 1,3-dipolar cycloaddition with a chloro oxime which contains the appropriate amine substitution. Removal of the amino protecting group PG from compounds of Formula **E-ii** occurs under standard conditions known to those skilled in the art to generate intermediates **E-vi**. Alternatively, such a PG deprotection can be performed from compounds of Formula **E-iv** to provide compounds of Formula **E-v**, prior to amine displacement which will furnish compounds of Formula **E-vi**.

[00235] From compounds of Formula **E-ii**, the pyridone ring system is introduced under metal-mediated coupling conditions, including but not limited to Suzuki coupling with an appropriate boronic ester or boronic acid to provide compounds of Formula **E-iii**. Removal of the amino protecting group PG from compounds of Formula **E-iii** takes place under standard conditions known to those skilled in the art such as, but not limited to, treatment with HCl or TFA to provide compounds of Formula **I** in which Ring D is isoxazole.

[00236] Alternatively, the pyridone ring system can be introduced on compounds of Formula **E-vi** using conditions as described above to give directly compounds of Formula **I**. In addition, compounds of Formula **I** can undergo further functional group transformations on substituent R_4, using reactions known to those skilled in the art such as, but not limited to, hydrolysis, nucleophilic displacement reactions, acylation reactions, amide bond formation reactions, or further deprotection to reveal additional functionality.

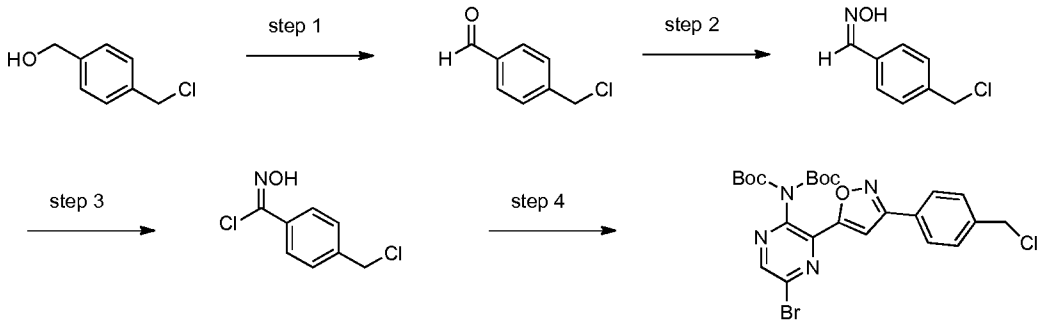
Preparations 17-24 and Examples 9-11 relate to schemes E-1.

Preparation 17. Synthesis of *Di-tert*-butyl (5-bromo-3-ethynylpyrazin-2-yl)carbamate



[00237] Step 1: Sodium carbonate (77.30 mL of 2 M, 154.6 mmol) was added to a suspension of tert-butyl N-[5-bromo-3-(2-trimethylsilylethynyl)pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate (60.6 g, 128.8 mmol) in DMF (303.0 mL) and heated at 75 °C for 45 min. The reaction mixture was allowed to cool to room temperature and then diluted with water (900 mL). The precipitate was left to stand for 30 min and was isolated by filtration and washed with water (300 mL). The yellow powder was transferred to a flask and triturated with ethyl acetate (300 mL) to give the sub-titled product as a white powder (48.39 g, 94% yield). ^{1}H NMR (400.0 MHz, DMSO-d_6) 1.43 (18H, s), 3.53 (1H, s), 8.55 (1H, s); MS (ES^+) 243.9, MS (ES^-) 334.2.

Preparation 18. Synthesis of *Di-tert*-butyl (5-bromo-3-(3-(4-(chloromethyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)carbamate



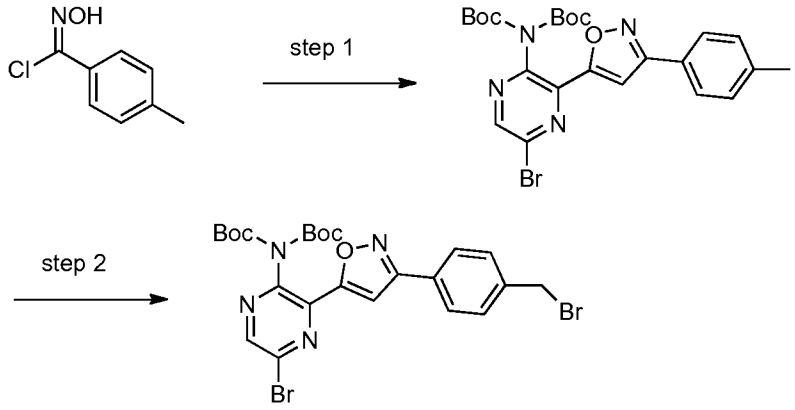
[00238] Step 1: MnO_2 (51.08 g, 587.5 mmol) was added to a solution of [4-(chloromethyl)phenyl]methanol (9.2 g, 58.75 mmol) in DCM (608 mL) . The mixture was stirred at room temperature for 48 h. The oxidant was removed by filtration, and the filtrate was concentrated *in vacuo* to give 4-(chloromethyl)benzaldehyde as a white solid (7.5 g, 83% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) 4.65 (2H, s), 7.58 (2H, d), 7.91 (2H, d) and 10.05 (H, s).

[00239] Step 2: Hydroxlamine hydrochloride (10.11 g, 145.5 mmol) was added to a solution of 4-(chloromethyl)benzaldehyde (7.5 g, 48.51 mmol) in ethanol. The mixture was heated at 50 °C for 3 h. After this time the reaction mixture was concentrated in vacuo. The residue was partitioned between DCM and water. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give (1E)-4-(chloromethyl)benzaldehyde oxime as a white solid (8.1 g, 98% yield). ^{1}H NMR (400.0 MHz, DMSO-d_6) 4.75 (2H, s), 7.45 (2H, d), 7.60 (2H, d), 8.15 (1H, s), 11.3 (H, s)

[00240] Step 3: (1E)-4-(chloromethyl)benzaldehyde oxime (1.662 g, 9.801 mmol) was dissolved in DMF (34.99 mL), N-chlorosuccinimide (1.570 g, 11.76 mmol) was added followed by a solution of HCl in dioxane (15.70 mL of 4 M, 62.82 mmol). The mixture was stirred at room temperature for 30 min. After this time water was added, and the mixture was extracted with ethyl acetate. The organic layer was separated, washed with water, saturated brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give (1Z)-4-(chloromethyl)-N-hydroxy-benzimidoyl chloride as a solid (2.0 g, 100% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) 4.63 (2H, s), 7.45 (2H, d), 7.86 (2H, d) and 8.36 (H, s).

[00241] Step 4: Triethylamine (1.128 g, 1.554 mL, 11.15 mmol) was added to a solution of tert-butyl N-(5-bromo-3-ethynyl-pyrazin-2-yl)-N-tert-butoxycarbonyl-carbamate (3.7 g, 9.291 mmol) and (1Z)-4-(chloromethyl)-N-hydroxy-benzimidoyl chloride (1.994 g, 9.774 mmol) in DCM (26.24 mL) . The mixture was stirred at room temperature for 18 h. The reaction mixture was partitioned between DCM and water. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as an oil. Purification by silica chromatography eluting with 10-40% ethyl acetate/petroleum ether gave the sub-titled product as a pale yellow solid (3.19 g, 66% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) 1.41 (18H, s), 4.66 (2H, s), 7.37 (1H, s), 7.54 (2H, d, J = 8.2), 7.90 (2H, d, J = 8.2 Hz) and 8.66 (1H, s); MS (ES^+) 410.9, MS (ES^-) 464.8.

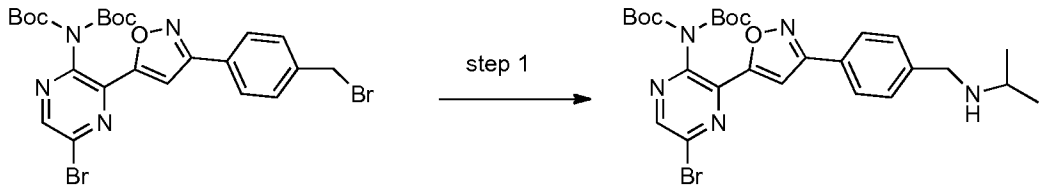
Preparation 19. Synthesis of *Di-tert*-butyl (5-bromo-3-(3-(4-(bromomethyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)carbamate



[00242] Step 1: N-hydroxy-4-methyl-benzimidoyl chloride (1.548 g, 9.127 mmol) and tert-butyl N-(5-bromo-3-ethynyl-pyrazin-2-yl)-N-tert-butoxycarbonyl-carbamate (4 g, 10.04 mmol) were dissolved in DMF (5.540 mL). Et_3N (1.108 g, 1.526 mL, 10.95 mmol) was added dropwise. The mixture was stirred at room temperature for 45 min followed by heating to 65 °C for 1 h. After this time the reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 mL) and water (5 mL) and the layers separated. The aqueous layer was extracted further with ethyl acetate (2 x 5 mL) and the combined organic extracts were washed with water (3 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product. Purification by silica chromatography eluting with 0–30% ethyl acetate/petroleum ether to give tert-butyl N-[5-bromo-3-[3-(p-tolyl)isoxazol-5-yl]pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate as a solid (3.5 g, 60% yield). ^1H NMR (400.0 MHz, $CDCl_3$) 1.4 (18H, s), 2.45 (3H, s), 7.35 (1H, s), 7.35 (2H, d), 7.8 (2H, d) and 8.65 (1H, s); MS (ES^+) 376.9, 431.0.

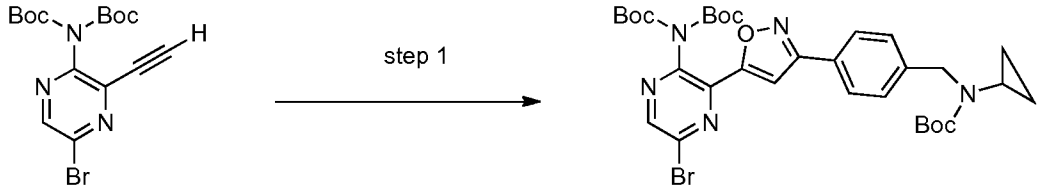
[00243] Step 2: Tert-butyl N-[5-bromo-3-[3-(p-tolyl)isoxazol-5-yl]pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate (1.800 g, 3.387 mmol) was dissolved in fluorobenzene (15 mL) . 2-(1-cyano-1-methyl-ethyl)azo-2-methyl-propanenitrile (111.2 mg, 0.6774 mmol) and 1-bromopyrrolidine-2,5-dione (723.3 mg, 4.064 mmol) were added. The mixture was heated to 90 °C for 1 h. After this time the solids were removed by filtration and the filtrate was concentrated *in vacuo* to give the sub-titled product as an oil (2 g, 70% purity, 68% yield). ^1H NMR (400.0 MHz, $CDCl_3$) 1.5 (18H, s), 4.55 (2H, s), 7.35 (1H, s), 7.55 (2H, d), 7.85 (2H, d) and 8.65 (1H, s), MS (ES^+) 454.8, 510.8.

Preparation 20. Synthesis of *Di-tert*-butyl (5-bromo-3-(3-(4-((isopropylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)carbamate



[00244] Step 1: Tert-butyl N-[5-bromo-3-[3-[4-(bromomethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate (100 mg, 0.1639 mmol) was added to a solution of propan-2-amine (96.88 mg, 140.8 µL, 1.639 mmol) in DMF (2 mL) . The mixture was stirred at room temperature for 1 h. After this time the reaction mixture was diluted with ethyl acetate, washed with water and brine. The organic layer was separated and concentrated *in vacuo* to give the crude product. Purification by silica chromatography eluting with 20% ether/petroleum ether gave the sub-titled product as a solid. This material was not completely clean and was used as such in the next step (90 mg, 93% yield). MS (ES^+) 590.0.

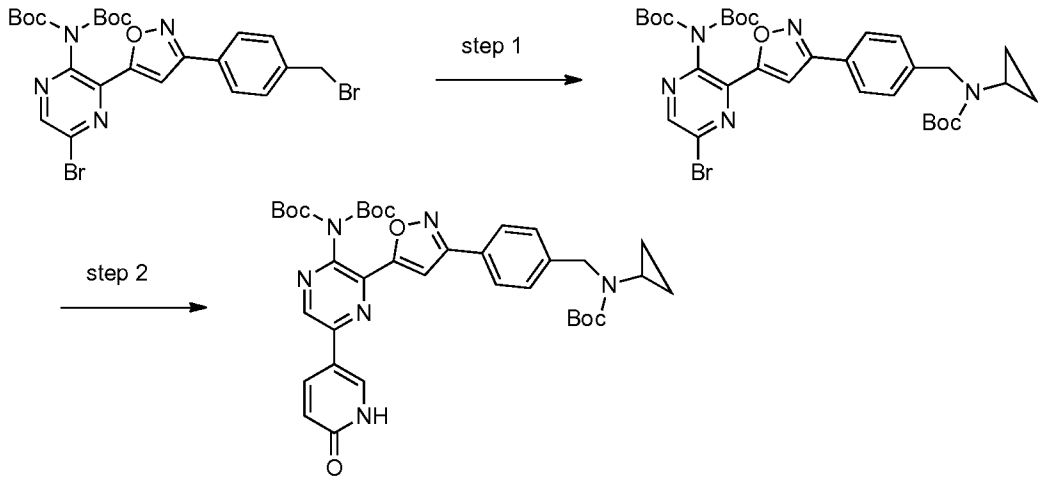
Preparation 21. Synthesis of tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-bromo-pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-cyclopropyl-carbamate



[00245] Step 1: NCS (204.6 mg, 1.532 mmol) was added to a solution of tert-butyl N-cyclopropyl-N-[[4-[(E)-hydroxyiminomethyl]phenyl]methyl]carbamate in DMF (3 mL) and the mixture heated at 55 °C for 30 min. The reaction mixture was allowed to cool to room temperature, and tert-butyl N-(5-bromo-3-ethynyl-pyrazin-2-yl)-N-tert-butoxycarbonyl-carbamate (610 mg, 1.532 mmol) and TEA (186.0 mg, 256.2 µL, 1.838 mmol) was added dropwise. The mixture was stirred at room temperature for 45 min followed by heating to 65 °C for 2 hr. After this time the reaction mixture was allowed to cool to room temperature and diluted with ethyl acetate (5 mL) and water (5 mL) and the layers separated. The aqueous layer was extracted further with ethyl acetate (2 x 5 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a solid. Purification by silica chromatography eluting with 10-30% ethyl

acetate/petroleum ether gave the sub-titled product (430 mg, 41% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) 0.66 - 0.77 (4H, m), 1.40 (18H, s), 1.48 (9H, s), 2.51 (1H, m), 3.25-3.31 (2H, m), 4.50 (2H, s), 7.35-7.38 (3H, m), 7.83–7.89 (2H, m) and 8.65 (1H, s); MS (ES^+) 532.0, 588.1.

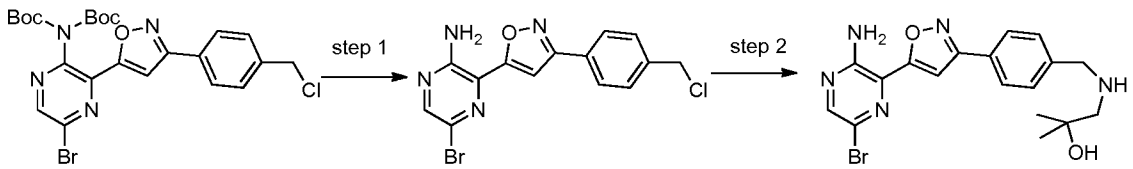
Preparation 22. Synthesis of *Di-tert*-butyl (3-(3-(4-((cyclopropylamino)methyl)phenyl)isoxazol-5-yl)-5-(6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yl)carbamate



[00246] Step 1: Tert-butyl N-[5-bromo-3-[3-[4-(bromomethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate (100 mg, 0.1639 mmol) was added to a solution of cyclopropanamine (93.58 mg, 113.6 µL, 1.639 mmol) in DMF (2 mL). The mixture was stirred at room temperature for 1 hr. After this time the reaction mixture was diluted with ethyl acetate, washed with water and brine and concentrated to a solid in vacuo. The solid was dissolved in DCM (10 mL) and triethylamine (16.59 mg, 22.85 µL, 0.1639 mmol) and di-tert-butyl carbonate (35.77 mg, 37.65 µL, 0.1639 mmol) was added. The resulting mixture was stirred at room temperature for 1 h and then concentrated to an oil *in vacuo*. Purification by silica chromatography eluting with 20% ether/petroleum gave tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-bromo-pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-cyclopropyl-carbamate (80mg, 71% yield). ^{1}H NMR (400.0 MHz, $CDCl_3$) 0.66 - 0.77 (4H, m), 1.40 (18H, s), 1.48 (9H, s), 2.51 (1H, m), 3.25-3.31 (2H, m), 4.50 (2H, s), 7.35-7.38 (3H, m), 7.83–7.89 (2H, m) and 8.65 (1H, s); MS (ES^+) 532.0, 588.1.

[00247] Step 2: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-bromo-pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-cyclopropyl-carbamate (800 mg, 1.165 mmol) was dissolved in dioxane (4 mL) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol (257.5 mg, 1.165 mmol) was added. The reaction mixture was degassed with 3 x nitrogen/vacuum cycles. Pd(dppf)Cl_2.DCM (23.78 mg, 0.02912 mmol) was added and the reaction was degassed a further 3 times. An aqueous solution of sodium carbonate (1.747 mL of 2 M, 3.495 mmol) was added and the reaction mixture was heated at 80 °C for 4 h. The reaction was cooled to room temperature and diluted with ethyl acetate and water. The aqueous layer was further extracted with ethyl acetate and the combined organic extracts were washed with brine (x 2), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by automated silica chromatography eluting with 0–100% ethyl acetate/petroleum ether gave *the* sub-titled product as a beige solid (505mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 0.69 - 0.78 (4H, m), 1.42 (18H, s), 1.50 (9H, s), 2.54 (1H, m), 4.52 (2H, s), 6.82 – 6.85 (H, d), 7.35 (H, s), 7.40 – 7.42 (2H, d), 7. 88 – 7.90 (2H, d), 8.29 – 8.32 (1H, m), 8.42 (1H, s), 8.83 (1H, s) and 12.75 (1H, m); MS (ES^+) 545.1, 601.2, 701.2, MS (ES^-) 701.2.

Preparation 23. Synthesis of 1-((4-(5-(3-amino-6-bromopyrazin-2-yl)isoxazol-3-yl)benzyl)amino)-2-methylpropan-2-ol

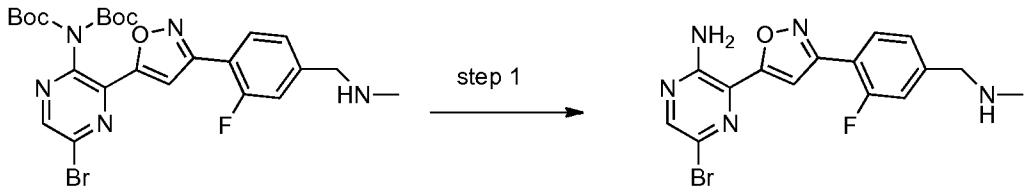


[00248] Step 1: Tert-butyl N-[5-bromo-3-[3-[4-(chloromethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-N-tert-butoxycarbonyl-carbamate (500 mg, 0.8836 mmol) was dissolved in DCM (25 mL). TFA (2.500 mL) was added and the mixture was stirred at room temperature for 15 min. The reaction mixture was concentrated *in vacuo* to give 5-bromo-3-[3-[4-(chloromethyl)phenyl]isoxazol-5-yl]pyrazin-2-amine as a yellow solid that was used without further purification (330 mg, 99% yield). MS (ES^-) 364.9.

[00249] Step 2: 1-amino-2-methyl-propan-2-ol (78.75 mg, 0.8835 mmol), 5-bromo-3-[3-[4-(chloromethyl)phenyl]isoxazol-5-yl]pyrazin-2-amine (32.30 mg, 0.08835 mmol) and DIPEA (22.84 mg, 30.78 µL, 0.1767 mmol) were combined in NMP (1 mL) and the reaction

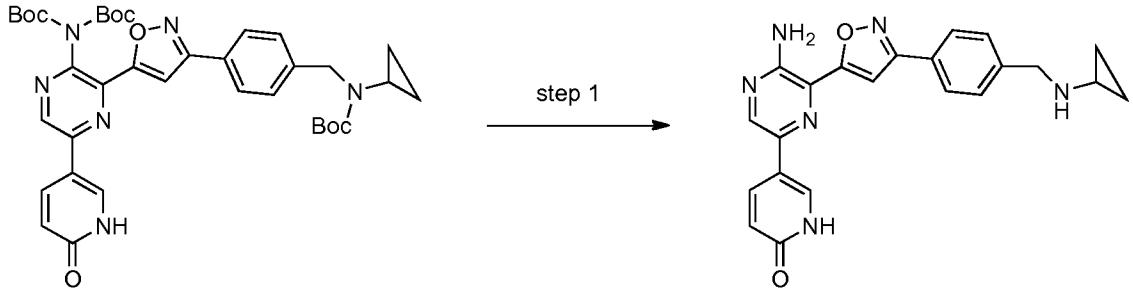
mixture was heated in a microwave reactor at 110 °C for 30 min. The reaction mixture was concentrated *in vacuo* and the sub-titled product was used crude. MS (ES^+) 420.5 (ES^-) 418.6.

