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(54) Title: DIKETO AZOLOPIPERIDINES AND AZOLOPIPERAZINES AS ANTI-HIV AGENTS

(57) Abstract: Compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use are set forth. In particular, diketo fused azolopiperidine and azolopiperazine derivatives that possess unique antiviral activity are provided. These compounds are useful the treatment of HIV and AIDS.

DIKETO AZOLOPIPERIDINES AND AZOLOPIPERAZINES AS ANTI-HIV AGENTS

FIELD OF THE INVENTION

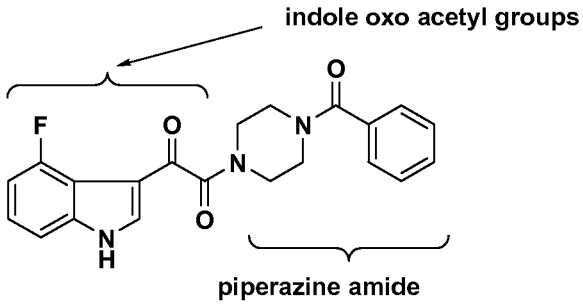
[0001] This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and methods of use. In particular, the disclosure is directed to diketo fused azolopiperidine and azolopiperazine derivatives that possess unique antiviral activity. More particularly, the present disclosure relates to compounds useful for the treatment of HIV and AIDS.

BACKGROUND OF THE INVENTION

[0002] HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 45 million people infected worldwide at the end of 2007. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2005, approximately 5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations: zidovudine (or AZT or RETROVIR®), didanosine (or VIDEX®), stavudine (or ZERIT®), lamivudine (or 3TC or EPIVIR®), zalcitabine (or DDC or HIVID®), abacavir succinate (or ZIAGEN®), tenofovir disoproxil fumarate salt (or VIREAD®), emtricitabine (or FTC - EMTRIVA®), COMBIVIR® (contains - 3TC plus AZT), TRIZIVIR® (contains abacavir, lamivudine, and zidovudine), Epzicom (contains abacavir and lamivudine), TRUVADA® (contains VIREAD® and EMTRIVA®); non-nucleoside reverse transcriptase inhibitors: nevirapine (or VIRAMUNE®), delavirdine (or RESCRIPTOR®) and efavirenz (or SUSTIVA®), Atripla (TRUVADA® + SUSTIVA®), and etravirine, and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, KALETRA® (lopinavir and Ritonavir), darunavir, atazanavir (REYATAZ®) and tipranavir (APTIVUS®), and integrase inhibitors such as raltegravir (Isentress), and entry inhibitors such as enfuvirtide (T-20) (FUZEON®) and maraviroc (Selzentry).

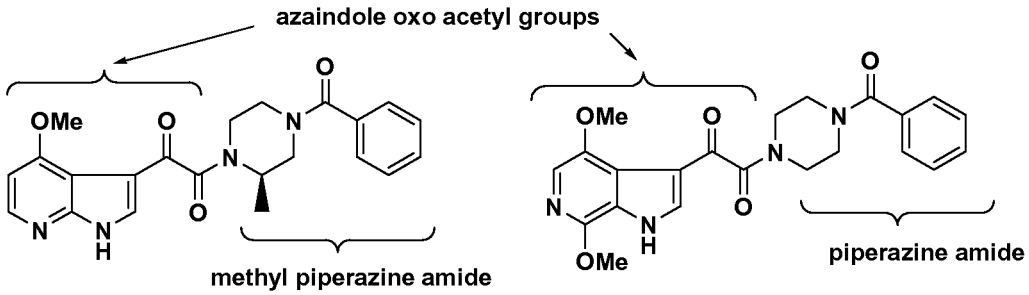
[0003] Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients may ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (*e.g.*, most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present. Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options. Improved HIV fusion inhibitors and HIV entry coreceptor antagonists are two examples of new classes of anti-HIV agents further being studied by a number of investigators.

[0004] HIV attachment inhibitors are a novel subclass of antiviral compounds that bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents. A disclosure describing indoles of which the structure shown below for BMS-705 is representative, has been disclosed (Antiviral Indoleoxoacetyl Piperazine Derivatives).



BMS-705

[0005] Two other compounds, referred to in the literature as BMS-806 and BMS-043 have been described in both the academic and patent art:



BMS-806 **BMS-043**

[0006] Some description of their properties in human clinical trials has been disclosed in the literature.

[0007] It should be noted that in all three of these structures, a piperazine amide (in these three structures a piperazine phenyl amide) is present and this group is directly attached to an oxoacetyl moiety. The oxoacetyl group is attached at the 3-position of 4-fluoro indole in BMS-705 and to the 3 position of substituted azaindoles in BMS-806 and BMS-043.

[0008] In an effort to obtain improved anti-HIV compounds, later publications described in part, modified substitution patterns on the indoles and azaindoles. Examples of such efforts include: (1) novel substituted indoleoxoacetic piperazine derivatives, (2) substituted piperazinyloxoacetylindole derivatives, and (3) substituted azaindoleoxoacetic piperazine derivatives.

[0009] Replacement of these groups with other heteroaromatics or substituted heteroaromatics or bicyclic hydrocarbons was also shown to be feasible. Examples include: (1) indole, azaindole and related heterocyclic amidopiperazine derivatives; (2) bicyclo 4.4.0 antiviral derivatives; and (3) diazaindole derivatives.

[0010] A select few replacements for the piperazine amide portion of the molecules have also been described in the art and among these examples are (1) some piperidine alkenes; (2) some pyrrolidine amides; (3) some N-aryl or heteroaryl piperazines; (4) some piperazinyl ureas; and (5) some carboline containing compounds.

[0011] Method(s) for preparing prodrugs for this class of compounds are disclosed in Prodrugs of Piperazine and Substituted Piperidine Antiviral Agents (Ueda et al., U.S. non-provisional application Serial. No. 11/066,745, filed February 25, 2005 or U.S. Publication No. 2005/0209246 or WO 2005/090367 A1).

[0012] A published PCT patent application WO 2003/103607 A1 (June 11, 2003) disclosures an assay useful for assaying some HIV inhibitors.

[0013] Several published patent applications describe combination studies with piperazine benzamide inhibitors, for example, U.S. Publication No. 2005/0215543 (WO 2005/102328 A1), U.S. Publication No. 2005/0215544 (WO 2005/102391 A1), and U.S. Publication No. 2005/0215545 (WO 2005/102392 A2).

[0014] A publication on new compounds in this class of attachment inhibitors (Wang, J. et al., *Org. Biol. Chem.*, 3:1781-1786 (2005)) and a patent application on some more remotely related compounds have appeared WO 2005/016344 published on February 24, 2005.

[0015] Published patent applications WO 2005/016344 and WO 2005/121094 also describe piperazine derivatives which are HIV inhibitors. Other references in the HIV attachment area include U.S. Publication Nos. 2007/0155702, 2007/0078141 and 2007/0287712, WO 2007/103456, as well as U.S. Patent Nos. 7,348,337 and 7,354,924. A literature reference is *J. Med. Chem.*, 50:6535 (2007).

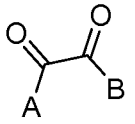
[0016] What is therefore needed in the art are new HIV attachment inhibitor compounds, and compositions thereof, which are efficacious against HIV infection. The compounds described in the foregoing references are structurally distinct from the compounds of the present invention hereinafter described.

SUMMARY OF THE INVENTION

[0017] The present invention provides compounds of Formula I below, the pharmaceutically acceptable salts and/or solvates (*e.g.*, hydrates) thereof, their

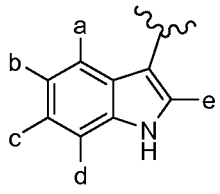
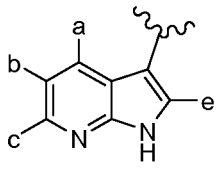
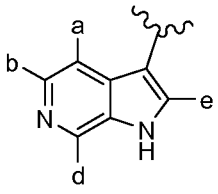
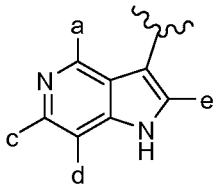
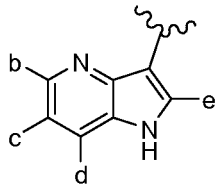
pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, their pharmaceutically acceptable salts and/or solvates are effective antiviral agents, particularly as inhibitors of HIV. They are useful for the treatment of HIV and AIDS.

[0018] One embodiment of the present invention is directed to a compound of Formula I, including pharmaceutically acceptable salts thereof:

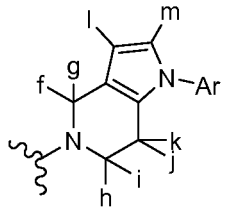
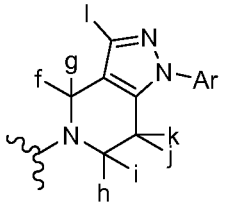
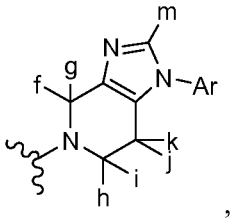
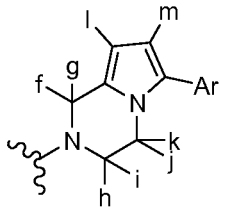
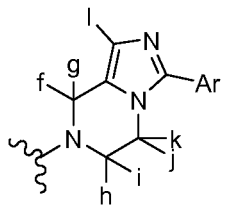
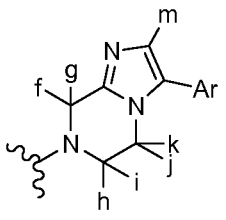
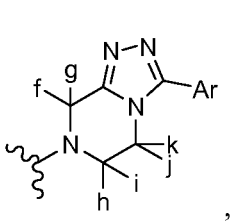
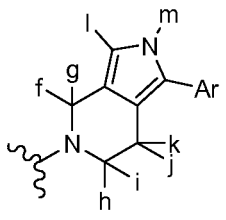


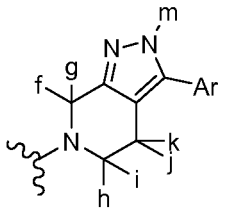
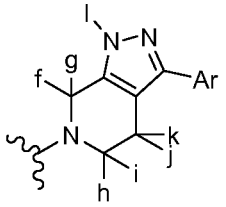
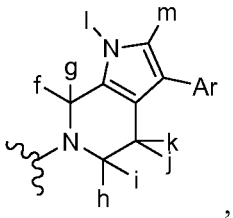
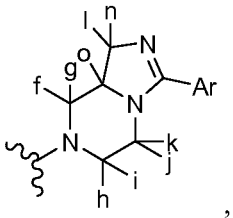
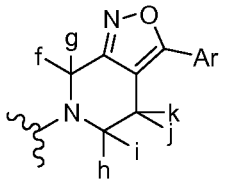
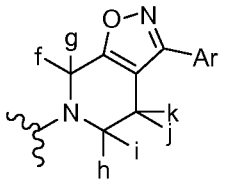
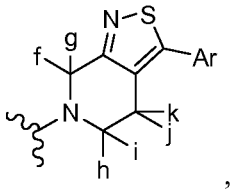
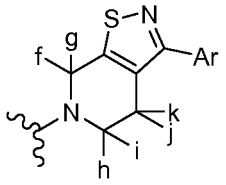
I

wherein A is selected from the group consisting of:


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and 
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wherein B is selected from the group consisting of:


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, and

;

and further wherein

a is selected from the group consisting of H, halogen and methoxy;

b and c are selected from the group consisting of H and halogen;

d is selected from the group consisting of H, halogen, methoxy and Group C;

e is H;

f and g are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein f and g can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

h and i are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein h and i can be connected by a carbon, oxygen, nitrogen or sulfur atom to form a ring;

j and k are selected from the group consisting of H, F, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein j and k can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

and further wherein j + k is C=O;

l and m are selected from the group consisting of H, OH, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, OR, halogen (attached to carbon only), OR, NR_1R_2, COOR, $CONR_1R_2$, and Group D;

n and o are selected from the group consisting of H, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$), COOR, $CONR_1R_2$ and Group D;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

Group C is selected from the group consisting of COOR, $CONR_1R_2$, and Group D;

Group D is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

Group E is selected from the group consisting of OH, OR, NR_1R_2, CN, COOR, $CONR_1R_2$, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, N R_1R_2, COOR, and $CONR_1R_2$;

R, R_1 and R_2 are independently H, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl group; and wherein R_1 and R_2 can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring.

[0019] Another embodiment of the present invention is directed to a method for treating mammals infected with a virus, especially wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I above, and one or more pharmaceutically acceptable carriers, excipients or diluents. Optionally, the compound of Formula I can be administered in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

[0020] Another embodiment of the present invention is a pharmaceutical composition comprising an antiviral effective amount of a compound of Formula I and one or more pharmaceutically acceptable carriers, excipients, diluents and optionally in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) other HIV entry inhibitors.

[0021] In another embodiment of the invention there is provided one or more methods for making the compounds of Formula I.

[0022] The present invention is directed to these, as well as other important ends, hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0023] Since the compounds of the present disclosure may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the present disclosure includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

Definitions

[0024] Unless otherwise specifically set forth elsewhere in the application, one or more of the following terms may be used herein, and shall have the following meanings:

[0025] The term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, amyl, hexyl and the like.

[0026] "C_1 –C_4 fluoroalkyl" refers to F-substituted C_1 –C_4 alkyl wherein at least one H atom is substituted with F atom, and each H atom can be independently substituted by F atom;

[0027] "Halogen" refers to chlorine, bromine, iodine or fluorine.

[0028] An "aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic(*i.e.*, rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and $-NR^xR^y$, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

[0029] As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (*i.e.*, rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an N-oxide is chemically

feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl. diazinyl, pyrazine, triazinyl, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thioalkoxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

[0030] As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encompass systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

[0031] An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; *e.g.*, "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3

carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

[0032] A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (*i.e.*, rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexene, cycloheptane, cycloheptene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

[0033] An "alkenyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon double bond.

[0034] An "alkynyl" group refers to an alkyl group, as defined herein, having at least two carbon atoms and at least one carbon-carbon triple bond.

[0035] A "hydroxy" group refers to an –OH group.

[0036] An "alkoxy" group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

[0037] An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

[0038] A "heteroaryloxy" group refers to a heteroaryl-O- group with heteroaryl as defined herein.

[0039] A "heteroalicycloxy" group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

[0040] A "thiohydroxy" group refers to an –SH group.

[0041] A "thioalkoxy" group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

[0042] A "thioaryloxy" group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

[0043] A "thioheteroaryloxy" group refers to a heteroaryl-S- group with heteroaryl as defined herein.

[0044] A "thioheteroalicycloxy" group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

[0045] A "carbonyl" group refers to a –C(=O)-R″ group, where R″ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

[0046] An "aldehyde" group refers to a carbonyl group where R″ is hydrogen.

[0047] A "thiocarbonyl" group refers to a –C(=S)-R″ group, with R″ as defined herein.

[0048] A "Keto" group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroalicyclic group.

[0049] A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

[0050] A "C-carboxy" group refers to a –C(=O)O-R″ groups, with R″ as defined herein.

[0051] An "O-carboxy" group refers to a R″C(-O)O-group, with R″ as defined herein.

[0052] A "carboxylic acid" group refers to a C-carboxy group in which R″ is hydrogen.

[0053] A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

[0054] A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

[0055] A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^x$- group with Z as defined above and R^x being H or (C_{1-6})alkyl.

[0056] A "sulfinyl" group refers to a $-S(=O)-R''$ group, with R″ being (C_{1-6})alkyl.

[0057] A "sulfonyl" group refers to a $-S(=O)_2R''$ group with R″ being (C_{1-6})alkyl.

[0058] A "S-sulfonamido" group refers to a $-S(=O)_2NR^XR^Y$, with R^X and R^Y independently being H or (C_{1-6})alkyl.

[0059] A "N-Sulfonamido" group refers to a $R''S(=O)_2NR_X$- group, with R_x being H or (C_{1-6})alkyl.

[0060] A "O-carbamyl" group refers to a $-OC(=O)NR^xR^y$ group, with R^X and R^Y independently being H or (C_{1-6})alkyl.

[0061] A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0062] A "O-thiocarbamyl" group refers to a $-OC(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0063] A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$- group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0064] An "amino" group refers to an $-NH_2$ group.

[0065] A "C-amido" group refers to a $-C(=O)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0066] A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0067] A "N-amido" group refers to a $R^xC(=O)NR^y$- group, with R^x and R^y independently being H or (C_{1-6})alkyl.

[0068] An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

[0069] A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

[0070] A "guanyl" group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^y independently being H or (C_{1-6})alkyl.

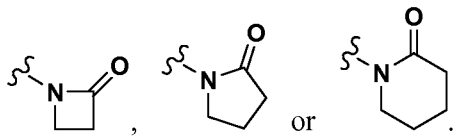
[0071] A "cyano" group refers to a –CN group.

[0072] A "silyl" group refers to a $-Si(R'')_3$, with R'' being (C_{1-6})alkyl or phenyl.

[0073] A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x being (C_{1-6})alkyl.

[0074] A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group, with R^x, R^y, and R^{y2} independently being H or (C_{1-6})alkyl.

[0075] A "4, 5, or 6 membered ring cyclic N-lactam" group refers to



[0076] Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

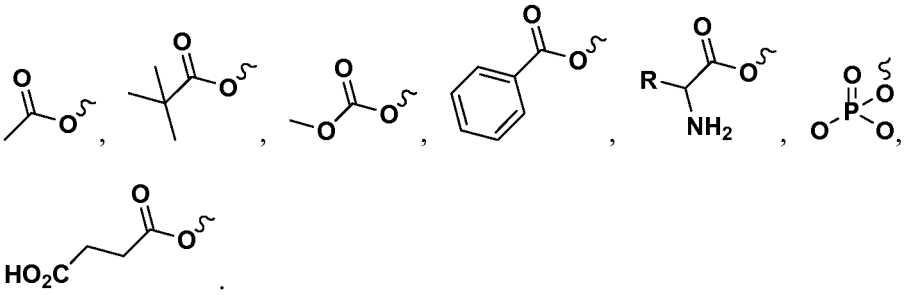
[0077] It is known in the art that nitrogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present disclosure are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

[0078] Pharmaceutically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this disclosure. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid,

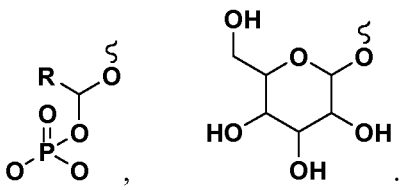
and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (*e.g.*, hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)-aminomethane), or with bases such as piperidine or morpholine.

[0079] As stated above, the compounds of the invention also include "prodrugs". The term "prodrug" as used herein encompasses both the term "prodrug esters" and the term "prodrug ethers". The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of Formula I with either alkyl, alkoxy, or aryl substituted acylating agents or phosphorylating agent employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates, amino acid esters, phosphates, half acid esters such as malonates, succinates or glutarates, and the like. In certain embodiments, amino acid esters may be especially preferred.

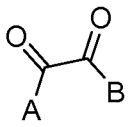
[0080] Examples of such prodrug esters include



[0081] The term "prodrug ethers" include both phosphate acetals and O-glucosides. Representative examples of such prodrug ethers include

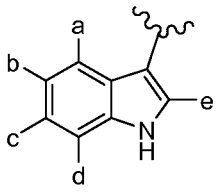
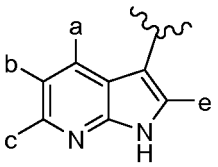
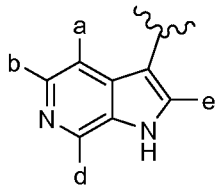
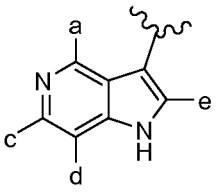
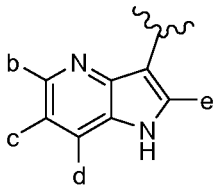


[0082] As set forth above, the invention is directed to compounds of Formula I, including pharmaceutically acceptable salts thereof:

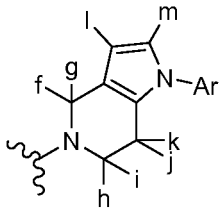
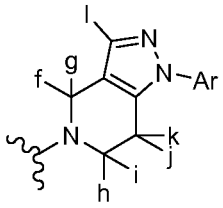
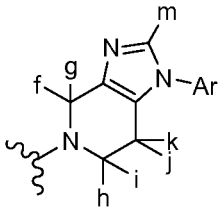
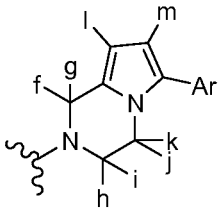


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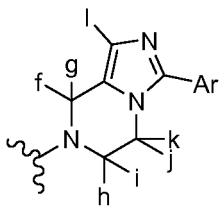
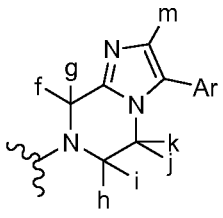
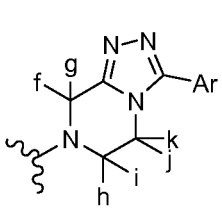
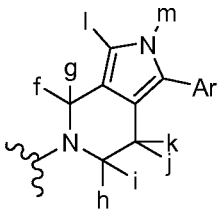
wherein A is selected from the group consisting of:

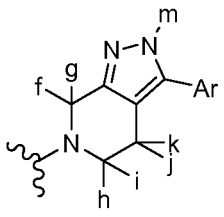
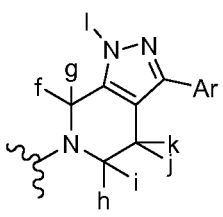
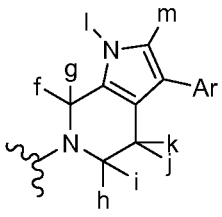
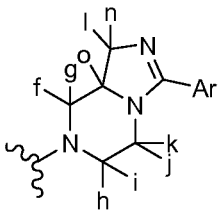

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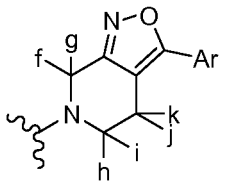
wherein B is selected from the group consisting of:

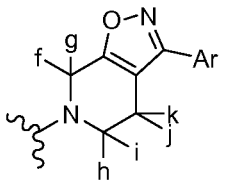

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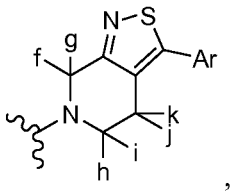
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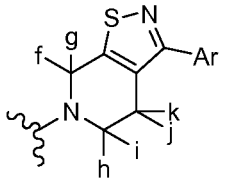

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and further wherein

a is selected from the group consisting of H, halogen and methoxy;

b and c are selected from the group consisting of H and halogen;

d is selected from the group consisting of H, halogen, methoxy and Group C;

e is H;

f and g are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein f and g can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

h and i are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group. wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein h and i can be connected by a carbon, oxygen, nitrogen or sulfur atom to form a ring;

j and k are selected from the group consisting of H, F, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein j and k can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

and further wherein j + k is C=O;

l and m are selected from the group consisting of H, OH, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, OR, halogen (attached to carbon only), OR, NR_1R_2, COOR, $CONR_1R_2$, and Group D;

n and o are selected from the group consisting of H, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$), COOR, $CONR_1R_2$ and Group D;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

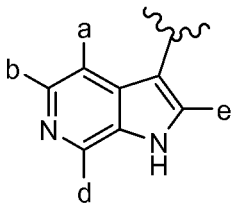
Group C is selected from the group consisting of COOR, $CONR_1R_2$, and Group D;

Group D is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

Group E is selected from the group consisting of OH, OR, NR_1R_2, CN, COOR, $CONR_1R_2$, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, N R_1R_2, COOR, and $CONR_1R_2$;

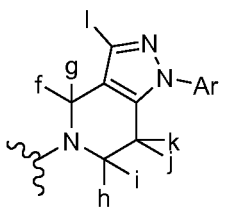
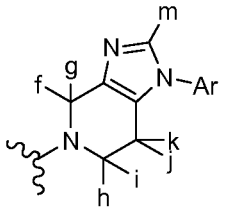
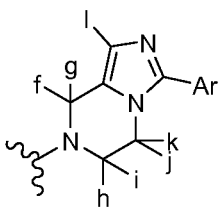
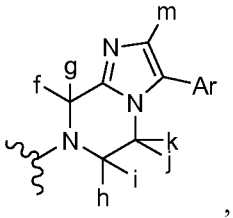
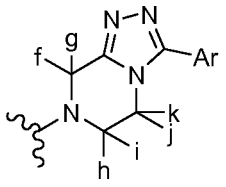
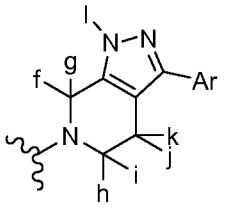
R, R_1 and R_2 are independently H, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl group; and wherein R_1 and R_2 can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring.

[0083] More preferred compounds of the Formula I include those wherein A =



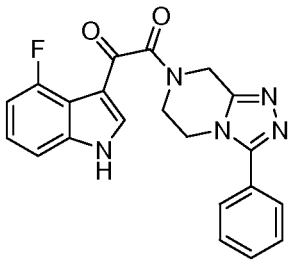
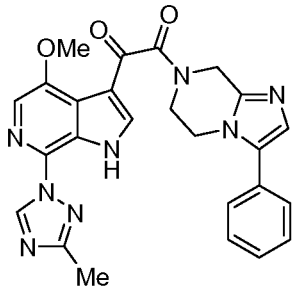
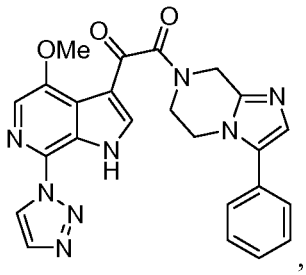
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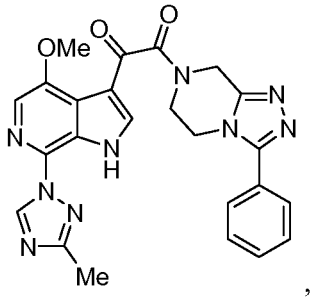
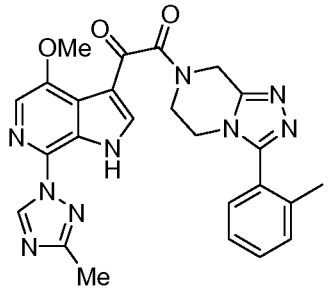
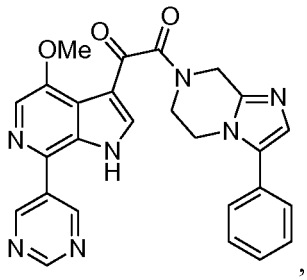
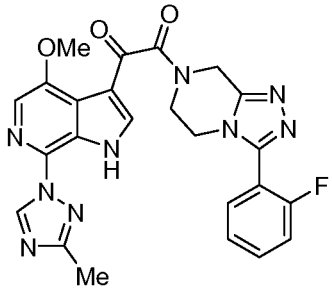
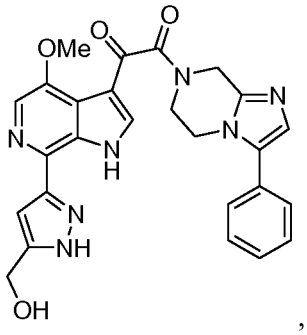
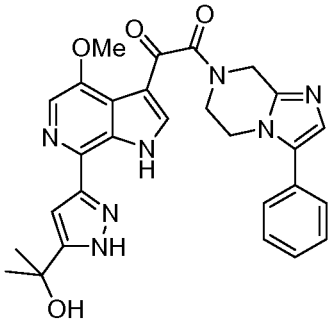
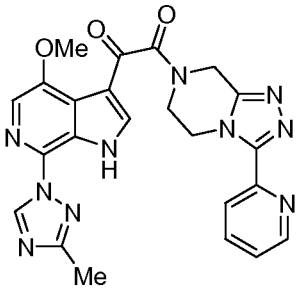
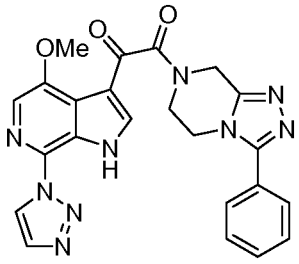
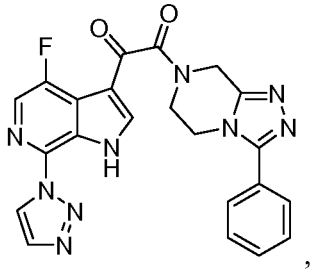
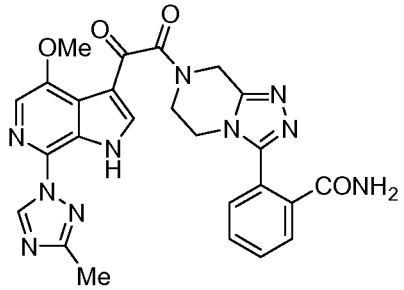
[0084] Also preferred compounds of the Formula I include those wherein B =


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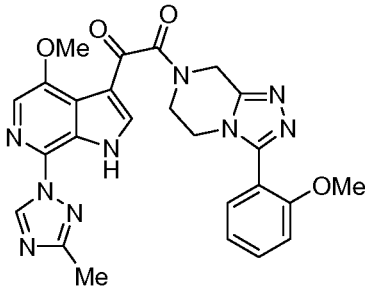
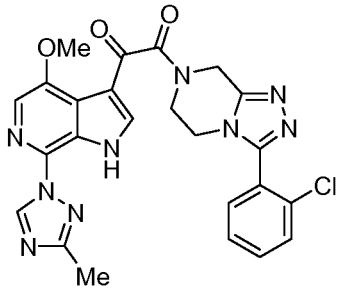
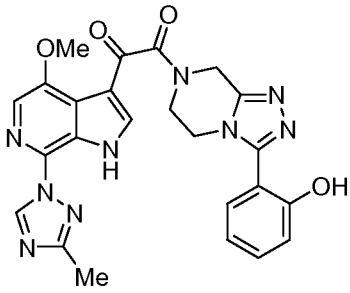
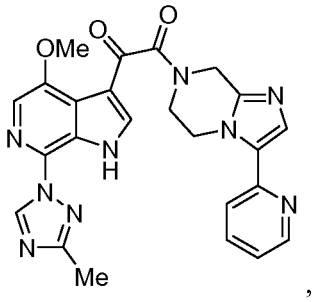
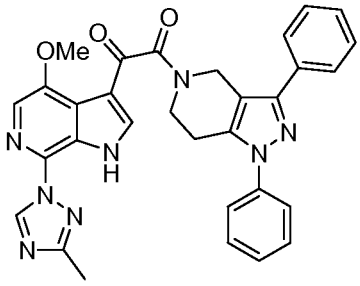
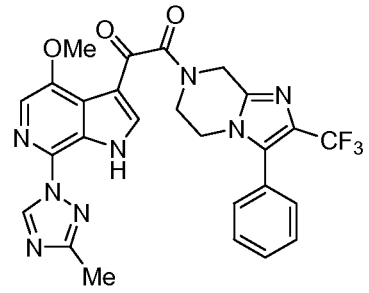
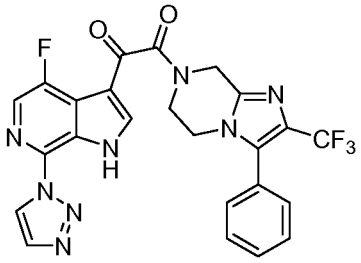
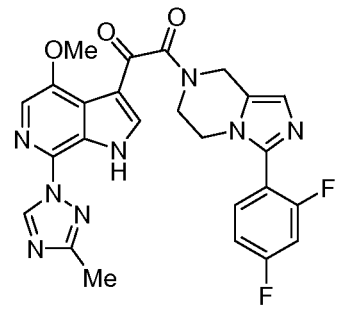
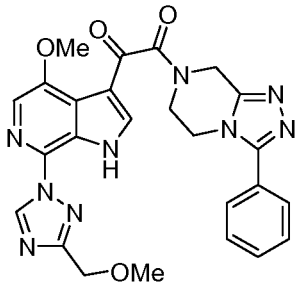
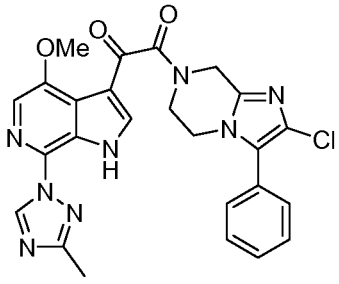
[0085] In another embodiment, both the preferred forms of A and B in the compound of Formula I are as set forth above.

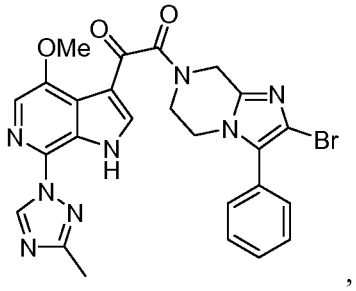
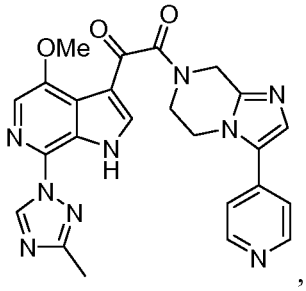
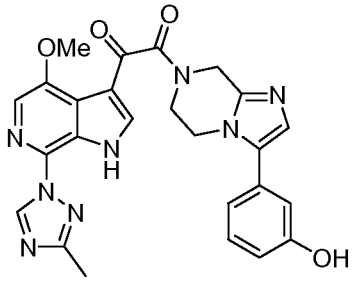
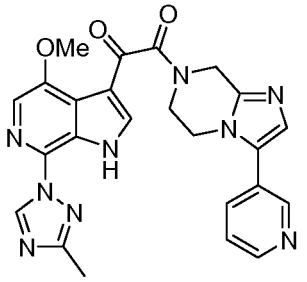
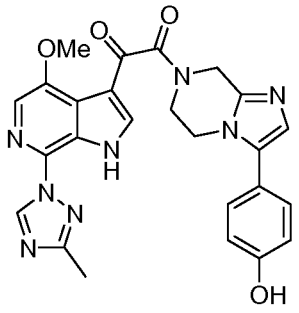
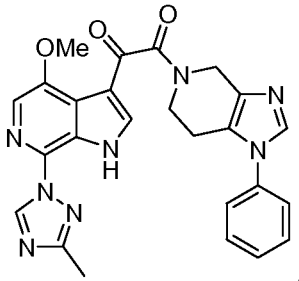
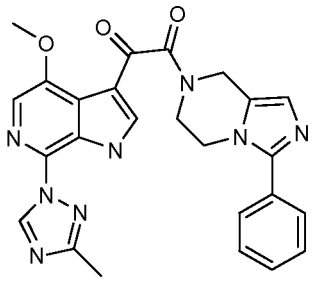
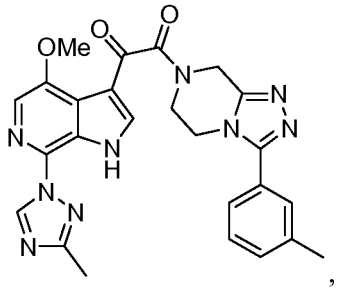
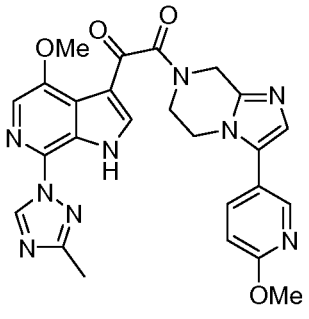
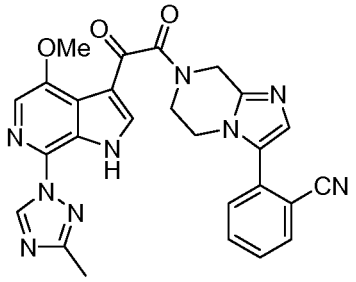
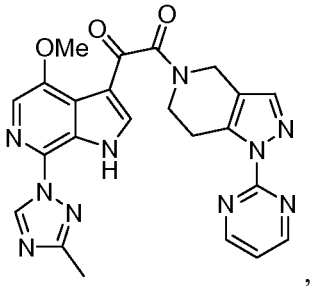
[0086] Particularly preferred compounds of the invention as part of Formula I include the following:


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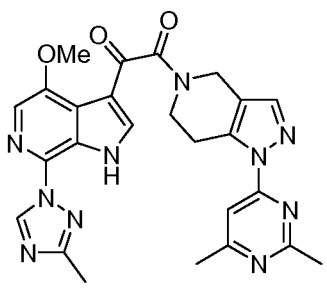
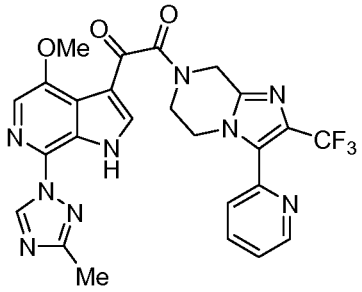
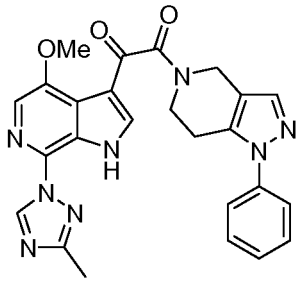
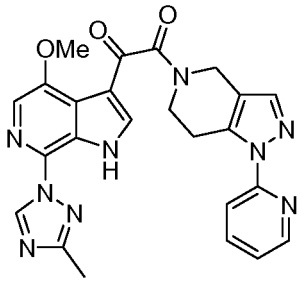
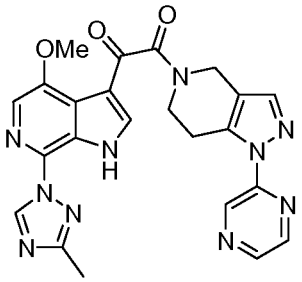
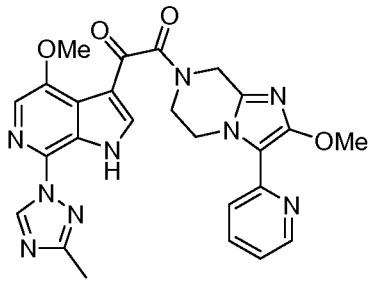
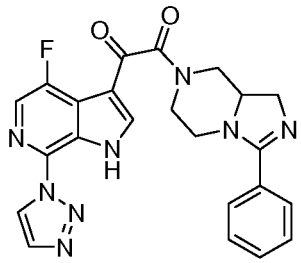
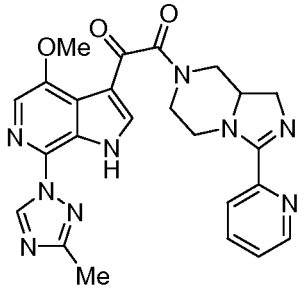
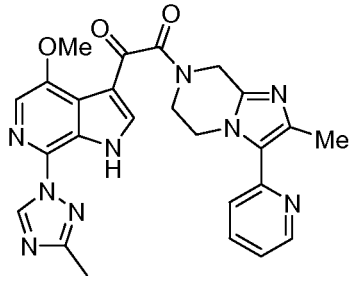
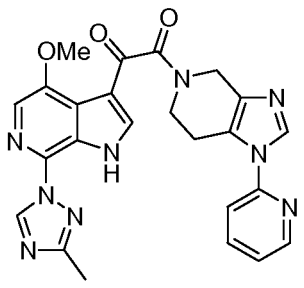
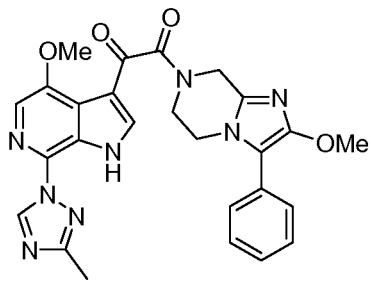

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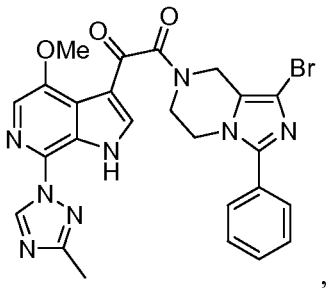
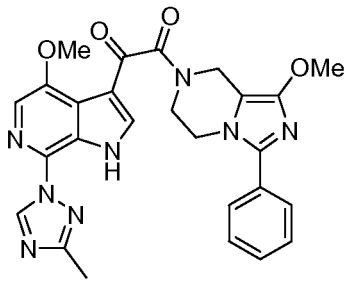
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[0087] The compounds of the present invention, according to all the various embodiments described above, may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, and by other means, in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, excipients and diluents available to the skilled artisan. One or more adjuvants may also be included.

[0088] Thus, in accordance with the present disclosure, there is further provided a method of treatment, and a pharmaceutical composition, for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition which contains an antiviral effective amount of one or more of the compounds of Formula I, together with one or more pharmaceutically acceptable carriers, excipients or diluents. As used herein, the term "antiviral effective amount" means the total amount of each active component of the composition and method that is sufficient to show a meaningful patient benefit, *i.e.*, inhibiting, ameliorating, or healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing, ameliorating or healing diseases associated with HIV infection.

[0089] The pharmaceutical compositions of the invention may be in the form of orally administrable suspensions or tablets; as well as nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleaginous suspensions or

suppositories. Pharmaceutically acceptable carriers, excipients or diluents may be utilized in the pharmaceutical compositions, and are those utilized in the art of pharmaceutical preparations.

[0090] When administered orally as a suspension, these compositions are prepared according to techniques typically known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

[0091] The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

[0092] The compounds of this disclosure can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses, usually over an extended period, such as days, weeks, months, or even years. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

[0093] Also contemplated herein are combinations of the compounds of Formula I herein set forth, together with one or more agents useful in the treatment of AIDS. For example, the compounds of this disclosure may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with

effective amounts of the AIDS antivirals, immunomodulators, anti-infectives, or vaccines, such as those in the following non-limiting table:

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
Amprenavir 141 W94 GW 141	GlaxoWellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	GlaxoWellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection, ARC, PGL, HIV positive, AIDS
Alpha Interferon	GlaxoWellcome	Kaposi's sarcoma, HIV in combination with RETROVIR®

Drug Name	Manufacturer	Indication
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-234475 (CGP-61755)	Bristol-Myers Squibb / Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral CMV retinitis
Darunavir (Prezista)	Tibotec- J & J	HIV infection, AIDS, ARC (protease inhibitor)
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC

Drug Name	Manufacturer	Indication
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266, SUSTIVA®) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, Stocrin	Bristol Myers Squibb	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Etravirine	Tibotec/ J & J	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Famciclovir	SmithKline	Herpes zoster, herpes simplex
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm	HIV infection, AIDS, ARC

Drug Name	Manufacturer	Indication
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	GlaxoWellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS

Drug Name	Manufacturer	Indication
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-Thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Tipranavir	Boehringer Ingelheim	HIV infection, AIDS, ARC (protease inhibitor)
Valaciclovir	GlaxoWellcome	Genital HSV and CMV infections
VIRAZOLE® (Ribavirin)	Viratek/ICN (Costa Mesa, CA)	Asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	GlaxoWellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (VIREAD®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)
EMTRIVA® (Emtricitabine) (FTC)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

Drug Name	Manufacturer	Indication
COMBIVIR®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
Abacavir succinate (or ZIAGEN®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
REYATAZ® (or atazanavir)	Bristol-Myers Squibb	HIV infection, AIDS, protease inhibitor
FUZEON® (enfuvirtide or T-20)	Roche/Trimeris	HIV infection AIDS, viral fusion inhibitor
LEXIVA® (or fosamprenavir calcium)	GSK/Vertex	HIV infection, AIDS, viral protease inhibitor
Selzentry (maraviroc) (UK 427857)	Pfizer	HIV infection, AIDS, (CCR5 antagonist, in development)
TRIZIVIR®	GSK	HIV infection, AIDS, (three drug combination)
Bevirimat	Panacos	HIV infection, AIDS, (maturation inhibitor, in development)
Sch-417690 (vicriviroc)	Schering-Plough	HIV infection, AIDS, (CCR5 antagonist, in development)
TAK-652	Takeda	HIV infection, AIDS, (CCR5 antagonist, in development)
GSK 873140 (ONO-4128)	GSK/ONO	HIV infection, AIDS, (CCR5 antagonist, in development)

Drug Name	Manufacturer	Indication
Integrase Inhibitor MK-0518 Raltegravir	Merck	HIV infection, AIDS
TRUVADA®	Gilead	Combination of Tenofovir disoproxil fumarate salt (VIREAD®) and EMTRIVA® (Emtricitabine)
Integrase Inhibitor GS917/JTK-303 Elvitegravir	Gilead / Japan Tobacco	HIV infection, AIDS, viral integrase inhibitor in development
Triple drug combination Atripla	Gilead / Bristol-Myers Squibb	Combination of Tenofovir disoproxil fumarate salt (VIREAD®), EMTRIVA® (Emtricitabine), and SUSTIVA® (Efavirenz)

IMMUNOMODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	Wyeth Lederle Labs	AIDS, Kaposi's sarcoma
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination with TNF (tumor necrosis factor)

Drug Name	Manufacturer	Indication
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination with AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination with AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination with AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination with AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering-Plough	Kaposi's sarcoma with AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma

Drug Name	Manufacturer	Indication
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination with AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma, AIDS, ARC, in combination with AZT
SK&F106528 Soluble T4	SmithKline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination with gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP

Drug Name	Manufacturer	Indication
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia associated with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia associated with AIDS
Testosterone	ALZA®, SmithKline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

[0094] Additionally, the compounds of the disclosure herein set forth may be used in combination with other HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in *Drugs of the Future*, 24(12):1355-1362 (1999); *Cell*, 9:243-246 (Oct. 29, 1999); and *Drug Discovery Today*, 5(5):183-194 (May 2000) and Meanwell, N.A. et al., "Inhibitors of the entry of HIV into host cells", *Curr. Op. Drug Disc. Dev*, 6(4):451-461 (2003). Specifically the compounds can be utilized in

combination with other attachment inhibitors, fusion inhibitors, and chemokine receptor antagonists aimed at either the CCR5 or CXCR4 coreceptor.

[0095] It will be understood that the scope of combinations of the compounds of this disclosure with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table but includes, in principle, any combination with any pharmaceutical composition useful for the treatment of AIDS.

[0096] Preferred combinations are simultaneous or alternating treatments with a compound of the present disclosure and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is REYATAZ® (active ingredient Atazanavir). Typically a dose of 300 to 600mg is administered once a day. This may be co-administered with a low dose of Ritonavir (50 to 500mgs). Another preferred inhibitor of HIV protease is KALETRA®. Another useful inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N′-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. Patent No. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine. (The preparation of ddC, ddI and AZT are also described in EP 0 484 071.)

[0097] In such combinations the compound of the present disclosure and other active agents may be administered separately or in conjunction. In addition, the

administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

GENERAL CHEMISTRY (METHODS OF SYNTHESIS)

[0098] The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof. General procedures to construct compounds of Formula I and intermediates useful for their synthesis are described in the following Schemes (after the Abbreviations).

Abbreviations

[0099] One or more of the following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, may be used throughout the description of the disclosure and the examples:

h = hour(s)

rt = room temperature

mol = mole(s)

mmol = millimole(s)

g = gram(s)

mg = milligram(s)

mL = milliliter(s)

TFA = trifluoroacetic Acid

DCE = 1,2-Dichloroethane

CH_2Cl_2 = dichloromethane

TPAP = tetrapropylammonium perruthenate

THF = tetrahydrofuran

DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one

DMAP = 4-dimethylaminopyridine

P-EDC = polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

DMF = *N,N*-dimethylformamide

Hunig's Base = *N,N*-diisopropylethylamine

MCPBA = *meta*-chloroperbenzoic acid

azaindole = 1*H*-pyrrolo-pyridine

4-azaindole = 1*H*-pyrrolo[3,2-*b*]pyridine

5-azaindole = 1*H*-pyrrolo[3,2-*c*]pyridine

6-azaindole = 1*H*-pyrrolo[2,3-*c*]pyridine

7-azaindole = 1*H*-pyrrolo[2,3-*b*]pyridine

PMB = 4-methoxybenzyl

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

OTf = trifluoromethanesulfonoxy

NMM = 4-methylmorpholine

PIP-COPh = 1-benzoylpiperazine

NaHMDS = sodium hexamethyldisilazide

EDAC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

TMS = trimethylsilyl

DCM = dichloromethane

DCE = dichloroethane

MeOH = methanol

THF = tetrahydrofuran

EtOAc = ethyl acetate

LDA = lithium diisopropylamide

TMP-Li = 2,2,6,6-tetramethylpiperidinyl lithium

DME = dimethoxyethane

DIBALH = diisobutylaluminum hydride

HOBT = 1-hydroxybenzotriazole

CBZ = benzyloxycarbonyl

PCC = pyridinium chlorochromate

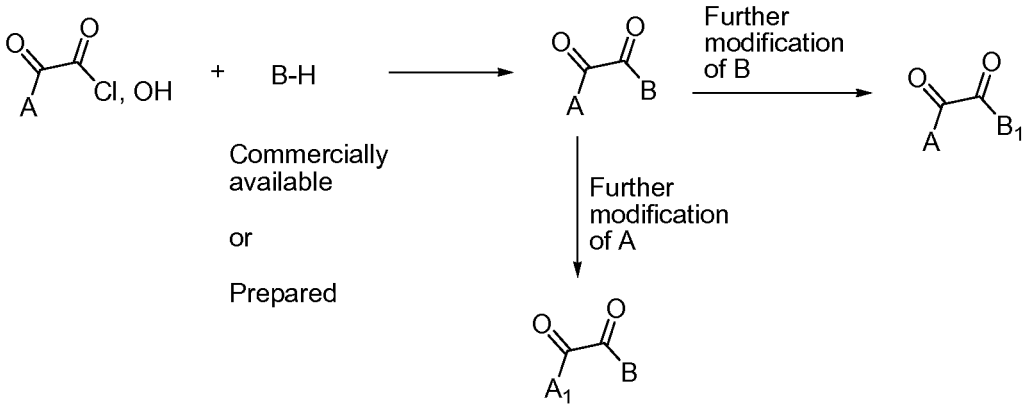
TBTU = O-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate

DEBPT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one

BOP = benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate

Preparation of Compounds of Formula I, Chemistry Schemes

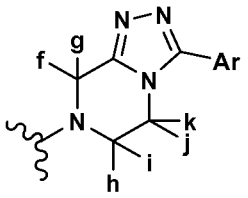
[00100] A general reaction scheme is set forth as follows:



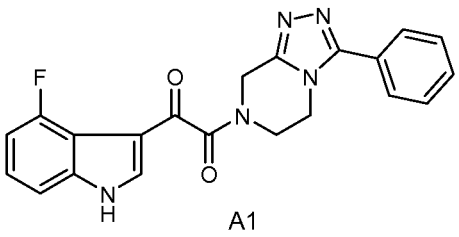
[00101] For the preparation of substituent "A" above, the procedures set forth in U.S. Patent Nos. 6,476,034, 6,573,262, 6,469,006 and 7,354,924, as well as WO 2004/004337 are useful, and are incorporated herein by reference in their entirety.

[00102] Other specialized procedures are as follows:

When B =

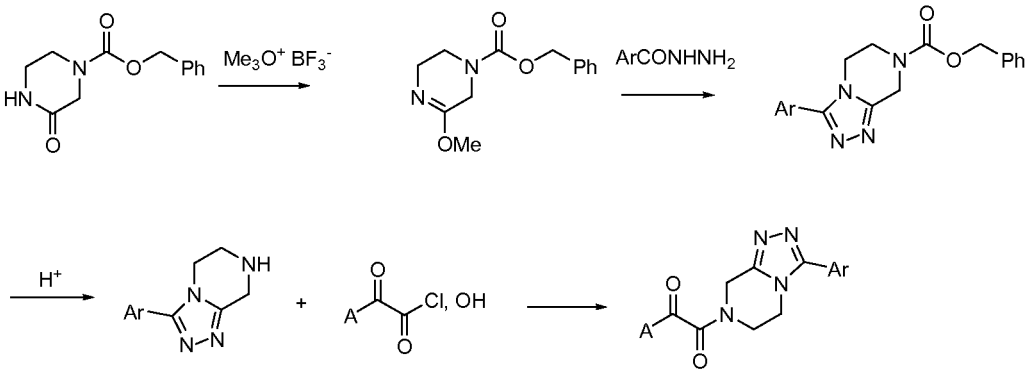


for the preparation of the following compound:

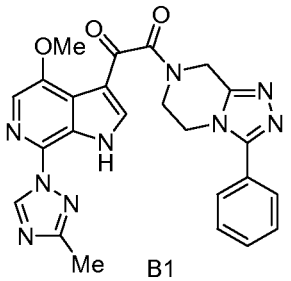


A1

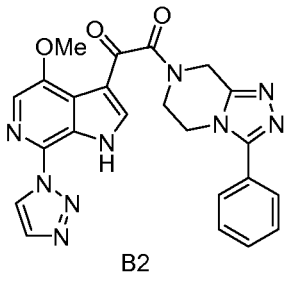
the following reaction scheme may be useful:



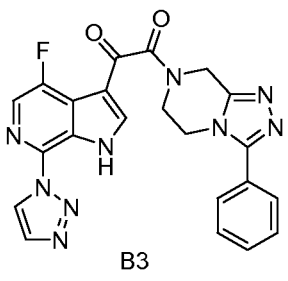
[00103] In another embodiment, for the preparation of the following compounds:



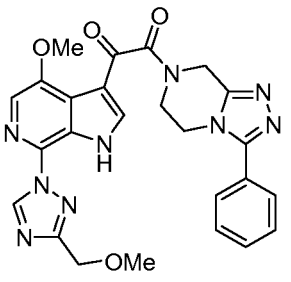
B1



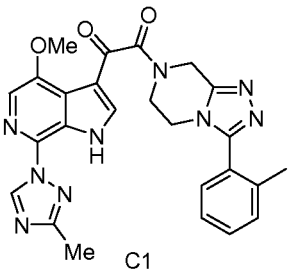
B2



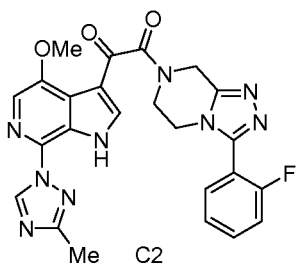
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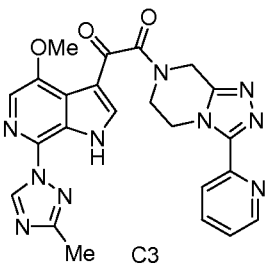
B4