Preparation 24. Synthesis of 5-bromo-3-(3-(2-fluoro-4-((methylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-amine



[00250] Step 1: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-bromo-pyrazin-2-yl]isoxazol-3-yl]-3-fluoro-phenyl]methyl]-N-methyl-carbamate (50 mg, 0.07369 mmol) was stirred at room temperature for 2 h in a mixture of DCM (5 mL) and TFA (0.5 mL). The reaction mixture was concentrated *in vacuo*. The residue was partitioned between DCM and saturated aqueous bicarbonate solution. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the sub-titled product as an oil. The product was used without any further purification. MS (ES^+) 380.5

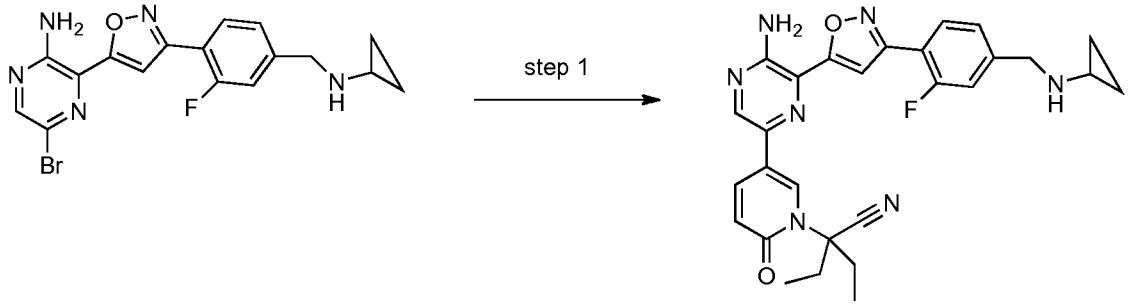
Example 9: Synthesis of 5-[5-amino-6-[3-[4-[(cyclopropylamino)methyl]phenyl]isoxazol-5-yl]pyrazin-2-yl]-1H-pyridin-2-one **(Compound I-111)**



[00251] Step 1: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-(6-oxo-1H-pyridin-3-yl)pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-cyclopropyl-carbamate (29.99 mg, 0.04280 mmol) was dissolved in DCM (3 mL) followed by the addition of TFA (146.4 mg, 98.92 µL, 1.284 mmol). The mixture was stirred at room temperature for 1 h and then

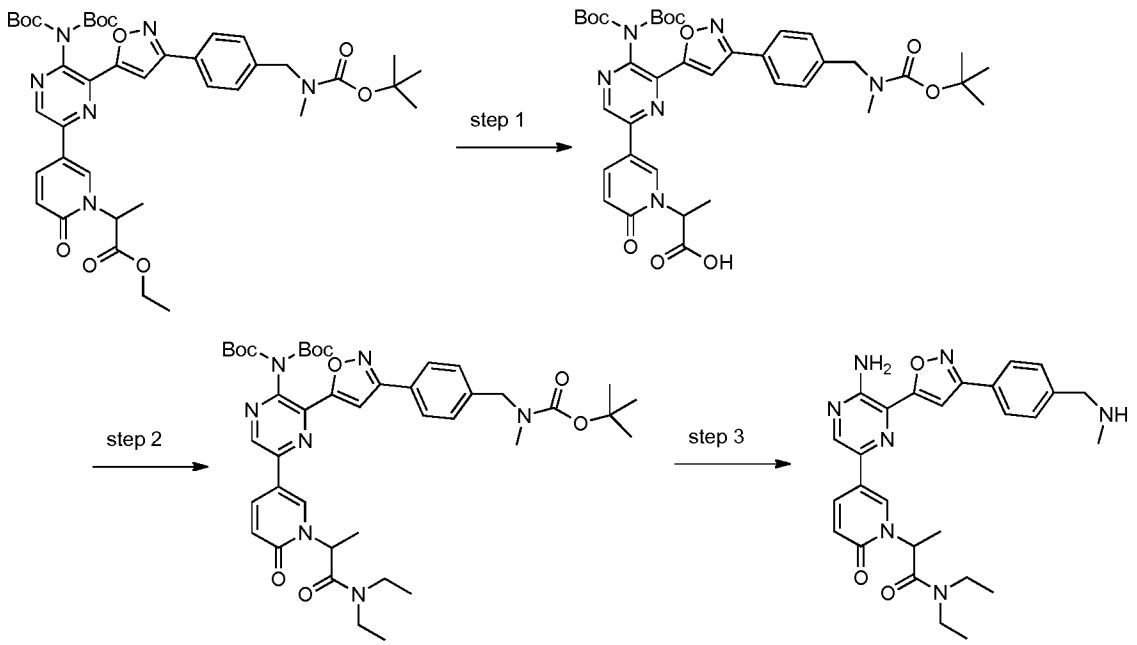
concentrated to an oil. Purification was purified by reverse phase preparative HPLC [Waters Sunfire C18, 10mM, 100 Å column, gradient 10% - 95% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 16 minutes at 25 mL/min] gave the sub-titled product (9.5 mg, 44% yield). H^1 NMR (400.0 MHz, DMSO-d_6) 0.8-0.9 (4H, m), 2.6-2.65 (1H, m), 4.25-4.3 (2H, m), 6.5 (1H, d), 6.9 (2H, s), 7.65 (2H, d), 7.78 (1H, s), 8.05 (2H, d), 8.1-8.12 (1H, m), 8.7 (1H, s), 8.8 (2H, brs); MS (ES^+) 401.1, MS (ES^-) 399.1

Example 10: Synthesis of 2-[5-[5-amino-6-[3-[4-[(cyclopropylamino)methyl]-2-fluoro-phenyl]isoxazol-5-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]-2-ethyl-butanenitrile **(Compound I-135)**



[00252] Step 1: 5-bromo-3-[3-[4-[(cyclopropylamino)methyl]-2-fluoro-phenyl]isoxazol-5-yl]pyrazin-2-amine (28.70 mg, 0.071 mmol) , 2-ethyl-2-[2-oxo-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-pyridyl]butanenitrile (35 mg, 0.1107 mmol) , K_3PO_4 (106.5 µL of 2 M, 0.2130 mmol) , $Pd(PPh_3)_4$ (8.204 mg, 0.007 mmol) in toluene (2 mL) and EtOH (0.5 mL) was degassed and then heated in a microwave reactor a 80 °C for 20 min. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between DCM and water. The layers were separated and the organic extract was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give an oil. Purification was purified by reverse phase preparative HPLC [Waters Sunfire C18, 10mM, 100 Å column, gradient 10% - 95% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 16 minutes at 25 mL/min] gave the sub-titled product (3.44 mg, 9.44% yield). H^1 NMR (400.0 MHz, $CDCl_3$) 8.44 (d, J = 2.2 Hz, 1H), 8.33 (s, 1H), 7.93-7.87 (m, 2H), 7.39 (d, J = 3.3 Hz, 1H), 7.18-7.15 (m, 3H), 6.59 (d, J = 9.5 Hz, 1H), 5.78 (s, 2H), 3.84 (s, 2H), 2.88 (m, 2H), 2.18 (m, 2H), 2.12 (m, 1H), 1.00 (t, J = 7.4 Hz, 6H) and 0.41-0.33 (m, 4H) ppm; MS (ES^+) 514.0, MS (ES^-) 512.0.

Example 11: Synthesis of 2-(5-(5-amino-6-(3-(4-((methylamino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)-2-oxopyridin-1(2*H*)-yl)-*N*,*N*-diethylpropanamide **(Compound I-101)**



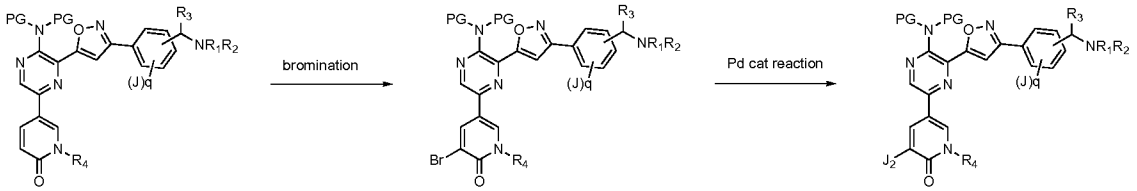
[00253] Step 1: To a solution of ethyl 2-[5-[5-[bis(tert-butoxycarbonyl)amino]-6-[3-[4-[[tert-butoxycarbonyl(methyl)amino]methyl]phenyl]isoxazol-5-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanoate (2.7 g, 3.485 mmol) in THF (30 mL) was added LiOH (8.710 mL of 2 M, 17.42 mmol) . The resulting solution was stirred at 40 °C for 4 hr. After this time the reaction mixture was neutralised with HCl and then extracted with EtOAc. The organics layer was separated, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give 2-[5-[5-[bis(tert-butoxycarbonyl)amino]-6-[3-[4-[[tert-butoxycarbonyl(methyl)amino]methyl]phenyl]isoxazol-5-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanoic acid as a yellow solid (1.2 g, 46% yield).

[00254] Step 2: To a solution of 2-[5-[5-[bis(tert-butoxycarbonyl)amino]-6-[3-[4-[[tert-butoxycarbonyl(methyl)amino]methyl]phenyl]isoxazol-5-yl]pyrazin-2-yl]-2-oxo-1-pyridyl]propanoic acid (100 mg, 0.1339 mmol) , diethoxyphosphorylformonitrile (21.84 mg, 0.1339 mmol) , and Et_3N (40.65 mg, 55.99 µL, 0.4017 mmol) in 1,2-dimethoxyethane (1 mL) was added N-diethylamine solution in THF (133.9 µL of 2 M, 0.2678 mmol) and the resulting solution was stirred overnight at room temperature. After this time, water was added, followed by DCM (5 mL) and the organic layer separated and the organic solution

containing *di-tert*-butoxycarbonyl(3-(3-(4-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)phenyl)isoxazol-5-yl)-5-(1-(1-(diethylamino)-1-oxopropan-2-yl)-6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yl)carbamate was used directly in the next step.

[00255] Step 3: HCl (1 mL of 1M, 1.000 mmol) was added the solution of DCM containing *di-tert*-butoxycarbonyl(3-(3-(4-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)phenyl)isoxazol-5-yl)-5-(1-(1-(diethylamino)-1-oxopropan-2-yl)-6-oxo-1,6-dihydropyridin-3-yl)pyrazin-2-yl)carbamate and the resulting solution was stirred for 1 hr. After this time the reaction mixture was passed through an SCX cartridge and the cartridge was washed with MeOH. The product mixture was eluted off with MeOH/NH_3. Purification was purified by reverse phase preparative HPLC [Waters Sunfire C18, 10mM, 100 Å column, gradient 10% - 95% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 16 minutes at 25 mL/min] gave the sub-titled product (3.89 mg, 6% yield). MS (ES^+) 502.0, MS (ES^-) 500.0.

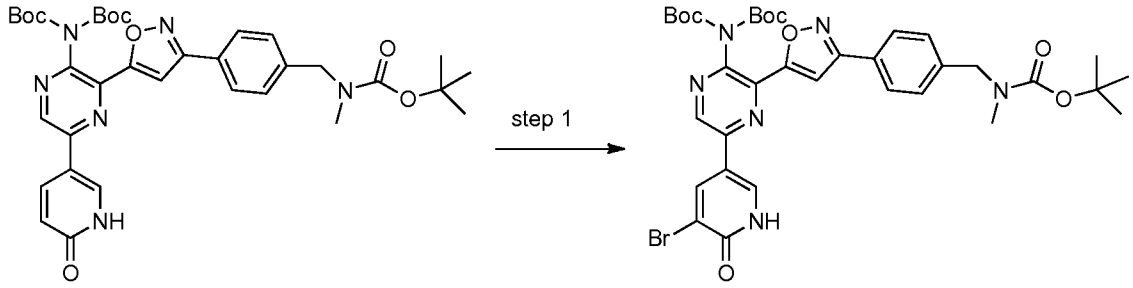
Scheme E-2



[00256] Scheme E-2 depicts a general method for the preparation of compounds of Formula **E-iii** where the pyridone nucleus is further functionalized by substituent J_2 (with $J_2 \neq H$). Compounds of Formula **E-iii** can be subjected to halogenation with reagent such as, but not limited to NBS to give compounds of Formula **E-vii**. Compounds of Formula **E-vii** were used as coupling partners in metal-mediated coupling reactions, including but not limited to Suzuki coupling, with an appropriate boronic ester or boronic acid to provide compounds of Formula **E-iii** where the pyridone nucleus is further functionalized by substituent J_2 (with $J_2 \neq H$).

Preparation 25 and Example 12 relate to Scheme E-2

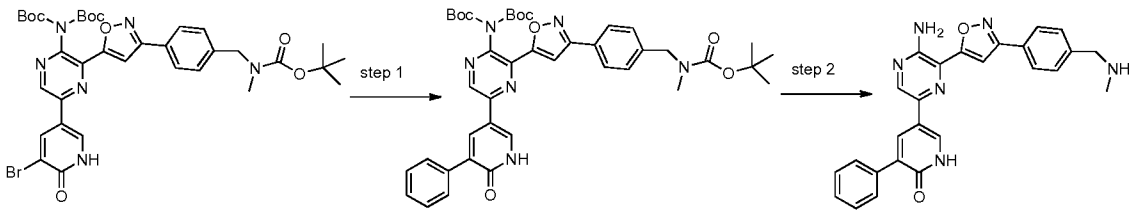
Preparation 25: Synthesis of *tert*-butyl (5-(5-bromo-6-oxo-1,6-dihydropyridin-3-yl)-3-(3-(4-(((*tert*-butoxycarbonyl)(methyl)amino)methyl)phenyl)isoxazol-5-yl)pyrazin-2-yl)(*tert*-butoxycarbonyl)carbamate



[00257] Step 1: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-(6-oxo-1H-pyridin-3-yl)pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-methyl-carbamate (500 mg, 0.7410 mmol) was dissolved in THF (5 mL) followed by the addition of NBS (158.3 mg, 0.8892 mmol) and the mixture stirred at room temperature for 1 hr. Additional NBS (39.58 mg, 0.222 mmol) was added and the reaction mixture was stirred for a further 30 min. The mixture was concentrated to an oil *in vacuo*. Purification by silica chromatography eluting with ether followed by 20% ethylacetate/diethyl ether gave the sub-titled product (370 mg, 65% yield).

H^1 NMR (400.0 MHz, $CDCl_3$) 1.34 (18H, s), 1.42 (9H, s), 2.72-2.84 (3H, m), 4.43 (2H, m), 7.32 (3H, m), 7.84-7.86 (2H, m), 8.4 (1H, s), 8.63 (1H, s) and 8.75 (1H, s); MS (ES^+) 597.0, 655.0, MS (ES^-) 753.0.

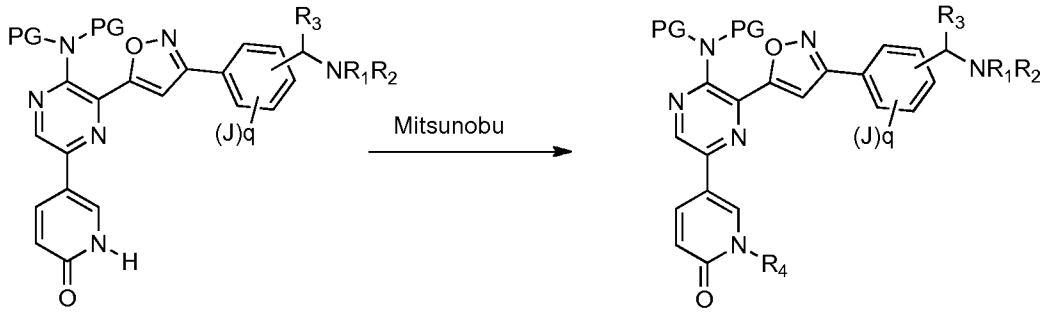
Example 12: Synthesis of 3-[4-(methylaminomethyl)phenyl]isoxazol-5-yl]pyrazin-2-yl]-3-phenyl-1H-pyridin-2-one **(Compound I-123)**



[00258] Step 1: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-(5-bromo-6-oxo-1H-pyridin-3-yl)pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-methyl-carbamate (50 mg, 0.06634 mmol) was added to dioxane (1.334 mL) followed by the addition of cyclopenta-1,4-dien-1-yl(diphenyl)phosphane (3.294 mg, 0.01327 mmol) , phenylboronic acid (10.52 mg, 0.08624 mmol) and sodium carbonate (21.09 mg, 0.1990 mmol) . The mixture heated to 80 °C for 2 hr. The mixture was filtered through celite and concentrated to an oil *in vacuo*. Purification by column chromatography eluting with 30% diethyl ether/petroleum ether gave the product (25mg, 50% yield). MS (ES^+) 651.3, 751.3, MS (ES^-) 749.2.

[00259] Step 2: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-(6-oxo-5-phenyl-1H-pyridin-3-yl)pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-methyl-carbamate (25 mg, 0.03330 mmol) was dissolved in DCM (3 mL) followed by the addition of TFA (189.8 mg, 128.2 µL, 1.665 mmol). The mixture was stirred for 1 hr at room temperature and then concentrated to an oil *in vacuo*. The residue was purified by reverse phase preparative HPLC [Waters Sunfire C18, 10mM, 100 Å column, gradient 10% - 95% B (solvent A: 0.05% TFA in water; solvent B: CH_3CN) over 16 minutes at 25 mL/min] to give sub-titled product (6 mg, 31% yield). H^1 NMR (400.0 MHz, DMSO-d_6) 2.62-2.68 (3H,s), 4.22 (2H,s), 6.9 (2H,s), 7.47 (1H,t), 7.45 (2H,t), 7.68 (2H,d), 7.74 (1H,s), 7.82 (2H,d), 8.08-8.12 (3H,m), 8.31 (1H,d), 8.77-8.83 (3H,m), 12.2 (1H,s). MS (ES^+) 451.2, MS (ES^-) 449.2.

Scheme E-3



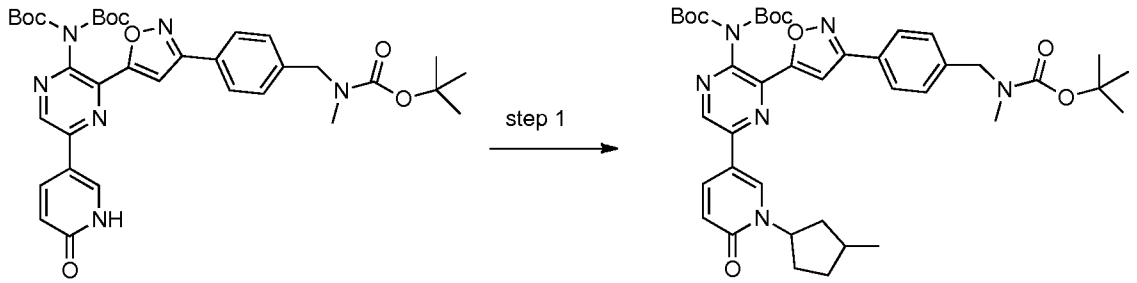
E-iii (R_4 = H) **E-iii ($R_4 \neq$ H)**

[00260] Scheme E-3 depicts another general method for the preparation of intermediates of Formula **E-iii**, where $R_4 \neq H$. Compounds of Formula **E-iii**, where $R_4 = H$, are reacted with an alcohol R_4OH under Mitsunobu conditions to give rise to compounds of Formula **E-**

iii, where $R_4 \neq H$. Suitable Mitsunobu conditions include, but are not limited to, Bu_3P / DIAD in an appropriate solvent such as $CHCl_3$ or THF. Alternatively, compounds of Formula **E-iii**, where $R_4 \neq H$, may be obtained from compounds of Formula **E-iii**, where $R_4 = H$, using alkylation conditions known to those skilled in the art such as, but not limited to, treatment of compounds of Formula **E-iii**, where $R_4 = H$, with R_4-LG and a base (eg triethylamine), where LG is an appropriate leaving group such as halogen, mesylate, or triflate.

Preparation 26 relate to Scheme E-3

Preparation 26: Synthesis of tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-[1-(3-methylcyclopentyl)-6-oxo-3-pyridyl]pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-methyl-carbamate



[00261] Step 1: Tert-butyl N-[[4-[5-[3-[bis(tert-butoxycarbonyl)amino]-6-(6-oxo-1H-pyridin-3-yl)pyrazin-2-yl]isoxazol-3-yl]phenyl]methyl]-N-methyl-carbamate (130 mg, 0.1927 mmol) and DIAD (77.93 mg, 75.88 µL, 0.3854 mmol) were dissolved in Chloroform (2 mL) and cooled to 0 °C in an ice bath and tributylphosphane (77.97 mg, 96.02 µL, 0.3854 mmol) was added slowly. The reaction was stirred at room temperature for 30 min then 3-methylcyclopentanol (28.96 mg, 31.82 µL, 0.2891 mmol) was added and the mixture stirred at room temperature for 16 h. The reaction mixture was purified directly by silica chromatography eluting with 0-100% EtOAc/Petroleum Ether to give the sub-titled product as a yellow solid (33.8 mg, 23% yield). H^1 NMR (400.0 MHz, DMSO-d_6) d 1.18 (d, 3H), 1.30 (s, 18H), 1.35 – 1.41 (m, 3H), 1.49 (2 x s, 9H), 2.02 – 2.14 (m, 4H), 2.82 (s, 3H), 4.46 (s, 2H), 5.24 – 5.28 (m, 1H), 6.60 (2 x s, 1H), 7.40 (d, 2H), 7.41 (2 x s, 1H), 8.00 (d, 2H), 8.40 (d, 1H), 8.70 (2 x d, 1H) and 9.33 (2 x s, 1H); MS (ES^+) 757.45.