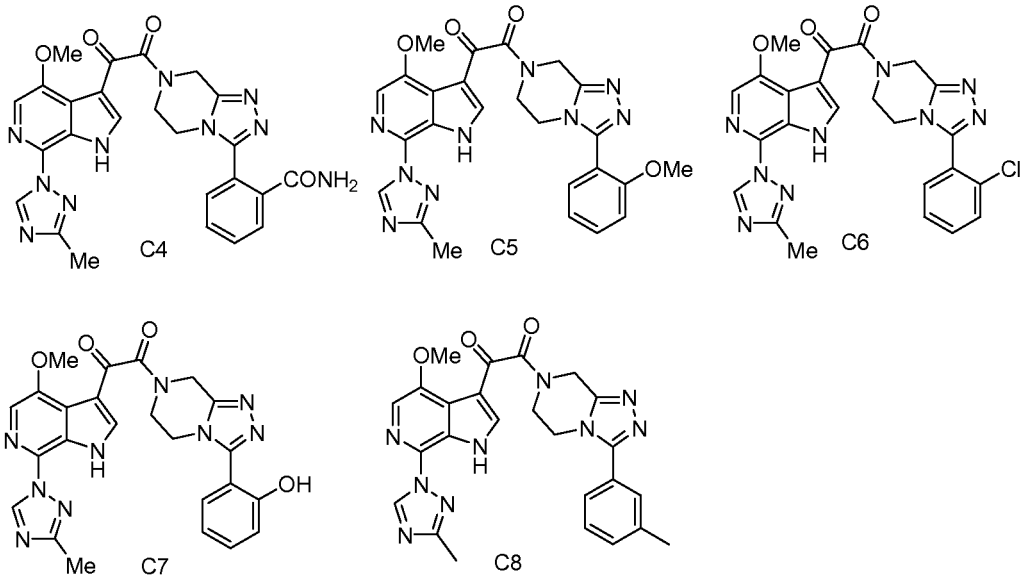
C1



C2

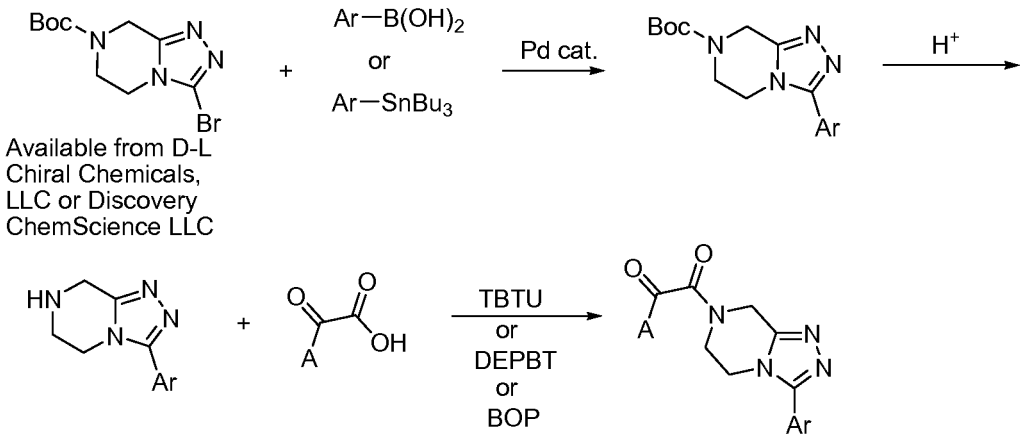


C3

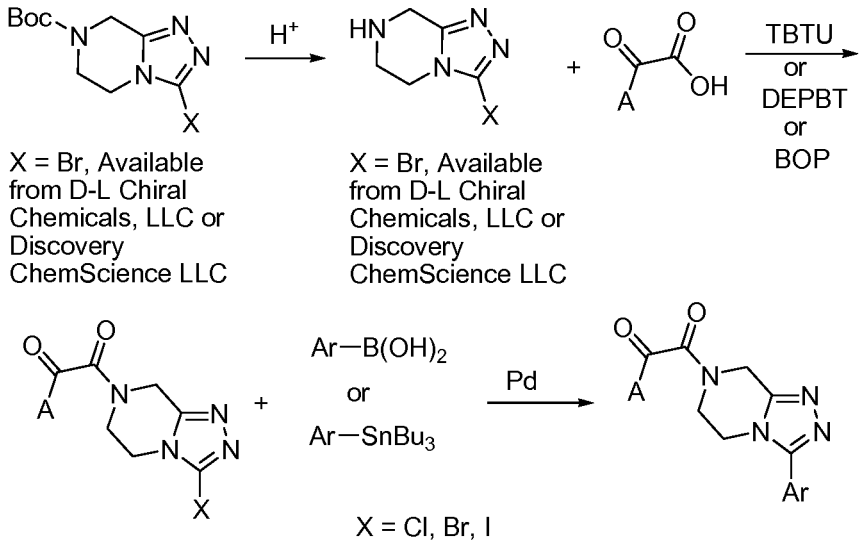


the following schemes may be useful:

Route 1

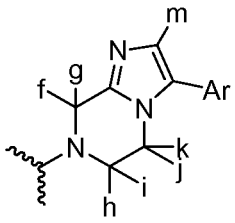


Route 2

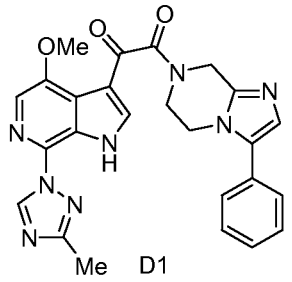


[00104] In another embodiment,

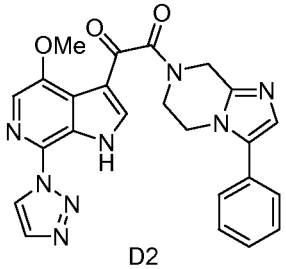
When B =



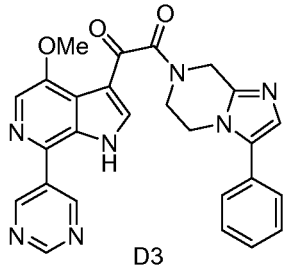
for the following compounds:



D1

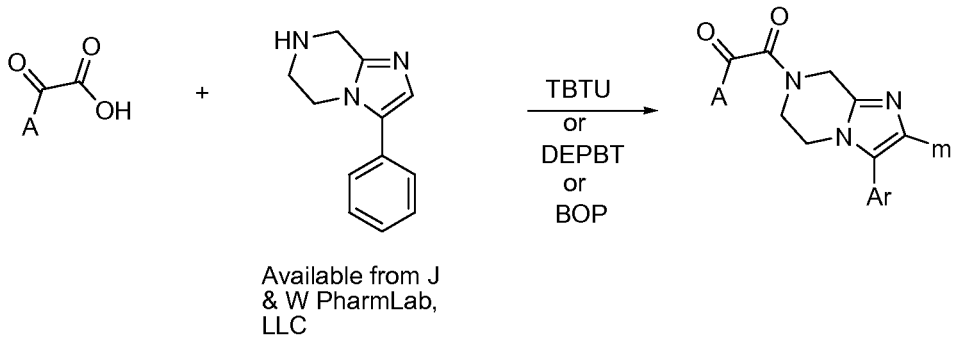


D2

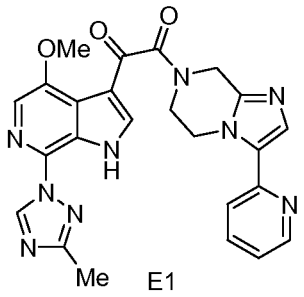


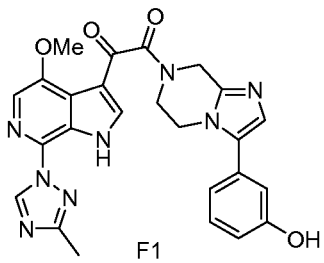
D3

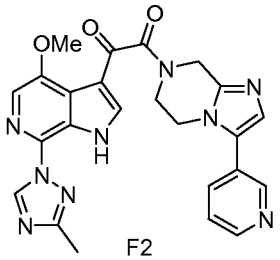
this reaction scheme may be useful:

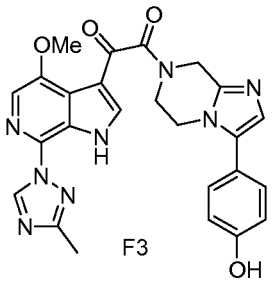


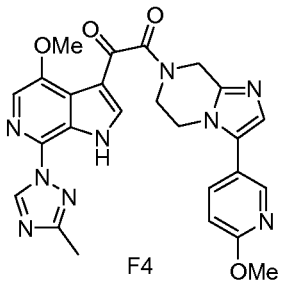
[00105] In another embodiment, to prepare the following compounds

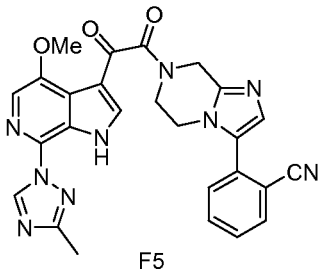

E1

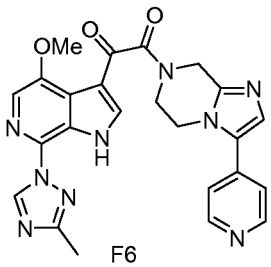

F1


F2


F3

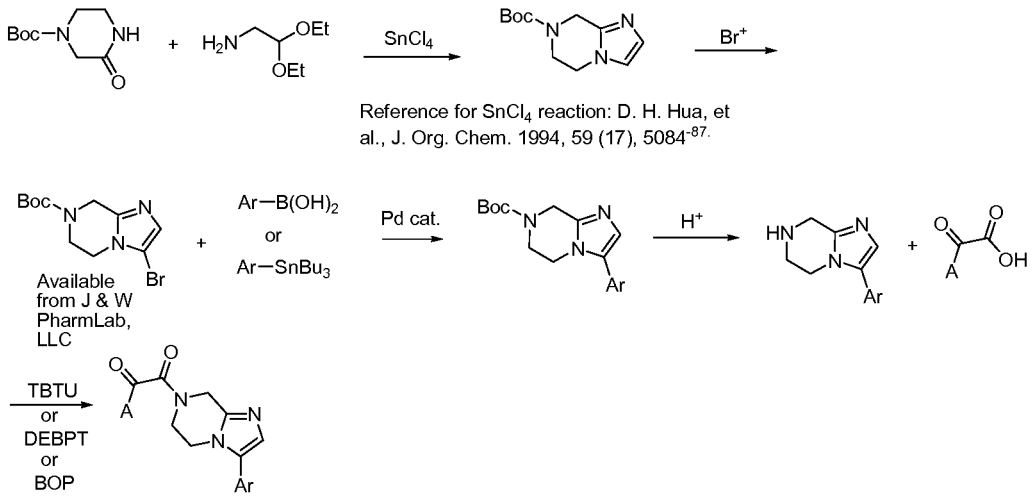

F4


F5

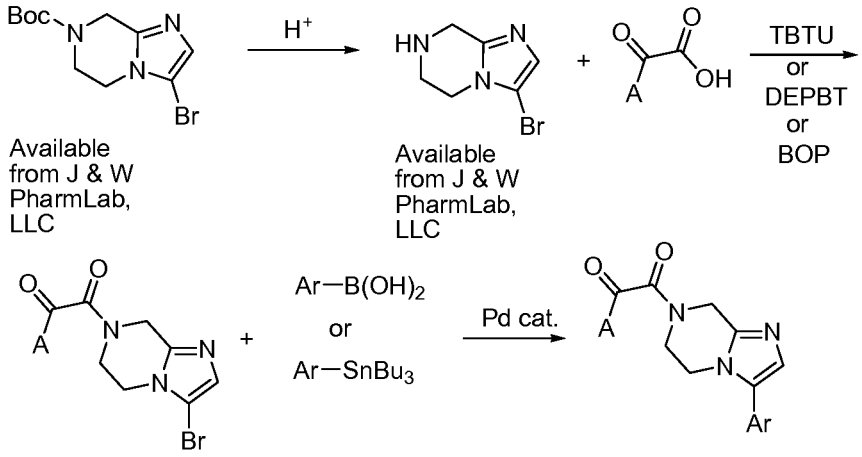

F6

the following reaction schemes may be useful:

Route 1

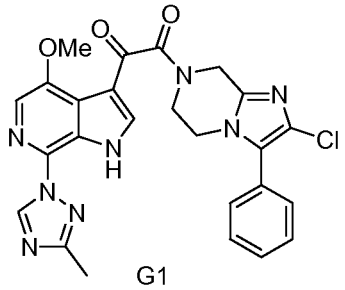


Route 2

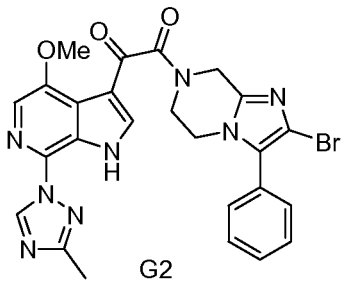


5

[00106] In another embodiment, for the preparation of the following compounds:

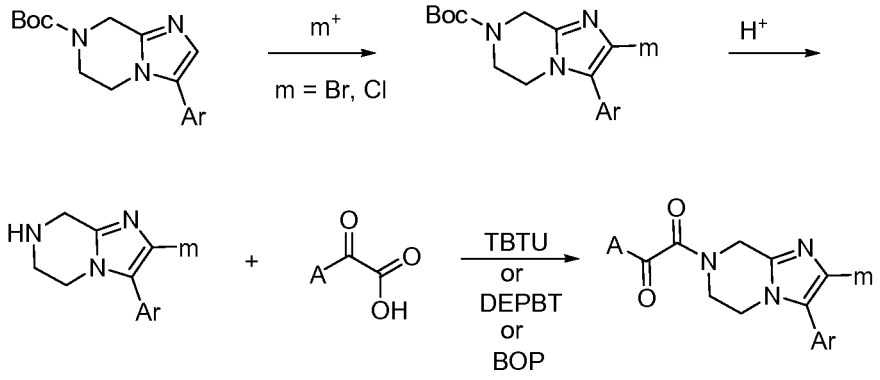


G1

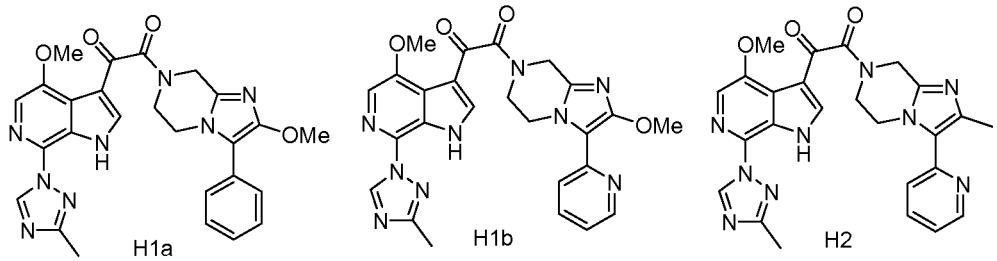


G2

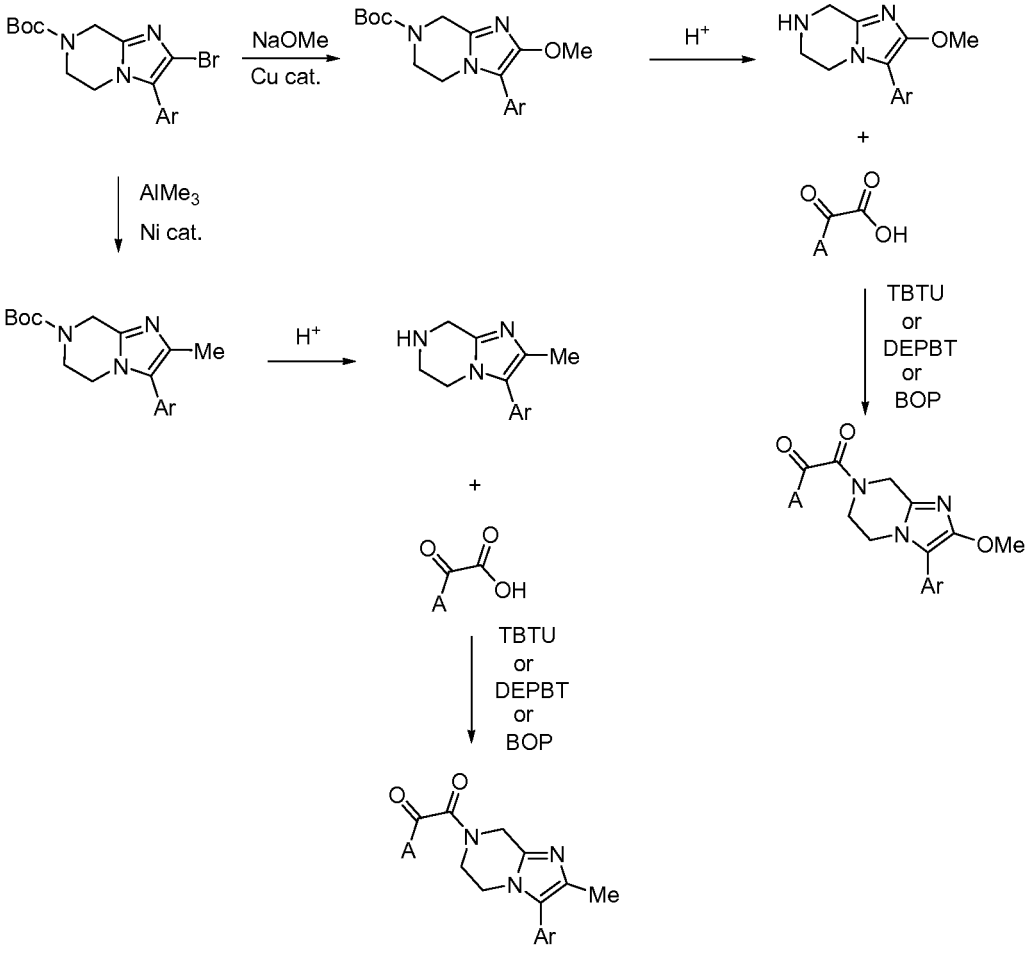
the following reaction may be useful:



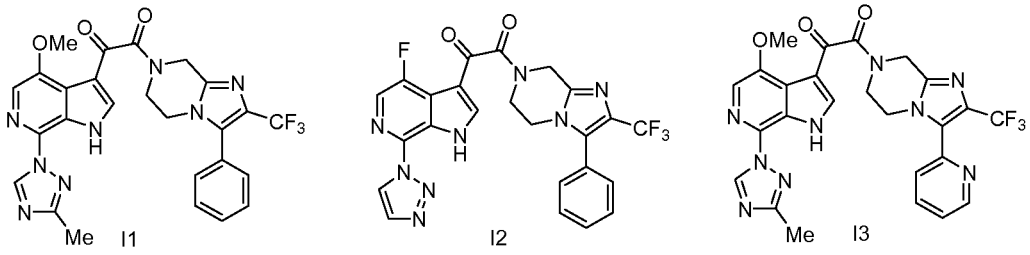
[00107] In another embodiment, for the preparation of the following compounds:



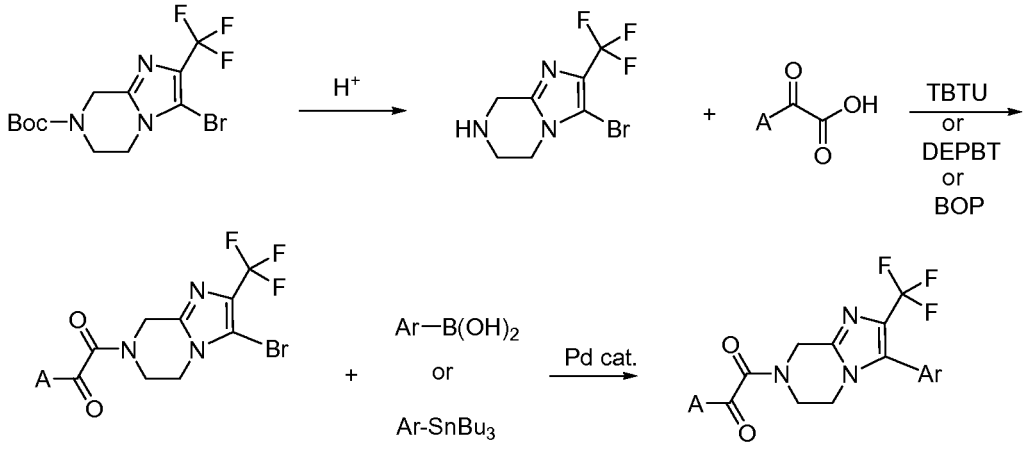
the following reaction schemes may be useful:



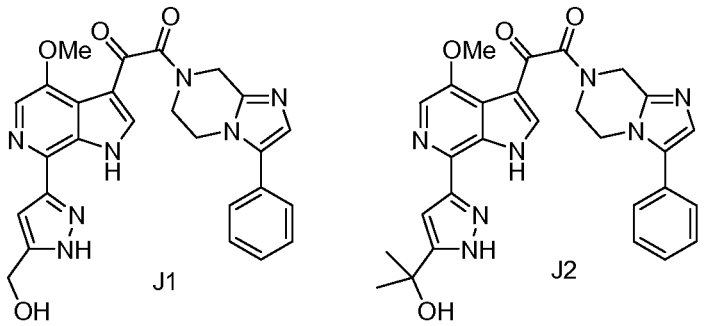
[00108] In another embodiment, for the preparation of the following compounds



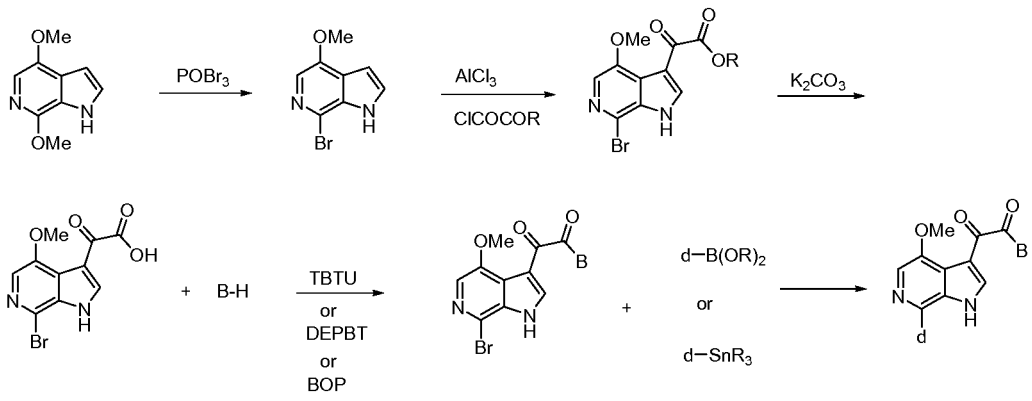
the following reaction scheme may be useful:



[00109] In another embodiment, for the preparation of the following compounds:

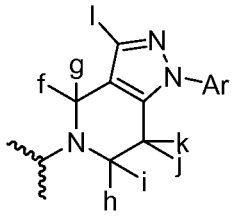


the following reaction scheme may be used:

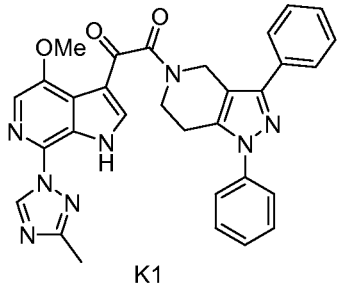


[00110] In another embodiment,

When B =

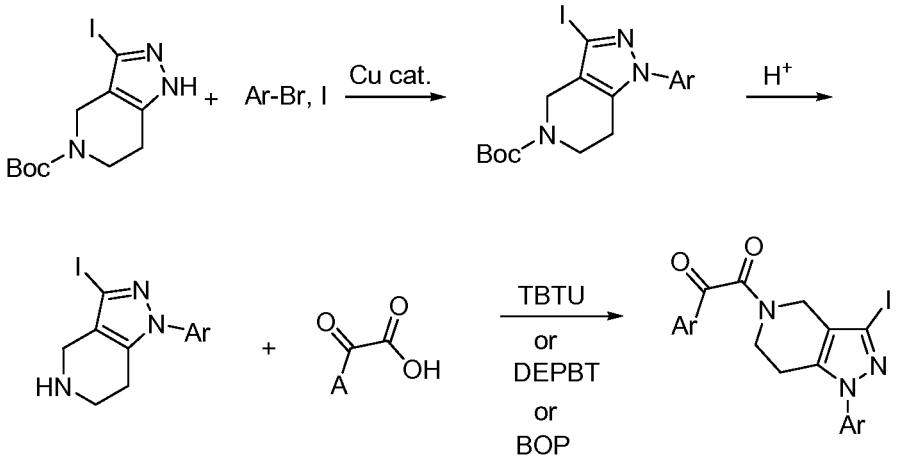


for the following compound:

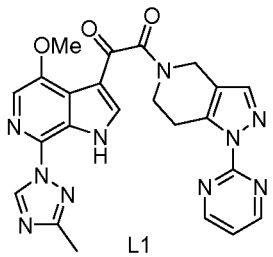


K1

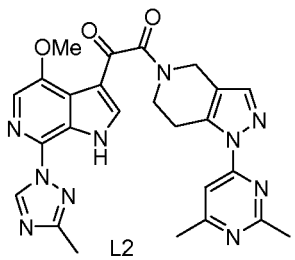
the following reaction scheme may be used:



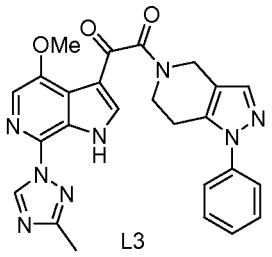
[00111] In another embodiment, for the preparation of the following compounds:



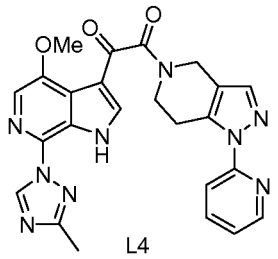
L1

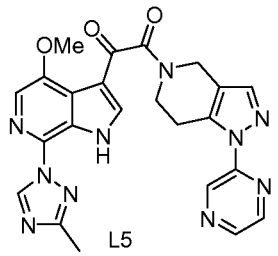


L2

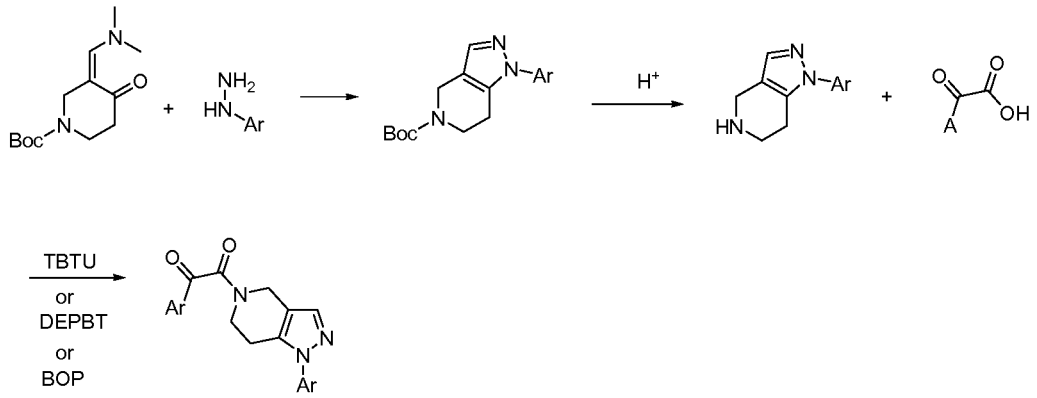


L3


L4

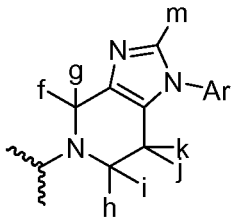

L5

the following reaction may be used:

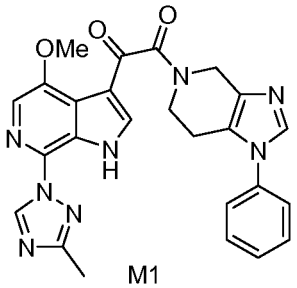


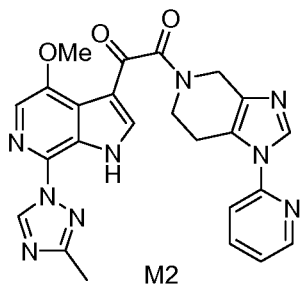
5 **[00112]** In another embodiment,

When B =

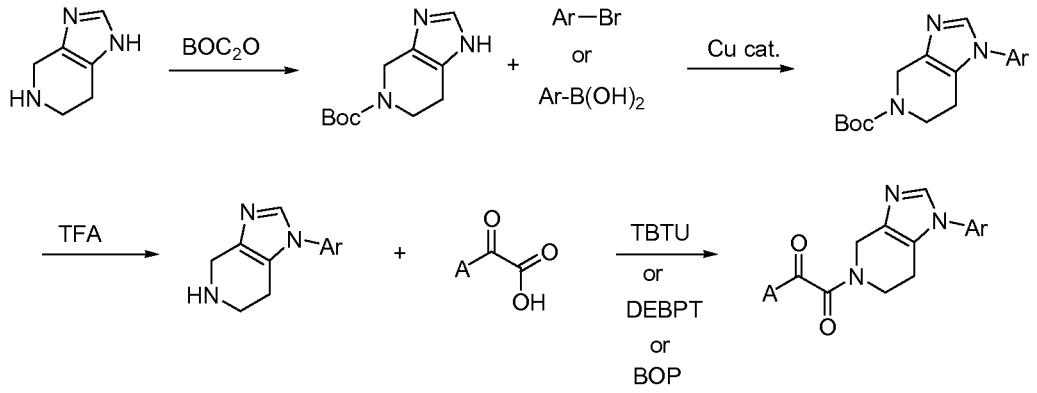


for the preparation of the following compounds:


M1

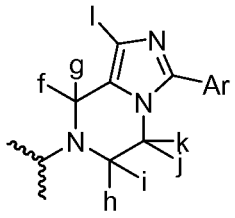

M2

10 the following reaction scheme may be used:

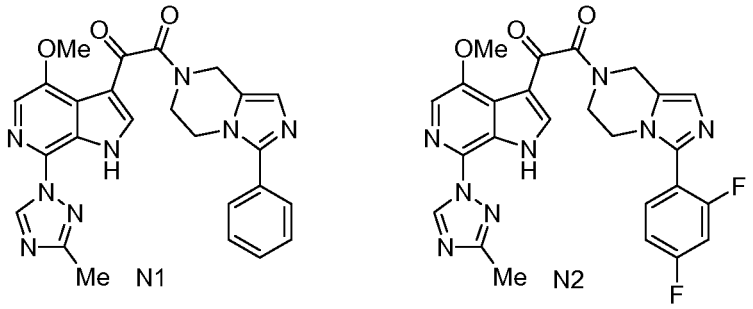


[00113] In another embodiment,

When B =

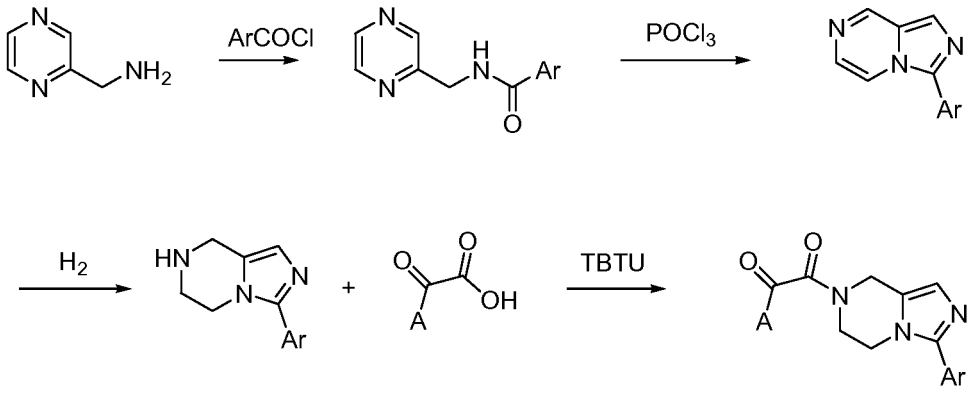


for the preparation of the following compounds:

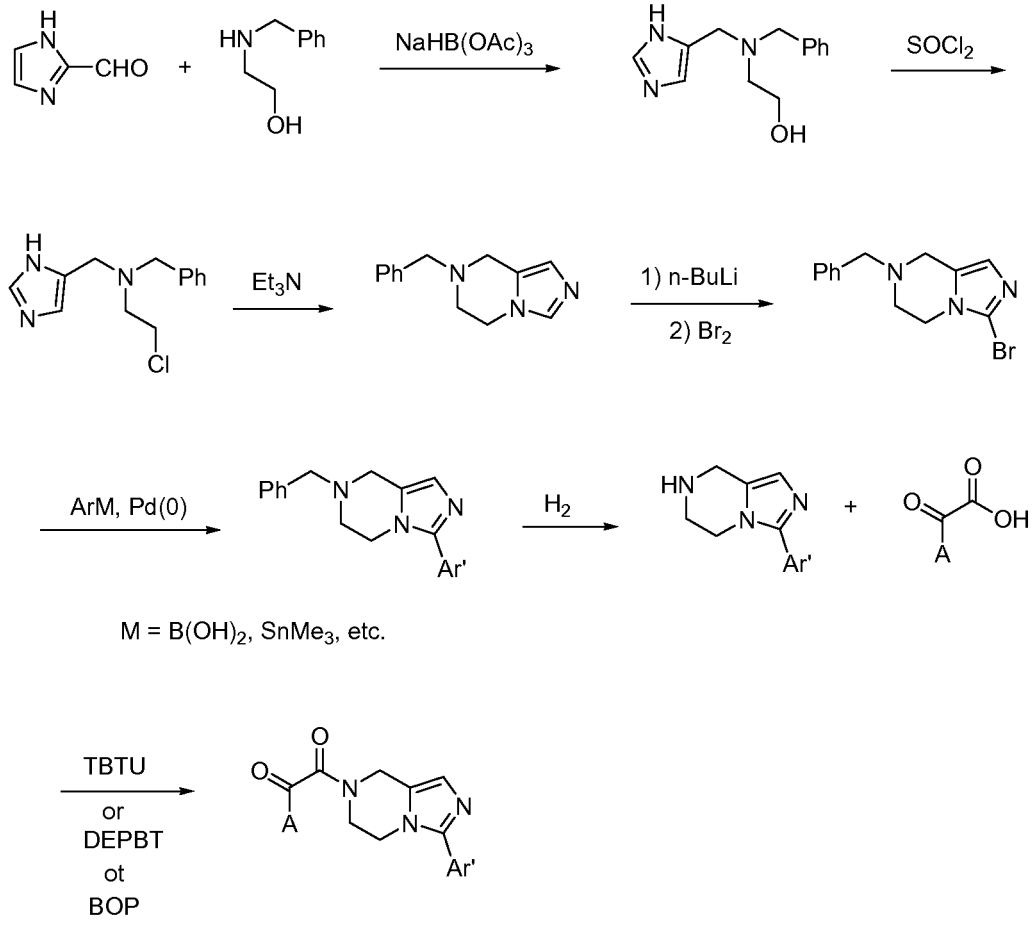


the following reaction schemes may be utilized:

Route 1



Route 2

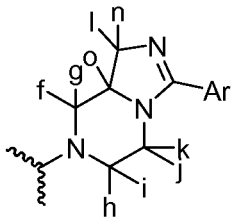


M = $B(OH)_2$, $SnMe_3$, etc.

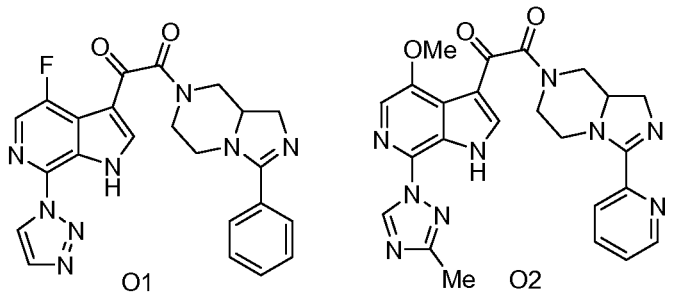
5

[00114] In another embodiment,

When B =

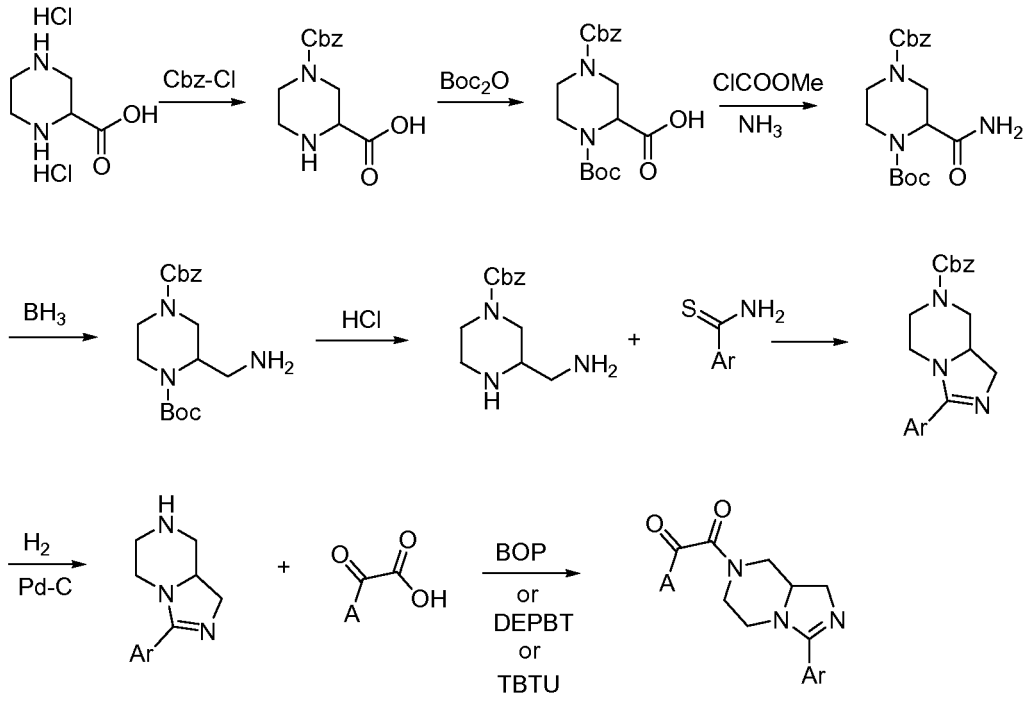


for the preparation of the following compounds:



O1 O2

the following reaction scheme may be used:



EXAMPLES

[00115] The following examples illustrate typical syntheses of the compounds of Formula I as described generally above. These examples are illustrative only and are

not intended to limit the disclosure in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Chemistry

Typical Procedures and Characterization of Selected Examples:

[00116] Unless otherwise stated, solvents and reagents were used directly as obtained from commercial sources, and reactions were performed under a nitrogen atmosphere. Flash chromatography was conducted on Silica gel 60 (0.040-0.063 particle size; EM Science supply). ^{1}H NMR spectra were recorded on Bruker DRX-500f at 500 MHz (or Bruker DPX-300B or Varian Gemini 300 at 300 MHz as stated). The chemical shifts were reported in ppm on the δ scale relative to δTMS = 0. The following internal references were used for the residual protons in the following solvents: $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.30), and DMSO-d_6 (δ_H 2.50). Standard acronyms were employed to describe the multiplicity patterns: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad), app (apparent). The coupling constant (*J*) is in Hertz. All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a MICROMASS® Platform for LC in electrospray mode.

LC/MS Methods (*i.e.*, compound identification)

Method 1:

Start %B = 0, Final %B = 100 over 3 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 5% ACN - 95% H_2O - 10 mm Ammonium Acetate

Solvent B = 95% ACN - 5% H_2O - 10 mm Ammonium Acetate

Column: PHENOMENEX® Luna 4.6 x 50 mm S10

Method 2:

Start %B = 0, Final %B = 100 over 3 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 10% MeOH - 90% H_2O - 0.1% TFA

Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA

Column: PHENOMENEX® Luna 10u C18 3.0 X 50 mm

Method 3:

Start %B = 0, Final %B = 100 over 3 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 90% H_2O – 10% ACN – 0.1% TFA

Solvent B = 10% H_2O – 90% ACN – 0.1% TFA

Column: SunFire C18 5u 4.6 x 50 mm

Method 4:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 90% H_2O – 10% ACN – 0.1% TFA

Solvent B = 10% H_2O – 90% ACN – 0.1% TFA

Column: PHENOMENEX® Luna 4.6 x 50 mm S10

Method 5:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Wavelength = 220

Flow Rate = 4 mL/min

Solvent A = 90% H_2O - 10% MeOH - 0.1% TFA

Solvent B = 10% H_2O - 90% MeOH - 0.1% TFA

Column: PHENOMENEX® LUNA 4.6 x 30 mm S10

Method 6:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Wavelength = 220

Flow Rate = 4 mL/min

Solvent A = 5% ACN - 95% H_2O - 10 mm Ammonium Acetate

Solvent B = 95% ACN - 5% H_2O - 10 mm Ammonium Acetate

Column: PHENOMENEX® LUNA 4.6 x 30 mm S10

Method 7:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Flow Rate = 5 mL/Min

Solvent A = 5% ACN - 95% H_2O - 10 mm Ammonium Acetate

Solvent B = 95% ACN - 5% H_2O - 10 mm Ammonium Acetate

Column: PHENOMENEX® 5u C18 4.6 x 30 mm S10

Method 8:

Start %B = 0, Final %B = 100 over 3 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 10% MeOH - 90% H_2O - 0.1% TFA

Solvent B = 90% MeOH - 10% H_2O - 0.1% TFA

Column: PHENOMENEX® Luna 4.6 X 50 mm S10

Method 9:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Flow Rate = 4 mL/Min

Solvent A = 90% H_2O – 10% MeOH – 0.1% TFA

Solvent B = 10% H_2O – 90% MeOH – 0.1% TFA

Column: PHENOMENEX® LUNA 4.6 x 50 mm S10

Method 10:

Start %B = 0, Final %B = 100 over 2 minute gradient (1 minutes collected after run)

Wavelength = 220

Flow Rate = 4 mL/min

Solvent A = 5% H_2O - 95% MeOH - 0.1% TFA

Solvent B = 95% H_2O - 5% MeOH - 0.1% TFA

Column: PHENOMENEX® LUNA 3.0 x 50 mm S10

Method 11:

Start %B = 0, Final %B = 30 over 2 minute gradient (1 minutes collected after run)
Wavelength = 220
Flow Rate = 4 mL/min
Solvent A = 90% H_2O - 10% MeOH - 0.1% TFA
Solvent B = 10% H_2O - 90% MeOH - 0.1% TFA
Column: PHENOMENEX® LUNA 4.6 x 30 mm S10

Method 12:
Start %B = 0, Final %B = 50 over 2 minute gradient (1 minutes collected after run)
Wavelength = 220
Flow Rate = 4 mL/min
Solvent A = 90% H_2O - 10% MeOH - 0.1% TFA
Solvent B = 10% H_2O - 90% MeOH - 0.1% TFA
Column: PHENOMENEX® LUNA 4.6 x 30 mm S10

[00117] Compounds purified by preparative HPLC were diluted in methanol (1.2 ml) and purified using the following methods on a Shimadzu LC-10A automated preparative HPLC system.

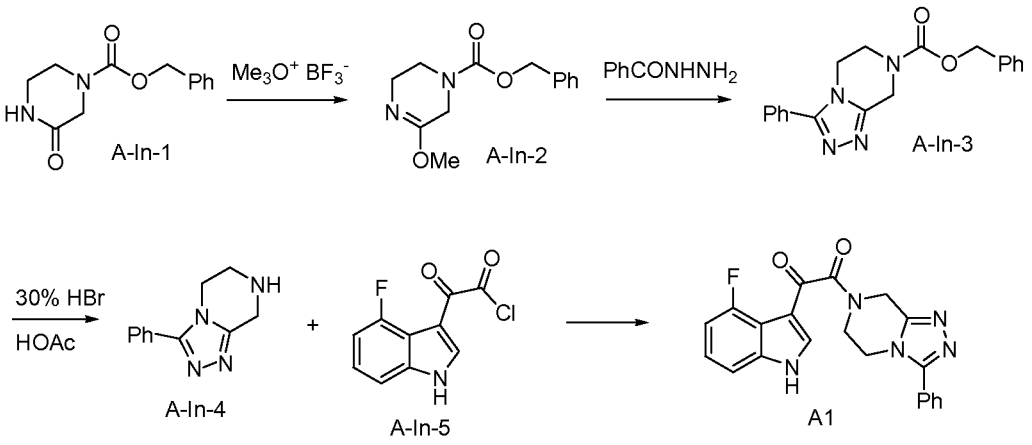
Preparative HPLC Method (*i.e.*, compound purification)

Purification Method: Initial gradient (40% B, 60% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A:	10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid
Solvent B:	10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid
Column:	YMC C18 S5 20x100 mm column
Detector Wavelength:	220 nm

EXAMPLE A

Preparation of Compound A of Formula 1



Process for the Preparation of Compound A-In-2:

[00118] This compound was prepared by the method described by Bryant, H.J. et al., in WO 01/44250.

[00119] To a stirred and cold (ice-bath cooling) suspension of benzyl 3-oxopiperazine-1-carboxylate (A-In-1) (1.00 g) and K_2CO_3 (11.8 g) in CH_2Cl_2 (40 mL) was added under N_2 trimethyloxonium tetrafluoroborate (2.20 g, from Aldrich) in one portion. The cooling bath was removed and the mixture was stirred at room temperature under N_2 for 19 h. This mixture was poured into water (40 mL) under ice-cooling and the organic phase was collected. The aqueous phase was extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were washed with water (20 mL), then with brine, dried (Na_2SO_4) and concentrated. The crude residual oil was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to give the title compound A-In-2 as colorless oil.

Process for the Preparation of Compound A-In-3 from A1-In-2:

[00120] A mixture of A1-In-2 (248 mg) and benzoic acid hydrazide (136 mg) in toluene (25 mL) was heated at reflux with a Dean-Stark trap for 24h. After cooling, the mixture was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2), followed by crystallization from Et_2O gave the title compound A-In-3 as white crystals.

Process for the Preparation of Compound A-In-4 from A-In-3:

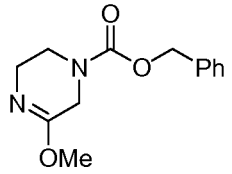
[00121] A mixture of A1-In-3 in 30% HBr in HOAc (1.7 mL) was stirred at room temperature for 3h. Concentration under vacuum provided an aqueous solution which was extracted with CH_2Cl_2 (15 mL). The organic layer was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (10% of 10% c-NH_4OH/MeOH in CH_2Cl_2) to give A-In-4 as white solid.

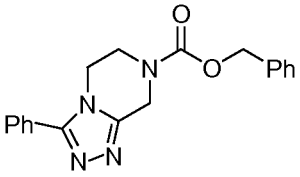
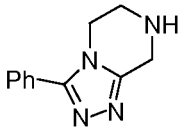
Process for the Preparation of Compound A1 from A-In-4:

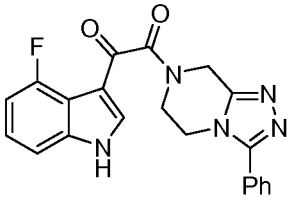
[00122] To a stirred solution of A-In-4 (30 mg) and A-In-5 (40 mg) in CH_2Cl_2 (2 mL) under N_2 was injected diisopropylethylamine (31 μL) and the mixture was stirred for 1h. After removal of solvents under vacuum, the residue was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2), followed by trituration from Et_2O to provide the title compound A1 as off-white crystalline powder.

Characterization of A-In and A (Table A):

TABLE A

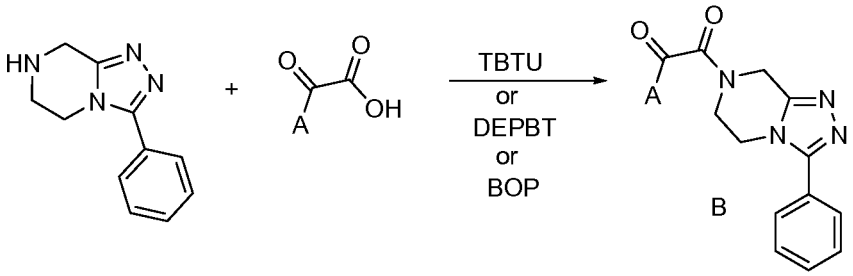
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
A-In-2		249	249. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ ppm 3.46-3.49 (2H, m), 3.56 (2H, m), 3.74 (3H, br.s), 3.99 (2H, br.s), 5.15 (2H, s), 7.33-7.38 (5H, m).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
A-In-3		335	335. ^{1}H-NMR ($CDCl_3$): δppm 3.87 (2H, br.s), 4.08 (2H, br.s), 4.95 (2H, s), 5.18 (2H, s), 7.35 (5H, s), 7.46 (3H, br.s), 7.63 (2H, br). ^{13}C-NMR ($CDCl_3$): δppm 41.0, 41.7, 44.0, 68.2, 126.5, 128.2, 128.6, 128.8, 129.2, 130.3, 135.9, 148.3, 153.4, 155.0.
A-in-4		201	201. ^{1}H-NMR ($CDCl_3$): δppm 2.37 (1H, br.s), 3.17 (2H, t, J = 5.5 Hz), 4.00 (2H, t, J = 5.5 Hz), 4.20 (2H, s), 7.38-7.48 (3H, m), 7.63 (2H, dd, J = 6.6, 2.9 Hz).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
A1		390	390. ^{1}H-NMR (300 MHz, DMSO-d_6): δppm 3.81 (1.5H, t, J = 5 Hz), 4.05-4.09 (0.5H, m), 4.12 (1.5H, t, J = 5 Hz), 4.32 (0.5H, t, J = 5 Hz), 4.84 (0.5H, s), 5.03 (1.5H, s), 7.03 (1H, m), 7.24-7.34 (1H, m), 7.37, 7.40 (1H, 2s, 3:1), 7.49-7.60 (3H, m), 7.68-7.76 (2H, m), 8.29 (0.25H, d, J = 3 Hz), 8.43 (0.75H, d, J = 2 Hz), 12.68 (1H, br.s).

EXAMPLE B

Preparation of Compounds B of Formula 1



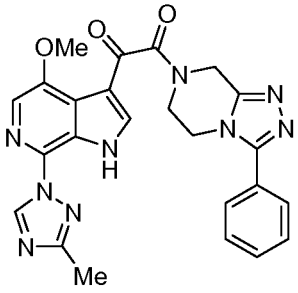
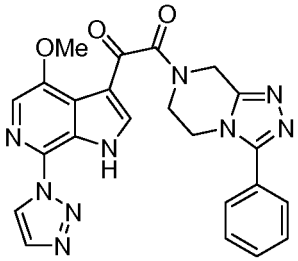
General Process for the Preparation of Compound B from 3-Phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine:

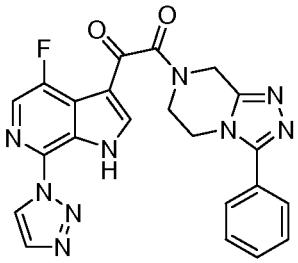
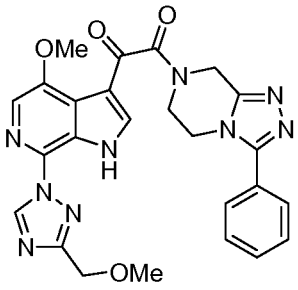
[00123] 2-Keto acid (1 eq.), 3-phenyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10%

Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

Characterization of B-In and B (Table B):

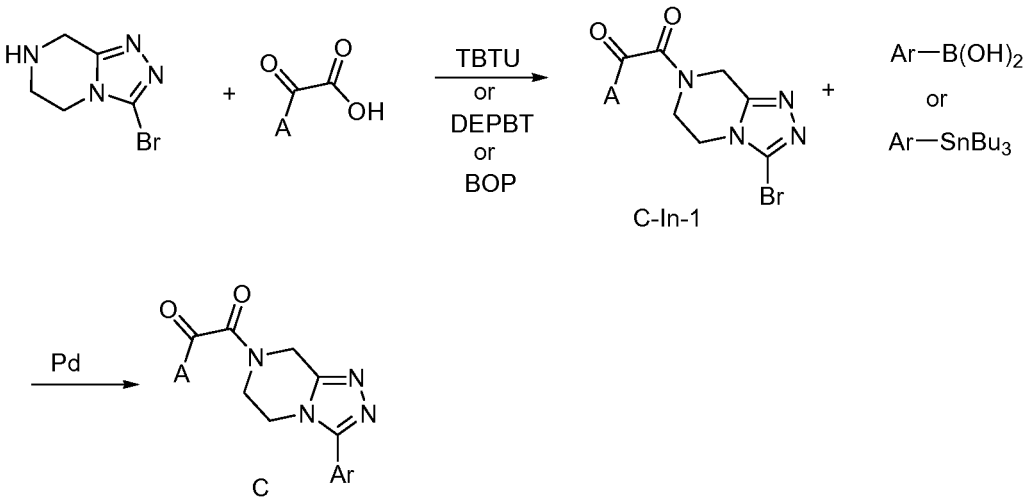
TABLE B

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
B1		484	484, Rf = 1.36 min (Method 5). ^1H NMR (500 MHz, MeOD): δppm 9.10 (s, 1H), 8.30 - 8.32 (m, 1 H), 7.75 (s, 1H), 7.63 - 7.68 (m, 2H), 7.51 - 7.56 (m, 3H), 5.02 - 5.20 (m, 2H), 3.93 - 4.32 (m, 7H), 2.53 (s, 3H).
B2		470	470, Rf = 1.40 min (Method 5). ^1H NMR (500 MHz, DMSO-d_6): δppm 12.84 (s, 1H), 8.93 (s, 1H), 8.29 - 8.40 (m, 1H), 8.05 - 8.10 (m, 1H), 7.93 - 8.00 (m, 1H), 7.71 - 7.81 (m, 2H), 7.50 - 7.58 (m, 3H), 4.87 - 5.10 (m, 2H), 3.85 - 4.33 (m, 7H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
B3		458	458, Rf = 1.53 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 13.10 (s, 1H), 9.01 (s, 1H), 8.41 - 8.62 (m, 1H), 8.29 - 8.33 (m, 1H), 8.07 - 8.15 (m, 1H), 7.70 - 7.80 (m, 2H), 7.49 - 7.58 (m, 3H), 4.91 - 5.09 (m, 2H), 4.13 - 4.34 (m, 2H), 3.85 - 4.12 (m, 2H).
B4		514	514, Rf = 1.41 min (Method 1). ^{1}H NMR (500 MHz, MeOD): δppm 9.25 (s, 1H), 8.33 - 8.40 (m, 1H), 7.81 - 7.85 (m, 1H), 7.66 - 7.74 (m, 2H), 7.53 - 7.60 (m, 3H), 5.02 - 5.24 (m, 2H), 4.70 (s, 2H), 3.93 - 4.37 (m, 7H), 3.52 (s, 3H).

EXAMPLE C

Preparation of Compounds C of Formula 1



General Process for the Preparation of Compound C-In-1 from 3-Bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine:

[00124] 2-Keto acid (1 eq.), 3-bromo-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford C-In-1.

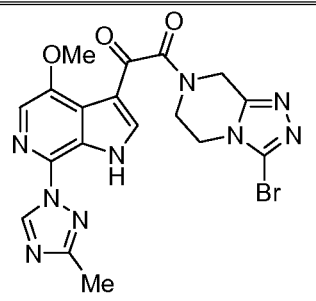
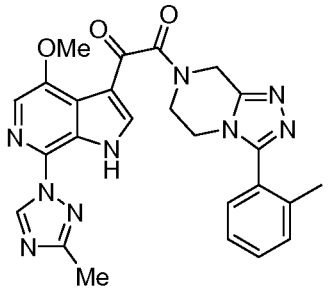
General Process for the Preparation of Compound C from C-In-1:

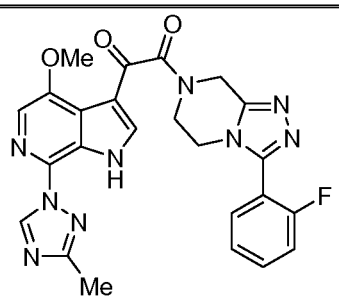
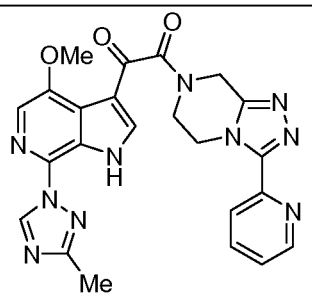
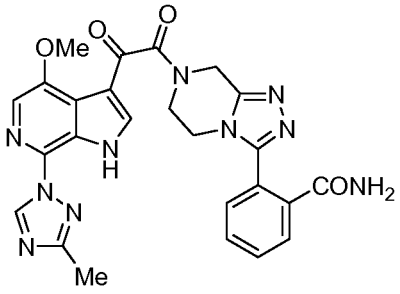
[00125] C-In-1 (1 eq.), boronic or stannane agent (1-10 eq.) and palladium catalyst (*e.g.*, tetrakis(triphenylphosphine)palladium, bis(diphenylphosphino)ferrocene palladium (II) chloride, bis(triphenylphosphine)palladium(II) chloride) (0.05-1 eq.) with or without base (*e.g.*, Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK, *t*-BuONa) were combined in DMF or dioxane, with or

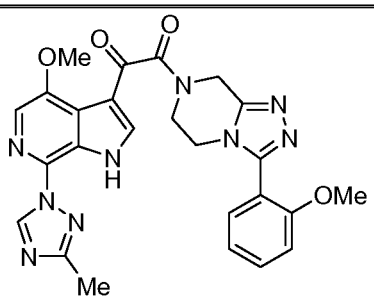
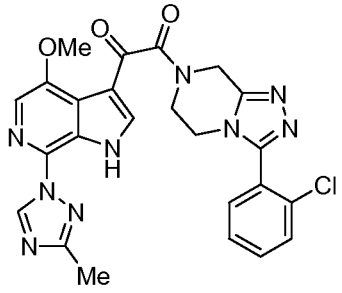
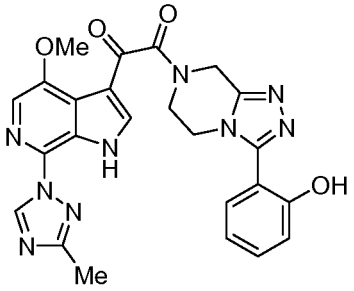
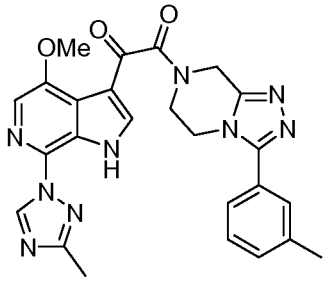
without water. The reaction was either heated to 100 °C to 200 °C in sealed tube or carried out in the microwave synthesizer for 20 minutes to 72 hours. The mixture was diluted with MeOH and filtered. The filtration was concentrated and purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound C.