Analytical Data Table

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-1	----	390.2	1.53
I-2	----	434.4	1.72
I-3	----	418.2	1.78
I-4	----	420.5	1.52
I-5	----	433.3	0.37
I-6	1H NMR (400 MHz, DMSO) d 9.31 (s, 2H), 8.90 (d, J = 2.3 Hz, 1H), 8.36 (s, 1H), 8.15 – 8.08 (m, 1H), 8.03 (dd, J = 7.9, 2.2 Hz, 1H), 7.61 (s, 2H), 7.30 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 9.3 Hz, 1H), 5.23 – 5.05 (m, 1H), 4.23 (s, 2H), 2.60 (s, 3H), 1.40 (d, J = 6.8 Hz, 7H).	448.5	1.25
I-7	----	415.4	1.39
I-8	----	476.2	2.13
I-9	----	446.2	2.03
I-10	1H NMR (400 MHz, DMSO) d 9.29 (s, 2H), 8.93 (s, 1H), 8.39 (d, J = 2.4 Hz, 1H), 8.25 (t, J = 7.8 Hz, 1H), 8.13 (dd, J = 9.5, 2.5 Hz, 1H), 7.76 (d, J = 11.5 Hz, 1H), 7.63 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.14 (dt, J = 13.8, 6.8 Hz, 1H), 4.27 (s, 2H), 2.60 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H).	436.5	1
I-11	1H NMR (400 MHz, DMSO) d 9.30 (d, J = 4.5 Hz, 2H), 8.80 (s, 1H), 8.34 (d, J = 2.3 Hz, 1H), 8.17 (dd, J = 9.5, 2.5 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.77 (s, 1H), 7.73 (d, J = 8.2 Hz, 2H), 6.54 (d, J = 9.5 Hz, 1H), 5.13 (m, 1H), 4.20 (t, J = 5.8 Hz, 2H), 2.57 (t, J = 5.3 Hz, 3H), 1.41 (d, J = 6.8 Hz, 6H).	417.5	1.1
I-12	----	432.2	1.14
I-13	----	488.24	1.07
I-14	----	458.1	0.82
I-15	H NMR (400.0 MHz, DMSO) d 1.80 (d, 3H), 2.89 (s, 3H), 3.72 (s, 2H), 5.86 (q, 1H), 6.65 (d, 1H), 6.97 (br s, 2H), 7.51 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.30 (dd, 1H), 8.49 (d, 1H) and 8.73 (s, 1H) ppm	428.1	1.14
I-16	1H NMR (400 MHz, CDCl3) d 8.49 (s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.02 (dd, J = 9.6, 2.5 Hz, 1H), 7.42 – 7.31 (m, 2H), 6.75 (d, J = 9.6 Hz, 1H), 6.16 (q, J = 7.1 Hz, 1H), 3.83 (s, 2H), 2.82 (s, 3H), 2.50 (s, 3H), 1.82 (d, J = 7.1 Hz, 3H).	443.5	1.05
I-17	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 – 9.34 (m, 2H), 8.87 (s, 1H), 8.36 (d, J = 2.2 Hz, 1H), 8.20 – 8.07 (m, 2H), 7.72 – 7.59 (m, 3H), 6.57 (d, J = 9.5 Hz, 1H), 5.27 – 5.15 (m, J = 5.2 Hz, 1H), 4.20 (t, J = 5.6 Hz, 2H), 3.84 – 3.72 (m, 1H), 3.57 (dd, J = 10.2, 5.1 Hz, 1H), 3.26 (s, 3H), 2.75 (s, 3H), 2.57 (t, J = 5.3 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H).	462	0.83

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-18	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (s, 2H), 8.92 (s, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.22 – 8.09 (m, 2H), 7.69 – 7.55 (m, 4H), 6.56 (d, J = 9.5 Hz, 1H), 4.42 – 4.09 (m, 12H), 2.75 (s, 3H), 2.59 (t, J = 5.3 Hz, 3H), 1.45 (d, J = 6.8 Hz, 4H), 1.18 (d, J = 6.2 Hz, 1H), 0.69 (s, 1H), 0.53 – 0.42 (m, 2H), 0.22 (d, J = 4.7 Hz, 1H).	458.1	0.87
I-19	1H NMR (400 MHz, DMSO) d 9.46 (s, 2H), 8.82 (s, 1H), 8.48 (d, J = 2.5 Hz, 1H), 8.13 (dd, J = 9.5, 2.5 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.31 (d, J = 8.1 Hz, 1H), 6.56 (d, J = 9.5 Hz, 1H), 4.23 (t, J = 5.7 Hz, 2H), 4.02 (d, J = 7.1 Hz, 2H), 4.00 (s, 3H), 2.58 (t, J = 5.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H).	434.5	0.96
I-20	1H NMR (400 MHz, DMSO) d 9.01 (s, 2H), 8.91 (s, 1H), 8.38 (d, J = 2.5 Hz, 1H), 8.14 (dd, J = 13.9, 5.1 Hz, 2H), 7.67 – 7.60 (m, 2H), 6.56 (d, J = 9.5 Hz, 1H), 5.22 – 5.07 (m, 1H), 4.23 (s, 2H), 3.41 – 3.33 (m, 1H), 2.77 (s, 3H), 1.40 (d, J = 6.8 Hz, 6H), 1.32 (d, J = 6.5 Hz, 6H).	460.5	1.16
I-21	1H NMR (400 MHz, DMSO) d 9.09 (s, 2H), 8.91 (s, 1H), 8.38 (s, 1H), 8.14 (dd, J = 13.7, 5.2 Hz, 2H), 7.74 (s, 1H), 7.70 (d, J = 8.5 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.19 – 5.08 (m, 1H), 4.19 (s, 2H), 2.77 (s, 3H), 1.41 (s, 11H), 1.39 (s, 4H).	474.5	1.15
I-22	H NMR (400.0 MHz, DMSO) d 1.05 (d, 1.2H), 1.12 (d, 1.8H), 1.21 – 1.30 (m, 1H), 1.54 – 1.72 (m, 2H), 1.85 – 1.97 (m, 1H), 2.01 – 2.14 (m, 3H), 2.29 (s, 3H), 3.71 (s, 2H), 5.14 – 5.30 (m, 1H), 6.52 (d, 1H), 6.89 (br s, 2H), 7.50 (d, 2H), 7.70 (d, 1H), 7.95 (d, 2H), 8.14 – 8.18 (m, 1H), 8.29 (d, 0.6H), 8.34 (d, 0.4H), 8.76 (s, 0.6H) and 8.78 (s, 0.4H) ppm	457.2	1.19
I-23	DMSO 1.42 (6H,d), 2.1-2.15 (1H,m), 2.23-2.33 (1H,m), 3.7-3.75 (1H,m), 3.8-3.85 (1H,m), 3.9-4.0 (3H,m), 4.3-4.35 (2H,m), 5.1-5.2 (1H,m), 6.55 (1H,d), 6.9 (2H,brs), 7.7 (2H,d), 7.75 (1H,s), 8.1 (2H,d), 8.15-8.2 (1H,m), 8.35-8.38 (1H,m), 8.72 (1H,s), 9.1 (2H,brs)	473.1	0.64
I-24	^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 – 10.23 (m, 1H), 9.38 – 9.28 (m, 2H), 8.84 (s, 1H), 8.57 (d, J = 2.4 Hz, 1H), 8.27 – 8.10 (m, 2H), 7.65 (d, J = 9.8 Hz, 4H), 6.65 (d, J = 9.5 Hz, 1H), 4.41 (t, J = 6.3 Hz, 2H), 4.20 (t, J = 5.8 Hz, 3H), 3.57 – 3.45 (m, 4H), 2.87 (d, J = 4.7 Hz, 7H), 2.75 (s, 3H), 2.58 (t, J = 5.3 Hz, 4H).	461.1	0.56
I-25	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (s, 2H), 8.90 (s, 1H), 8.30 (d, J = 2.3 Hz, 1H), 8.11 (dd, J = 9.5, 2.3 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.65 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 9.5 Hz, 1H), 4.96 (dd, J = 14.2, 7.1 Hz, 1H), 4.00 (s, 4H), 2.58 (t, J = 5.2 Hz, 3H), 1.91 – 1.73 (m, 2H), 1.39 (d, J = 6.8 Hz, 3H), 0.80 (t, J = 7.3 Hz, 3H).	462.1	0.81

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-26	1H NMR (400 MHz, DMSO) d 9.44 (s, 2H), 8.81 (s, 1H), 8.40 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 9.5, 2.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 4.23 (t, J = 5.9 Hz, 2H), 4.00 (s, 3H), 3.83 (d, J = 7.5 Hz, 2H), 2.59 (t, J = 5.3 Hz, 3H), 2.22 – 2.04 (m, 1H), 0.91 (d, J = 6.7 Hz, 6H).	462.5	1.06
I-27	1H NMR (400 MHz, DMSO) d 9.08 (s, 2H), 8.78 (s, 1H), 8.47 (d, J = 1.5 Hz, 1H), 8.24 (dd, J = 9.6, 2.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H), 7.60 (d, J = 9.0 Hz, 1H), 6.68 (d, J = 9.7 Hz, 1H), 4.99 (q, J = 9.3 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 2.75 (s, 3H), 2.60 (t, J = 5.3 Hz, 3H).	472.5	1.15
I-28	1H NMR (400 MHz, DMSO) d 9.10 (s, 2H), 8.77 (s, 1H), 8.44 (s, 1H), 8.22 (d, J = 9.6 Hz, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.69 (s, 2H), 7.55 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 6.68 (d, J = 9.6 Hz, 1H), 5.07 – 4.89 (m, 2H), 4.24 (t, J = 4.1 Hz, 2H), 3.99 (s, 3H), 2.61 (s, 3H).	488.5	1.08
I-29	1H NMR (400 MHz, DMSO) d 9.43 (bs, 2H), 8.80 (s, 1H), 8.34 (d, J = 2.4 Hz, 1H), 8.14 (dd, J = 9.5, 2.4 Hz, 1H), 8.08 (t, J = 7.8 Hz, 1H), 7.70 (d, J = 11.6 Hz, 1H), 7.61 – 7.53 (m, 2H), 6.53 (d, J = 9.5 Hz, 1H), 5.14 – 5.08 (m, 1H), 4.23 (t, J = 5.8 Hz, 2H), 2.58 (t, J = 5.4 Hz, 3H), 1.40 (d, J = 6.8 Hz, 6H).	435.5	1.08
I-30	1H NMR (400 MHz, DMSO) d 9.12 (s, 2H), 8.87 (s, 1H), 8.59 (d, J = 2.1 Hz, 1H), 8.26 – 8.07 (m, 2H), 7.63 (dd, J = 23.0, 10.5 Hz, 4H), 6.59 (d, J = 9.4 Hz, 1H), 5.82 (s, 1H), 4.21 (s, 2H), 2.76 (s, 3H), 2.59 (t, J = 5.0 Hz, 3H), 1.87 (d, J = 1.8 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H).	456.1	0.88
I-31	1H NMR (400 MHz, DMSO) d 9.12 (s, 2H), 8.87 (s, 1H), 8.59 (d, J = 2.1 Hz, 1H), 8.26 – 8.07 (m, 2H), 7.63 (dd, J = 23.0, 10.5 Hz, 4H), 6.59 (d, J = 9.4 Hz, 1H), 5.82 (s, 1H), 4.21 (s, 2H), 2.76 (s, 3H), 2.59 (t, J = 5.0 Hz, 3H), 1.87 (d, J = 1.8 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H).	450.1	0.77
I-32	1H NMR (400 MHz, DMSO) d 9.30 (s, 2H), 8.87 (s, 1H), 8.33 (s, 1H), 8.13 (s, 0H), 8.07 (dd, J = 36.3, 8.1 Hz, 2H), 7.60 (s, 3H), 7.30 (d, J = 7.6 Hz, 1H), 6.55 (d, J = 9.4 Hz, 1H), 5.17 (s, 2H), 4.24 (s, 2H), 3.99 (s, 3H), 2.60 (s, 3H), 2.33 – 2.14 (m, 0H), 1.93 (dd, J = 113.0, 39.6 Hz, 8H).	474.1	0.79
I-33	1H NMR (400 MHz, DMSO) d 9.11 (s, 2H), 8.94 (s, 1H), 8.45 (s, 1H), 8.15 (d, J = 8.3 Hz, 3H), 7.94 – 7.50 (m, 6H), 6.53 (d, J = 9.6 Hz, 1H), 5.30 – 4.99 (m, 2H), 4.21 (s, 6H), 2.77 (s, 4H), 2.59 (t, J = 5.3 Hz, 7H), 2.39 (t, J = 9.0 Hz, 5H), 1.83 (s, 3H).	444.1	0.76

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-34	1H NMR (400 MHz, DMSO) d 8.83 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.21 (dd, J = 9.6, 2.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.68 (s, 2H), 7.29 (s, 1H), 7.13 (d, J = 8.1 Hz, 1H), 6.67 (d, J = 9.6 Hz, 1H), 5.90 (q, J = 7.1 Hz, 1H), 3.96 (s, 3H), 3.76 (s, 2H), 2.32 (s, 3H), 1.79 (d, J = 7.1 Hz, 3H).	459.5	0.98
I-35	1H NMR (400 MHz, DMSO) d 9.08 (s, 2H), 8.90 (s, 1H), 8.36 (d, J = 2.4 Hz, 1H), 8.11 (dd, J = 9.5, 2.5 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.67 (s, 1H), 7.37 (d, J = 8.1 Hz, 1H), 6.57 (d, J = 9.4 Hz, 1H), 5.18 – 5.09 (m, 1H), 4.24 (d, J = 12.5 Hz, 2H), 4.01 (s, 3H), 1.54 – 0.96 (m, 15H).	490.5	1.04
I-36	---	464	0.63
I-37	1H NMR (400 MHz, DMSO) d 9.42 (s, 2H), 8.91 (s, 1H), 8.52 (s, 1H), 8.20 – 8.08 (m, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.31 (d, J = 6.9 Hz, 1H), 6.56 (d, J = 9.5 Hz, 1H), 4.23 (s, 3H), 3.99 (s, 3H), 2.59 (s, 3H), 1.45 (d, J = 6.7 Hz, 3H), 0.68 (m, 1H), 0.47 (m, 2H), 0.22 (m, 1H).	474.3	1.1
I-38	1H NMR (400 MHz, DMSO) d 9.36 (s, 2H), 8.86 (d, J = 2.1 Hz, 1H), 8.43 (d, J = 2.3 Hz, 0.6H), 8.37 (d, J = 2.4 Hz, 0.4H), 8.26 – 8.10 (m, 2H), 7.67 (m, 3H), 7.37 (s, 1H), 7.27 (d, J = 16.8 Hz, 1H), 7.12 (s, 1H), 6.58 (t, J = 9.9 Hz, 1H), 5.50 (m, 0.4H), 5.29 (m, 0.6H), 4.20 (t, J = 5.7 Hz, 2H), 2.75 (s, 3H), 2.57 (t, J = 5.3 Hz, 3H), 1.74 – 1.56 (m, 3H).	462.5	0.98
I-39	---	443.7	1.09
I-40	---	485.4	1.07
I-41	1H NMR (400 MHz, DMSO) d 9.50 (s, 2H), 8.90 (s, 1H), 8.32 (s, 1H), 8.21 (dd, J = 9.6, 2.4 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.66 (s, 1H), 7.32 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 9.6 Hz, 1H), 6.21 – 5.67 (m, 1H), 4.23 (t, J = 5.8 Hz, 2H), 3.99 (s, 3H), 2.58 (t, J = 5.3 Hz, 3H), 1.73 (d, J = 7.3 Hz, 3H).	502.1	0.74
I-42	1H NMR (400 MHz, DMSO) d 8.97 – 8.92 (m, 1H), 8.47 (dd, J = 4.8, 4.4 Hz, 3H), 8.42 – 8.37 (m, 1H), 8.35 – 8.28 (m, 1H), 8.22 – 8.11 (m, 2H), 7.86 – 7.81 (m, 1H), 7.79 – 7.73 (m, 1H), 6.61 – 6.54 (m, 1H), 5.20 – 5.10 (m, 1H), 4.63 (td, J = 11.0, 5.4 Hz, 1H), 1.58 (d, J = 6.7 Hz, 3H), 1.41 (d, J = 6.8 Hz, 6H).	418.5	1.26
I-43	1H NMR (400 MHz, DMSO) d 9.42 (s, 2H), 8.78 (s, 1H), 8.31 (d, J = 2.2 Hz, 1H), 8.17 (dd, J = 9.6, 2.1 Hz, 1H), 8.08 (d, J = 8.0 Hz, 3H), 7.81 – 7.68 (m, 5H), 6.53 (d, J = 9.4 Hz, 1H), 4.20 (t, J = 5.7 Hz, 2H), 3.57 (s, 2H), 2.56 (t, J = 5.2 Hz, 4H), 2.22 – 1.94 (m, 2H), 1.94 – 1.54 (m, 6H).	443.7	1.11

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-44	1H NMR (400 MHz, DMSO) d 9.18 (s, 2H), 8.81 (s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.18 (dd, J = 9.5, 2.5 Hz, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.87 – 7.76 (m, 3H), 6.54 (d, J = 9.5 Hz, 1H), 5.13 (dt, J = 13.4, 6.7 Hz, 1H), 4.19 (d, J = 6.2 Hz, 2H), 1.40 (d, J = 4.6 Hz, 16H).	459.7	1.36
I-45	1H NMR (400 MHz, DMSO) d 8.94 (s, 1H), 8.62 (s, 3H), 8.39 (d, J = 2.3 Hz, 1H), 8.19 (m, 3H), 7.81 (d, J = 8.2 Hz, 2H), 7.65 (s, 1H), 6.58 (d, J = 9.5 Hz, 1H), 5.14 (dt, J = 13.5, 6.8 Hz, 1H), 4.64 – 4.48 (m, 1H), 1.57 (d, J = 6.7 Hz, 3H), 1.41 (d, J = 6.8 Hz, 6H).	418.5	0.92
I-46	1H NMR (400 MHz, DMSO) d 9.08 (s, 2H), 8.95 (s, 1H), 8.40 (s, 2H), 8.23 – 8.14 (m, 2H), 7.90 (d, J = 7.5 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.67 (s, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.21 – 5.07 (m, 1H), 4.30 (s, 2H), 1.42 (t, J = 3.1 Hz, 15H).	460.5	0.98
I-47	1H NMR (400 MHz, DMSO) d 9.26 (s, 2H), 8.95 (s, 1H), 8.44 – 8.29 (m, 2H), 8.24 – 8.13 (m, 2H), 7.84 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.66 (s, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.21 – 5.06 (m, 1H), 4.29 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 5.2 Hz, 3H), 1.42 (d, J = 6.8 Hz, 6H).	418.5	0.92
I-48	1H NMR (400 MHz, DMSO) d 9.27 (s, 2H), 8.81 (s, 1H), 8.36 (s, 2H), 8.17 (dd, J = 9.5, 2.4 Hz, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.64 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 9.5 Hz, 1H), 5.18 – 5.08 (m, 1H), 4.22 (s, 2H), 1.46 – 1.37 (m, 15H).	459.7	1.05
I-49	1H NMR (400 MHz, DMSO) d 9.37 (s, 2H), 8.81 (s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.25 (s, 1H), 8.16 (dd, J = 9.5, 2.5 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.75 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 6.54 (d, J = 9.5 Hz, 1H), 5.13 (dt, J = 13.7, 6.9 Hz, 1H), 4.23 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.3 Hz, 3H), 1.42 (t, J = 9.3 Hz, 6H).	417.5	1
I-50	1H NMR (400 MHz, MeOD) d 8.58 (d, J = 7.6 Hz, 8H), 8.42 – 8.26 (m, 12H), 8.12 (s, 1H), 8.09 (d, J = 8.2 Hz, 14H), 7.75 – 7.60 (m, 20H), 6.74 (d, J = 9.3 Hz, 7H), 5.35 – 5.21 (m, 6H), 4.28 (s, 17H), 2.22 (s, 12H), 1.90 (d, J = 75.9 Hz, 38H), 1.50 (s, 65H).	485.2	0.86
I-51	1H NMR (400 MHz, DMSO) d 8.78 (s, 1H), 8.31 (d, J = 2.5 Hz, 1H), 8.16 (dd, J = 9.5, 2.5 Hz, 1H), 8.10 (d, J = 8.3 Hz, 2H), 7.79 (s, 1H), 7.77 (s, 2H), 6.89 (s, 2H), 6.53 (d, J = 9.5 Hz, 1H), 5.18 – 5.09 (m, 1H), 4.43 (d, J = 5.8 Hz, 2H), 3.14 – 3.05 (m, 5H), 2.10 – 1.99 (m, 4H), 1.92 – 1.86 (m, 5H), 1.72 – 1.64 (m, 2H).	483.5	1.12

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-52	1H NMR (400 MHz, DMSO) d 8.86 (s, 2H), 8.78 (s, 1H), 8.31 (d, J = 2.4 Hz, 1H), 8.17 (dd, J = 9.5, 2.5 Hz, 1H), 8.08 (d, J = 8.3 Hz, 2H), 7.78 – 7.72 (m, 3H), 6.53 (d, J = 9.5 Hz, 1H), 5.18 – 5.06 (m, 1H), 4.19 (s, 2H), 3.56 (s, 2H), 2.09 – 1.98 (m, 2H), 1.96 – 1.79 (m, 4H), 1.77 – 1.60 (m, 2H), 1.33 (s, 6H).	501.5	1.31
I-53	1H NMR (400 MHz, DMSO) d 8.79 (s, 1H), 8.55 (s, 3H), 8.32 (d, J = 2.3 Hz, 1H), 8.22 (s, 1H), 8.16 (dd, J = 9.5, 2.5 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.76 (s, 1H), 7.66 (dt, J = 15.2, 7.7 Hz, 2H), 6.54 (d, J = 9.5 Hz, 1H), 5.18 – 5.06 (m, 1H), 4.57 – 4.47 (m, 1H), 2.08 – 1.97 (m, 2H), 1.94 – 1.83 (m, 4H), 1.73 – 1.64 (m, 2H), 1.58 (d, J = 6.7 Hz, 3H).	443.7	1.09
I-54	1H NMR (400 MHz, DMSO) d 9.39 (s, 2H), 8.80 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.19 – 8.04 (m, 2H), 7.69 (dd, J = 11.7, 1.3 Hz, 1H), 7.61 – 7.53 (m, 2H), 6.53 (d, J = 9.5 Hz, 1H), 4.43 – 4.17 (m, 3H), 2.58 (t, J = 5.4 Hz, 3H), 1.45 (d, J = 6.8 Hz, 3H), 0.67 (dd, J = 8.1, 5.8 Hz, 1H), 0.63 – 0.29 (m, 2H), 0.21 (dd, J = 9.4, 4.2 Hz, 1H).	461.1	0.78
I-55	1H NMR (400 MHz, DMSO) d 8.81 (s, 1H), 8.52 (d, J = 3.0 Hz, 3H), 8.35 (d, J = 2.5 Hz, 1H), 8.22 (s, 1H), 8.16 (dd, J = 9.5, 2.6 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.76 (s, 1H), 7.66 (dt, J = 15.1, 7.7 Hz, 2H), 6.54 (d, J = 9.5 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.54 (dt, J = 9.3, 4.7 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.41 (d, J = 6.8 Hz, 6H).	417.2	0.94
I-56	1H NMR (400 MHz, DMSO) d 9.36 (s, 4H), 8.77 (s, 2H), 8.30 (s, 2H), 8.19 – 7.99 (m, 3H), 7.69 (d, J = 11.8 Hz, 2H), 7.56 (d, J = 2.2 Hz, 3H), 6.52 (d, J = 9.5 Hz, 2H), 5.40 – 4.86 (m, 3H), 4.22 (d, J = 5.7 Hz, 4H), 2.58 (t, J = 5.2 Hz, 5H), 2.24 – 1.86 (m, 9H), 1.68 (s, 6H).	461.2	0.82
I-57	1H NMR (400 MHz, DMSO) d 8.82 (s, 1H), 8.57 – 8.47 (m, 4H), 8.22 (s, 1H), 8.17 (dd, J = 9.5, 2.6 Hz, 1H), 8.02 (t, J = 5.1 Hz, 1H), 7.77 (s, 1H), 7.72 – 7.60 (m, 2H), 6.54 (d, J = 9.5 Hz, 1H), 4.59 – 4.49 (m, 1H), 4.24 (tt, J = 13.6, 6.8 Hz, 1H), 1.58 (d, J = 6.8 Hz, 3H), 1.56 – 1.51 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H), 0.68 (dd, J = 14.3, 7.8 Hz, 1H), 0.52 – 0.41 (m, 2H), 0.26 – 0.15 (m, 1H).	443.1	1.04
I-58	DMSO 1.42 (6H,d), 2.1-2.15 (1H,m), 2.23-2.33 (1H,m), 3.7-3.75 (1H,m), 3.8-3.85 (1H,m), 3.9-4.0 (3H,m), 4.3-4.35 (2H,m), 5.1-5.2 (1H,m), 6.55 (1H,d), 6.9 (2H,brs), 7.7 (2H,d), 7.75 (1H,s), 8.1 (2H,d), 8.15-8.2 (1H,m), 8.35-8.38 (1H,m), 8.72 (1H,s), 9.1 (2H,brs)	473.1	0.64

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-59	H NMR (400.0 MHz, DMSO) d 1.41 (d, 6H), 4.67 – 4.77 (m, 1H), 4.82 – 4.89 (m, 2H), 5.13 (sept, 1H), 6.54 (d, 1H), 6.91 (s, 2H), 7.70 (d, 2H), 7.78 (s, 1H), 8.13 (d, 2H), 8.17 (dd, 1H), 8.35 (d, 1H), 8.73 (s, 3H) and 8.82 (s, 1H) ppm	435.1	0.65
I-60	DMSO 1.36 (6H,d), 1.42 (6H,d), 3.37-3.42 (1H,m), 4.25-4.3 (2H,m), 5.1-5.2 (1H,m), 6.55 (1H,d), 6.9 (2H,brs), 7.7 (2H,d), 7.8 (1H,s), 8.12 (2H,d), 8.15-8.2 (1H,m), 8.35-8.38 (1H,m), 8.75 (2H,brs), 8.82 (1H,s)	445.2	0.61
I-61	DMSO 0.6-0.7 (4H,m), 1.3 (6H,d), 2.6-2.7 (1H,m), 4.1 (2H,s), 4.95-5.0 (1H,m), 6.4 (1H,d), 6.75 (2H,brs), 7.55 (2H,d), 7.65 (1H,s), 7.95 (2H,d), 8.05-8.1 (1H,m), 8.18-8.22 (1H,m), 8.68 (1H,s), 8.9 (2H,brs)	443.2	0.7
I-62	H NMR (400.0 MHz, DMSO) d 0.44 – 0.53 (m, 4H), 1.28 – 1.36 (m, 1H), 2.29 (s, 3H), 3.72 (s, 2H), 3.86 (d, 2H), 6.54 (d, 1H), 6.89 (br s, 2H), 7.52 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.21 (dd, 1H), 8.48 (d, 1H) and 8.70 (s, 1H) ppm [1]	428.196	1.15
I-63	DMSO 1.25 (3H,t), 1.42 (6H,d), 3.0-3.1 (2H,m), 4.2-4.25 (2H,m), 5.1-5.2 (1H,m), 6.55 (1H,d), 6.9 (2H,brs), 7.7 (2H,d), 7.8 (1H,s), 8.12 (2H,d), 8.15-8.2 (1H,m), 8.35-8.38 (1H,m), 8.8-8.85 (3H,m), [1]	430.212	0.58
I-64	(DMSO) 1.24 (6H, m), 2.47 (3H, t), 3.79 (3H, s), 4.06 (2H, m), 4.97 (1H, m), 6.37 (1H, d), 6.72 (2H, br s), 7.04 (1H, m), 7.24 (1H, d), 7.34 (1H, s), 7.73 (1H, d), 7.95 (1H, dd), 8.18 (1H, d), 8.62 (1H, s) and 8.70 (2H, br s) ppm [1]	446.207	0.57
I-65	DMSO 1.42 (6H,m), 4.37 (2H,s), 5.1-5.2 (1H,m), 6.5-6.55 (2H,m), 6.6 (2H,d), 6.85-6.9 (2H, brs), 7.05 (2H,t), 7.55 (2H,d), 7.7 (1H,s), 7.97 (2H,d), 8.08-8.2 (2H,m), 8.37-8.4 (1H,m), 8.8 (1H,s), [1]	478.212	0.92
I-66	H NMR (400.0 MHz, DMSO) d 1.68 – 1.72 (m, 2H), 2.05 – 2.16 (m, 2H), 2.25 (s, 3H), 3.48 (t, 2H), 3.68 (s, 2H), 4.00 (dd, 2H), 4.93 – 5.00 (m, 1H), 6.54 (d, 1H), 6.86 (s, 2H), 7.47 (d, 2H), 7.69 (s, 1H), 7.92 (d, 2H), 8.18 (dd, 1H), 8.33 (d, 1H) and 8.80 (s, 1H) ppm [1]	458.207	1.08
I-67	DMSO 1.42 (6H,d), 2.63 (3H,s), 4.18 (2H,s), 5.17-5.21 (1H,m), 5.25-5.3 (1H,m), 6.0-6.1 (1H,m), 6.3-6.38 (2H,m), 7.48 (1H,s), 7.55 (2H,d), 8.0 (2H,d), 8.17-8.22 (2H,m), 8.53 (1H,s) [1]	442.212	0.66
I-68	H NMR (400.0 MHz, DMSO) d 0.09 – 0.12 (m, 2H), 0.50 – 0.52 (m, 2H), 0.78 (s, 3H), 2.05 (s, 3H), 3.48 (s, 2H), 3.72 (s, 2H), 6.31 (d, 1H), 6.66 (br s, 2H), 7.27 (d, 2H), 7.48 (s, 1H), 7.71 (d, 2H), 7.96 (dd, 1H), 8.18 (d, 1H) and 8.45 (s, 1H) ppm [1]	442.212	1.18

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-69	H NMR (400.0 MHz, DMSO) d 2.29 (s, 3H), 3.72 (s, 2H), 5.04 (s, 2H), 6.55 – 6.57 (m, 2H), 6.91 (br s, 2H), 7.51 (d, 2H), 7.63 (t, 1H), 7.72 (s, 1H), 7.75 (s, 1H), 7.95 (d, 2H), 8.21 (dd, 1H), 8.55 (d, 1H) and 8.68 (s, 1H) ppm [1]	454.175	1.15
I-70	H NMR (400.0 MHz, DMSO) d 1.85 – 1.92 (m, 2H), 2.10 (t, 2H), 2.29 (s, 3H), 3.42 (t, 2H), 3.55 (t, 2H), 3.71 (s, 2H), 4.14 (t, 2H), 6.50 (d, 1H), 6.89 (br s, 2H), 7.51 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.17 (dd, 1H), 8.35 (d, 1H) and 8.67 (s, 1H) ppm [1]	485.218	1.11
I-71	---	494.107	0.63
I-72	H NMR (400.0 MHz, DMSO) d -0.01 – 0.03 (m, 1H), 0.35 – 0.43 (m, 1H), 0.59 – 0.66 (m, 2H), 0.75 (d, 3H), 2.04 (s, 3H), 3.47 (s, 2H), 3.54 (dd, 1H), 3.68 (dd, 1H), 6.29 (d, 1H), 6.63 (br s, 2H), 7.26 (d, 2H), 7.47 (s, 1H), 7.70 (d, 2H), 7.96 (dd, 1H), 8.22 (d, 1H) and 8.44 (s, 1H) ppm [1]	442.212	1.17
I-73	H NMR (400.0 MHz, DMSO) d 2.29 (s, 3H), 3.07 (t, 2H), 3.72 (s, 2H), 4.28 (t, 2H), 6.59 (d, 1H), 6.93 (br s, 2H), 7.51 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.25 (dd, 1H), 8.52 (d, 1H) and 8.67 (s, 1H) ppm [1]	427.176	1.08
I-74	H NMR (400.0 MHz, DMSO) d 0.94 (t, 3H), 1.48 – 1.54 (m, 2H), 2.29 (s, 3H), 3.21 (s, 3H), 3.48 – 3.53 (m, 1H), 3.71 (s, 2H), 3.90 (dd, 1H), 4.19 (dd, 1H), 6.54 (d, 1H), 6.89 (br s, 2H), 7.51 (d, 2H), 7.72 (s, 1H), 7.95 (d, 2H), 8.21 (dd, 1H), 8.35 (d, 1H) and 8.67 (s, 1H) ppm [1]	460.222	1.15
I-75	DMSO 1.2 (3H,t), 1.4 (6H,d), 2.6-2.7 (2H,m), 4.2-4.3 (2H,m), 5.1-5.2 (1H,m), 6.85-6.9 (2H,brs), 7.65 (2H,d), 7.7 (1H,s), 7.97-8.0 (1H,m), 8.12 (2H,d), 8.1-8.12 (1H,m), 8.87-8.92 (2H,m), [1]	444.227	0.65
I-76	H NMR (400.0 MHz, DMSO) d 2.34 (s, 3H), 3.19 (s, 2H), 6.47 (d, 1H), 6.85 (br s, 2H), 7.53 (d, 2H), 7.73 (s, 1H), 7.99 (d, 2H), 8.11 (d, 1H), 8.23 (dd, 1H), 8.69 (s, 1H) and 11.91 (br s, 1H) ppm [1]	374.149	1.09
I-77	H NMR (400.0 MHz, DMSO) d 0.87 (t, 3H), 0.94 (d, 3H), 1.17 – 1.24 (m, 1H), 1.35 – 1.45 (m, 2H), 1.48 – 1.57 (m, 1H), 1.68 – 1.75 (m, 1H), 2.29 (s, 3H), 3.71 (s, 2H), 4.01 (t, 2H), 6.52 (d, 1H), 6.88 (br s, 2H), 7.50 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.19 (dd, 1H), 8.46 (d, 1H) and 8.70 (s, 1H) ppm [1]	458.243	1.28
I-78	MEOH 2.8 (3H,s), 4.35 (2H,s), 7.6 (1H,s), 7.71 (2H,d), 8.1 (2H,d), 8.13-8.15 (1H,m), 8.45 (1H,s), 8.73 (1H,d) [1]	452.06	0.52

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-79	H NMR (400.0 MHz, DMSO) d 0.10 – 0.20 (m, 1H), 0.35 – 0.50 (m, 2H), 0.60 – 0.70 (m, 1H), 1.26 (d, J = 6.8 Hz, 1H), 1.40 – 1.50 (m, 4H), 2.29 (s, 2H), 3.13 (d, J = 9.4 Hz, 1H), 3.65 (s, 2H), 4.15 – 4.25 (m, 1H), 6.49 – 6.50 (d, 1H), 6.90 (s, 2H), 7.49 – 7.50 (d, 2H), 7.75 (d, J = 8.2 Hz, 1H), 7.90 – 8.00 (m, 2H), 8.15 (d, 1H) and 8.75 (s, 1H) ppm [1], H NMR (400.0 MHz, DMSO) d 0.00 (m, 1H), 0.05 – 0.30 (m, 2H), 0.40 – 0.50 (m, 1H), 1.00 – 1.10 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 1.30 – 1.35 (m, 1H), 2.40 (d, J = 5.3 Hz, 3H), 4.02 (s, 4H), 6.33 (d, J = 9.5 Hz, 1H), 6.70 (br s, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.56 (s, 1H), 7.89 (d, J = 8.2 Hz, 2H), 7.95 (d, 1H), 8.30 (s, 1H) and 8.61 (s, 2H) ppm [2]	442.212	0.61 , 0.61 [2]
I-80	H NMR (400.0 MHz, DMSO) d 0.43 – 0.46 (m, 2H), 0.71 – 0.73 (m, 2H), 2.29 (s, 3H), 3.22 (d, 2H), 3.71 (s, 2H), 4.06 (s, 2H), 4.81 (t, 1H), 6.57 (d, 1H), 6.91 (br s, 2H), 7.51 (d, 2H), 7.71 (s, 1H), 7.94 (d, 2H), 8.21 (dd, 1H), 8.41 (d, 1H) and 8.66 (s, 1H) ppm [1]	458.207	1.12
I-81	dmso d6 1.30 (3H, t), 2.29 (3H, s), 3.72 (2H, s), 4.03 (2H, q), 6.52 (1H, d), 6.89 (2H, s), 7.50 (2H, d), 7.75 (1H, s), 7.96 (2H, d), 8.20 (1H, dd), 8.48 (1H, d), 8.70 (1H, s) [1]	402.18	2.51
I-82	dmso d6 0.80 (3H, t), 1.39 (3H, d), 2.24 (3H, s), 3.73 (2H, s), 4.90-4.98 (1H, m), 6.54 (1H, d), 6.90 (2H, s), 7.50 (1H, d), 7.72 (1H, s), 7.96 (2H, d), 8.18 (1H, dd), 8.28 (1H, d), 8.79 (1H, s) [1]	430.212	2.66
I-83	dmso d6 0.76 (6H, t), 1.75-1-85 (4H, m), 2.30 (3H, s), 3.73 (2H, s), 4.75-4.86 (1H, m), 6.55 (1H, d), 6.89 (2H, s), 7.50 (2H, d), 7.72 (1H, s), 7.96 (2H, d), 8.17-8.21 (2H, m), 8.78 (1H, s) [1]	444.227	2.72
I-84	H NMR (400.0 MHz, DMSO) d 2.28 (s, 3H), 3.71 (s, 2H), 5.53 (s, 2H), 6.61 (d, 1H), 6.93 (br s, 2H), 7.51 (d, 2H), 7.72 (d, 1H), 7.74 (s, 1H), 7.78 (d, 1H), 7.94 (d, 2H), 8.28 (dd, 1H), 8.67 (d, 1H) and 8.68 (s, 1H) ppm [1]	471.148	0.98
I-85	H NMR (400.0 MHz, DMSO) d 2.28 (s, 3H), 3.71 (s, 2H), 3.76 (s, 3H), 5.24 (s, 2H), 6.53 (d, 1H), 6.80 (d, 1H), 6.91 (br s, 2H), 7.12 (d, 1H), 7.51 (d, 2H), 7.70 (s, 1H), 7.94 (d, 2H), 8.22 (dd, 1H), 8.55 (d, 1H) and 8.66 (s, 1H) ppm [1]	468.202	1.08
I-86	H NMR (400.0 MHz, DMSO) d 1.58 – 1.63 (m, 1H), 1.80 – 2.01 (m, 3H), 2.29 (s, 3H), 3.65 (q, 1H), 3.71 (s, 2H), 3.82 (q, 1H), 3.91 (q, 1H), 4.16 – 4.20 (m, 2H), 6.54 (d, 1H), 6.89 (br s, 2H), 7.50 (d, 2H), 7.72 (s, 1H), 7.95 (d, 2H), 8.20 (dd, 1H), 8.38 (d, 1H) and 8.66 (s, 1H) ppm [1]	458.207	1.13

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-87	H NMR (400.0 MHz, DMSO) d 1.23 – 1.31 (m, 1H), 1.46 (br s, 3H), 1.62 (br d, 1H), 1.77 – 1.84 (m, 1H), 2.29 (s, 3H), 3.23 – 3.34 (m, 1H), 3.63 – 3.71 (m, 1H), 3.71 (s, 2H), 3.82 – 3.88 (m, 2H), 4.16 (dd, 1H), 6.53 (d, 1H), 6.89 (br s, 2H), 7.50 (d, 2H), 7.73 (s, 1H), 7.95 (d, 2H), 8.20 (dd, 1H), 8.33 (d, 1H) and 8.66 (s, 1H) ppm [1]	472.222	1.18
I-88	MeOH 2.6-2.7 (3H,m), 4.1-4.2 (2H,m), 4.6 (2H,s), 7.6-7.65 (3H,m), 8.0-8.1 (3H,m), 8.4-8.42 (1H,m), 8.58 (1H,s) [1]	404.16	0.43
I-89	DMSO 1.2 (3H,t), 2.6-2.65 (3H,m), 4.2-4.25 (2H,m), 6.85 (1H,s), 7.68 (2H,d), 7.75 (1H,s), 7.95-8.0 (1H,m), 8.05-8.08 (1H,m), 8.1 (2H,d), 8.7 (1H,s), 8.8 (2H,brs) [1]	402.18	0.54
I-90	DMSO 2.6-2.65 (3H,m), 4.2-4.25 (2H,m), 6.9 (1H,s), 7.68 (2H,d), 7.78 (1H,s), 8.08 (2H,d), 8.1-8.12 (1H,m), 8.5-8.52 (1H,m), 8.7 (1H,s), 8.8 (2H,brs) [1]	408.11	0.5
I-91	H NMR (400.0 MHz, DMSO) d 8.85 (s, 2H), 8.75 (s, 1H), 8.35 (d, J = 2.5 Hz, 1H), 8.22 (dd, J = 2.6, 9.5 Hz, 2H), 8.10 (d, J = 8.3 Hz, 2H), 7.77 (s, 1H), 7.67 (d, J = 8.2 Hz, 2H), 6.92 (s, 1H), 6.55 (d, J = 9.5 Hz, 1H), 5.47 (q, J = 7.2 Hz, 1H), 4.24 – 4.21 (m, 2H), 2.63 – 2.61 (m, 6H) and 1.63 (d, J = 7.4 Hz, 3H) ppm [1]	459.202	2.11
I-92	dmso d6 0.25-0.28 (2H, m), 0.33-0.39 (2H, m), 1.61-1.71 (2H, m), 1.81-1.91 (4H, m), 1.96-2.06 (3H, m), 3.80 (2H, s), 5.58-5.68 (1H, m), 6.53 (1H, d), 6.89 (2H, s), 7.51 (2H, d), 7.71 (1H, s), 7.95 (2H, d), 8.17 (1H, dd), 8.31 (1H, s), 8.77 (1H, s) [1]	468.227	2.52
I-93	dmso d6 0.23-0.27 (2H, m), 0.32-0.38 (2H, m), 0.76 (6H, t), 1.80-1.85 (4H, m), 2.05-2.07 (1H, m), 3.80 (2H, s), 4.75-4.86 (1H, m), 6.55 (1H, d), 6.89 (2H, s), 7.51 (2H, d), 7.72 (1H, s), 7.95 (2H, d), 8.17-8.21 (2H, m), 8.78 (1H, s) [1]	470.243	2.53
I-94	(DMSO) 0.76 (6H, t), 1.57 (3H, d), 1.83 (4H, m), 4.56 (1H, m), 4.83 (1H, m), 6.56 (1H, m), 6.93 (2H, br s), 7.66 (2H, m), 7.73 (1H, s), 8.03 (1H, m), 8.15-8.18 (2H, m), 8.23 (1H, m), 8.32 (3H, br s) and 8.82 (1H, s) ppm [1], (DMSO) d 0.76 (6H, t), 1.56 (3H, d), 1.84 (4H, m), 4.54 (1H, m), 4.82 (1H, m), 6.56 (1H, d), 6.93 (2H, br s), 7.65 (2H, m), 7.27 (1H, s), 8.04 (1H, m), 8.15-8.23 (3H, m), 8.32 (3H, br s) and 8.82 (1H, s) ppm [2]	444.227	0.65 , 0.65 [2]
I-95	H NMR (400.0 MHz, DMSO) d 2.62 (s, 3H), 3.27 (s, 3H), 3.65 (t, 2H), 4.18 (t, 2H), 4.22 (s, 2H), 6.54 (d, 1H), 6.92 (br s, 2H), 7.67 (d, 2H), 7.78 (s, 1H), 8.11 (d, 2H), 8.21 (dd, 1H), 8.40 (d, 1H), 8.69 (s, 1H) and 8.77 (br s, 2H) ppm [1]	432.191	0.95