Characterization of C-In and C (Table C):

TABLE C

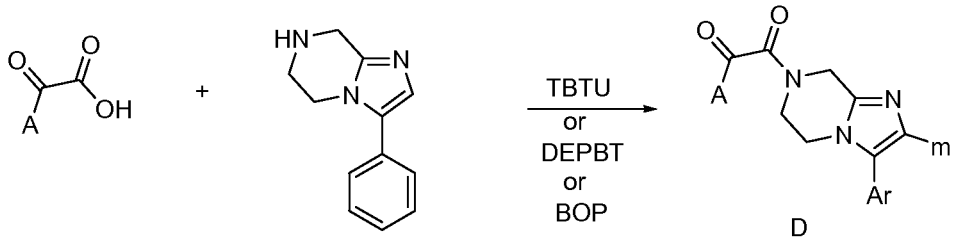
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
C-In-1		486	486, Rf = 1.35 min (Method 9).
C1		498	498, Rf = 1.45 min (Method 5). ^{1}H NMR (500 MHz, MeOD): δppm 9.12 - 9.18 (m, 1H), 8.34 (s, 1H), 7.78 - 7.84 (m, 1H), 7.31 - 7.47 (m, 4H), 5.01 - 5.25 (m, 2H), 3.98 - 4.23 (m, 4H,) 3.92 - 3.95 (m, 3H), 2.50 - 2.58 (m, 3H), 2.25 - 2.32 (m, 3H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
C2		502	502, Rf = 1.40 min (Method 5). ^{1}H NMR (500 MHz, MeOD): δppm 9.15 (s, 1H), 8.31 - 8.39 (m, 1H), 7.76 - 7.83 (m, 1H), 7.23 - 7.62 (m, 4H), 5.00 - 5.26 (m, 2H), 3.98 - 4.23 (m, 4H), 3.84 - 3.98 (m, 3H), 2.54 (s, 3H).
C3		485	485, Rf = 1.12 min (Method 6).
C4		527	527, Rf = 1.70 min (Method 8).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
C5		514	514, Rf = 1.44 min (Method 1).
C6		518	518, Rf = 1.52 min (Method 1).
C7		498 (M-H)	498 $(M-H)^+$, Rf = 1.36 min (Method 1).
C8		498	498.

Example D

Preparation of Compounds D of Formula 1



D-In-1

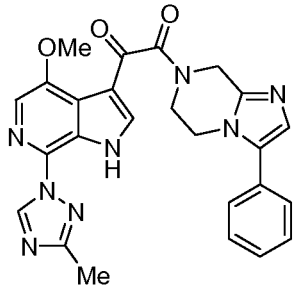
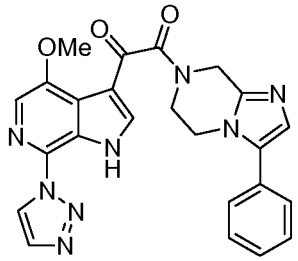
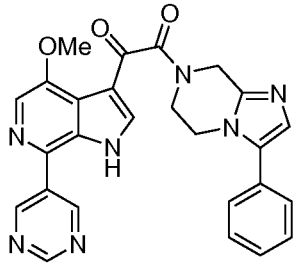
D

General Process for the Preparation of Compound D from D-In-1:

[00126] 2-Keto acid (1 eq.), D-In-1 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

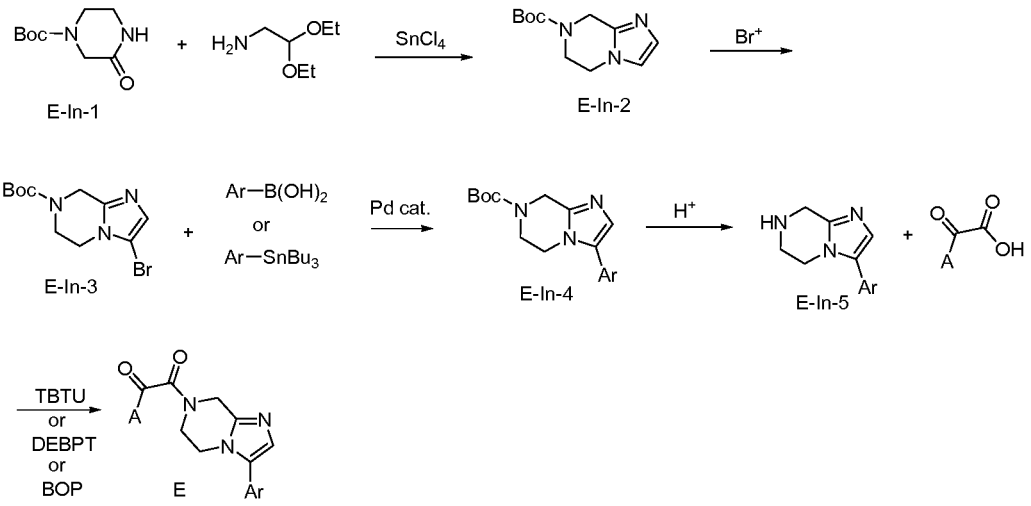
Characterization of D (Table D):

TABLE D

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
D1		483	483, Rf = 1.32 min (Method 5). ^{1}H NMR (500 MHz, $CDCl_3$) δppm 11.07 - 11.13 (m, 1H), 9.08 (s, 1H), 8.22 - 8.27 (m, 1H), 7.34 - 7.45 (m, 5H), 7.10 - 7.17 (m, 1H), 4.93 - 5.10 (m, 2H), 3.94 - 4.15 (m, 4H,) 3.85 - 3.91 (m, 3H), 2.55 (s, 3H).
D2		469	469, Rf = 1.31 min (Method 5). ^{1}H NMR (500 MHz, MeOD): δppm 8.74 (s, 1H), 8.31 - 8.39 (m, 1H), 7.89 (s, 1H), 7.83 (s, 1H), 7.34 - 7.44 (m, 5H), 7.03 - 7.08 (m, 1H), 4.87 - 5.05 (m, 2H), 3.89 - 4.20 (m, 7H).
D3		480	480, Rf = 1.00 min (Method 5). ^{1}H NMR (500 MHz, MeOD): δppm 9.27 - 9.32 (m, 1H), 9.15 - 9.21 (m, 2H), 8.43 - 8.49 (m, 1H), 8.18 (s, 1H), 7.49 - 7.58 (m, 6H), 5.19 - 5.32 (m, 2H), 4.06 - 4.34 (m, 7H).

EXAMPLE E

Preparation of Compounds E of Formula 1



General Process for the Preparation of Compound E-In-2 from E-In-1:

[00127] A round bottom flask was charged with E-In-1 (1 eq.), CH_2Cl_2, mesitylene and Tin(IV) chloride (0.3 eq.). The mixture was brought to reflux then aminoacetaldehyde diethyl acetal (2 eq.) was added slowly. The reaction was refluxed for 2 – 3d. The reaction was diluted with CH_2Cl_2 and filtered through activated charcoal and the filtrate was evaporated giving a solid which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford E-In-2.

General Process for the Preparation of Compound E-In-3 from E-In-2:

[00128] A round bottom flask was charged with E-In-2 (1 eq.), CCl_4 and N-bromosuccinimide (1 eq.). The solution was refluxed for 30 minutes then allowed to cool. The CCl_4 solution was decanted off a brown solid and evaporated. The residue was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford E-In-3.

General Process for the Preparation of Compound E-In-4 from E-In-3:

[00129] E-In-3 (1 eq.), boronic or stannane agent (1-10 eq.) and palladium catalyst (*e.g.*, tetrakis(triphenylphosphine)palladium, bis(diphenylphosphino)ferrocene

palladium (II) chloride, bis(triphenylphosphine)palladium(II) chloride) (0.05-1 eq.) with or without base (*e.g.*, Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK, *t*-BuONa) were combined in DMF or dioxane, with or without water. The reaction was either heated to 100 °C to 200 °C in sealed tube or carried out in the microwave synthesizer for 20 minutes to 72 hours. The mixture was diluted with MeOH and filtered. The filtration was concentrated and purified by HPLC or recrystallization to offer Compound E-In-4.

General Process for the Preparation of Compound E-In-5 from E-In-4:

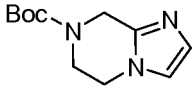
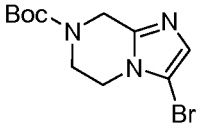
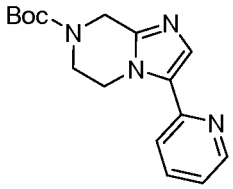
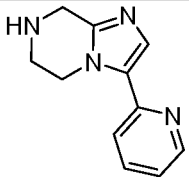
[00130] E-In-4 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford E-In-5.

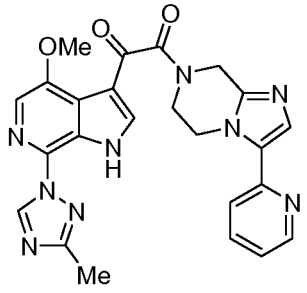
General Process for the Preparation of Compound E from E-In-5:

[00131] 2-Keto acid (1 eq.), E-In-5 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

Characterization of E-In and E (Table E):

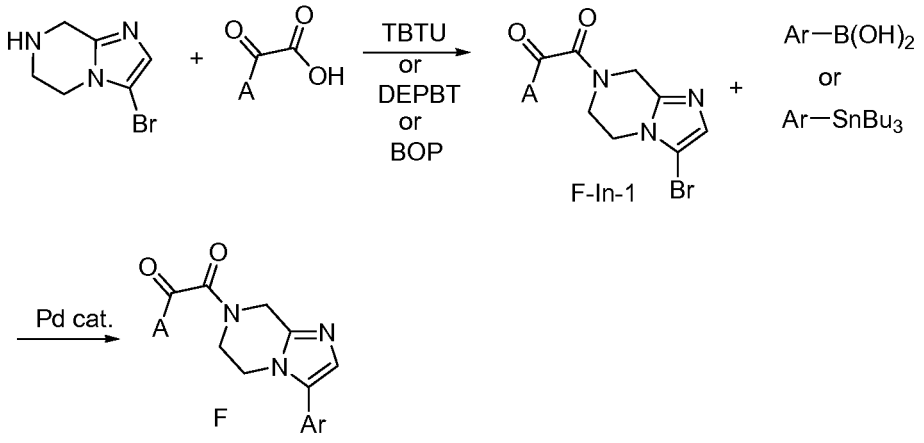
TABLE E

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
E-In-2		224	224. ^{1}H NMR (DMSO-d_6): δ1.46 (s, 9H), 3.82 - 3.84 (m, 2H), 3.97 - 3.99 (m, 2H), 4.68 (s, 2H), 6.85 (s, 1H), 7.04 (s, 1H).
E-In-3		302	302. ^{1}H NMR (DMSO-d_6): δ1.46 (s, 9H), 3.85 (s, 4H), 4.65 (s, 2H), 6.99 (s, 1H).
E-In-4		301	301. ^{1}H NMR (DMSO-d_6) δ1.47 (s, 9H), 3.82 - 3.84 (t, 2H, J = 5Hz), 4.51 - 4.53 (t, 2H, J = 5Hz), 4.78 (s, 2H), 7.11 - 7.13 (dd, 1H, J = 7, 5Hz), 7.43 (s, 1H), 7.51 - 7.53 (d, 1 H, J = 8Hz), 7.64 - 7.68 (dd, 1H, J = 8, 2Hz), 8.53 - 8.54 (d, 1H, J = 5Hz).
E-In-5		201	201.

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
E1		484	484. ^{1}H NMR (DMSO-d_6): δ2.52 (s, 3H), 3.85 & 3.93 (s, 3H), 3.97 - 3.99 & 4.16 - 4.18 (t, 2H, J = 5Hz), 4.51 - 4.53 & 4.67 - 4.69 (t, 2H, J = 5Hz), 5.10 & 4.93 (s, 2H), 7.37 - 7.42 (m, 1H), 7.86 - 7.95 (m, 3H), 8.07 (s, 1H), 8.40 - 8.41 & 8.32 - 8.33 (d, 1H, J = 3Hz), 8.61 - 8.61 & 8.68 - 8.69 (d, 1H, J = 3Hz), 9.25 (s, 1H), 12.51 & 12.46 (s, 1H).

EXAMPLE F

Preparation of Compounds F of Formula 1



General Process for the Preparation of Compound F-In-1 from 3-Bromo-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine:

[00132] 2-Keto acid (1 eq.), 3-bromo-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100

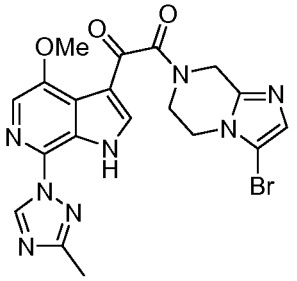
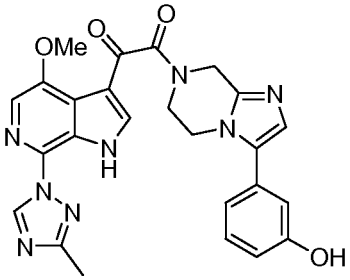
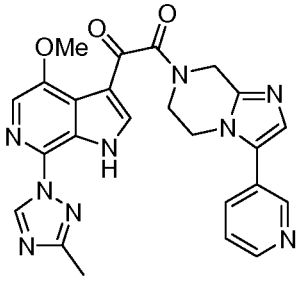
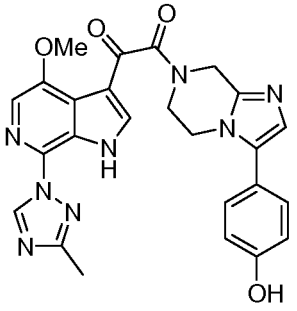
eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

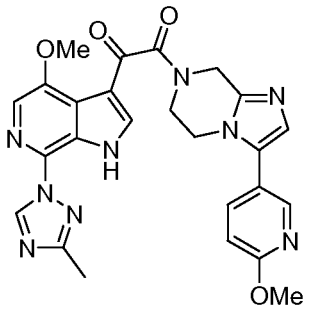
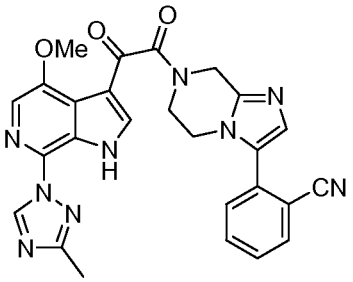
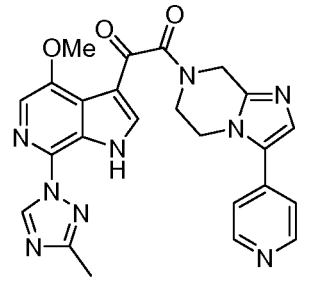
General Process for the Preparation of Compound F from F-In-1:

[00133] F-In-1 (1 eq.), boronic or stannane agent (1-10 eq.) and palladium catalyst (*e.g.*, tetrakis(triphenylphosphine)palladium, bis(diphenylphosphino)ferrocene palladium (II) chloride, bis(triphenylphosphine)palladium(II) chloride) (0.05-1 eq.) with or without base (*e.g.*, Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK, *t*-BuONa) were combined in DMF or dioxane, with or without water. The reaction was either heated to 100 °C to 200 °C in sealed tube or carried out in the microwave synthesizer for 20 minutes to 72 hours. The mixture was diluted with MeOH and filtered. The filtration was concentrated and purified by HPLC or recrystallization to offer Compound F.

Characterization of F-In and F (Table F):

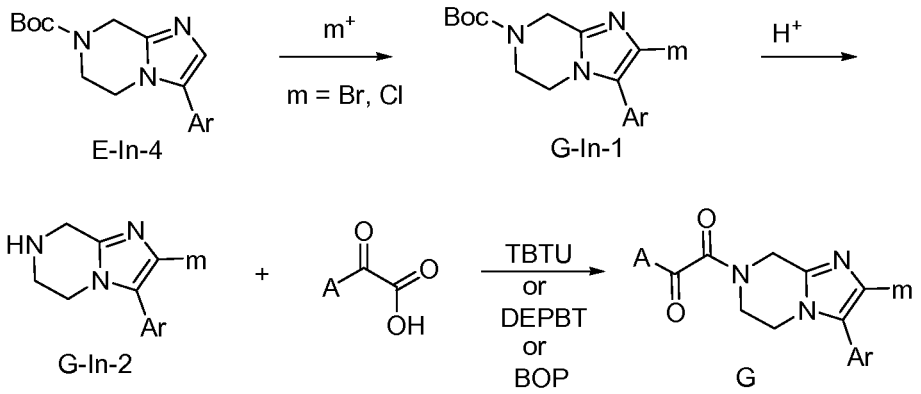
TABLE F

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
F-In-1		485	485, Rf = 1.26 min (Method 9).
F1		499	499, Rf = 1.32 min (Method 9).
F2		484	484, Rf = 1.11 min (Method 9).
F3		499	499, Rf = 1.27 min (Method 9).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
F4		514	514, Rf = 1.48 min (Method 1).
F5		508	508, Rf = 1.52 min (Method 1).
F6		484	484, Rf = 1.33 min (Method 8).

EXAMPLE G

Preparation of Compounds G of Formula 1



5

General Process for the Preparation of Compound G-In-1 from E-In-4:

[00134] A round bottom flask was charged with acetonitrile, 2-propanol, E-In-4 (1 eq.) and N-chlorosuccinimide or N-bromosuccinimide (1.05 eq.). The reaction was refluxed under nitrogen for 0.25h. The reaction was diluted with ether, washed with water then brine, dried over $MgSO_4$ and evaporated giving a creamy white powder which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

General Process for the Preparation of Compound G-In-2 from G-In-1:

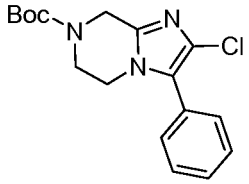
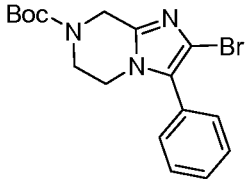
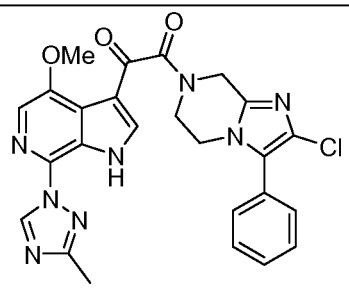
[00135] G-In-1 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford G-In-2.

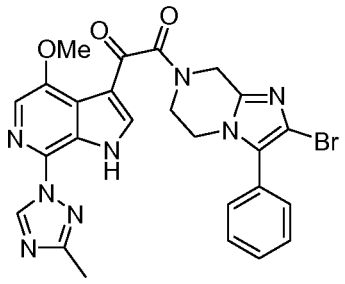
General Process for the Preparation of Compound G from G-In-2:

[00136] 2-Keto acid (1 eq.), G-In-2 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

Characterization of G-In and G (Table G):

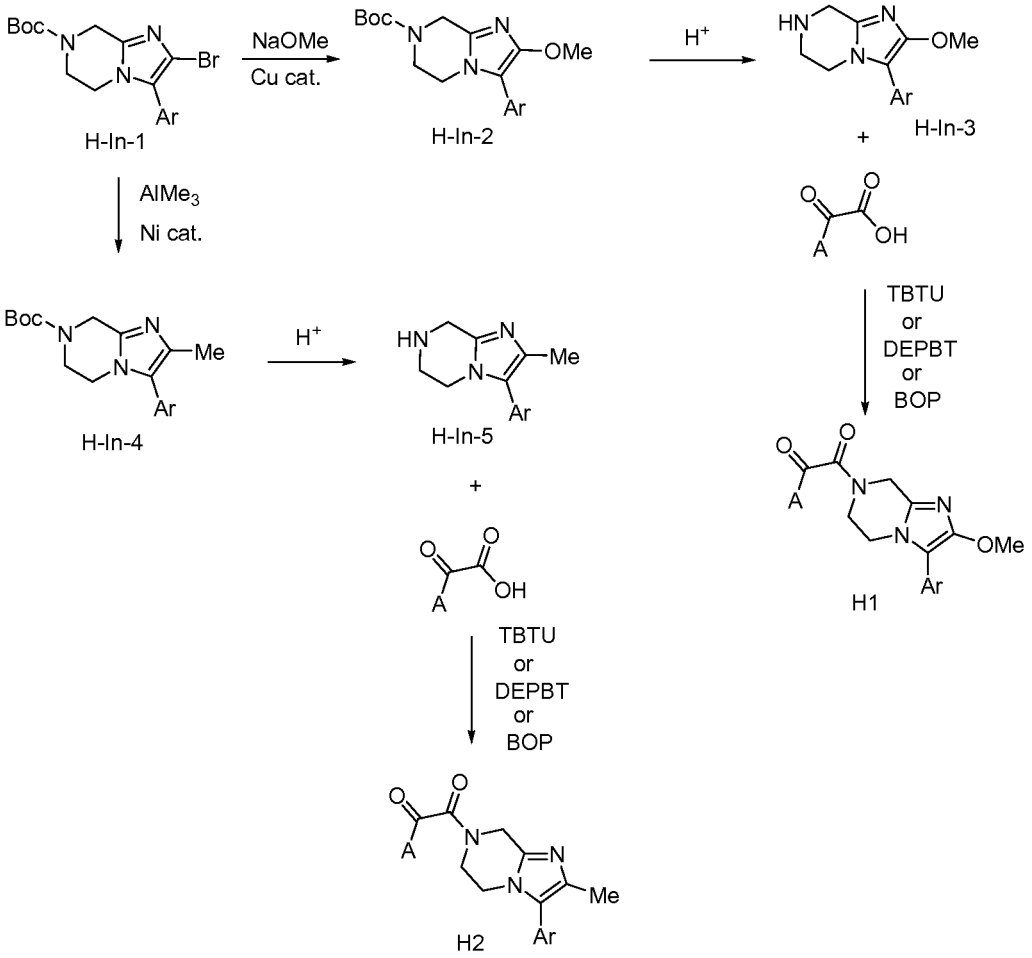
TABLE G

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
G-In-1a		334	334. ^{1}H NMR (DMSO-d_6): δ1.49 (s, 9H), 3.78 - 3.80 (m, 2H), 3.86 - 3.88 (m, 2H), 4.71 (s, 2H), 7.38 - 7.40 (m, 3H), 7.44 - 7.47 (m, 2H).
G-In-1b		378	^{1}H NMR (DMSO-d_6): δ1.48 (s, 9H), 3.79 - 3.80 (m, 2H), 3.86 - 3.88 (m, 2H), 4.79 (s, 2H), 7.38 - 7.48 (m, 5H).
G1		517	517. ^{1}H NMR (DMSO-d_6): δ3.17 (s, 3H), 3.18 (s, 3H), 3.89 - 3.91 (q, 2H), 4.08 - 4.11 (q, 2H), 4.89 & 4.72 (s, 2H), 7.43 - 7.55 (m, 5H), 7.89 & 7.90 (s, 1H), 8.36 & 8.32 (s, 1H), 9.25 (s, 1H), 12.47 (s, 1H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
G2		561	561. ^{1}H NMR (DMSO-d_6): δ2.52 (s, 3H), 3.83 & 3.94 (s, 3H), 3.50 - 3.90 & 4.05 - 4.09 (m, 2H), 4.90 & 4.72 (s, 2H), 7.42 - 7.55 (m, 5H), 7.89 & 7.90 (s, 1H), 8.36 & 8.32 (s, 1H), 9.25 (s, 1H), 12.47 (s, 1H).

EXAMPLE H

Preparation of Compounds H of Formula 1



General Process for the Preparation of Compound H-In-2 from H-In-1:

[00137] Copper or CuBr or CuCl or CuI was added in the mixture of H-In-1 and sodium methoxide in methanol solution (0.5 - 4N) in a sealed tube. The reaction mixture was heated to 100 – 150 °C for 30 minutes to 18 hours. 1N HCl was then added to adjust pH value to 7. The solution was extracted with EtOAc or Ether or dichloromethane. The combined organic layer was washed with brine and then dried over $MgSO_4$. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford H-In-2.

General Process for the Preparation of Compound H-In-4 from H-In-1:

[00138] [1,3-Bis(diphenylphosphino)nickel(II) chloride was added in the mixture of H-In-1 and 2N trimethylalumnium in toluene in a sealed tube. The reaction mixture was heated to 100 – 150 °C for 30 minutes to 18 hours. 1N HCl was then added to adjust pH value to 7. The solution was extracted with EtOAc or Ether or dichloromethane. The combined organic layer was washed with brine and then dried over $MgSO_4$. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford H-In-4.

General Process for the Preparation of Compound H-In-3 or H-In-5 from H-In-2 or H-In-4:

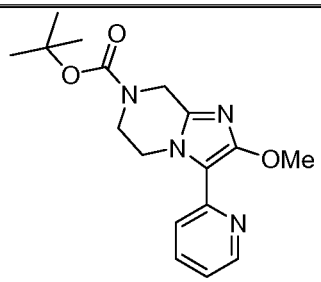
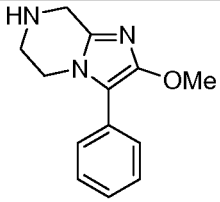
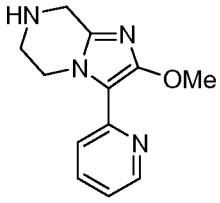
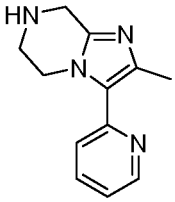
[00139] H-In-2 or H-In-4 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford H-In-3 or H-In-5.

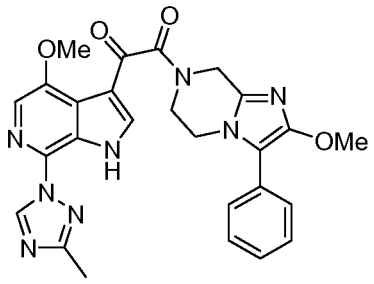
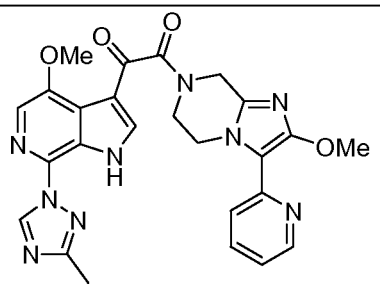
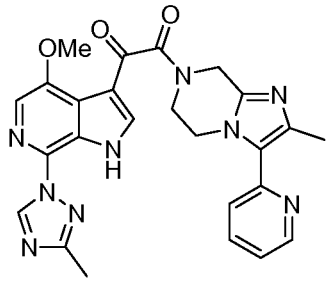
General Process for the Preparation of Compound H from H-In-3 or H-In-5:

[00140] 2-Keto acid (1 eq.), H-In-3 or H-In-5 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system.

Characterization of H-In and H (Table H):

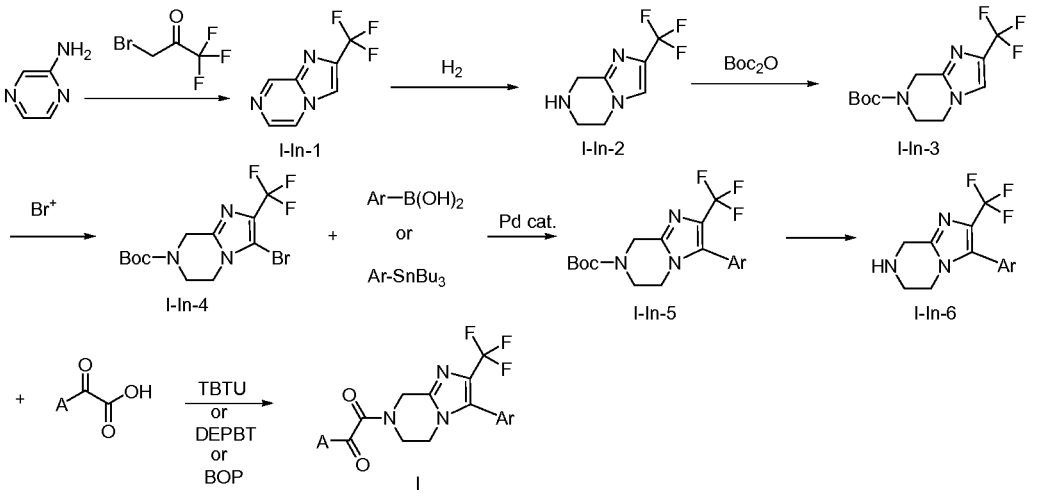
TABLE H

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
H-In-2b		331	331, Rf = 2.16 min (Method 1).
H-In-3a		230	230.
H-In-3b		231	231, Rf = 1.38 min (Method 1).
H-In-5a		215	215, Rf = 0.48 min (Method 9).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
H1a		HRMS: 513.1993	HRMS: 513.1992. ^{1}H NMR (DMSO-d_6): δ2.50 (s, 3H), 3.81 & 3.78 (s, 3H), 3.86 & 3.92 (s, 3H), 3.87 - 3.89 & 4.08 - 4.10 (t, 2H, J = 5Hz), 3.97 - 3.99 & 4.14 - 4.16 (t, 2H, J = 5Hz), 4.86 & 4.67 (s, 2H), 7.42 - 7.55 (m, 5H), 7.89 & 7.90 (s, 1H), 8.36 & 8.32 (s, 1H), 9.25 (s, 1H), 12.47 (s, 1H).
H1b		514	514, Rf = 1.68 min (Method 1).
H2		498	498, Rf = 1.71 min (Method 8).

EXAMPLE I

Preparation of Compounds I of Formula 1



Process for the Preparation of Compound I-In-1 from Pyrazin-2-amine:

[00141] 3-Bromo-1,1,1-trifluoroacetone (1 eq.) was added to a solution of pyrazin-2-amine (1 eq.) in dioxane and the mixture was heated at 40 - 110 °C for 20h. The solid formed was collected by filtration and washed twice with EtOAc. This solid was heated in isopropanol at reflux for 3 hours. Reaction mixture cooled to room temperature and partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The aqueous phase was extracted once more with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a solid containing 2-(trifluoromethyl)imidazo[1,2-a]pyrazine, I-In-1. This material could be purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, or used as is without further purification.

Process for the Preparation of Compound I-In-2 from I-In-1:

[00142] The crude material containing 2-(trifluoromethyl)imidazo[1,2-a]pyrazine, I-In-1 was dissolved in MeOH and was treated with Pd/C and hydrogen at 1atm of pressure. The mixture was stirred at room temperature for 2h. Reaction transferred to a Parr shaker reactor and kept under 50psi for 20h. Solution filtered through CELITE® to remove catalyst and concentrated *in vacuo*. Residue containing 2-

(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine, I-In-2, could be purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, or used as is without further purification.

Process for the Preparation of Compound I-In-3 from I-In-2:

[00143] The solution of 2-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (1 eq.), Hunig's Base (1 – 20 eq.) and BOC_2O (1 -5 eq.) was stirred in CH_2Cl_2 at room temperature for 1 – 20h. The volume was reduced to half *in vacuo* and then the solution was partitioned between ethyl acetate and 0.5N HCl. Aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified on silica gel to afford I-In-3.

Process for the Preparation of Compound I-In-4 from I-In-3:

[00144] I-In-3 (1 eq.) in chloroform was cooled to 0 °C and bromine (1 eq.) was added slowly. The reaction was stirred at this temperature for 30min and then placed at room temperature for 1.5h. Bromine (1 eq.) was added and the stirring continued for 2h. The reaction was quenched with aq. sat. $NaHCO_3$, extracted with AcOEt, dried over Na_2SO_4, and purified on silica gel (hexanes-10%EtOAc/Hex) to afford I-In-4.

General Process for the Preparation of Compound I-In-5 from I-In-4:

[00145] I-In-4 (1 eq.), boronic or stannane agent (1-10 eq.) and palladium catalyst (*e.g.*, tetrakis(triphenylphosphine)palladium, bis(diphenylphosphino)ferrocene palladium (II) chloride, bis(triphenylphosphine)palladium(II) chloride) (0.05-1 eq.) with or without base (*e.g.*, Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK, *t*-BuONa) were combined in DMF or dioxane, with or without water. The reaction was either heated to 100 °C to 200 °C in sealed tube or carried out in the microwave synthesizer for 20 minutes to 72 hours. The mixture was diluted with MeOH and filtered. The filtration was concentrated and purified by HPLC or recrystallization to offer I-In-5.

General Process for the Preparation of Compound I-In-6 from I-In-5:

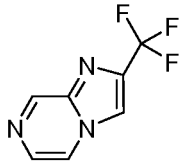
[00146] I-In-5 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford I-in-6.

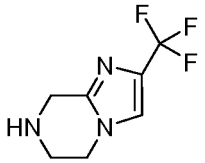
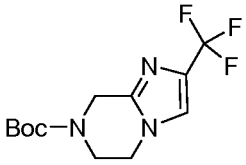
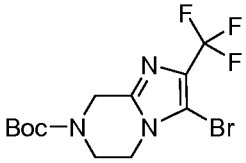
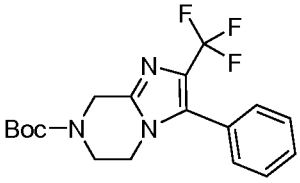
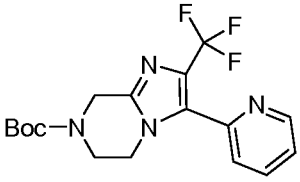
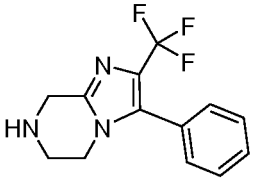
General Process for the Preparation of Compound I from I-In-6:

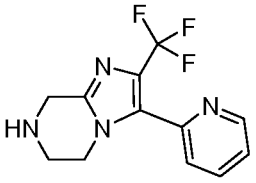
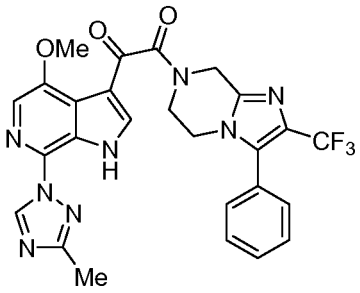
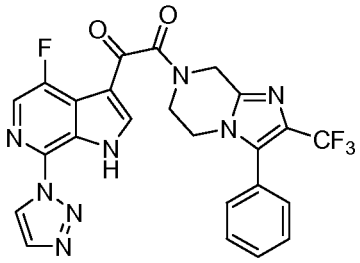
[00147] 2-Keto acid (1 eq.), I-In-6 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound I.

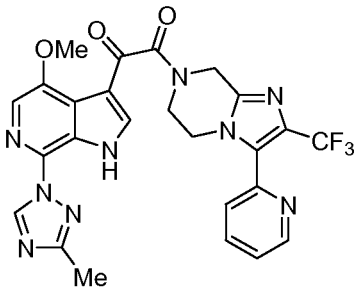
Characterization of I-In and I (Table I):

TABLE I

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
I-In-1		188	188, Rf = 1.19 min (Method 2). ^1H NMR (500 MHz, $CDCl_3$) δppm 9.21 (s, 1H), 8.11 (s, 1H), 7.94 - 8.08 (m, 2H).

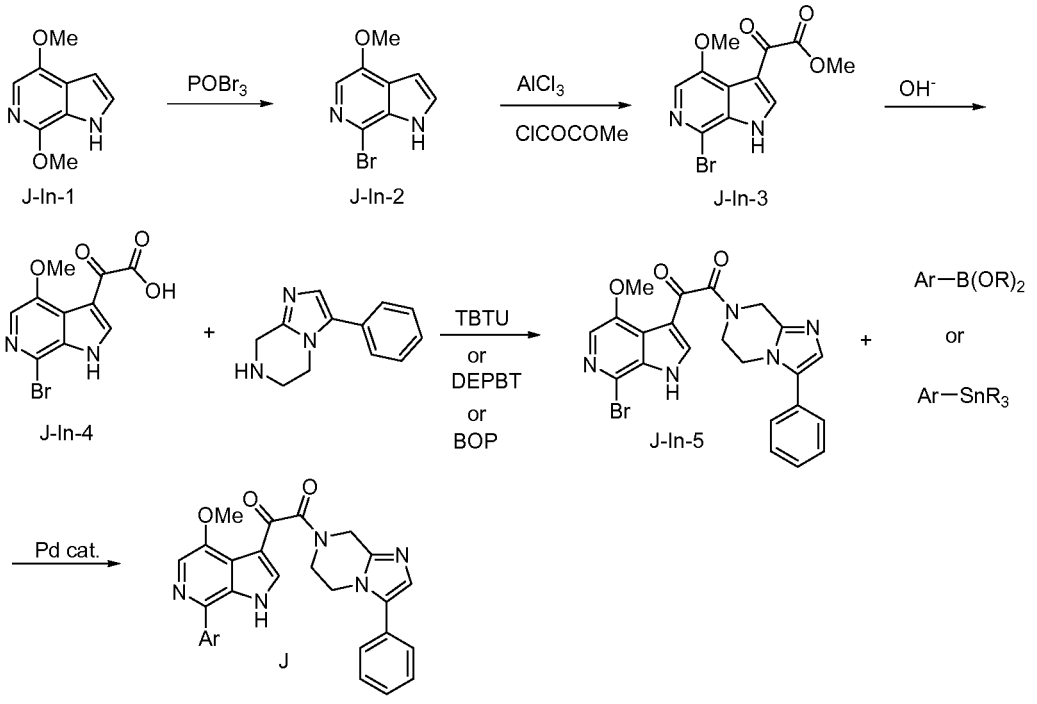
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
I-In-2		192	192, Rf = 0.24 min (Method 2).
I-In-3		292	292, Rf = 2.99 min. (Method 2). ^{1}H NMR (500 MHz, $CDCl_3$): δppm 7.20 (s, 1 H), 4.71 (s, 2H), 3.97 - 4.07 (m, 2H), 3.78 - 3.93 (m, 2H), 1.47 (s, 9H).
I-In-4		370	^{1}H NMR (500 MHz, $CDCl_3$): δppm 4.70 (s, 2H), 3.91 – 3.90 (m, 4H), 1.49 (s, 9H).
I-In-5a		368	368, Rf = 2.35 min. (Method 2).
I-In-5b		369	369, Rf = 2.10 min (Method 3).
I-In-6a		268	268, Rf = 1.67 min. (Method 2).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
I-In-6b		269	269, Rf = 1.39 min (Method 3).
I1		551	551, Rf = 2.77 min (Method 2). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.45 - 12.52 (m, 1H), 9.22 - 9.27 (m, 1H), 8.30 - 8.38 (m, 1H), 7.87 - 7.92 (m, 1H), 7.41 - 7.58 (m, 5H), 4.74 - 4.98 (m, 2H), 3.74 - 4.14 (m, 10H).
I2		525	525, Rf = 2.00 min (Method 1). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 13.07 - 13.18 (m, 1H), 8.99 - 9.06 (m, 1H), 8.42 - 8.61 (m, 1H), 8.31 - 8.37 (m, 1H), 8.13 (s, 1H), 7.41 - 7.59 (m, 5H), 4.79 - 4.98 (m, 2H), 3.76 - 4.13 (m, 4H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
I3		552	552, Rf = 1.23 min (Method 4). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 2.51 (s, 3H), 3.69 - 4.33 (m, 7H), 4.71 - 5.16 (m, 2H), 7.43 - 7.71 (m, 2 H), 7.81 - 7.95 (m, 1H) 7.92 - 8.15 (m, 1H) 8.19 - 8.48 (m, 1H), 8.70 (d, J = 4.27 Hz, 1H), 9.24 (s, 1H), 12.49 (s, 1H).

EXAMPLE J

Preparation of Compounds J of Formula 1



Process for the Preparation of Compound J-In-2 from J-In-1:

[00148] To a stirred solution of 4, 7-dimethoxy azaindole (1 eq.) in anisole was added phosphorus oxybromide (1 eq.) portion wise and the reaction mixture was slowly heated to 120 °C. Reaction mixture was allowed to stir at 120 °C for about 18h. Then, the reaction mixture was cooled to 10 °C and slowly quenched with ice-water mixture. The resulting mixture was neutralized with saturated sodium bicarbonate solution and then extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography using 60-120 silica gel and 15% ethyl acetate in hexane as eluent to afford J-In-2.

Process for the Preparation of Compound J-In-3 from J-In-2:

[00149] To a stirred solution of aluminum chloride (4 eq.) in dry dichloromethane under nitrogen atmosphere was added J-In-2 (1 eq.) portion wise and the reaction mixture was stirred at room temperature for 2h. In a separate flask, to a stirred solution of aluminum chloride (6 eq.) in dry dichloromethane under nitrogen atmosphere was added methoxy oxalylchloride (3 eq.) drop wise. The reaction mixture was allowed to stir at room temperature for 2hrs. Then this reaction mixture was added slowly to the above reaction mixture for about 30min and stirred for 16h at room temperature. The reaction mixture was quenched with saturated ammonium acetate solution to pH-7. The resulting mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography using 60-120 silica gel and 25% ethyl acetate in hexane as eluent to afford J-In-3.

General Process for the Preparation of Compound J-In-4 from J-In-3:

[00150] J-In-3 (1 eq.) was dissolved in THF/water or acetone/water mixture (1:1), LiOH or NaOH or K_2CO_3 (2 – 10 eq.) and the reaction was stirred for 20h at room temperature. The volatiles were removed under reduced pressure and acidified the mixture using dilute HCl (pH ~6). The resulting solid (J-In-4) was filtered, dried and used for the next step without further purification.

General Process for the Preparation of Compound J-In-5 from J-In-4:

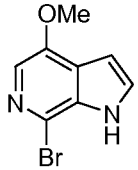
[00151] 2-Keto acid (1 eq.), J-In-4 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford J-In-5.

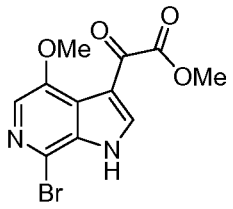
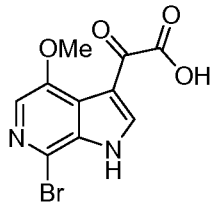
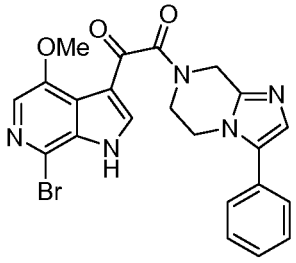
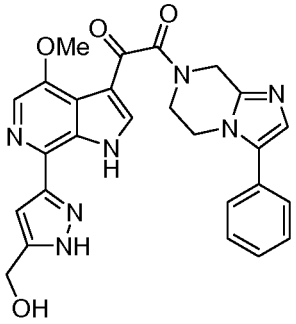
General Process for the Preparation of Compound J from J-In-5:

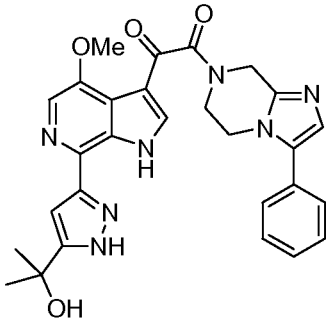
[00152] J-In-5 (1 eq.), boronic or stannane agent (1-10 eq.) and palladium catalyst (*e.g.*, tetrakis(triphenylphosphine)palladium, bis(diphenylphosphino)ferrocene palladium (II) chloride, bis(triphenylphosphine)palladium(II) chloride) (0.05-1 eq.) with or without base (*e.g.*, Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK, *t*-BuONa) were combined in DMF or dioxane, with or without water. The reaction was either heated to 100 °C to 200 °C in sealed tube or carried out in the microwave synthesizer for 20 minutes to 72 hours. The mixture was diluted with MeOH and filtered. The filtration was concentrated and purified by HPLC or recrystallization to offer Compound J.

Characterization of J-In and J (Table J):

TABLE J

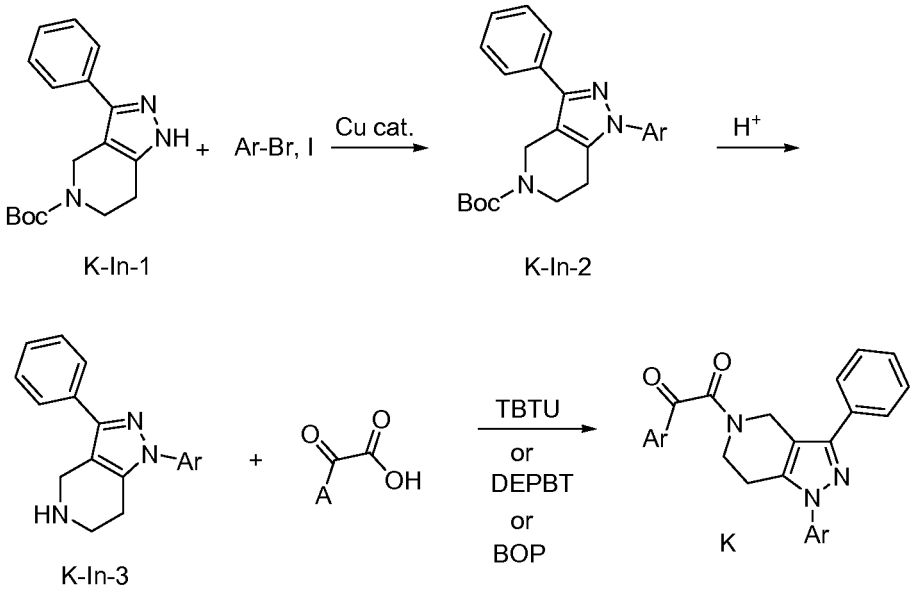
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
J-In-2		227	227.

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
J-In-3		313	313.
J-In-4		299	299.
J-In-5		480	480.
J1		498	498, Rf = 1.72 min (Method 2). ^{1}H NMR (500 MHz, MeOD): δppm 4.08 - 4.22 (m, 5H), 4.30 - 4.46 (m, 2H), 4.81 (s, 2H), 5.23 - 5.40 (m, 2H), 7.19 (s, 1H), 7.53 - 7.67 (m, 5H), 7.70 - 7.80 (m, 1H), 7.99 - 8.07 (m, 1H), 8.68 - 8.79 (m, 1H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
J2		526	526, Rf = 1.92 min (Method 2). ^{1}H NMR (500 MHz, MeOD): δppm 1.69 (s, 6H), 4.15 (m, 5H), 4.29 - 4.48 (m, 2H), 5.27 - 5.39 (m, 2H), 7.14 (s, 1H), 7.54 - 7.69 (m, 5H), 7.71 - 7.83 (m, 1H), 8.04 (s, 1H), 8.72 - 8.82 (m, 1H).

EXAMPLE K

Preparation of Compounds K of Formula 1



General Process for the Preparation of Compound K-In-2 from K-In-1:

[00153] K-In-1 (1 eq.), base selected from Cs_2CO_3, K_2CO_3, $NaCO_3$, Na_3PO_4, NaH_2PO_4, Na_2HPO_4, Et_3N, iPr_2NEt, *t*-BuOK and *t*-BuONa (1-10 eq.), copper agent selected from Cu, CuCl, CuBr and CuI (0.01-2 eq.), (1R,2R)-

diaminomethylcyclohexane (0.02-4 eq.), and aryl bromide or aryl iodide (1-5 eq.) were combined in a sealable flask. The mixture was diluted with 1,4-dioxane. The flask was flushed with N_2, sealed, and heated to 100 °C for 2-24h. The mixture was cooled to room temperature and was filtered through a pad of CELITE® to remove solids. The organic solution was concentrated under reduced pressure, and the residue was purified by silica chromatography or HPLC to afford K-In-2.

General Process for the Preparation of Compound K-In-3 from K-In-2:

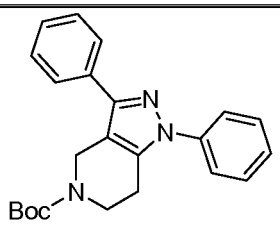
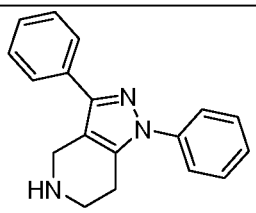
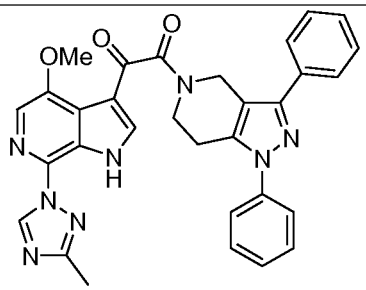
[00154] K-In-2 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford K-In-3.

General Process for the Preparation of Compound K from K-In-3:

[00155] 2-Keto acid (1 eq.), K-In-3 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound K.

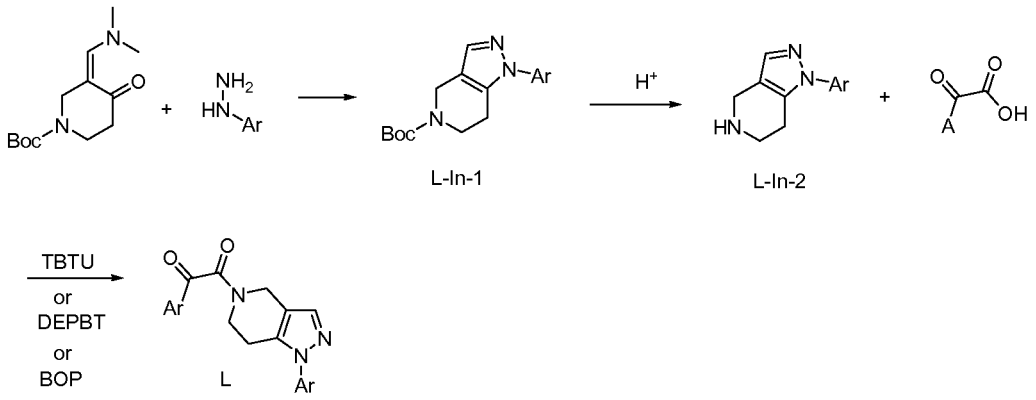
Characterization of K-In and K (Table K):

TABLE K

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
K-In-2		376	376, Rf = 3.405 min (Method 2). ^{1}H NMR (500 MHz, $CDCl_3$): δppm 7.77 (d, J=7.02 Hz, 2H), 7.26 - 7.61 (m, 8H), 4.75 (br. s., 2H), 3.74 (br. s., 2H), 2.85 - 2.94 (m, 2H), 1.48 - 1.55 (m, 9H).
K-In-3		276	276, Rf = 2.06 min (Method 2). ^{1}H (500 MHz, MeOD): δppm 7.40 - 7.74 (m, 10H), 4.54 (s, 2H), 3.60 (t, J = 6.10 Hz, 2H), 3.20 (t, J = 6.10 Hz, 2H).
K1		559	559, Rf = 2.09 min (Method 1). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.44 (br. s., 1H), 9.21 - 9.28 (m, 1H), 8.19 - 8.35 (m, 1H), 7.27 - 7.98 (m, 11H), 4.73 - 4.98 (m, 2H), 3.70 - 4.04 (m, 5H), 2.91 - 3.12 (m, 2H), 2.44 - 2.55 (m, 3H).

EXAMPLE L

Preparation of Compounds L of Formula 1



General Process for the Preparation of Compound L-In-1 from *tert*-Butyl 3-((dimethylamino)methylene)-4-oxopiperidine-1-carboxylate:

[00156] *tert*-Butyl 3-((dimethylamino)methylene)-4-oxopiperidine-1-carboxylate (1 eq.) and hydrazine (1 – 2eq.) were mixed in ethanol. The reaction mixture was heated at 115°C for 16h. After removal of the solvents under vacuum, the residue was purified using silica gel column chromatography or Shimadzu automated preparative HPLC system, to afford L-In-1.

General Process for the Preparation of Compound L-In-2 from L-In-1:

[00157] L-In-1 was added to a solution of TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford L-In-2.

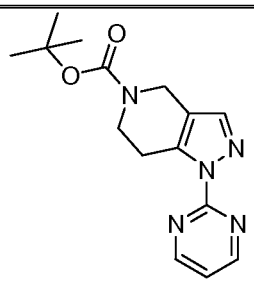
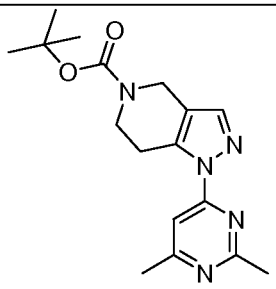
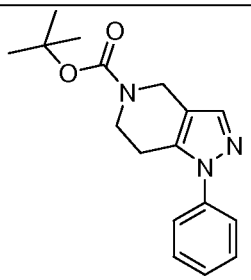
General Process for the Preparation of Compound L from L-In-2:

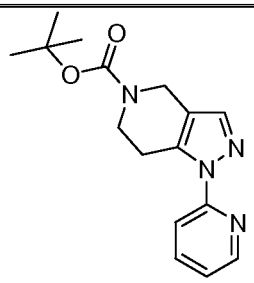
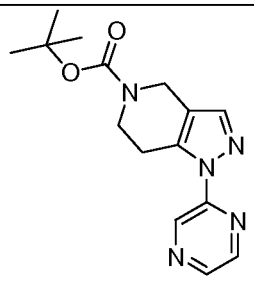
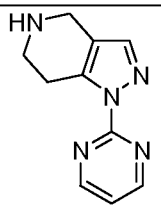
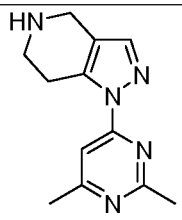
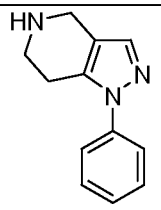
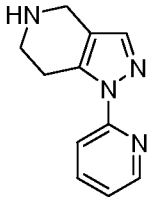
[00158] 2-Keto acid (1 eq.), L-In-2 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer

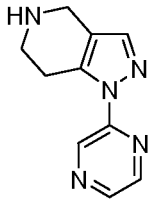
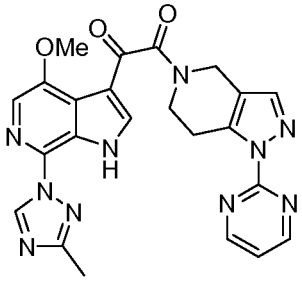
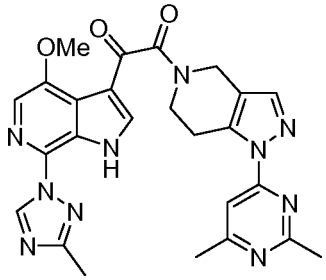
was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound L.

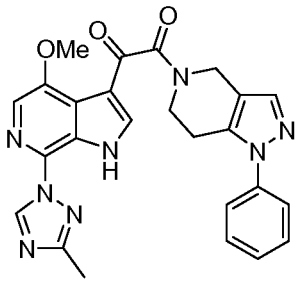
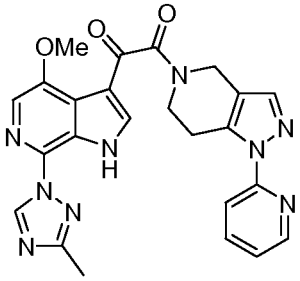
Characterization of L-In and L (Table L):

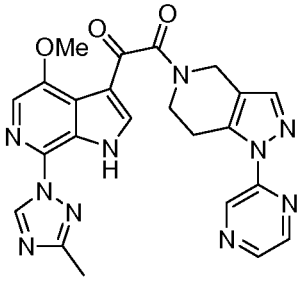
TABLE L

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
L-In-1a		302	302, Rf = 1.72 min (Method 4).
L-In-1b		330	330, Rf = 1.72 min (Method 4).
L-In-1c		300	300, Rf = 1.91 min (Method 4).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
L-In-1d		301	301, Rf = 1.94 min (Method 4).
L-In-1e		302	302, Rf = 1.86 min (Method 4).
L-In-2a		202	202, Rf = 0.26 min (Method 10).
L-In-2b		230	230, Rf = 0.46 min (Method 11).
L-In-2c		200	200, Rf = 1.01 min (Method 12).
L-In-2d		201	201, Rf = 0.65 min (Method 4).