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-96	H NMR (400.0 MHz, DMSO) d -0.01 (d, J = 4.6 Hz, 2H), 0.36 (d, J = 6.8 Hz, 2H), 0.72 – 0.74 (m, 1H), 1.56 (d, J = 7.1 Hz, 2H), 2.24 (s, 3H), 3.66 (s, 2H), 4.02 (s, 2H), 6.47 (d, J = 9.5 Hz, 1H), 6.83 (s, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.90 (d, J = 8.0 Hz, 2H), 8.42 (d, J = 2.3 Hz, 1H), 8.64 (s, 1H) and 8.71 (s, 1H) ppm [1]	442.212	0.61
I-97	H NMR (400.0 MHz, DMSO) d 0.85 – 0.92 (m, 6H), 1.12 – 1.24 (m, 1H), 1.33 – 1.45 (m, 2H), 1.45 – 1.99 (m, 1H), 2.29 (s, 3H), 3.72 (s, 2H), 3.76 – 3.81 (m, 1H), 3.92 – 3.96 (m, 1H), 6.53 (d, J = 9.5 Hz, 1H), 6.89 (s, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.73 (s, 1H), 7.95 (d, J = 8.1 Hz, 2H), 8.21 (d, 1H), 8.40 (d, 1H) and 8.69 (s, 1H) ppm [1]	444.227	0.65
I-98	H NMR (400.0 MHz, DMSO) d 2.25 (s, 2H), 2.63 (s, 1H), 3.67 (s, 2H), 4.58 (s, 2H), 6.48 (d, J = 9.5 Hz, 1H), 6.85 (s, 2H), 7.23 (s, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.70 (s, 2H), 7.91 (d, J = 8.2 Hz, 2H), 8.37 (s, 1H), 8.40 (s, 1H) and 8.61 (s, 1H) ppm [1]	431.171	0.43
I-99	dmso d6 0.32-0.37 (2H, m), 1.81 (3H, d), 2.01-2.08 (1H, m), 3.80 (2H, s), 5.80-5.88 (1H, m), 6.65 (1H, d), 6.97 (2H, s), 7.51 (2H, d), 7.73 (1H, s) 7.94 (2H, d), 8.27 (1H, d), 8.49 (1H, s), 8.74 (1H, s) [1]	453.191	0.57
I-100	MeOH 1.2 (6H,d), 2.6-2.65 (3H,m), 4.2-4.25 (2H,m), 7.45 (1H,s), 7.55 (2H,d), 7.85 (1H,d), 7.92-8.0 (3H,m), 8.45 (1H,s), [1]	416.196	0.57
I-101		501.249	0.59
I-102		499.233	0.55
I-103	(DMSO) 1.57 (3H, d), 4.56 (1H, m), 6.48 (1H, d), 6.89 (2H, br s), 7.65 (2H, m), 7.72 (1H, s), 8.03 (1H, m), 8.12 (1H, br s), 8.15 (1H, s), 8.20 (1H, dd), 8.32 (3H, br s), 8.72 (1H, s) and 12.03 (1H, br s) ppm [1]	374.149	0.48
I-104	(DMSO) 1.41 (3H, d), 1.50 (3H, d), 4.41 (1H, m), 5.33 (1H, m), 6.40 (1H, d), 6.78 (2H, br s), 7.16 (1H, s), 7.50 (1H, m), 7,57 (2H, m), 7.88 (1H, m), 7,90 (1H, m), 8.04 (1H, dd), 8.06 (4H, m) and 8.62 (1H, s) ppm [1]	445.186	0.49
I-105	(DMSO) d 0.35 (2H, m), 0.75 (2H, m), 1.03 (3H, s), 1.33 (3H, d), 3.96 (2H, s), 4.14 (1H, m), 6.55 (1H, d), 6.90 (2H, br s), 7.48-7.56 (2H, m), 7.71 (1H, s), 7.84 (1H, d), 8.02 (1H, m), 8.18-8.21 (1H, dd), 8.42 (1H, m) and 8.69 (1H, s) ppm [1]	442.212	0.64
I-106	(DMSO) d 0.02 (1H, m), 0.39 (1H, m), 0.62 (1H, m), 0.75 (3H, d), 0.81 (1H, m), 1.33 (3H, m), 3.52 (masked signal), 3.69 (1H, m), 4.31 (1H, m), 6.30 (1H, m), 6.68 (2H, br s), 7.41 (2H, m), 7.48 (1H, m), 7.77-7.80 (1H, m), 7.91 (1H, s), 7.94 (1H, dd), 8.08 (3H, br s), 8.24 (1H, m) and 8.47 (1H, s) ppm [1]	442.212	0.65

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-107	DMSO 1.6-1.7 (4H,m), 1.75-1.8 (2H,m), 1.95-2.0 (2H,m), 2.6-2.65 (3H,m), 3.05-3.15 (1H,m), 4.2-4.25 (2H,m), 6.85 (2H,s), 7.68 (2H,d), 7.73 (1H,s), 7.95-8.02 (2H,m), 8.12 (2H,d), 8.7 (1H,s), 8.85 (2H,brs) [1]	442.212	0.63
I-108	H NMR (400.0 MHz, DMSO) d 2.62 (t, 3H), 3.56 (s, 3H), 4.23 (t, 2H), 6.54 (d, 1H), 6.91 (br s, 2H), 7.67 (d, 2H), 7.80 (s, 1H), 8.10 (d, 2H), 8.21 (dd, 1H), 8.51 (d, 1H), 8.70 (s, 1H) and 8.81 (br s, 2H) ppm [1]	388.165	0.93
I-109	H NMR (400.0 MHz, DMSO) d 0.92 (t, 3H), 1.74 (sept, 2H), 2.62 (t, 3H), 3.95 (t, 2H), 4.23 (t, 2H), 6.54 (d, 1H), 6.91 (br s, 2H), 7.67 (d, 2H), 7.79 (s, 1H), 8.10 (d, 2H), 8.20 (dd, 1H), 8.46 (d, 1H), 8.71 (s, 1H) and 8.80 (br s, 2H) ppm [1]	416.196	1
I-110	H NMR (400.0 MHz, DMSO) d 2.62 (t, 3H), 3.70 (t, 2H), 4.07 (t, 2H), 4.23 (t, 2H), 4.96 (br s, 1H), 6.54 (d, 1H), 6.90 (br s, 2H), 7.67 (d, 2H), 7.78 (s, 1H), 8.10 (d, 2H), 8.20 (dd, 1H), 8.39 (d, 1H), 8.68 (s, 1H) and 8.81 (br s, 2H) ppm [1]	418.175	0.89
I-111	DMSO 0.8-0.9 (4H,m), 2.6-2.65 (1H,m), 4.25-4.3 (2H,m), 6.5 (1H,d), 6.9 (2H,s), 7.65 (2H,d), 7.78 (1H,s), 8.05 (2H,d), 8.1-8.12 (1H,m), 8.7 (1H,s), 8.8 (2H,brs) [1]	400.165	0.57
I-112	DMSO 0.8-0.9 (4H,m), 2.6-2.65 (1H,m), 4.25-4.3 (2H,m), 6.9 (1H,s), 7.68 (2H,d), 7.78 (1H,s), 8.08 (2H,d), 8.1-8.12 (1H,m), 8.5-8.52 (1H,m), 8.7 (1H,s), 8.95 (2H,brs) [1]	434.126	0.63
I-113	H NMR (400.0 MHz, MeOH) d 1.21 (s, 3H), 2.45 (s, 3H), 3.64 (s, 2H), 3.83 (s, 2H), 4.48 – 4.53 (m, 2H), 4.71 – 4.74 (m, 2H), 7.54 – 7.59 (m, 3H), 7.72 (s, 1H), 7.98 (d, 2H), 8.78 (s, 1H) and 8.99 – 9.02 (m, 2H) ppm [1]	458.207	0.82
I-114	MeOH 1.6-1.65 (2H,m), 1.67-1.7 (2H,m), 2.1-2.15 (2H,m), 2.3-2.35 (2H,m), 2.7 (3H,s), 3.4-3.5 (1H,m), 4.2 (2H,s), 6.2-6.22 (1H,m), 7.42 (1H,s), 7.55 (2H,d), 7.9 (1H,d), 8.0-8.1 (3H,m), 8.42 (1H,s), [1]	454.212	0.65
I-115	DMSO 1.2-1.4 (4H,m), 1.65-1.85 (6H,m), 2.6-2.7 (3H,m), 4.2-4.25 (2H,m), 6.85 (2H,m), 7.6 (2H,d), 7.7 (1H,s), 7.85-7.95 (2H,m), 8.15 (2H,d), 8.65 (1H,s), 8.8 (2H,brs) [1]	456.227	0.66
I-116	DMSO 0.78 (3H,t), 0.85 (3H,t), 1.18-1.22 (2H,m), 1.6-1.72 (4H,m), 2.6-2.65 (3H,m), 2.78-2.83 (1H,m), 4.20-4.22 (2H,m), 6.85 (2H,s), 7.67 (2H,d), 7.7 (1H,s), 7.8-7.91 (1H,m), 7.92-7.95 (1H,m), 8.1 (2H,d), 8.7 (1H,s), 8.8 (2H,brs) [1]	458.243	0.68

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-117	H NMR (400.0 MHz, DMSO) d 2.31 (s, 3H), 3.75 – 3.86 (m, 6H), 4.98 (t, J = 5.4 Hz, 3H), 6.54 (d, J = 9.5 Hz, 1H), 6.85 (s, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.68 (s, 1H), 7.96 (d, J = 8.1 Hz, 2H), 8.17 (dd, J = 2.5, 9.4 Hz, 1H), 8.29 (d, J = 2.4 Hz, 1H) and 8.69 (s, 1H) ppm [1]	448.186	0.43
I-118	(DMSO) d 1.38-1.42 (12H, m), 2.63 (3H, t), 4.20 (2H, t), 4.78 (1H, m), 5.14 (1H, m), 6.52 (1H, d), 6.85 (2H, br s), 7.16 (1H, m), 7.38 (1H, s), 7.53 (1H, s), 7.92 (1H, d), 8.07 (1H, dd), 8.03 (1H, d), 8.75 (1H, s) and 8.81 (2H, br s) ppm [1]	474.238	0.63
I-119	MeOH 0.9-1.0 (4H,m), 1.7-1.8 (5H,m), 1.87-1.92 (2H,m), 2.08-2.13 (1H,m), 2.8-2.88 (1H,m), 4.42 (2H,s), 7.55 (1H,s), 7.7 (2H,d), 7.95 (1H,d), 8.1 (2H,d), 8.12-8.14 (1H,m), 8.55 (1H,s) [1]	468.227	0.75
I-120	MeOH 0.83-1.0 (10H,m), 1.28-1.33 (2H,m), 1.7-1.8 (4H,m), 2.8-2.85 (1H,m), 2.92-2.98 (1H,m), 4.42 (2H,s), 7.55 (1H,s), 7.7 (2H,d), 7.97 (1H,d), 8.08 (1H,d), 8.12 (2H,d), 8.55 (1H,s) [1]	484.259	0.82
I-121	MeOH 1.55 (6H,d), 2.77 (3H,s), 4.3 (2H,s), 7.65 (2H,d), 7.67-7.7 (1H,m), 8.1-8.2 (2H,m), 8.18-8.21 (1H,m), 8.67 (1H,s) [1]	434.187	0.59
I-122	H NMR (400.0 MHz, DMSO) d 1.10 – 1.20 (br s , 1H), 1.45 – 1.65 (m, 5H), 1.70 – 1.85 (m, 5H), 2.29 (s, 3H), 3.72 (s, 2H), 3.95 – 4.05 (m, 2H), 6.50 (d, 1H), 6.85 (br s, 2H), 7.49 – 7.55 (m, 2H), 7.72 (s, 1H), 7.75 (s, 1H), 7.95 – 8.00 (m, 2H), 8.15 – 8.25 (m, 1H), 8.45 (d, 1H) and 8.70 (s, 1H) ppm [1]	470.243	0.7
I-123	DMSO 2.62-2.68 (3H,s), 4.22 (2H,s), 6.9 (2H,s), 7.47 (1H,t), 7.45 (2H,t), 7.68 (2H,d), 7.74 (1H,s), 7.82 (2H,d), 8.08-8.12 (3H,m), 8.31 (1H,d), 8.77-8.83 (3H,m), 12.2 (1H,s) [1]	450.18	0.6
I-124	(DMSO) d 1.04 (3H, d), 1.12 (1H, d), 1.19 (1H, d), 1.53-1.58 (5H, m), 1.76 (1H, m), 1.90-2.14 (4H, m), 2.42 (1H, m), 4.56 (1H, m), 5.26 (1H, m), 6.53 (1H, d), 6.92 (2H, br s), 7.66 (2H, m), 7.71 (1H, m), 8.03 (1H, m), 8.14 (2H, m), 8.30-8.35 (5H, m) and 8.79 (1H, d) ppm [1]	456.227	0.68
I-125	H NMR (400.0 MHz, DMSO) d 2.03 (s, 6H), 2.35 (s, 3H), 3.81 (s, 2H), 6.66 (d, J = 9.4 Hz, 1H), 6.93 (s, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.73 (s, 1H), 7.98 (d, J = 8.1 Hz, 2H), 8.24 – 8.29 (m, 2H) and 8.76 (s, 1H) ppm [1]	441.191	1.76 , 1.75 [2]
I-126	CDCl3 0.78-0.86 (6H, m), 1.68-1.86 (4H, m), 2.90 (2H, dt), 3.87 (2H, s), 4.53 (2H, dt), 4.92-5.02 (1H, m), 5.74 (2H, br s), 6.66 (1H, d), 7.20 (1H, s), 7.43 (2H, d), 7.74-7.88 (4H, m), 8.30 (1H, s) [1]	476.234	0.74

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-127	CDCl3 0.86 (6H, t), 1.59-1.70 (2H, m), 1.75-1.88 (2H, m), 2.18-2.32 (2H, m), 2.67-2.80 (2H, m), 3.17-3.27 (1H, m), 3.74 (1H, s), 4.91-5.01 (1H, m), 5.75 (2H, br s), 6.65 (1H, d), 7.19 (1H, s), 7.40 (1H, d), 7.73-7.88 (4H, m), 8.30 (1H, s) [1]	520.24	0.88
I-128	DMSO 0.77-0.9 (10H,m), 1.8-1.9 (4H,m), 2.75-2.8 (1H,m), 4.37 (2H,s), 4.8-4.85 (1H,m), 6.55 (1H,d), 6.95 (2H,brs), 7.5-7.7 (4H,m), 8.08-8.18 (2H,m), 8.22 (1H,d), 8.8 (1H,s), 9.1 (2H,brs) [1]	488.234	0.83
I-129	DMSO 0.85-0.95 (6H,m), 1.8-1.9 (4H,m), 2.62 (3H,s), 4.35 (2H,s), 5.85-5.95 (1H,m), 6.6 (1H,d), 7.9-8.0 (2H,m), 7.5-7.7 (3H,m), 8.15-8.3 (3H,m), 8.8 (1H,s), 8.9-9.0 (2H,m), [1]	462.218	0.64
I-130	dmso d 0.77 (6H, d), 1.45-2.25 (11H, m), 3.82 (2H, s), 4.77-4.90 (1H, m), 5.20 (1H, d), 6.55 (1H, d), 6.90 (2H, br s), 7.55 (2H, d), 7.73 (1H, s), 7.98 (2H, d), 8.17-8.21 (2H, m), 8.79 (1H, s) [1]	516.265	2.63
I-131	H NMR (400.0 MHz, DMSO) d 0.76 (t, 6H), 1.83 (quin, 4H), 4.20 – 4.27 (m, 1H), 4.36 – 4.45 (m, 1H), 4.48 – 4.57 (m, 1H), 4.82 (br, s, 1H), 6.56 (d, 1H), 6.91 (br s ,2H), 7.53 (t, 1H), 7.59 (d, 1H), 7.73 (s, 1H), 7.91 (d, 1H), 8.06 (s, 1H), 8.17 – 8.22 (m, 2H) and 8.79 (s, 1H) ppm [1]	462.218	1.08
I-132	DMSO 0.8 (3H,t), 1.58-1.75 (4H,m) 2.6-2.65 (3H,m), 2.7-2.78 (1H,m), 4.22-4.26 (2H,m), 6.8-6.83 (2H,m), 7.48-7.52 (2H,m), 7.55-7.65 (1H,m), 7.85-7.88 (1H,m), 7.93-7.98 (1H,m), 8.12 (1H,t), 8.72 (1H,s), 8.88 (2H,brs), 11.85 (1H,s) [1]	462.218	0.65
I-133	(DMSO) d 0.76 (6H, t), 0.82 (3H, t), 1.81-2.02 (6H, m), 4.30 (1H, m), 4.84 (1H, m), 6.56 (1H, d), 6.93 (2H, br s), 7.62-7.69 (2H, m), 7.72 (1H, s), 8.05 (1H, m), 8.14-8.16 (2H, m), 8.23 (1H, m), 8.34 (3H, br s) and 8.82 (1H, s) ppm [1]	458.243	0.68
I-134	H NMR (400.0 MHz, DMSO) d 8.74 (s, 1H), 8.27 (dd, J = 2.3, 9.5 Hz, 1H), 8.22 (d, J = 2.1 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.69 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 6.97 (s, 2H), 6.65 (d, J = 9.5 Hz, 2H), 3.71 (s, 2H), 2.55 – 2.47 (m, 2H), 2.32 – 2.27 (m, 2H), 2.30 (s, 3H) and 0.98 (t, J = 7.3 Hz, 6H) ppm [1]	469.223	2.06
I-135	H NMR (400.0 MHz, CDCl3) d 8.52 (d, J = 2.3 Hz, 1H), 8.41 (s, 1H), 8.02 – 7.96 (m, 2H), 7.48 (d, J = 3.4 Hz, 1H), 7.28 – 7.25 (m, 2H), 6.68 (d, J = 9.5 Hz, 1H), 5.89 (s, 2H), 3.84 (s, 2H), 2.96 (qn, J = 7.3 Hz, 2H), 2.50 (s, 3H), 2.26 (td, J = 14.6, 7.3 Hz, 2H) and 1.09 (t, J = 7.4 Hz, 6H) ppm [1]	487.213	2.09

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-136	H NMR (400.0 MHz, CDCl3) d 8.44 (d, J = 2.2 Hz, 1H), 8.33 (s, 1H), 7.93 – 7.87 (m, 2H), 7.39 (d, J = 3.3 Hz, 1H), 7.18 – 7.15 (m, 3H), 6.59 (d, J = 9.5 Hz, 1H), 5.78 (s, 2H), 3.84 (s, 2H), 2.88 (m, 2H), 2.18 (m, 2H), 2.12 (m, 1H), 1.00 (t, J = 7.4 Hz, 6H) and 0.41 – 0.33 (m, 4H) ppm [1]	513.229	2.74
I-137	(DMSO) d 0.61 (6H, t), 1.21 (4H, m), 1.68 (4H, t), 4.67 (1H, m), 6.41 (1H, d), 6.78 (2H, br s), 7.42 (1H, m), 7.49 (1H, t), 7.61 (1H, s), 7.86 (1H, m), 7.90 (1H, m), 8.00 (1H, dd), 8.08 (1H, m), 8.54 (3H, br s) and 8.66 (1H, s) ppm [1]	456.227	0.75
I-138	H NMR (400.0 MHz, MeOH) d 8.54 (s, 1H), 8.49 (s, 1H), 8.22 (d, J = 9.4 Hz, 1H), 7.92 (s, 1H), 7.79 (d, J = 7.1 Hz, 1H), 7.53 – 7.46 (m, 3H), 6.67 (d, J = 9.4 Hz, 1H), 4.16 – 4.13 (m, 1H), 2.79 (m, 2H), 2.33 (m, 2H), 1.47 (d, J = 6.6 Hz, 3H) and 1.10 (t, J = 7.3 Hz, 6H) ppm [1]	469.223	2.13
I-139	H NMR (400.0 MHz, MeOH) d 8.52 (d, J = 2.1 Hz, 1H), 8.48 (s, 1H), 8.21 (dd, J = 2.2, 9.4 Hz, 1H), 7.91 (s, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.53 – 7.44 (m, 3H), 6.66 (d, J = 9.4 Hz, 1H), 4.15 (d, J = 6.6 Hz, 1H), 2.76 (qn, J = 7.3 Hz, 2H), 2.33 (td, J = 14.7, 7.3 Hz, 2H), 1.47 (d, J = 6.7 Hz, 3H) and 1.10 (t, J = 7.4 Hz, 6H) ppm [1]	469.223	2.13
I-140	DMSO D6 0.29-0.32 (2H, m), 0.48-0.52 (2H, m), 1.24 (3H, s), 1.74-1.84 (4H, m), 3.80 (2H, s), 4.72-4.85 (1H, m), 6.53 (1H, d), 6.84 (2H, br s), 7.48 (2H, d), 7.68 (1H, s), 7.91 (2H, d), 8.12-8.20 (2H, m), 8.76 (1H, s) [1]	484.259	0.79
I-141	H NMR (400.0 MHz, DMSO) d 8.79 (s, 1H), 8.23 – 8.16 (m, 3H), 7.89 (s, 1H), 7.71 (s, 1H), 7.32 (s, 1H), 6.89 (s, 2H), 6.56 (d, J = 9.4 Hz, 1H), 4.85 (br s, 1H), 4.32 (d, J = 6.5 Hz, 1H), 2.15 (br s, 1H), 1.82 (t, J = 7.0 Hz, 4H), 1.32 (d, J = 6.5 Hz, 3H) and 0.76 (t, J = 7.2 Hz, 6H) ppm [1]	462.218	0.69
I-142	H NMR (400.0 MHz, DMSO) d 8.79 (s, 1H), 8.20 (d, J = 2.4 Hz, 1H), 8.11 (d, J = 9.4 Hz, 1H), 7.89 – 7.75 (m, 2H), 7.50 (s, 1H), 7.37 (d, J = 2.4 Hz, 1H), 6.94 (s, 2H), 6.50 (s, 1H), 4.80 (br s, 1H), 4.51 – 4.41 (m, 1H), 1.64 (t, J = 7.2 Hz, 4H), 1.35 (d, J = 6.6 Hz, 3H) and 0.58 (t, J = 7.3 Hz, 7H) ppm [1]	462.218	0.66
I-143	H NMR (400.0 MHz, DMSO) d 8.75 (s, 1H), 8.29 (d, 1H), 8.21 (d, J = 2.1 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.72 (s, 2H), 7.51 (d, J = 8.1 Hz, 2H), 6.95 (s, 2H), 6.66 (d, J = 9.5 Hz, 1H), 3.71 (s, 2H), 2.87 (m, 2H), 2.29 (s, 3H) and 1.90 (s, 4H) ppm [1]	467.207	1.93

Cmpd No.	HNMR	LCMS ES Plus	LCMS (Rt min)
I-144	H NMR (400.0 MHz, CDCl3) d 8.38 (s, 1H), 8.25 (d, J = 2.3 Hz, 1H), 7.96 (dd, J = 2.4, 9.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.30 (s, 1H), 6.74 (d, J = 9.5 Hz, 1H), 5.87 (s, 2H), 3.93 (s, 2H), 2.18 (m, 1H), 2.14 (s, 6H) and 0.48 – 0.41 (m, 4H) ppm [1]	467.207	2.23
I-145	H NMR (400.0 MHz, CDCl3) d 8.39 (s, 1H), 8.25 (d, J = 2.0 Hz, 1H), 7.98 (dd, J = 2.1, 9.5 Hz, 1H), 7.87 (d, J = 8.1 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.25 (s, 1H), 6.75 (d, J = 9.5 Hz, 1H), 5.90 (s, 2H), 3.98 (d, J = 7.2 Hz, 1H), 3.88 (s, 2H), 3.80 (m, 2H), 3.68 (dd, J = 3.8, 8.9 Hz, 1H), 3.50 – 3.48 (m, 1H), 2.14 (s, 6H), 2.11 (m, 1H) and 1.82 (m, 1H) ppm [1]	497.218	2.07
I-146	(DMSO) d 0.58 (6H, t), 1.53 (6H, s), 1.65 (4H, m), 4.64 (1H, m), 6.38 (1H, d), 6.74 (2H, br s), 7.47-7.54 (2H, m), 7.57 (1H, s), 7.84 (1H, m), 7.97-7.99 (2H, m), 8.04 (1H, m), 8.31 (3H, br s) and 8.63 (1H, s) [1]	458.243	0.67
I-147	-----	485.218	6.97
I-148	-----	375.144	1.45
I-149	-----	442.187	1.29
I-150	-----	445.223	1.1
I-151	-----	456.202	1.32

Example 2: Cellular ATR Inhibition Assay:

[00262] Compounds can be screened for their ability to inhibit intracellular ATR using an immunofluorescence microscopy assay to detect phosphorylation of the ATR substrate histone H2AX in hydroxyurea treated cells. HT29 cells are plated at 14,000 cells per well in 96-well black imaging plates (BD 353219) in McCoy's 5A media (Sigma M8403) supplemented with 10% foetal bovine serum (JRH Biosciences 12003), Penicillin/Streptomycin solution diluted 1:100 (Sigma P7539), and 2mM L-glumtamine (Sigma G7513), and allowed to adhere overnight at 37°C in 5% CO_2. Compounds are then added to the cell media from a final concentration of 25μM in 3-fold serial dilutions and the cells are incubated at 37°C in 5% CO_2. After 15min, hydroxyurea (Sigma H8627) is added to a final concentration of 2mM.