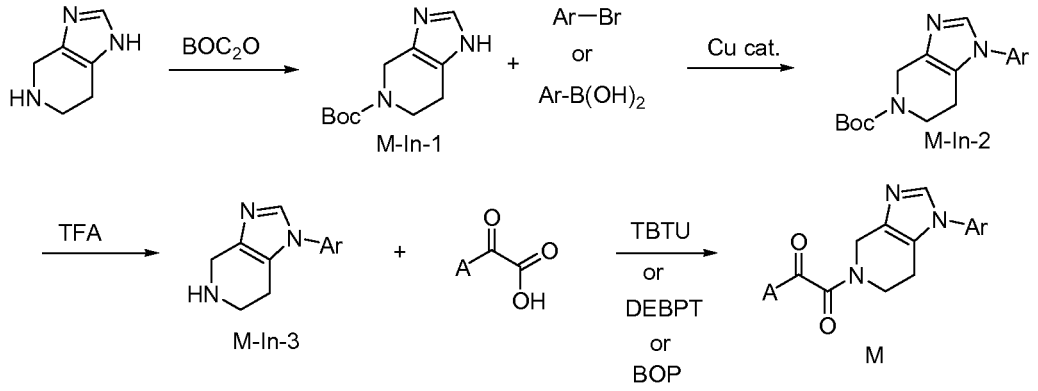
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
L-In-2e		202	202, Rf = 0.35 min (Method 10).
L1		485	485, Rf = 1.48 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.36 - 12.44 (m, 1H), 9.20 - 9.25 (m, 1H), 8.80 - 8.92 (m, 2H), 8.17 - 8.30 (m, 1H), 7.40 - 7.88 (m, 3H), 4.46 - 4.77 (m, 2H), 3.78 - 3.97 (m, 5H), 3.13 - 3.33 (m, 2H), 2.46 (s, 3H).
L2		513	513, Rf =1.49 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.30 - 12.49 (m, 1H), 9.16 - 9.30 (m, 1H), 8.12 - 8.32 (m, 1H), 7.55 - 7.88 (m, 3H), 4.45 - 4.75 (m, 2H), 3.66 - 3.99 (m, 6H), 3.25 - 3.44 (m, 3H), 2.50 - 2.61 (m, 3H), 2.46 - 2.48 (m, 4H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
L3		483	483, Rf = 1.69 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.35 - 12.48 (m, 1H), 9.18 - 9.26 (m, 1H), 8.19 - 8.33 (m, 1H), 7.82 - 7.90 (m, 1H), 7.60 - 7.72 (m, 1H), 7.46 - 7.59 (m, 4H), 7.34 - 7.40 (m, 1H), 4.48 - 4.74 (m, 2H), 3.65 - 3.96 (m, 5H), 2.85 - 3.04 (m, 2H), 2.47 - 2.48 (m, 3H).
L4		484	484, Rf = 1.68 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.33 - 12.44 (m, 1H), 9.18 - 9.27 (m, 1H), 8.36 - 8.50 (m, 1H), 8.17 - 8.29 (m, 1H), 7.93 - 8.00 (m, 1H), 7.81 - 7.90 (m, 2H), 7.58 - 7.77 (m, 1H), 7.28 - 7.36 (m, J = 6.87, 5.34 Hz, 1H), 4.47 - 4.73 (m, 2H), 3.68 - 3.97 (m, 5H), 3.19 - 3.38 (m, 2H), 2.46 - 2.48 (m, 3H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
L5		485	485, Rf = 1.58 min (Method 5). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.34 - 12.44 (m, 1H), 9.15 - 9.26 (m, 2H), 8.44 - 8.61 (m, 2H), 8.17 - 8.29 (m, 1H), 7.68 - 7.89 (m, 2H), 4.48 - 4.77 (m, 2H), 3.68 - 3.99 (m, 5H), 2.70 - 3.20 (m, 2H), 2.46 - 2.48 (m, 3H).

EXAMPLE M

Preparation of Compounds M of Formula 1



General Process for the Preparation of Compound M-In-1 from 4,5,6,7-Tetrahydro-1H-imidazo[4,5-c]pyridine:

[00159] 4,5,6,7-Tetrahydro-1H-imidazo[4,5-c]pyridine (1 eq.) was dissolved in CH_2Cl_2 and treated with TEA (2-10 eq.), BOC-Anhydride (2 eq.) and a catalytic amount of DMAP (0.01-1 eq.) and the mixture was stirred at room temperature for 1-7 days. The reaction mixture was quenched with 1N HCl, followed by extraction with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and concentrated. The

crude product containing both diboc-regioisomers drawn above was dissolved in MeOH and treated with ammonia in MeOH and the mixture was heated at 60 °C for 2-8h. Removal of solvents under vacuum afforded M-In-1 which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system. The crude M-In-1 could be used in the further reaction without any purification.

General Process for the Preparation of Compound M-In-2 from M-In-1:

[00160] M-In-1 (1 eq.), boronic acid (1-5 eq.), pyridine (0.01-5 eq.), $Cu(OAc)_2$ (0.01-2 eq.) and molecular sieves (4A) were stirred in CH_2Cl_2 at room temperature with open air for 1-10 days. The reaction mixture was filtered to remove solids and the filtrate was concentrated under vacuum provided a residue which was purified by HPLC to afford M-In-2.

General Process for the Preparation of Compound M-In-3 from M-In-2:

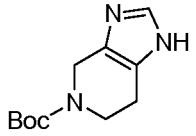
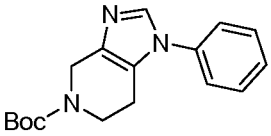
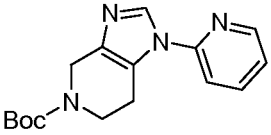
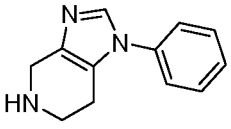
[00161] M-In-2 was added into a solution TFA in dichloromethane (1% to 100%) or HCl in ether (2N). The reaction mixture was stirred at room temperature for 30 minutes to 18 hours. Concentration under vacuum provided a residue which was purified by silica chromatography or HPLC to afford M-In-3.

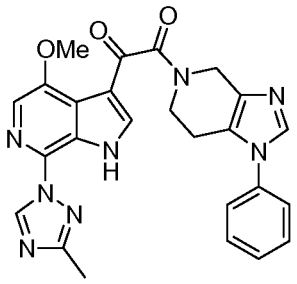
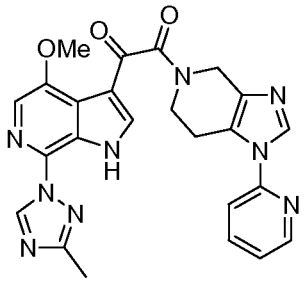
General Process for the Preparation of Compound M from M-In-3:

[00162] 2-Keto acid (1 eq.), M-In-3 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound M.

Characterization of M-In and M (Table M):

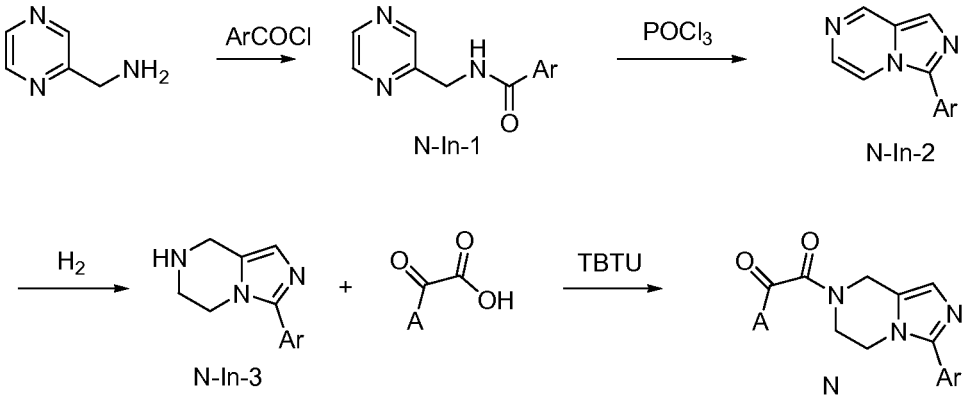
TABLE M

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
M-In-1		224	224, Rf = 0.96 (Method 1). ^{1}H NMR (500 MHz, $CDCl_3$): δppm 7.57 (s, 1H), 4.43 (brs, 2H), 3.66 (brs, 2H), 2.64 (brs, 2H), 1.42 (s, 9H).
M-In-2a		300	300, Rf = 1.41 min (Method 1). ^{1}H NMR (500 MHz, $CDCl_3$): δppm 8.68 (br. s., 1H), 7.32 - 7.73 (m, 6H), 4.66 (br. s., 2H), 3.76 (br. s., 2H), 2.60 - 2.80 (m, 2H), 1.37 - 1.60 (m, 12H).
M-In-2b		301	^{1}H NMR (500 MHz, $CDCl_3$): δ9.04 (s, 1H), 8.54 (m, 1H), 7.95 (m, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 4.62 (s, 2H). 3.74 (m, 2H), 3.00 (m, 2H), 1.45 (s, 9H).
M-In-3a		200	200, Rf = 0.77 min (Method 1).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
M1		483	483, Rf = 1.10 min (Method 1). ^{1}H NMR (500 MHz, MeOD): δppm 9.24 (s, 1H), 8.82 - 9.05 (m, 1H), 8.29 - 8.42 (m, 1H), 7.88 (s, 1H), 7.52 - 7.74 (m, 5H), 3 - 5.02 (m, 2H), 3.95 - 4.07 (m, 3H), 3.83 - 4.23 (m, 2H), 2.78 - 2.99 (m, 2H), 2.57 (s, 3H).
M2		484	484, Rf = 1.15 min (Method 1). ^{1}H NMR (500 MHz, DMSO-d_6): δppm 12.47 (s, 1H), 9.24 (s, 1H) 8.9 - 8.78 (m, 1H) 8.60 - 8.58 (m, 1H), 8.31 - 8.28 (m, 1H), 8.11 - 8.08 (m, 1H), 7.88 - 7.80 (m, 2H) 7.54 - 7.51 (m, 1H) 4.78 - 4.53 (m, 2H), 4.01 - 3.73 (m, 3H), 3.84 (s, 3H), 2.5 (s, 3H).

EXAMPLE N

Preparation of Compounds N of Formula 1



General Process for the Preparation of Compound N-In-1 from Pyrazin-2-ylmethanamine:

[00163] To a solution of 2-(aminomethyl)pyrazine dihydrochloride (1 eq.) [prepared as described by Dhar, T.G.M. et al., *Bioorg. Med. Chem. Lett.*, 17, 5019-5024 (2007)] and N,N-diisopropylethylamine (2-10 eq.) in DMF at 25°C was added aroyl chloride (1-2 eq.), and the mixture was stirred at 25 °C for 24h. The resulting mixture was concentrated under vacuum, and the residue was dissolved in ethyl acetate. The solution was washed with water and brine, dried over anhyd. sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-50% ethyl acetate/methylene chloride) N-In-1.

General Process for the Preparation of Compound N-In-2 from N-In-1:

[00164] To a suspension of N-In-1 (1 eq.) in toluene at room temperature was added phosphorous oxychloride (1-10 eq.) dropwise. The resulting mixture was heated at reflux for 2.5h. After cooling to room temperature the reaction mixture was diluted with ethyl acetate and water. The phases were separated. The aqueous phase was adjusted to pH 7 employing aqueous sodium bicarbonate solution and then extracted with ethyl acetate. The combined organic phases were washed with water and brine, dried over anhyd. sodium sulfate, filtered, and concentrated. Column chromatography on silica gel (elution: 0-5% isopropanol/chloroform) provided N-In-2.

General Process for the Preparation of Compound N-In-3 from N-In-2:

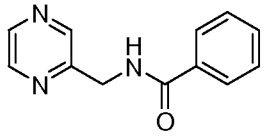
[00165] A mixture of N-In-2 (1 eq.) and 20% palladium hydroxide on carbon (0.01-0.5 eq.) in methanol was stirred at 25 °C under hydrogen gas (1.00 atm) for 26h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to provide N-In-3.

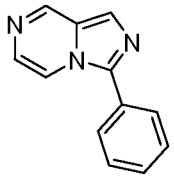
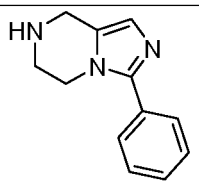
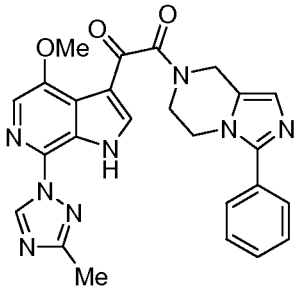
General Process for the Preparation of Compound N from N-In-3:

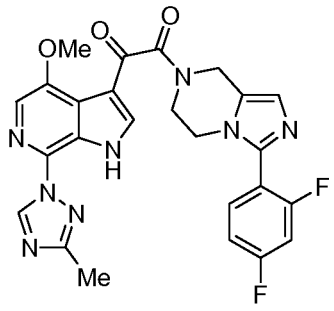
[00166] 2-Keto acid (1 eq.), N-In-3 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound N.

Characterization of N-In and N (Table N):

TABLE N

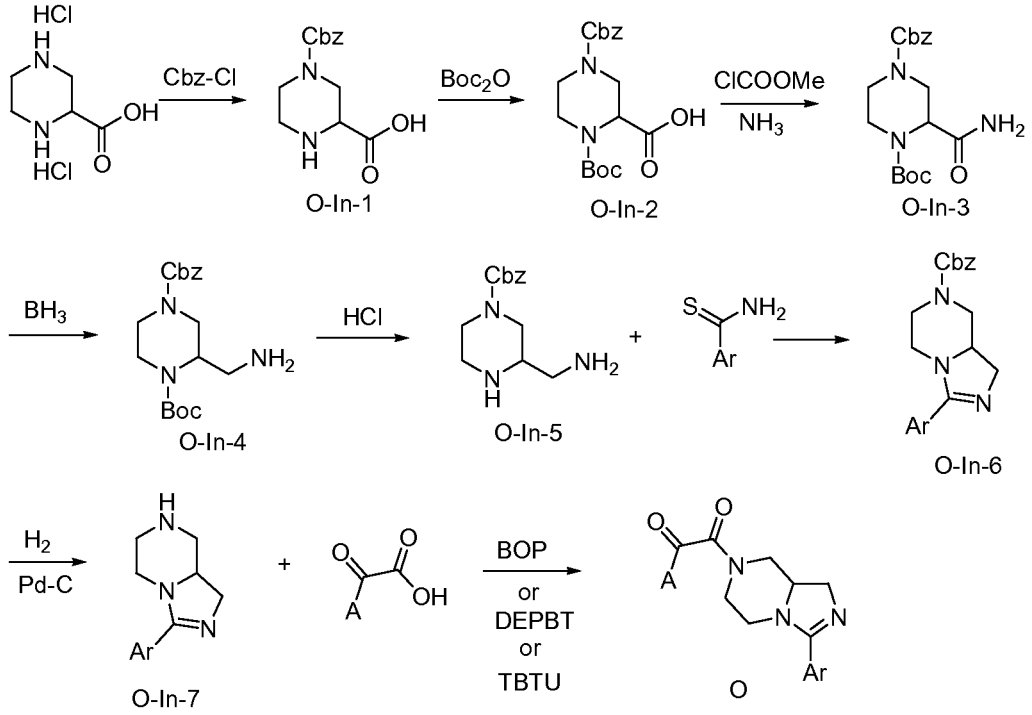
Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
N-In-1a		214	214. ^{1}H-NMR (500 MHz, $CDCl_3$): δ8.69 (s, 1H), 8.53 (m, 2H), 7.84 (m, 2H), 7.53 - 7.44 (m, 3H), 4.83 (d, 1H, J = 4.9Hz).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
N-In-2a		196	196.
N-In-3a		200	200.
N1		HRMS: 483.1888	HRMS: 483.1873. ^{1}H-NMR (500 MHz, DMSO-d_6): δ12.48 (br s, 1H), 9.25 (s, 1H), 8.36 - 8.31 (m, 1H), 7.90 (m, 1H), 7.80 - 7.73 (m, 2H), 7.62 - 7.57 (m, 3H), 7.45 (s, 2/3H), 7.27 (s, 1/3H), 5.00 (s, 4/3H), 4.84 (s, 2/3H), 4.41 (m, 2/3H), 4.26 (m, 4/3H), 4.05 (m, 2/3H), 3.92 (s, 1H), 3.88 (s, 2H), 3.86 (m, 4/3H), 2.50 (s, 3H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
N2		HRMS: 519.1699	HRMS: 519.1689. ^{1}H-NMR (500 MHz, DMSO-d_6): δ12.46 (br s, 1H), 9.24 (s, 1H), 8.34 - 8.30 (m, 1H), 7.88 - 7.86 (m, 1H), 7.69 - 7.60 (m, 1H), 7.50 - 7.40 (m, 1H), 7.29 - 7.21 (m, 1H), 7.10 (s, 2/3H), 6.94 (s, 1/3H), 4.96 (s, 4/3H), 4.79 (s, 2/3H), 4.09 (m, 2/3H), 3.98 (m, 2/3H), 3.91 (m, 4/3H), 3.84 (s, 1H), 3.81 (m, 4/3H), 3.77 (s, 2H), 2.50 (s, 3H).

EXAMPLE O

Preparation of Compounds O of Formula 1



General Process for the Preparation of Compound O-In-1 from Piperazine-2-carboxylic acid:

[00167] A three necked round bottom flask was charged with piperazine-2-carboxylic acid dihydrochloride (1 eq.), cupric carbonate (1.1 eq.) and water. The reaction mixture was refluxed for about 2h and it was filtered through CELITE® bed. The deep blue color filtrate was cooled to 0 °C and added sodium bicarbonate (3.7 eq.) into the reaction mixture very slowly. The reaction mixture was stirred at 0 °C for 30min and benzyl chloroformate (1.5 eq.) was added to the reaction mixture very slowly. The progress of the reaction was monitored by TLC. After consumption of starting material, the reaction mixture was filtered and a pale blue solid was washed with cold water, ethanol and diethyl ether. The pale blue solid was taken up in water and concentrated hydrochloric acid was added. To this solution, H_2S gas was purged for 1h under stirring at room temperature. The excess H_2S gas was removed by purging with nitrogen for 30min. The reaction mixture was filtered through

CELITE® bed and was washed with 1.5N HCl. The colorless filtrate was concentrated to afford desired O-In-1.

General Process for the Preparation of Compound O-In-2 from O-In-1:

[00168] A three necked round bottom flask was charged with O-In-1 (1 eq.), sodium hydroxide (2 eq.) and acetonitrile. The reaction mixture was cooled to 0 °C and Boc anhydride (1 eq.) was added into the reaction mixture very slowly. The reaction mixture was stirred at room temperature for 16h. The progress of the reaction was monitored by TLC. After consumption of starting material, the reaction mixture was washed with petroleum ether. The aqueous layer was acidified with citric acid to pH~6 and extracted with dichloro methane. The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated to afford O-In-2.

General Process for the Preparation of Compound O-In-3 from O-In-2:

[00169] A three necked round bottom flask was charged with O-In-2 (1 eq.), triethyl amine (2 eq.) and dry dichloromethane under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and methyl chloroformate (1.3 eq.) was added into the reaction mixture very slowly. The reaction mixture was stirred at -10 °C for 30min and further cooled to -30 °C. Ammonia gas was purged in the reaction mixture for 30min at -30 °C. The reaction mixture was allowed to stir at room temperature for 16h. After consumption of starting material, ice-cold water was added to reaction mixture. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined organic layers was washed with water, brine and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using 60-120 silica gel and chloroform\methanol (6%) as eluant to afford O-In-3.

General Process for the Preparation of Compound O-In-4 from O-In-3:

[00170] A three necked round bottom flask was charged with O-In-3 (1 eq.) in dry THF under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and

borane-dimethyl sulphide (4 eq.) was added into the reaction mixture very slowly. The reaction mixture was allowed to stir at room temperature for 16h. After consumption of starting material, methanol was added to the reaction mixture very slowly. The reaction mixture was stirred at room temperature for 30min and evaporated to remove volatiles. The residue was dissolved in dichloromethane and ice cold water. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined organic layers was washed with water, brine and dried over anhydrous sodium sulfate. The organic layer was filtered and concentrated under reduced pressure. The resulting crude product was purified by column chromatography using 60-120 silica gel and chloroform\methanol (10%) as eluant to afford O-In-4.

General Process for the Preparation of Compound O-In-5 from O-In-4:

[00171] To O-In-5 dissolved in dry methanol, excess of methanolic HCl was added at 0 °C. The reaction mixture was allowed to stir at room temperature for 3h. The volatiles were completely removed under vacuum to provide O-In-5 as an HCl salt which was used in the further reactions without any purification.

General Process for the Preparation of Compound O-In-6 from O-In-5:

[00172] To O-In-5 (1 eq.) dissolved in dry triethylamine, thiobenzamide (2 eq.) was added. The reaction mixture was heated to 100 °C for 3h. The volatiles were completely removed under vacuum and the residue was diluted with water. The aqueous layer was extracted with dichloromethane and the combined organic layer was washed with brine solution, dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography using 60-120 silica gel and chloroform\methanol (8%) as eluant to afford O-In-6.

General Process for the Preparation of Compound O-In-7 from O-In-6:

[00173] Palladium on carbon (0.01-0.5 eq.) was added into the solution of O-In-6 (1 eq.) in dry methanol under a nitrogen atmosphere. The reaction mixture was allowed to stir under a hydrogen atmosphere at 2kg pressure for 16h. After the completion of the reaction, the reaction mixture was filtered through a CELITE® bed

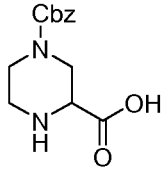
and washed repeatedly with methanol. The filtrate was concentrated under vacuum to afford O-In-7.

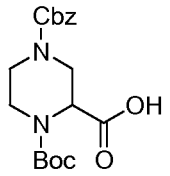
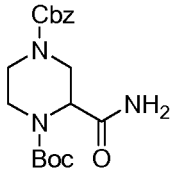
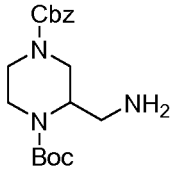
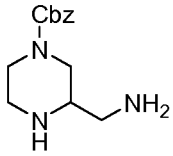
General Process for the Preparation of Compound O from O-In-7:

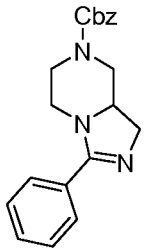
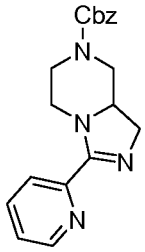
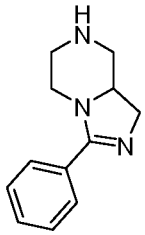
[00174] 2-Keto acid (1 eq.), O-In-7 (1 - 5 eq.), coupling agent (TBTU, DEPBT or BOP) (1 - 5 eq.) and Hunig's Base (1- 100 eq.) were combined in DMF or THF. The mixture was stirred at room temperature for 17 hours. DMF or THF was removed *via* evaporation at reduced pressure and the residue was partitioned between ethyl acetate and 5 - 10% Na_2CO_3 or 5% $NaHCO_3$ or NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate or methylene chloride. The organic phase combined and dried over anhydrous $MgSO_4$. Concentration in *vacuo* provided a crude product, which was purified by trituration, or recrystallization, or silica gel column chromatography, or Shimadzu automated preparative HPLC system, to afford Compound O.

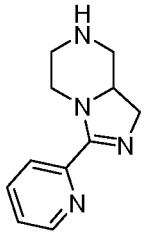
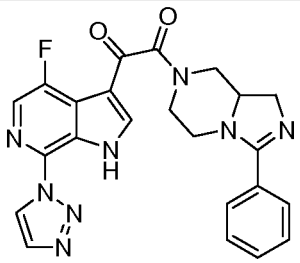
Characterization of O-In and O (Table O):

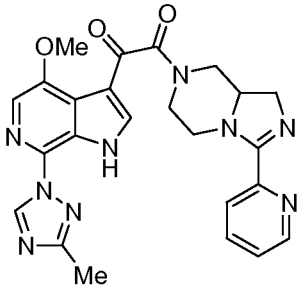
TABLE O

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
O-In-1		265	265. ^{1}H NMR (400 MHz, DMSO-d_6): δ3.24 (m, 2H), 3.89 (m, 2H), 4.14 - 4.20 (m, 2H), 5.11 (m, 1H), 7.30 - 7.42 (m, 5H), 9.86 (bs, 1H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
O-In-2		$(M-1)^+$ 363	363 $(M-1)^+$. ^{1}H NMR (400 MHz, DMSO-d_6): δ1.40 (s, 9H), 2.94 (m, 4H), 3.72 - 3.86 (m, 2H), 4.46 (m, 2H), 7.29 - 7.38 (m, 5H), 13.2 (bs, 1H).
O-In-3		364	^{1}H NMR (400 MHz, DMSO-d_6): δ1.48 (s, 9H), 2.90 (m, 1H), 3.15 - 3.18 (m, 2H), 3.6 - 3.68 (m, 2H), 3.71 - 3.81 (m, 2H), 4.57 - 4.67 (m, 2H), 5.07 - 5.10 (dd, 2H), 7.29 - 7.38 (m, 5H).
O-In-4		350	350. ^{1}H NMR (400 MHz, DMSO-d_6): δ1.48 (s, 9H), 2.90 - 3.1 (m, 2H), 3.2 - 3.33 (m, 3H), 3.6 - 3.68 (d, 1H), 3.71 - 3.81 (dd, 1H), 4.35 - 4.45 (m, 2H), 5.05 (s, 2H), 7.01 (bs, 1H), 7.35 - 7.38 (m, 5H).
O-In-5		250	250. ^{1}H NMR (400 MHz, DMSO-d_6): δ2.90 - 3.1 (m, 2H), 3.18 - 3.33 (m, 3H), 3.5 - 3.65 (m, 2H), 3.94 - 4.02 (dd, 1H), 4.18 - 4.23 (dd, 1H), 5.05 (s, 2H), 7.35 - 7.44 (m, 5H), 8.5 (bs, 3H), 10.12 (bs, 2H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
O-In-6a		336	336. ^{1}H NMR (400 MHz, DMSO-d_6): δ2.70 - 2.73 (m, 1H), 3.11 - 3.18 (m, 2H), 3.58 - 3.63 (m, 2H), 3.75 - 3.80 (m, 2H), 4.18 - 4.22 (m, 2H), 5.05 (s, 2H), 7.35 - 7.50 (m, 10H).
O-In-6b		337	337. ^{1}H NMR (400 MHz, DMSO-d_6): δ3.18 - 3.23 (m, 3H), 3.41 - 3.58 (m, 2H), 3.6 - 3.65 (m, 2H), 4.10 - 4.14 (m, 2H), 5.05 (s, 2H), 7.35 - 7.44 (m, 5H), 7.7 (m, 1H), 8.02 - 8.03 (m, 1H), 8.48 - 8.50 (d, 1H), 8.65 - 8.66 (d, 1H).
O-In-7a		202	202. ^{1}H NMR (400 MHz, DMSO-d_6): δ3.05 - 3.10 (m, 2H), 3.21 - 3.28 (m, 2H), 3.58 - 3.65 (m, 2H), 3.70 - 3.73 (m, 1H), 3.9 - 4.04 (m, 2H), 7.36 - 7.5 (m, 5H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
O-In-7b		203	203. ^{1}H NMR (400 MHz, DMSO-d_6): δ3.2 - 3.40 (m, 3H), 3.51 - 3.60 (m, 2H), 3.6 - 3.65 (m, 2H), 4.0 - 4.04 (m, 2H), 7.7 (m, 1H), 8.02 - 8.03 (m, 1H), 8.48 - 8.50 (d, 1H), 8.65 - 8.66 (d, 1H).
O1		459	459. ^{1}H NMR (400 MHz, DMSO-d_6): δ2.6 (m, 2H), 2.85 - 2.95 (m, 2H), 3.10 - 3.15 (m, 1H), 3.5 - 3.69 (m, 4H), 3.8 - 4.01 (m, 2H), 4.17 - 4.43 (m, 3H), 4.47 (dd, 1H), 7.17 (m, 1H), 7.40 - 7.60 (m, 2H), 7.70 - 7.97 (m, 3H), 8.04 - 8.09 (dd, 1H), 8.17 - 8.25 (m,1H), 8.29 - 8.32 (dd, 1H), 9.03 (m, 1H).

Compound No.	Structure	MS $(M+H)^+$ Calcd.	MS $(M+H)^+$ Observ. and Retention Time and NMR
O2		486	486. ^{1}H NMR (400 MHz, DMSO-d_6): δ2.4 (s, 3H), 3.11 - 3.13 (m, 1H), 3.49 - 3.59 (m, 3H), 3.6 - 3.69 (m, 1H), 4.01 (s, 3H), 4.17 - 4.43 (d, 2H), 4.47 (dd, 1H), 7.77 (m, 1H), 7.89 - 7.90 (d, 1H), 7.96 - 7.97 (m, 1H), 8.14 - 8.27 (m, 1H), 8.27 - 8.29 (d,1H), 8.80 - 8.9 (dd, 1H), 9.23 (s, 1H), 12.5 (bs, 1H).