[00263] After 45min of treatment with hydroxyurea, the cells are washed in PBS, fixed for 10min in 4% formaldehyde diluted in PBS (Polysciences Inc 18814), washed in 0.2% Tween-20 in PBS (wash buffer), and permeabilised for 10min in 0.5% Triton X-100 in PBS, all at room temperature. The cells are then washed once in wash buffer and blocked for 30min at room temperature in 10% goat serum (Sigma G9023) diluted in wash buffer (block buffer). To detect H2AX phosphorylation levels, the cells are then incubated for 1h at room

temperature in primary antibody (mouse monoclonal anti-phosphorylated histone H2AX Ser139 antibody; Upstate 05-636) diluted 1:250 in block buffer. The cells are then washed five times in wash buffer before incubation for 1h at room temperature in the dark in a mixture of secondary antibody (goat anti-mouse Alexa Fluor 488 conjugated antibody; Invitrogen A11029) and Hoechst stain (Invitrogen H3570); diluted 1:500 and 1:5000, respectively, in wash buffer. The cells are then washed five times in wash buffer and finally 100ul PBS is added to each well before imaging.

[00264] Cells are imaged for Alexa Fluor 488 and Hoechst intensity using the BD Pathway 855 Bioimager and Attovision software (BD Biosciences, Version 1.6/855) to quantify phosphorylated H2AX Ser139 and DNA staining, respectively. The percentage of phosphorylated H2AX-positive nuclei in a montage of 9 images at 20x magnification is then calculated for each well using BD Image Data Explorer software (BD Biosciences Version 2.2.15). Phosphorylated H2AX-positive nuclei are defined as Hoechst-positive regions of interest containing Alexa Fluor 488 intensity at 1.75-fold the average Alexa Fluor 488 intensity in cells not treated with hydroxyurea. The percentage of H2AX positive nuclei is finally plotted against concentration for each compound and IC50s for intracellular ATR inhibition are determined using Prism software(GraphPad Prism version 3.0cx for Macintosh, GraphPad Software, San Diego California, USA).

[00265] The compounds described herein can also be tested according to other methods known in the art (see Sarkaria et al, "Inhibition of ATM and ATR Kinase Activities by the Radiosensitizing Agent, Caffeine: *Cancer Research* 59: 4375-5382 (1999); Hickson et al, "Identification and Characterization of a Novel and Specific Inhibitor of the Ataxia-Telangiectasia Mutated Kinase ATM" *Cancer Research* 64: 9152-9159 (2004); Kim et al, "Substrate Specificities and Identification of Putative Substrates of ATM Kinase Family Members" *The Journal of Biological Chemistry*, 274(53): 37538-37543 (1999); and Chiang et al, "Determination of the catalytic activities of mTOR and other members of the phosphoinositide-3-kinase-related kinase family" *Methods Mol. Biol.* 281:125-41 (2004)).

Example 3: ATR Inhibition Assay:

[00266] Compounds were screened for their ability to inhibit ATR kinase using a radioactive-phosphate incorporation assay. Assays were carried out in a mixture of 50mM Tris/HCl (pH 7.5), 10mM $MgCl_2$ and 1mM DTT. Final substrate concentrations were 10μM

[γ-33P]ATP (3mCi 33P ATP/mmol ATP, Perkin Elmer) and 800 μM target peptide (ASELPASQPQPFSAKKK).

[00267] Assays were carried out at 25°C in the presence of 5 nM full-length ATR. An assay stock buffer solution was prepared containing all of the reagents listed above, with the exception of ATP and the test compound of interest. 13.5 μL of the stock solution was placed in a 96 well plate followed by addition of 2 μL of DMSO stock containing serial dilutions of the test compound (typically starting from a final concentration of 15 μM with 3-fold serial dilutions) in duplicate (final DMSO concentration 7%). The plate was pre-incubated for 10 minutes at 25°C and the reaction initiated by addition of 15 μL [γ-33P]ATP (final concentration 10 μM).

[00268] The reaction was stopped after 24 hours by the addition of 30μL 0.1M phosphoric acid containing 2mM ATP. A multiscreen phosphocellulose filter 96-well plate (Millipore, Cat no. MAPHN0B50) was pretreated with 100μL 0.2M phosphoric acid prior to the addition of 45μL of the stopped assay mixture. The plate was washed with 5 x 200μL 0.2M phosphoric acid. After drying, 100 μL Optiphase 'SuperMix' liquid scintillation cocktail (Perkin Elmer) was added to the well prior to scintillation counting (1450 Microbeta Liquid Scintillation Counter, Wallac).

[00269] After removing mean background values for all of the data points, Ki(app) data were calculated from non-linear regression analysis of the initial rate data using the Prism software package (GraphPad Prism version 3.0cx for Macintosh, GraphPad Software, San Diego California, USA).

[00270] Below is a chart showing the ATR Inhibition Ki values of compounds of the disclosure. Compounds with a Ki value of $\leq$ 5 nM are marked with "+++." Compounds with a Ki value > 5 nM but $\leq$ 50 nM are marked with "++." Compounds with a Ki value > 50 nM but < 100 nM are marked with "+."

Cmpd No.	Ki Value
I-1	++
I-2	++
I-3	++
I-4	++
I-5	+
I-6	+++
I-7	++
I-8	++
I-9	++
I-10	+++
I-11	+++
I-12	+++
I-13	+++
I-14	+++
I-15	+++
I-16	+++
I-17	+++
I-18	+++
I-19	+++
I-20	+++
I-21	+++
I-22	+++
I-23	+++
I-24	++
I-25	+++
I-26	+++
I-27	+++
I-28	+++
I-29	+++
I-30	+++
I-31	++
I-32	+++
I-33	+++
I-34	+++
I-35	+++
I-36	+++
I-37	+++
I-38	++
I-39	++
I-40	++
I-41	+++
I-42	+++
I-43	+++
I-44	++
I-45	++

Cmpd No.	Ki Value
I-46	+
I-47	++
I-48	+
I-49	++
I-50	+++
I-51	++
I-52	++
I-53	+++
I-54	+++
I-55	+++
I-56	+++
I-57	+++
I-58	+++
I-59	++
I-60	+++
I-61	+++
I-62	+++
I-63	+++
I-64	+++
I-65	+
I-66	+++
I-67	+
I-68	+++
I-69	+++
I-70	+++
I-71	++
I-72	+++
I-73	+++
I-74	+++
I-75	+
I-76	++
I-77	+++
I-78	+++
I-79	+++
I-80	+++
I-81	+++
I-82	+++
I-83	+++
I-84	+++
I-85	+++
I-86	+++
I-87	+++
I-88	+++
I-89	+++
I-90	+++

Cmpd No.	Ki Value
I-91	+++
I-92	+++
I-93	+++
I-94	+++
I-95	+++
I-96	+++
I-97	+++
I-98	+++
I-99	+++
I-100	+++
I-101	++
I-102	+++
I-103	+++
I-104	+++
I-105	+++
I-106	+++
I-107	+++
I-108	+++
I-109	+++
I-110	+++
I-111	+++
I-112	+++
I-113	+++
I-114	+++
I-115	+++
I-116	+++
I-117	+++
I-118	+++
I-119	+++
I-120	+++
I-121	++
I-122	+++
I-123	+++
I-124	+++
I-125	+++
I-126	+++
I-127	+++
I-128	+++
I-129	+++
I-130	+++
I-131	+++
I-132	+++
I-133	+++
I-134	+++
I-135	+++

Cmpd No.	Ki Value
I-136	+++
I-137	++
I-138	+++
I-139	+++
I-140	+++
I-141	+++

Cmpd No.	Ki Value
I-142	+++
I-143	+++
I-144	+++
I-145	+++
I-146	+++
I-147	+++

Cmpd No.	Ki Value
I-148	+++
I-149	++
I-150	+
I-151	++

Example 4: Cisplatin Sensitization Assay

[00271] Compounds can be screened for their ability to sensitize HCT116 colorectal cancer cells to Cisplatin using a 96h cell viability (MTS) assay. HCT116 cells, which possess a defect in ATM signaling to Cisplatin (see, Kim et al.; *Oncogene* 21:3864 (2002); see also, Takemura et al.; *JBC* 281:30814 (2006)) are plated at 470 cells per well in 96-well polystyrene plates (Costar 3596) in 150µl of McCoy's 5A media (Sigma M8403) supplemented with 10% foetal bovine serum (JRH Biosciences 12003), Penicillin/Streptomycin solution diluted 1:100 (Sigma P7539), and 2mM L-glumtamine (Sigma G7513), and allowed to adhere overnight at 37°C in 5% CO_2. Compounds and Cisplatin are then both added simultaneously to the cell media in 2-fold serial dilutions from a top final concentration of 10µM as a full matrix of concentrations in a final cell volume of 200µl, and the cells are then incubated at 37°C in 5% CO_2. After 96h, 40µl of MTS reagent (Promega G358a) is added to each well and the cells are incubated for 1h at 37°C in 5% CO_2. Finally, absorbance is measured at 490nm using a SpectraMax Plus 384 reader (Molecular Devices) and the concentration of compound required to reduce the IC50 of Cisplatin alone by at least 3-fold (to 1 decimal place) can be reported (CP3 shift).

Cmpd	CP3 shift (uM)
I-3	0.234
I-6	0.156
I-15	0.039
I-11	0.156
I-22	0.02
I-23	0.312
I-32	0.079
I-37	0.078
I-42	0.156
I-43	0.078
I-44	0.312
I-49	0.625
I-50	0.312
I-53	0.039
I-54	0.039
I-55	0.039
I-57	0.02
I-58	0.312
I-60	0.312
I-61	0.078
I-62	0.078
I-63	0.156
I-64	0.078

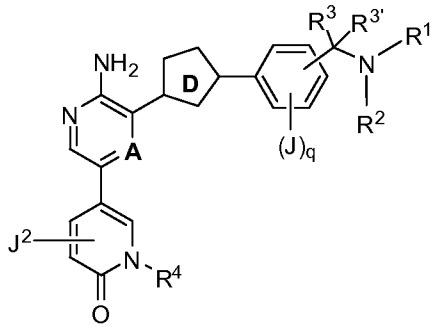
Cmpd	CP3 shift (uM)
I-68	0.039
I-72	0.078
I-73	0.156
I-74	0.078
I-77	0.039
I-78	0.625
I-80	0.078
I-81	0.156
I-82	0.079
I-83	0.02
I-87	0.078
I-89	0.312
I-90	0.625
I-92	0.078
I-93	0.02
I-94	0.007
I-96	0.078
I-97	0.078
I-102	0.078
I-105	0.02
I-106	0.039
I-107	0.039
I-116	0.02

Cmpd	CP3 shift (uM)
I-119	0.156
I-120	0.078
I-122	0.078
I-123	0.078
I-124	0.039
I-125	0.015
I-126	0.625
I-127	0.312
I-128	0.078
I-129	0.02
I-130	0.078
I-131	0.02
I-132	0.01
I-133	0.039
I-134	0.02
I-135	0.01
I-138	0.01
I-139	0.01
I-140	0.156
I-143	0.01
I-145	0.01

[00272] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds, methods, and processes 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 herein.

CLAIMS

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

A is C or N;

Ring D is isoxazolyl or oxadiazolyl;

J is -C_{1-3}alkyl, -O(C_{1-3}alkyl), halo, or CN;

q is 0 or 1;

R^1 is H, C_{1-6}aliphatic, phenyl, or tetrahydrofuranyl, wherein said C_{1-6}aliphatic is optionally substituted with one occurrence of OH and up to two occurrences of F;

R^2 is H or C_{1-3}alkyl;

or R^1 and R^2, together with the nitrogen atom to which they are attached, optionally form a 4-6 membered monocyclic heterocyclyl ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

R^3 is H or C_{1-3}alkyl, wherein said alkyl is optionally substituted with up to three occurrences of F;

$R^{3'}$ is H or C_{1-3}alkyl;

or R^3 and $R^{3'}$, together with the carbon atom to which they are attached, form a 3-4 membered monocyclic saturated carbocyclic ring;

R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', S, or CO; and wherein one methylene unit of the C_{1-2}alkyl can optionally be replaced with C(=O);

R^4 is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 1 occurrence of CN and up to 4 occurrences of F;

Q is 3-6 membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; Q is

optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 4 occurrences of F;

R' is H or C_{1-4}alkyl;

R is H or C_{1-4}alkyl;

or R and R', together with the nitrogen to which they are attached, optionally form a 3-6 membered heterocyclic ring having 1-2 heteroatoms selected from the group consisting of O, N, and S;

J^2 is H, C_{1-6}aliphatic, halo, phenyl, or CN, wherein said C_{1-6}aliphatic is optionally substituted with 1-2 occurrences of halo, OH, CN, or OR .

2. The compound of claim 1, wherein

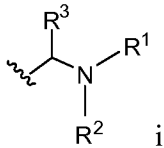
R^1 is H, C_{1-6}aliphatic, or tetrahydrofuranyl, wherein said C_{1-6}aliphatic is optionally substituted with one occurrence of OH and up to two occurrences of F; $R^{3'}$ is H;

R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', S, or CO;

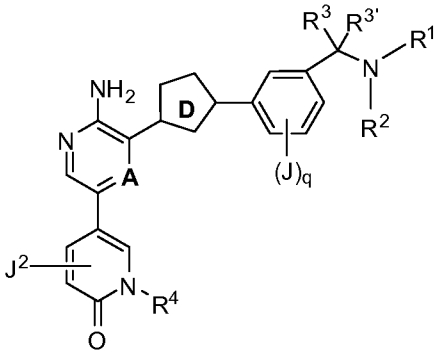
Q is 3-6 membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur; Q is optionally substituted with 1-3 occurrences of halo, CN, NRR', OR, or C_{1-3}aliphatic wherein said C_{1-3}aliphatic is optionally substituted with up to 4 occurrences of F;

J^2 is H.

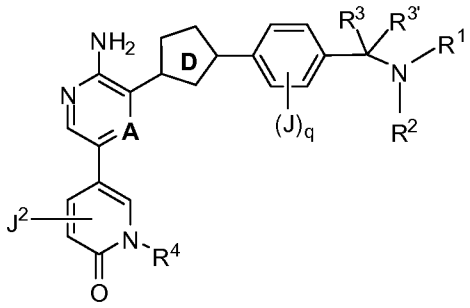
3. The compound of claim 1, wherein A is N.
4. The compound of claim 1 or claim 2, wherein R^2 is H.
5. The compound of any one of claims 1-4, wherein Ring D is isoxazolyl.
6. The compound of any one of claims 1-4, wherein Ring D is oxadiazolyl.
7. The compound of claim 5 or claim 6,



wherein is bonded at the meta or para position of the phenyl ring as shown in Formula Ia and Ib below:

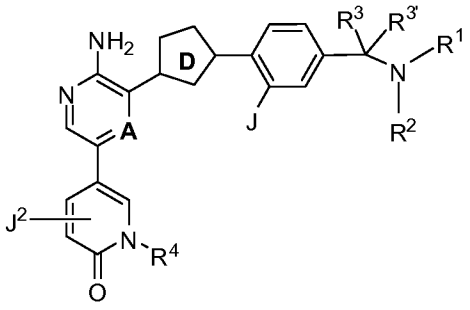


Ia



Ib.

8. The compound of claim 7, having formula Ib.
9. The compound of claim 8, wherein R^3 is H or methyl.
10. The compound of claim 9, wherein R^3 is H.
11. The compound of any one of claims 1-10, wherein R^1 is C_{1-6}aliphatic, phenyl, or tetrahydrofuranyl.
12. The compound of claim 11 wherein R^1 is C_{1-6}aliphatic or tetrahydrofuranyl.
13. The compound of claim 12 , wherein R^1 is C_{1-4}alkyl or tetrahydrofuranyl.
14. The compound of claim 13, wherein R^1 is C_{1-4}alkyl.
15. The compound of claim 13, wherein R^1 is methyl, isopropyl, tert-butyl, or tetrahydrofuranyl.
16. The compound according to any one of claims 11-15, wherein the C_{1-6}alkyl of R^1 is optionally substituted with 1-2 occurrences of OH or fluoro.
17. The compound of any one of claims 1-16, wherein q is 1.
18. The compound of claim 17, wherein J is bonded at the ortho position of the phenyl ring as shown in Formula Ic:

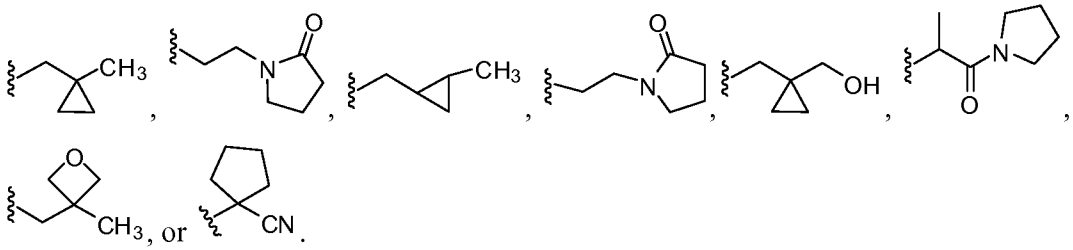


Ic.

19. The compound of claim 18, wherein J is fluoro, C_{1-3}alkyl, $O(C_{1-3}$alkyl), or CN.
20. The compound of claim 19, wherein the C_{1-3}alkyl is methyl or isopropyl.
21. The compound of claim 18, wherein J is fluoro, CH_3, OCH_3, or CN.

22. The compound of any one of claims 1-16, wherein q is 0.
23. The compound according to any one of claims 1-22, wherein R^4 is Q, -(C_{1-2}alkyl)-Q, or a C_{1-10}aliphatic wherein up to two methylene units of said C_{1-10}aliphatic are optionally replaced with O, NR', or CO; and wherein one methylene unit of the C_{1-2}alkyl can optionally be replaced with C(=O).
24. The compound of claim 23, wherein Q is a 5 membered heteroaryl having 1-2 heteroatoms selected from O, N, or S; 4-6 membered heterocyclyl having 1 heteroatoms selected from O or N; or a 3-6 membered cycloalkyl.
25. The compound of claim 24, wherein Q is furanyl, thiazoyl, imidazolyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinonyl, or 3-6 membered cycloalkyl.
26. The compound ofclaim 23, wherein R^4 is C_{1-10}aliphatic, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), -(C_{1-4}alkyl)-N(C_{1-3}alkyl)$_2$, -(C_{1-4}alkyl)-O(C_{1-3}alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted.
27. The compound of claim 26, wherein R^4 is C_{1-6}alkyl, -(C_{1-4}alkyl)-CF_3, -(C_{1-4}alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl.

28. The compound of claim 26, wherein R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, $CH(CH_3)COOH$, CH_2CONH_2, $CH(CH_3)CONH_2$, $CH(CH_3)CONHCH_3$, $CH(CH_3)CONCH_2CH_3)_2$, cyclobutyl, cyclopentyl, methylcyclopentyl, $CH(CH_3)$(cyclopropyl), CH_2(cyclopropyl), CH_2CH_2(cyclopropyl), CH_2CH_2(cyclopentyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $C(CH_3)_2CN$, $C(CH_2CH_3)_2CN$, $CH(CH_3)CN$, CH_2CN, $CH_2CH(CH_3)CH_2CH_3$, $CH(CH_2CH_3)_2$ $CH(CH_2OH)_2$ $CH(CH_3)CH_2OH$, $CH(CH_3)CH_2OCH_3$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NH_2$, tetrahydrofuranyl, tetrohydropyranyl, CH_2(furanyl), CH_2(thiazolyl), CH_2(imidazolyl), CH_2CH_2CN, $CH_2CH(OCH_3)CH_2CH_3$, $CH_2CH_2CH(CH_3)CH_2CH_3$,



29. The compound of claim 26, wherein R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, $CH(CH_3)COOH$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl),

$CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, $CH(CH_3)CH_2OH$, CH_2CH_2OH, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2CH_2NH_2$, $CH(CH_3)CH_2OCH_3$, or tetrahydrofuranyl.

30. The compound of claim 28, wherein R^4 is methyl, ethyl, isopropyl, sec-butyl, isobutyl, $CH(CH_3)C{\equiv}CCH_3$, cyclobutyl, cyclopentyl, $CH(CH_3)$(cyclopropyl), $CH(CH_3)CH_2F$, $CH(CH_3)CF_3$, CH_2CF_3, $CH(CH_3)CN$, CH_2CN, or tetrahydrofuranyl.

31. The compound of any one of claims 1-30, wherein J^2 is H, CN, F, Cl, Br, $CH{=}CH_2$, methyl, ethyl, isopropyl, CH_2OH, $CH(CH_2CH_3)CH_2CH_2CH_3$, $CH(CH_2CH_3)_2$, cyclopentyl, cyclohexyl, cyclohexenyl, or phenyl.

32. The compound of claim 1, wherein

A is N;

J^2 is H;

R^1 is methyl;

R^2 is H;

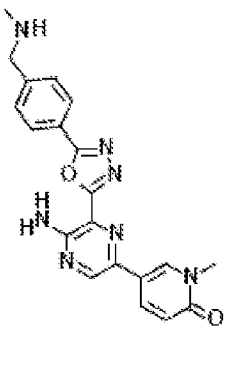
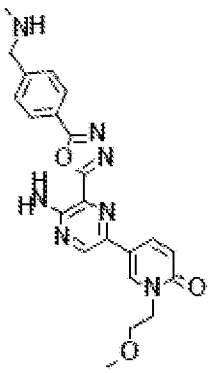
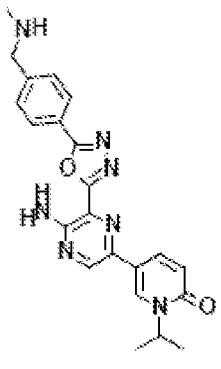
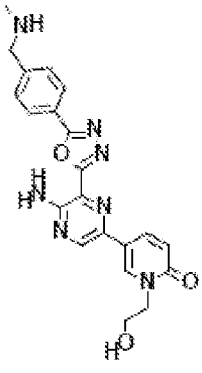
R^3 is H; and

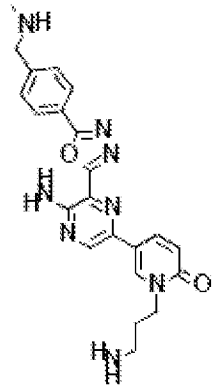
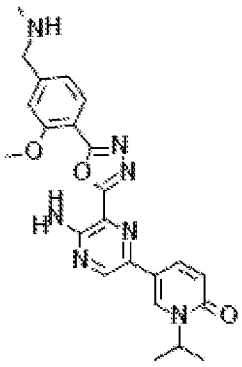
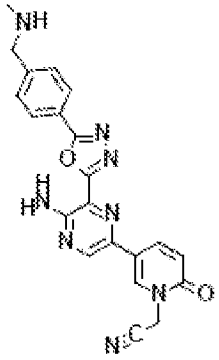
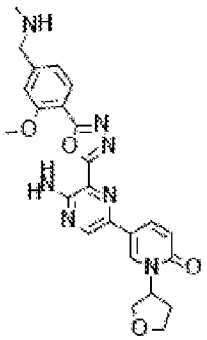
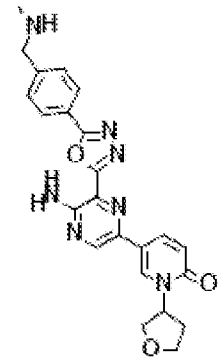
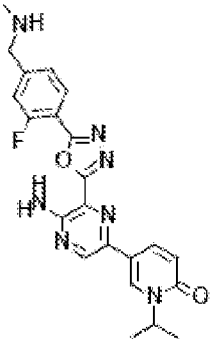
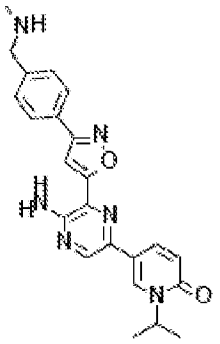
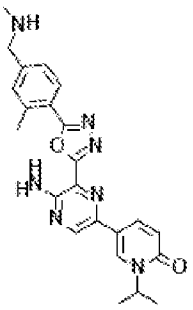
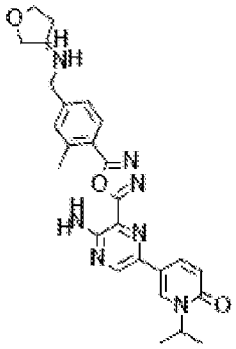
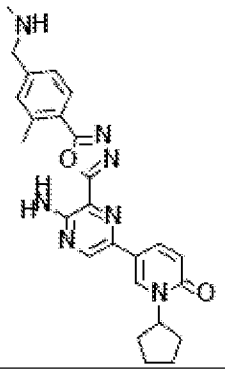
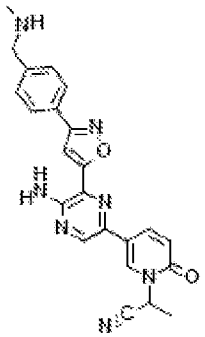
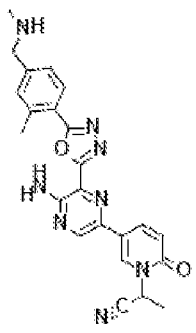
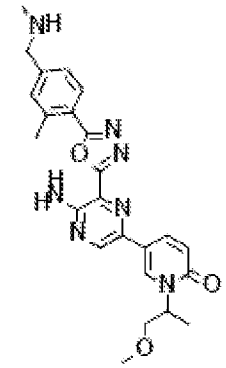
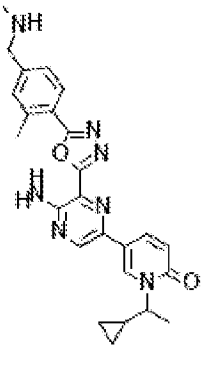
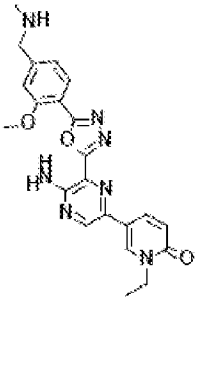
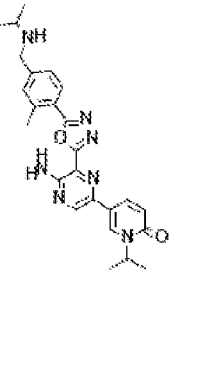
R^4 is $C_{1\text{-}10}$aliphatic, -($C_{1\text{-}4}$alkyl)-CF_3, -($C_{1\text{-}4}$alkyl)-(C_3-C_6cycloaliphatic), -($C_{1\text{-}4}$alkyl)-N($C_{1\text{-}3}$alkyl)$_2$, -($C_{1\text{-}4}$alkyl)-O($C_{1\text{-}3}$alkyl), C_3-C_6cycloaliphatic, or tetrahydrofuranyl, wherein said alkyl group is optionally substituted.

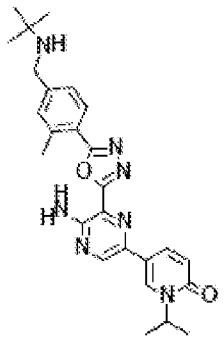
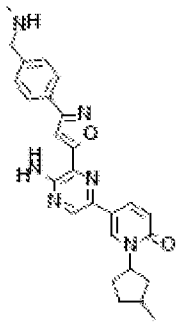
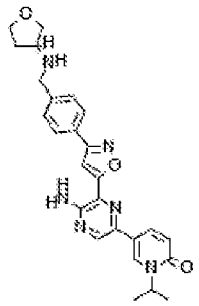
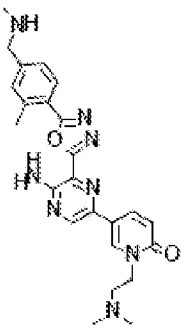
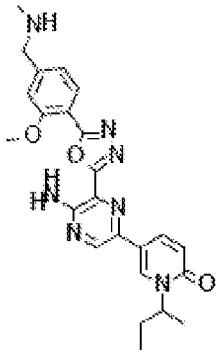
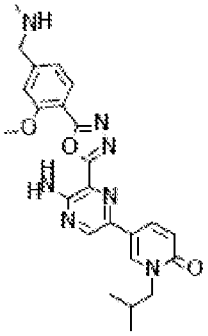
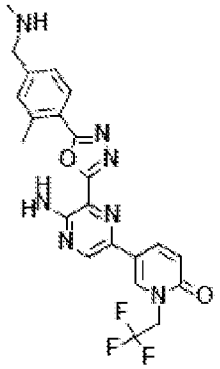
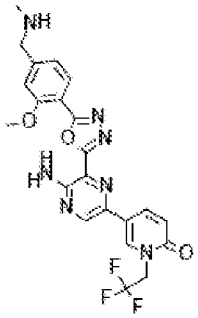
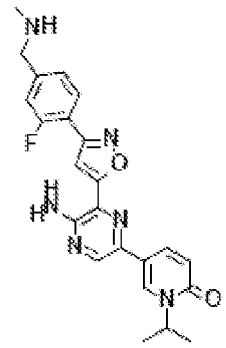
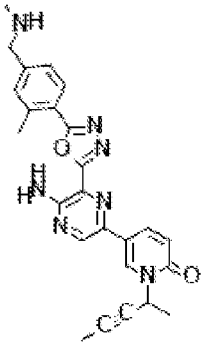
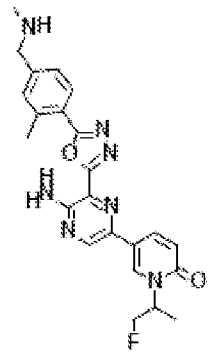
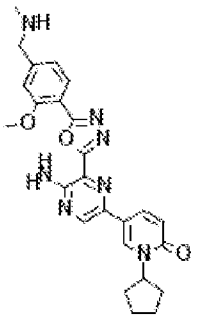
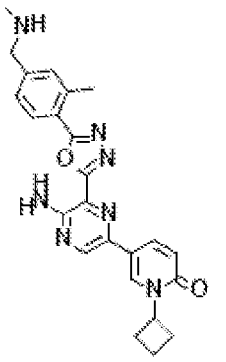
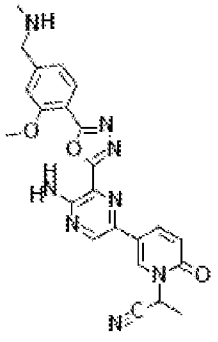
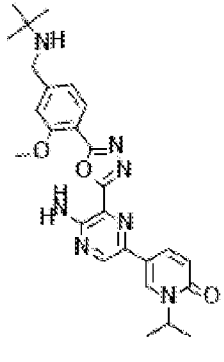
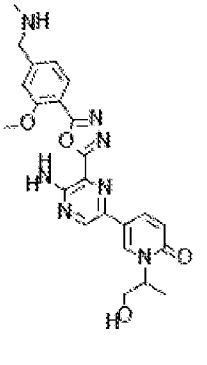
33. The compound of claim 32, wherein R^4 is $C_{1\text{-}10}$aliphatic, -($C_{1\text{-}4}$alkyl)-CF_3, -($C_{1\text{-}4}$alkyl)-(C_3-C_6cycloaliphatic), C_3-C_6cycloaliphatic, or tetrahydrofuranyl.

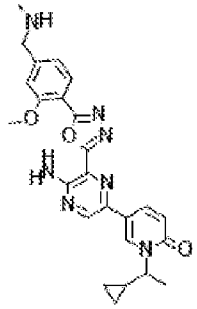
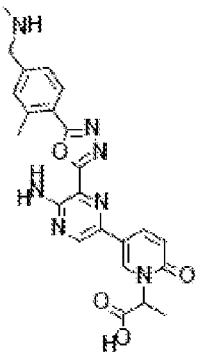
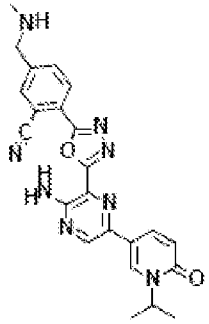
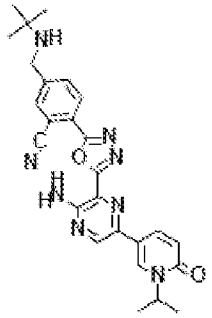
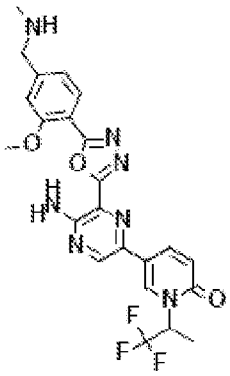
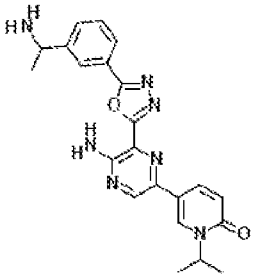
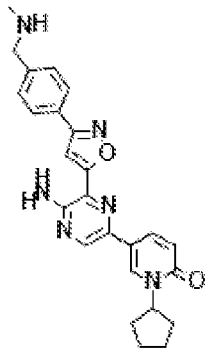
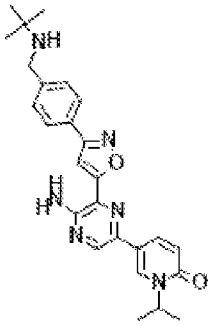
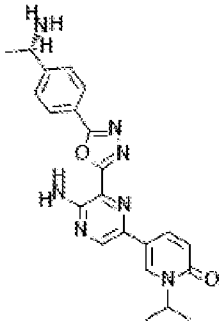
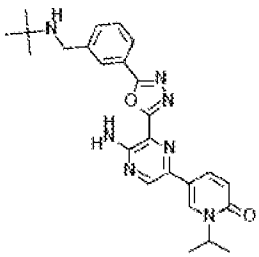
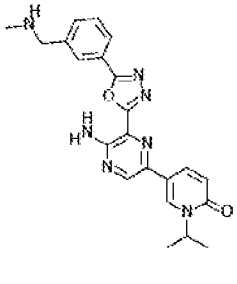
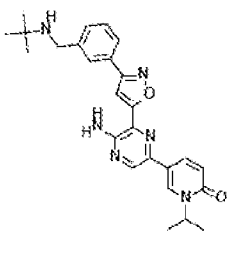
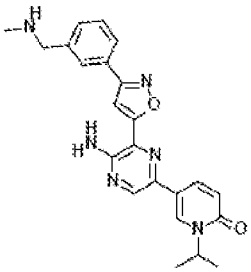
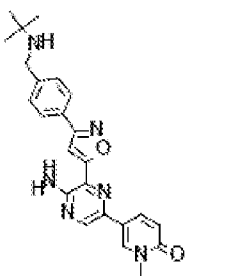
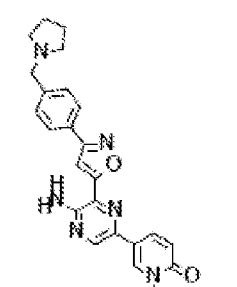
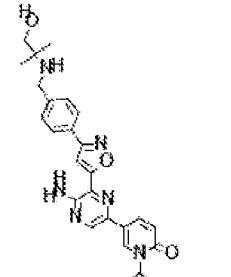
34. The compound of claim 33, wherein said alkyl group is optionally substituted with CH_3, OH, OCH_3, NH_2, CN, or tetrahydrofuranyl.

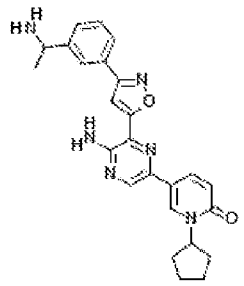
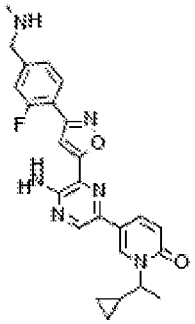
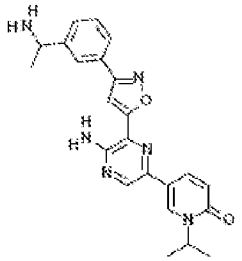
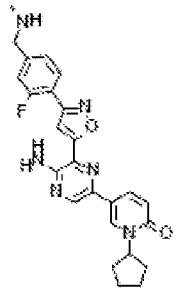
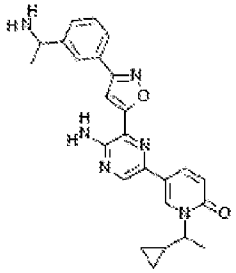
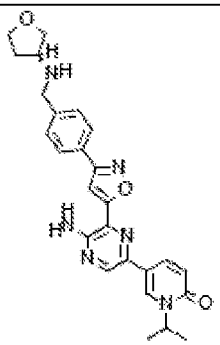
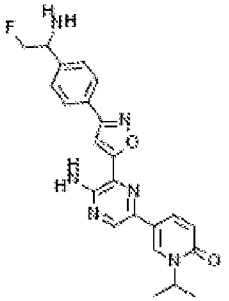
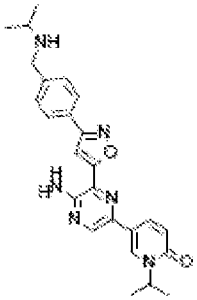
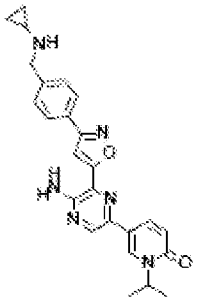
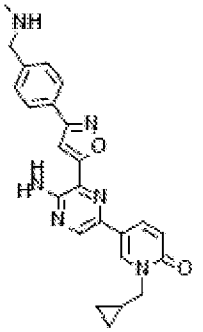
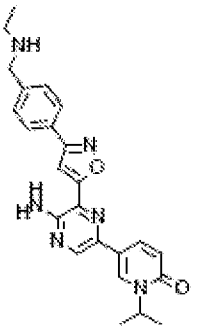
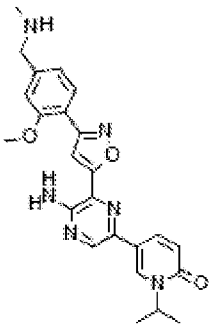
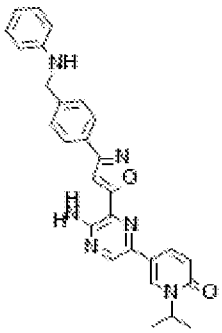
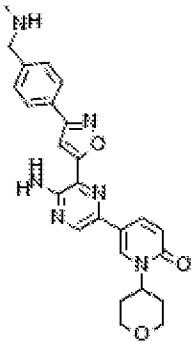
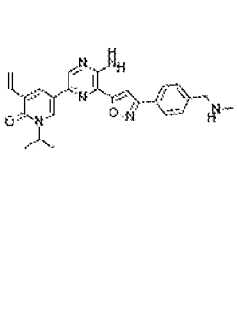
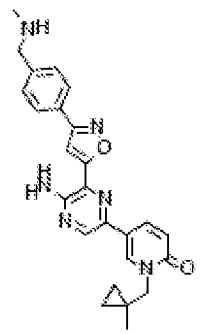
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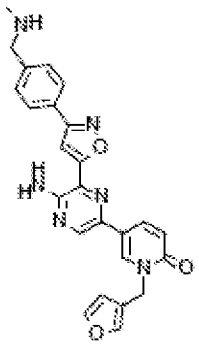
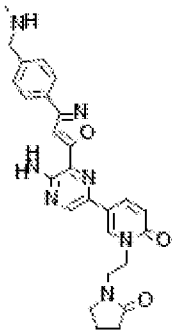
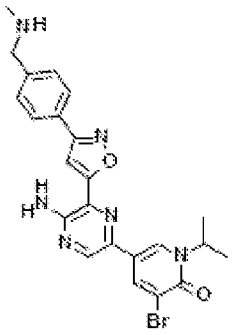
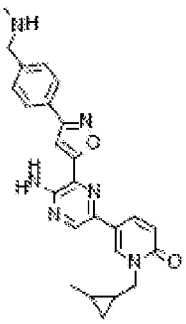
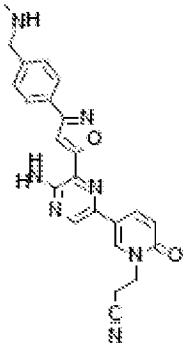
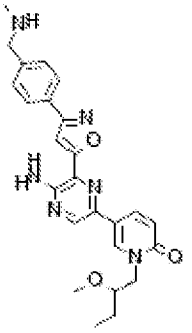
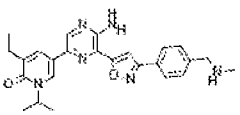
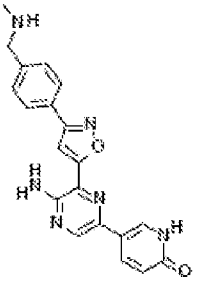
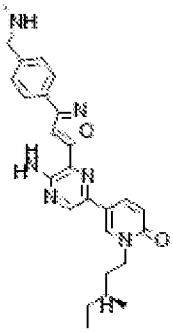
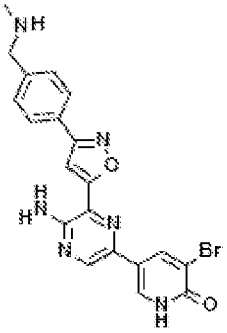
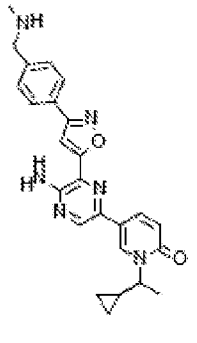
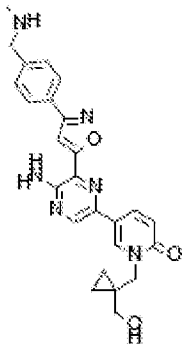
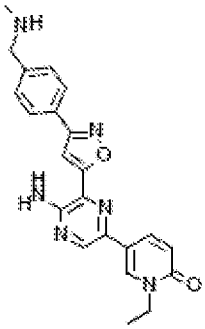
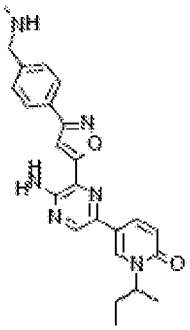
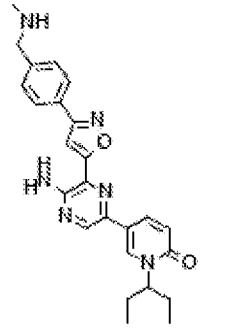
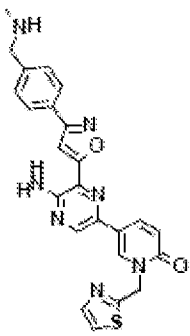
			
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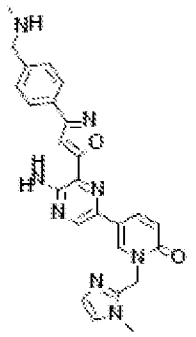
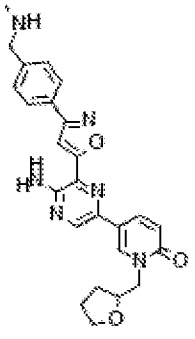
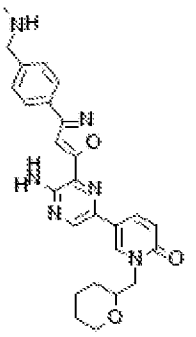
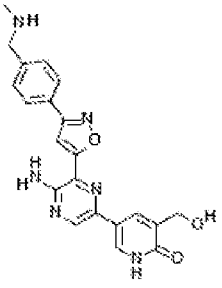
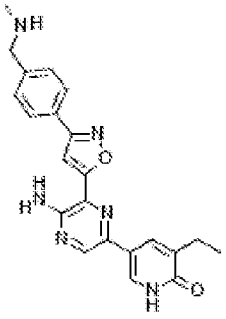
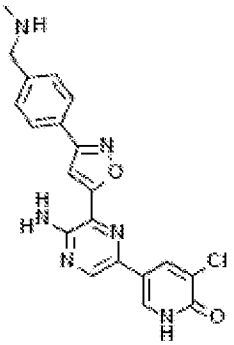
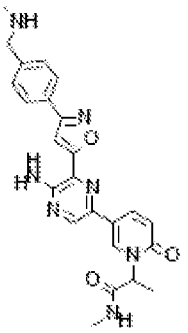
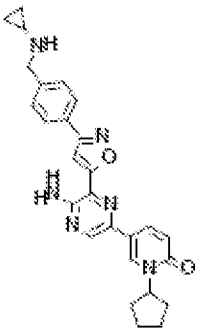
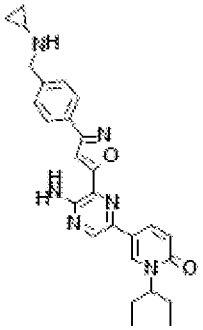
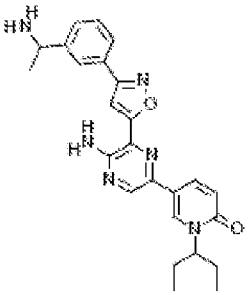
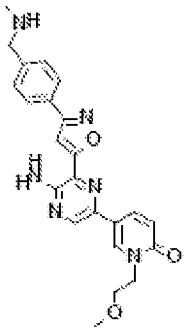
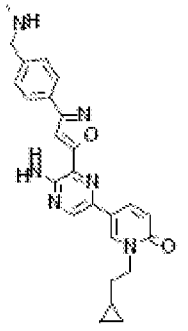
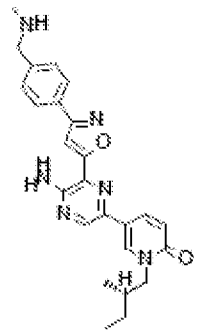
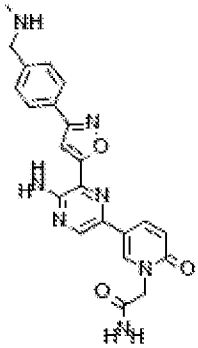
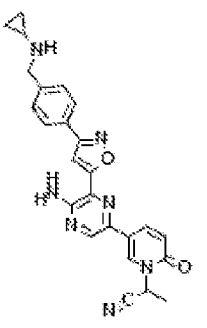
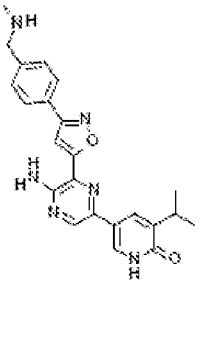
			
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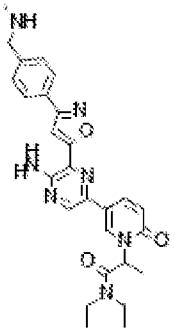
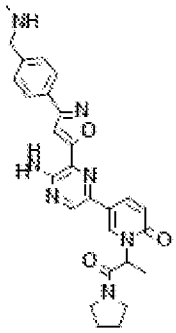
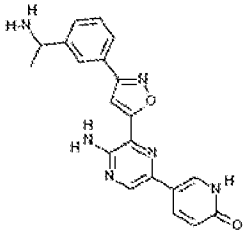
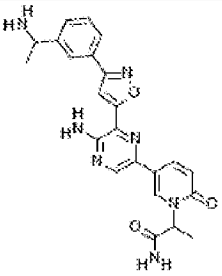
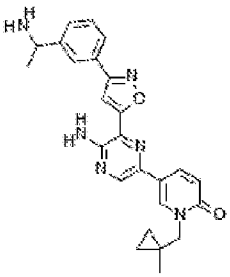
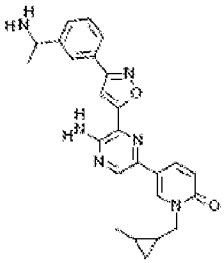
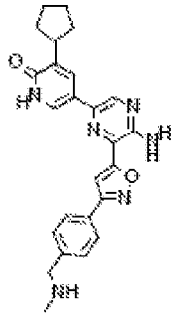
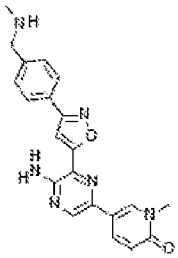
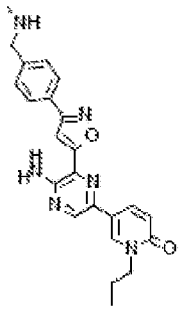
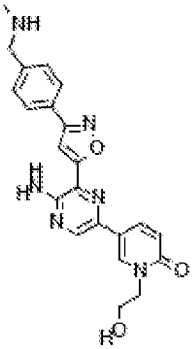
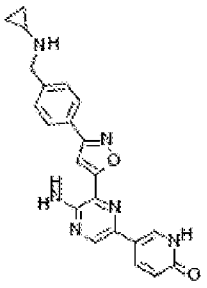
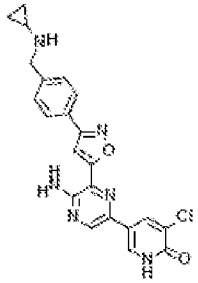
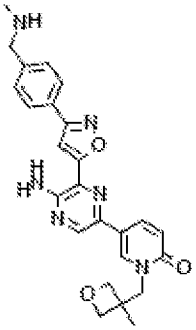
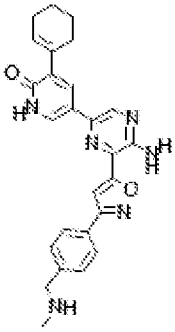
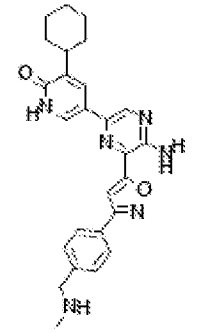
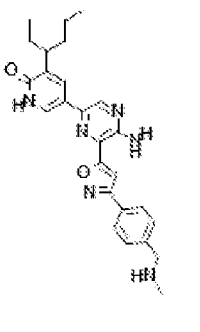
			
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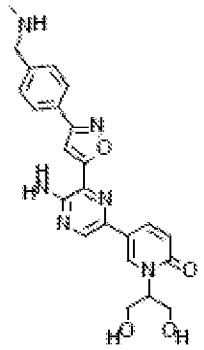
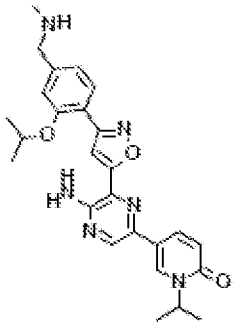
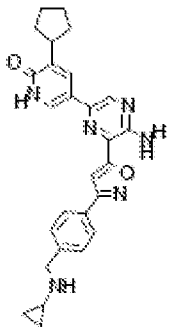
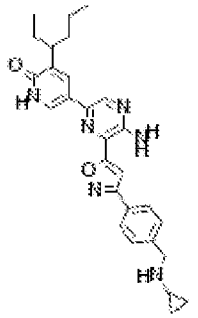
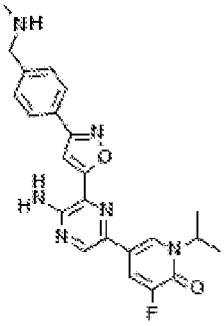
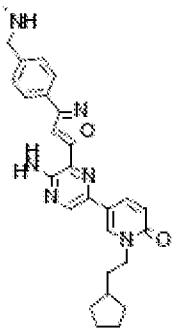
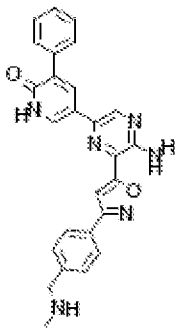
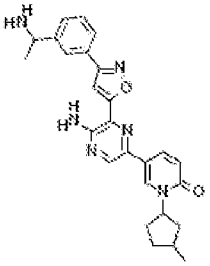
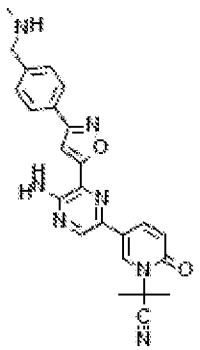
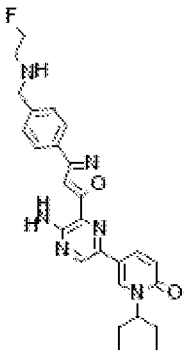
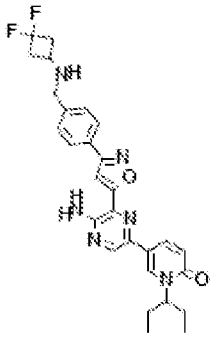
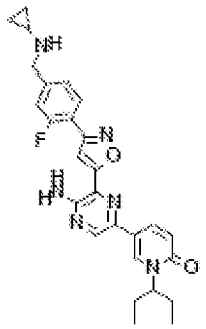
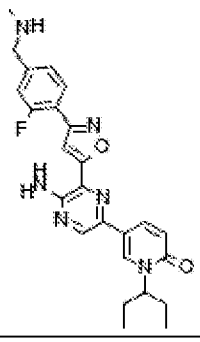
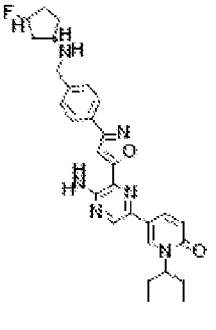
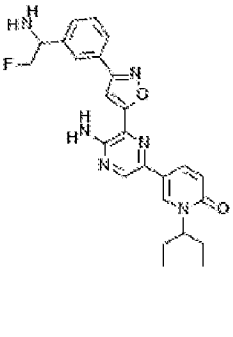
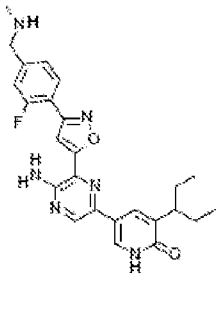
			
I-37	I-38	I-39	I-40
			
I-41	I-42	I-43	I-44
			
I-45	I-46	I-47	I-48
			
I-49	I-50	I-51	I-52

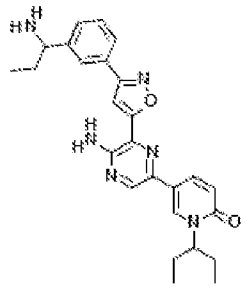
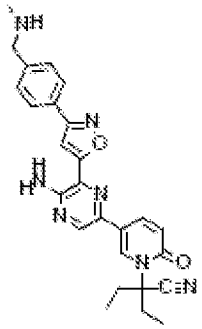
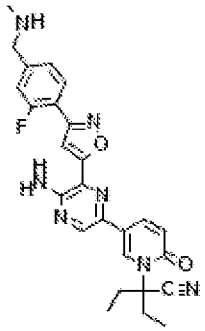
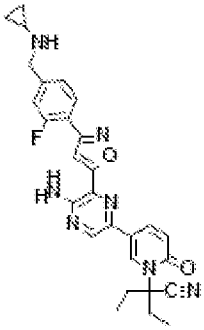
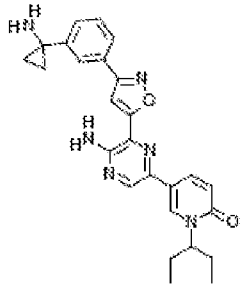
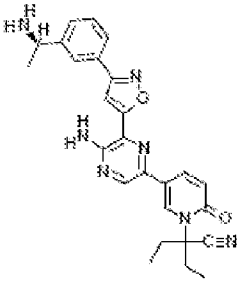
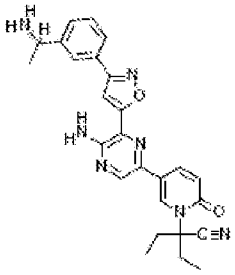
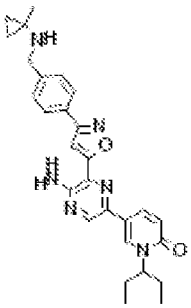
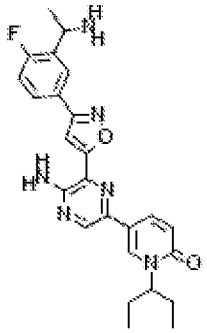
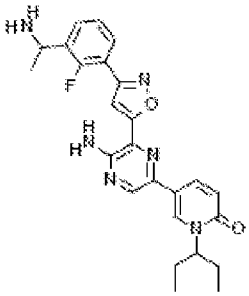
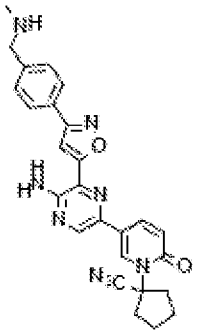
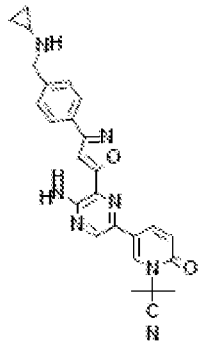
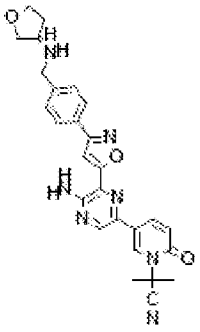
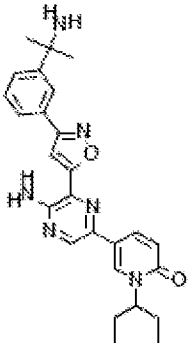
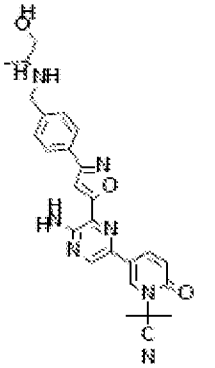
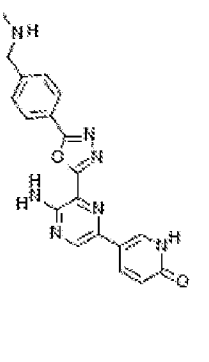
			
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I-57	I-58	I-59	I-60
			
I-61	I-62	I-63	I-64
			
I-65	I-66	I-67	I-68

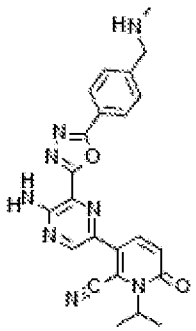
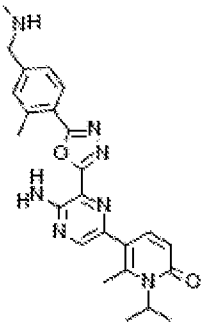
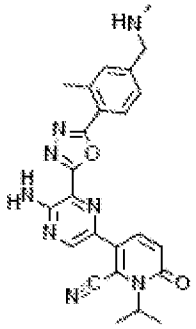
			
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I-77	I-78	I-79	I-80
			
I-81	I-82	I-83	I-84

			
I-85	I-86	I-87	I-88
			
I-89	I-90	I-91	I-92
			
I-93	I-94	I-95	I-96
			
I-97	I-98	I-99	I-100

			
I-101	I-102	I-103	I-104
			
I-105	I-106	I-107	I-108
			
I-109	I-110	I-111	I-112
			
I-113	I-114	I-115	I-116

			
I-117	I-118	I-119	I-120
			
I-121	I-122	I-123	I-124
			
I-125	I-126	I-127	I-128
			
I-129	I-130	I-131	I-132

			
I-133	I-134	I-135	I-136
			
I-137	I-138	I-139	I-140
			
I-141	I-142	I-143	I-144
			
I-145	I-146	I-147	I-148

			
I-149	I-150	I-151	

36. A pharmaceutical composition comprising a compound of any one of claims 1-35 and a pharmaceutically acceptable carrier.

37. A method for treating cancer in a patient comprising administering a compound of any one of claims 1-35 or a pharmaceutically acceptable derivative thereof.

38. The method of claim 37, further comprising administering to said patient an additional therapeutic agent selected from a DNA-damaging agent; wherein said additional therapeutic agent is appropriate for the disease being treated; and said additional therapeutic agent is administered together with said compound as a single dosage form or separately from said compound as part of a multiple dosage form.

39. The method of claim 38, wherein said DNA-damaging agent is selected chemotherapy or radiation treatment.

40. The method of claim 38, wherein said DNA-damaging agent is selected from ionizing radiation, radiomimetic neocarzinostatin, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, an antimetabolite, an alkylating agent, an alkyl sulphonates, or an antibiotic.

41. The method of claim 40, wherein said DNA-damaging agent is selected from ionizing radiation, a platinating agent, a Topo I inhibitor, a Topo II inhibitor, or an antibiotic.

42. The method of claim 41, wherein said platinating agent is selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, Lobaplatin, Triplatin Tetranitrate, Picoplatin, Satraplatin, ProLindac and Aroplatin; said Topo I inhibitor is selected from

Camptothecin, Topotecan, Irinotecan/SN38, Rubitecan and Belotecan; said Topo II inhibitor is selected from Etoposide, Daunorubicin, Doxorubicin, Aclarubicin, Epirubicin, Idarubicin, Amrubicin, Pirarubicin, Valrubicin, Zorubicin and Teniposide; said antimetabolite is selected from Aminopterin, Methotrexate, Pemetrexed, Raltitrexed, Pentostatin, Cladribine, Clofarabine, Fludarabine, Thioguanine, Mercaptopurine, Fluorouracil, Capecitabine, Tegafur, Carmofur, Floxuridine, Cytarabine, Gemcitabine, Azacitidine and Hydroxyurea; said alkylating agent is selected from Mechlorethamine, Cyclophosphamide, Ifosfamide, Trofosfamide, Chlorambucil, Melphalan, Prednimustine, Bendamustine, Uramustine, Estramustine, Carmustine, Lomustine, Semustine, Fotemustine, Nimustine, Ranimustine, Streptozocin, Busulfan, Mannosulfan, Treosulfan, Carboquone, ThioTEPA, Triaziquone, Triethylenemelamine, Procarbazine, Dacarbazine, Temozolomide, Altretamine, Mitobronitol, Actinomycin, Bleomycin, Mitomycin and Plicamycin.

43. The method of claim 42, wherein said platinating agent is selected from Cisplatin, Oxaliplatin, Carboplatin, Nedaplatin, or Satraplatin; said Topo I inhibitor is selected from Camptothecin, Topotecan, irinotecan/SN38, rubitecan; said Topo II inhibitor is selected from Etoposide; said antimetabolite is selected from methotrexate, pemetrexed, Thioguanine, Fludarabine, Cladribine, Cytarabine, gemcitabine, 6-Mercaptopurine, or 5-Fluorouracil; said alkylating agent is selected from nitrogen mustards, nitrosoureas, triazenes, alkyl sulfonates, Procarbazine, or aziridines; and said antibiotic is selected from Hydroxyurea, Anthracyclines, Anthracenediones, or Streptomyces family.

44. The method of claim 41 wherein said DNA-damaging agent is a platinating agent or ionizing radiation.

45. The method of any one of claims 37-44, wherein said cancer is a solid tumor selected from the following cancers: Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma),

stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal; rectum, Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma , undifferentiated thyroid cancer, medullary thyroid carcinoma, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma.

46. The method of claim 45, wherein said cancer is selected from lung cancer, head and neck cancer, pancreatic cancer, gastric cancer, and brain cancer.

47. A method of promoting cell death in cancer cells comprising administering to a patient a compound of any one of claims 1-35.

48. A method of preventing cell repair from DNA damage comprising administering to a patient a compound of any one of claims 1-35.

49. A method of inhibiting ATR in a biological sample comprising the step of contacting a compound of any one of claims 1-35 with said biological sample.

50. The method of claim 49, wherein said biological sample is a cell.

51. A method of sensitizing cells to DNA damaging agents comprising administering to a patient a compound of any one of claims 1-35.

52. The method of any one of claims 37-51, wherein said cell is a cancer cell having defects in the ATM signaling cascade.

53. The method of claim 52, wherein said defect is altered expression or activity of one or more of the following: ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1 or H2AX.

54. The method of any one of claims 37-51, wherein said cell is a cancer cell expressing DNA damaging oncogenes.

55. The method of claim 54, wherein said cancer cell has altered expression or activity of one or more of the following: K-Ras, N-Ras, H-Ras, Raf, Myc, Mos, E2F, Cdc25A, CDC4, CDK2, Cyclin E, Cyclin A and Rb.

56. Use of a compound of any one of claims 1-35 as a radio-sensitizer or a chemo-sensitizer.

57. Use of a compound according to any one of claims 1-35 as a single agent (monotherapy) for treating cancer.

58. Use of according to any one of claims 1-35 for treating patients having cancer with a DNA-damage response (DDR) defect.

59. The use according to claim 58, wherein said defect is a mutation or loss of ATM, p53, CHK2, MRE11, RAD50, NBS1, 53BP1, MDC1, or H2AX.