Biology Data for the Examples

- "μM" means micromolar
- "mL" means milliliter
- "μl" means microliter
- "mg" means milligram

[00175] The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

Cells:

- *Virus production* - Human embryonic Kidney cell line, 293T, was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, CA) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO).

- *Virus infection* - Human epithelial cell line, HeLa, expressing the HIV-1 receptor CD4 was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, CA) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO) and supplemented with 0.2 mg/mL GENETICIN® (Invitrogen, Carlsbad, CA).

- *Virus* - Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al., Ref. 41). Transfections were performed using Lipofectamine Plus reagent as described by the manufacturer (Invitrogen, Carlsbad, CA).

Experimental Procedure:

1. HeLa CD4 cells were plated in 96 well plates at a cell density of 1 X 10^4 cells per well in 100 µl Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum and incubated overnight.

2. Compound was added in a 2 µl dimethylsulfoxide solution, so that the final assay concentration would be ≤10 µM.

3. 100 µl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 µl per well.

4. Virally-infected cells were incubated at 37 °C, in a CO_2 incubator, and harvested 72 h after infection.

5. Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit, as described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, IN). Infected cell supernatants were removed and 50 µl of lysis buffer was added per well. After 15 minutes, 50 µl of freshly-reconstituted luciferase assay reagent was added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac MICROBETA® scintillation counter.

6. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

7. An EC_{50} provides a method for comparing the antiviral potency of the compounds of this disclosure. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four parameter logistic model (model 205). The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

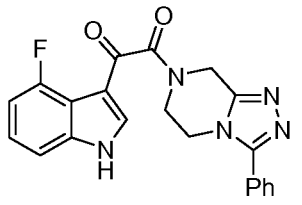
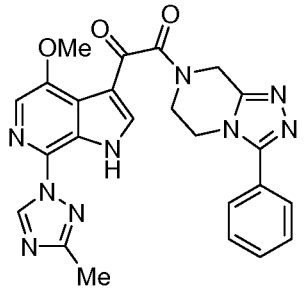
Results

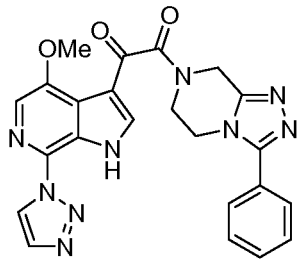
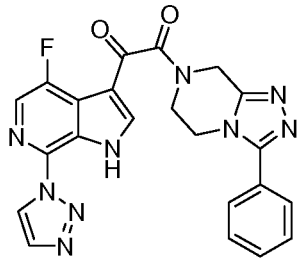
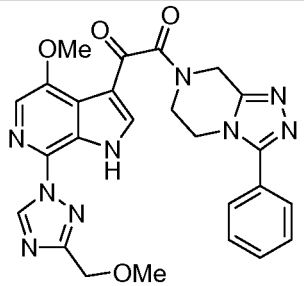
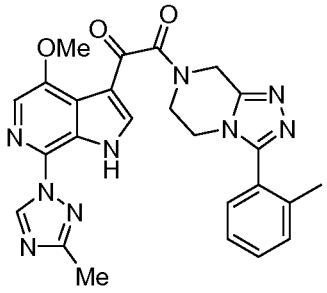
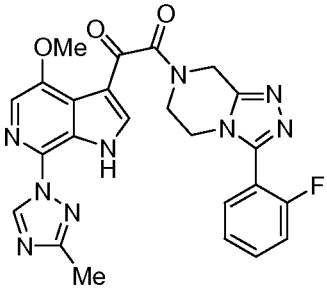
TABLE 1

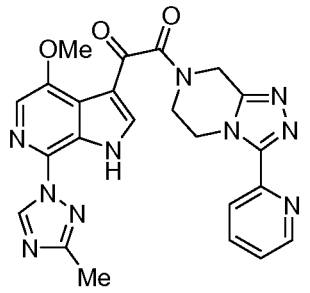
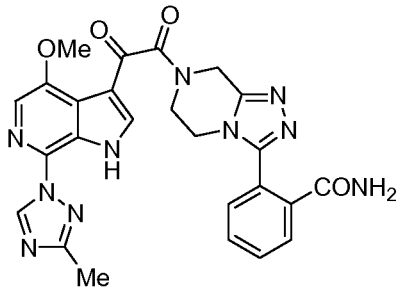
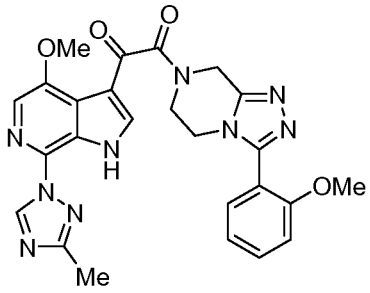
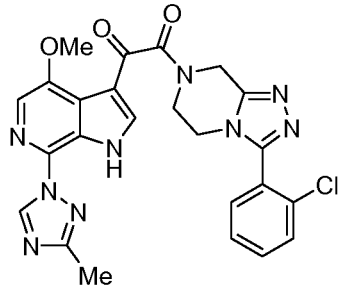
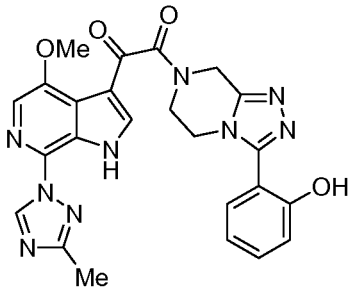
Biological Data Key for EC_{50}s

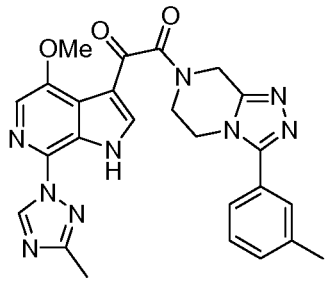
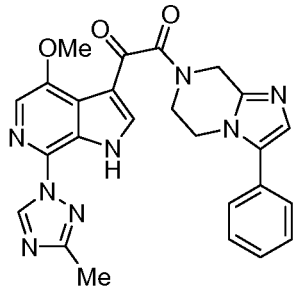
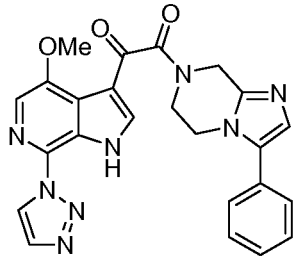
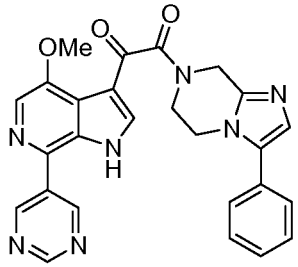
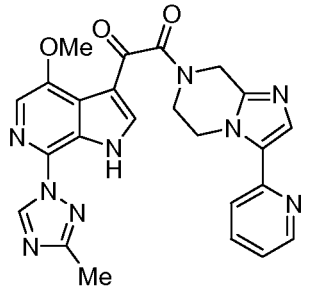
Compounds with EC_{50}s >0.5 μM	Compounds with EC_{50} < 0.5 μM
Group "B"	Group "A"

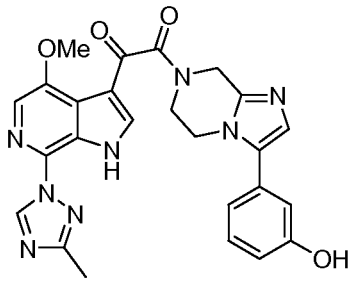
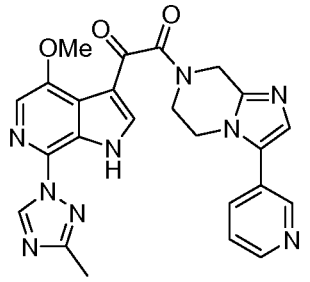
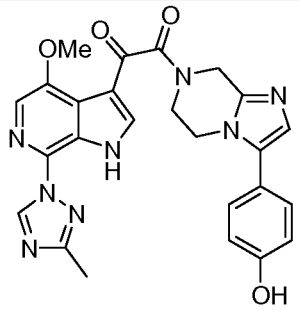
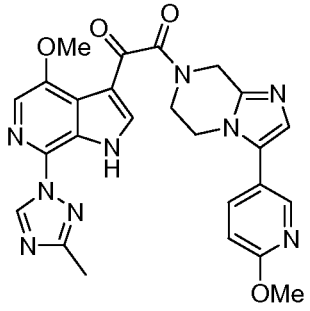
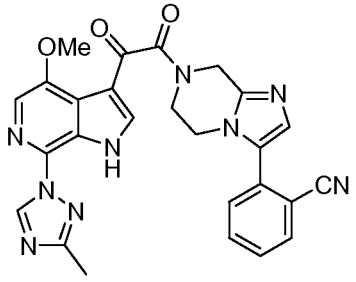
TABLE 2

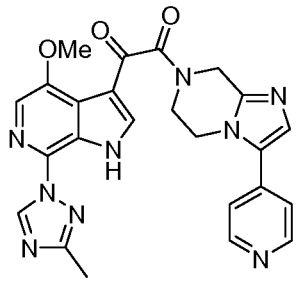
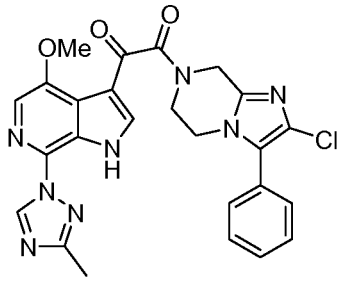
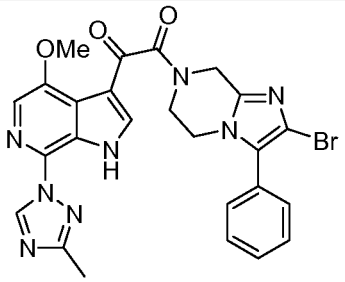
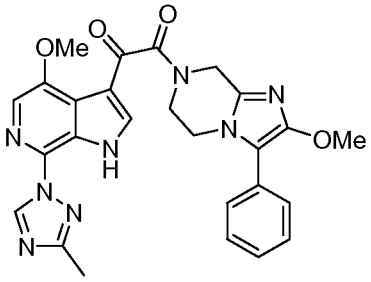
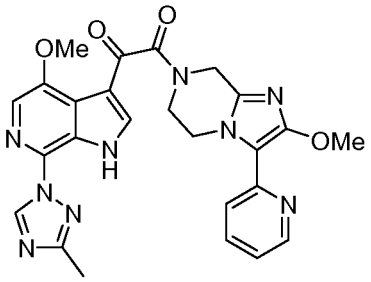
Compound No.	Structure	EC_{50} Group from Table 1
A1		217nM
B1		0.95nM

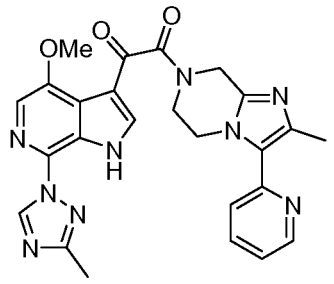
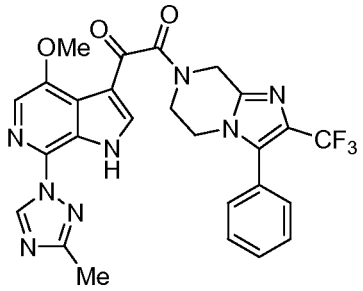
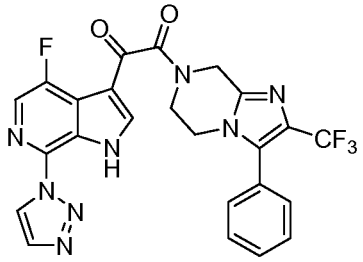
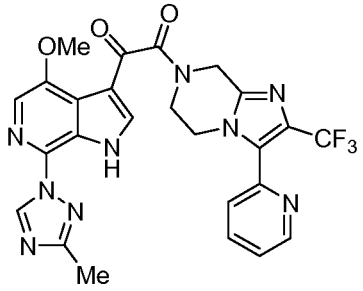
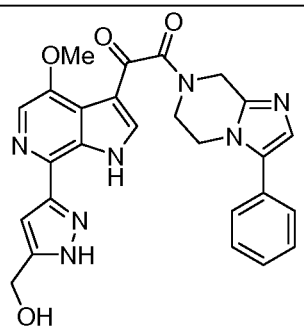
Compound No.	Structure	EC_{50} Group from Table 1
B2		A
B3		A
B4		A
C1		11.8nM
C2		0.29nM

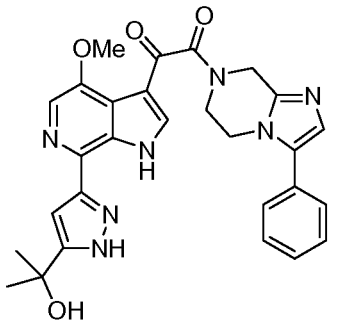
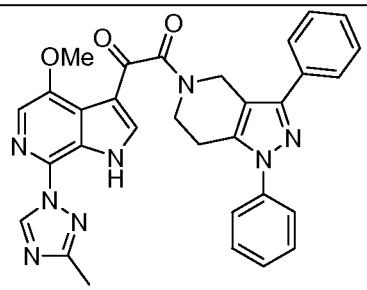
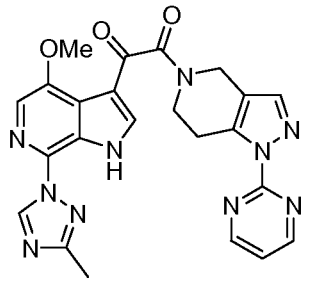
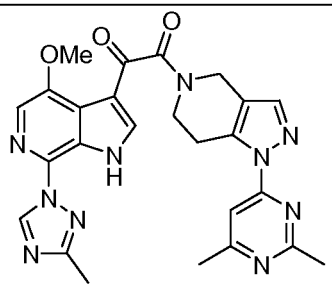
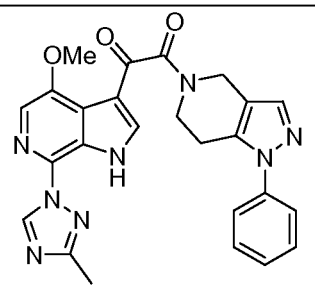
Compound No.	Structure	EC_{50} Group from Table 1
C3		A
C4		>500nM
C5		A
C6		A
C7		1.91nM

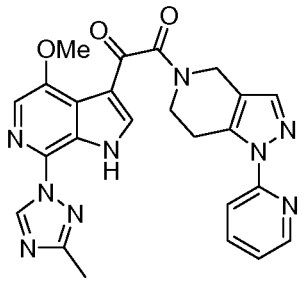
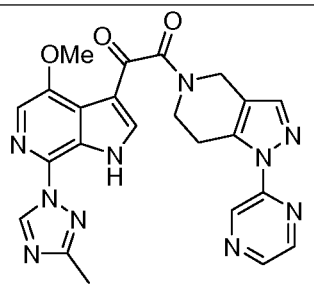
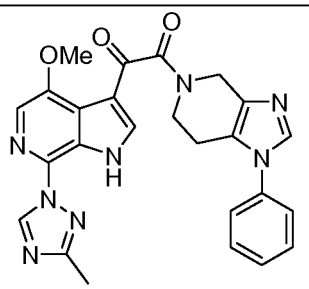
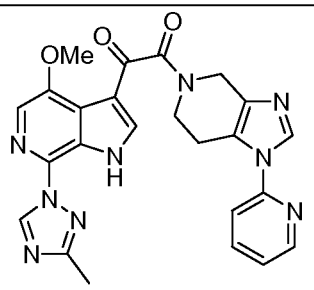
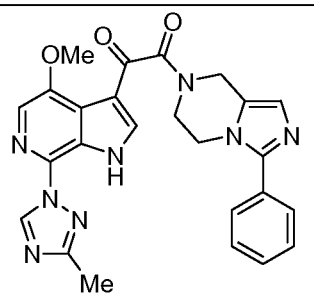
Compound No.	Structure	EC_{50} Group from Table 1
C8		A
D1		A
D2		0.05nM
D3		A
E1		A

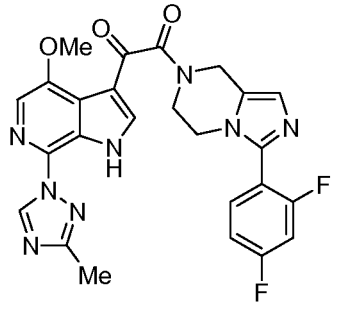
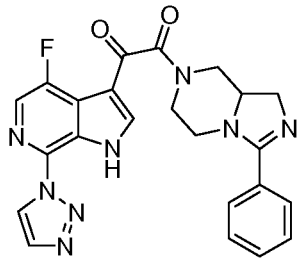
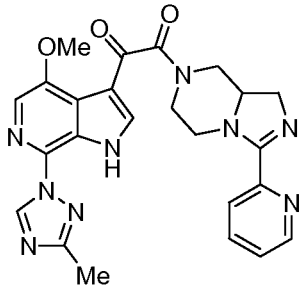
Compound No.	Structure	EC_{50} Group from Table 1
F1		A
F2		A
F3		A
F4		A
F5		98.9nM

Compound No.	Structure	EC_{50} Group from Table 1
F6		13.6nM
G1		A
G2		A
H1a		A
H1b		A

Compound No.	Structure	EC_{50} Group from Table 1
H2		1nM
I1		A
I2		A
I3		0.59nM
J1		0.05nM

Compound No.	Structure	EC_{50} Group from Table 1
J2		A
K1		2.6nM
L1		A
L2		331nM
L3		0.03nM

Compound No.	Structure	EC_{50} Group from Table 1
L4		A
L5		A
M1		0.07nM
M2		A
N1		0.06nM

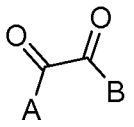
Compound No.	Structure	EC_{50} Group from Table 1
N2		A
O1		13nM
O2		A

[00176] The foregoing description is merely illustrative and should not be understood to limit the scope or underlying principles of the invention in any way. Indeed, various modifications of the invention, in addition to those shown and described herein, will become apparent to those skilled in the art from the following examples and the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

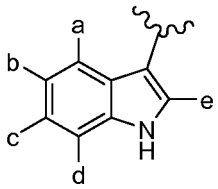
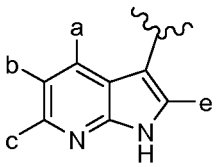
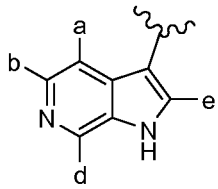
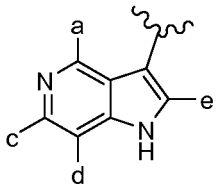
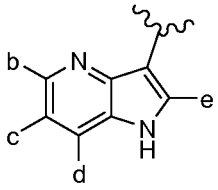
What is claimed is:

1. A compound of Formula I, including pharmaceutically acceptable salts thereof:

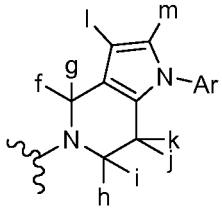
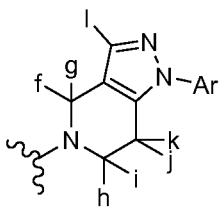
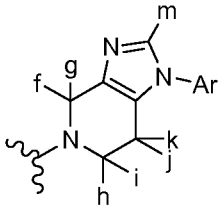
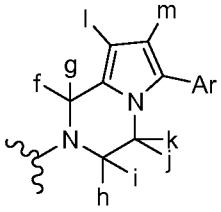
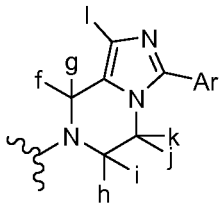
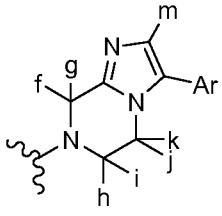
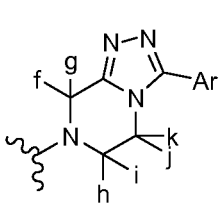
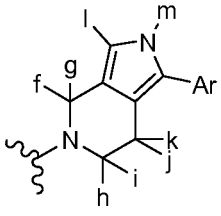


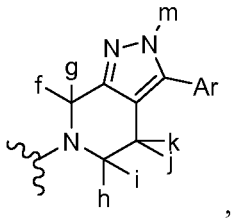
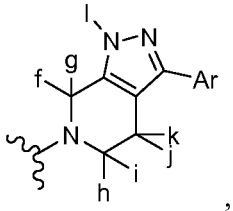
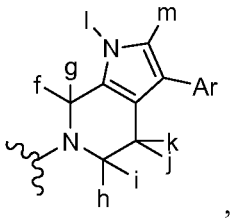
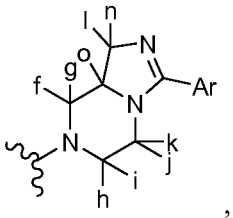
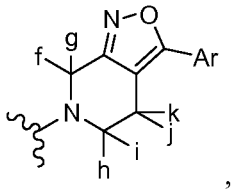
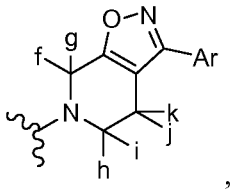
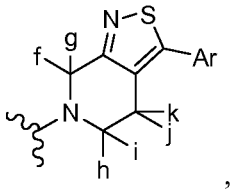
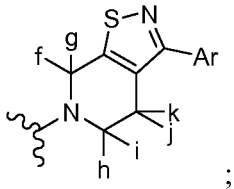
I

wherein A is selected from the group consisting of:


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and 
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wherein B is selected from the group consisting of:


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, and

;

and further wherein

a is selected from the group consisting of H, halogen and methoxy;

b and c are selected from the group consisting of H and halogen;

d is selected from the group consisting of H, halogen, methoxy and Group C;

e is H;

f and g are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein f and g can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

h and i are selected from the group consisting of H, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group. wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein h and i can be connected by a carbon, oxygen, nitrogen or sulfur atom to form a ring;

j and k are selected from the group consisting of H, F, (C_1-C_4) alkyl, and (C_3-C_6) cycloalkyl group, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, NR_1R_2, COOR, and $CONR_1R_2$;

and wherein j and k can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring;

and further wherein j + k is C=O;

l and m are selected from the group consisting of H, OH, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, OR, halogen (attached to carbon only), OR, NR_1R_2, COOR, $CONR_1R_2$, and Group D;

n and o are selected from the group consisting of H, (C_1-C_4) alkyl optionally substituted with one to three substitutions selected from F, OH, OR, NR_1R_2, COOR, CON R_1R_2, (C_3-C_6) cycloalkyl optionally substituted with one to three substitutions (selected from F, OH, OR, NR_1R_2, COOR, $CONR_1R_2$), COOR, $CONR_1R_2$ and Group D;

Ar is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

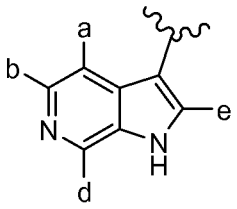
Group C is selected from the group consisting of COOR, $CONR_1R_2$, and Group D;

Group D is selected from the group consisting of phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from Group E; heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, and triazolyl;

Group E is selected from the group consisting of OH, OR, NR_1R_2, CN, COOR, $CONR_1R_2$, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, and wherein said alkyl or cycloalkyl group is optionally substituted with one to three substitutions selected from the group of F, OH, OR, N R_1R_2, COOR, and $CONR_1R_2$;

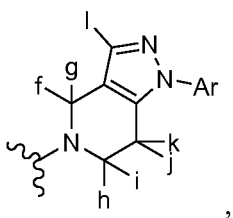
R, R_1 and R_2 are independently H, (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl group; and wherein R_1 and R_2 can be connected by carbon, oxygen, nitrogen or sulfur atom to form a ring.

2. The compound of claim 1, wherein A =

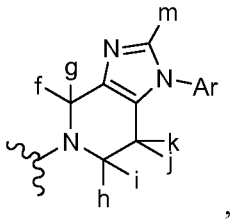


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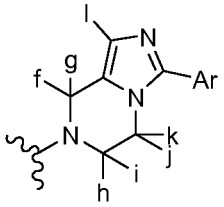
3. The compound of claim 1, wherein B =



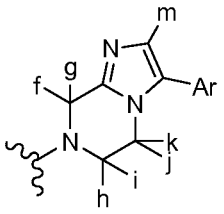
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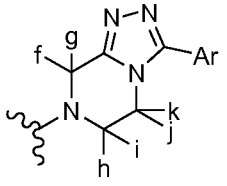
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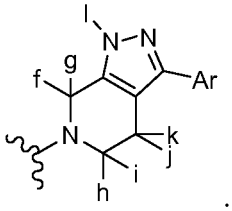
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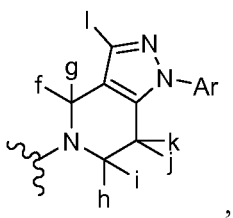


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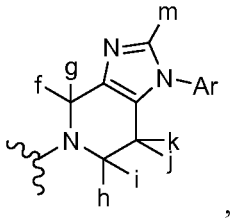


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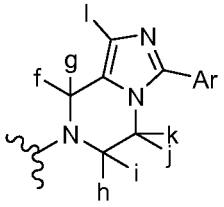
4. The compound of claim 2, wherein B =



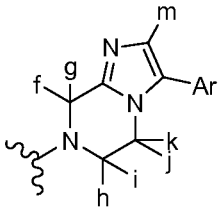
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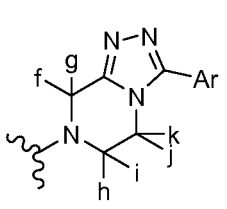
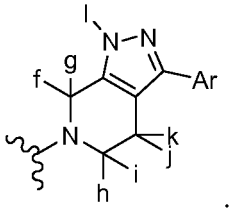
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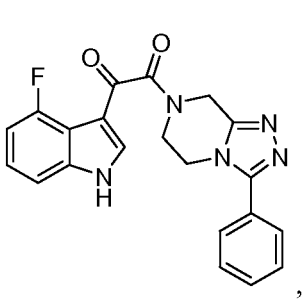
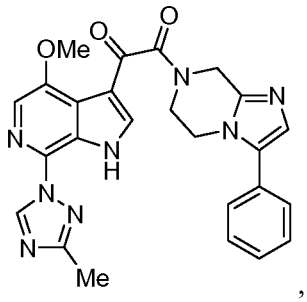
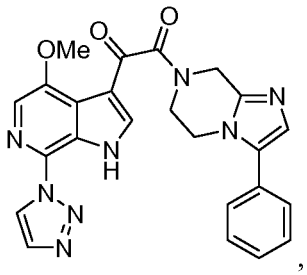
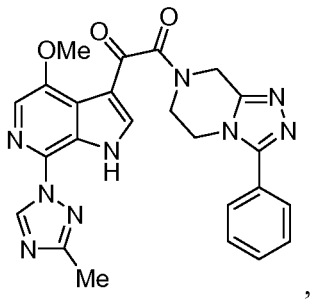
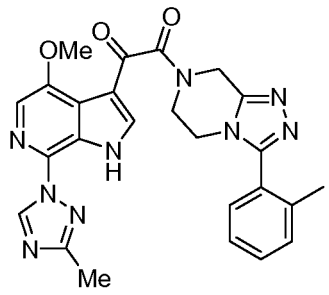
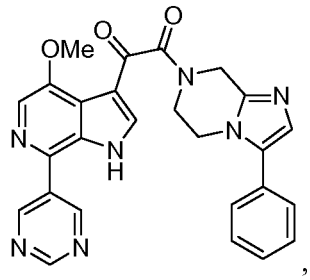
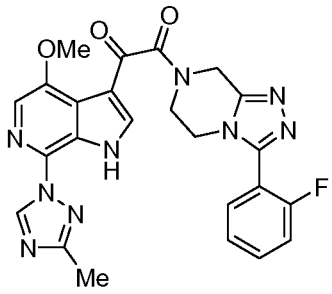
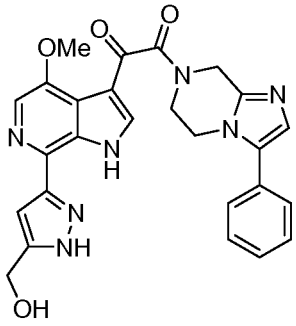
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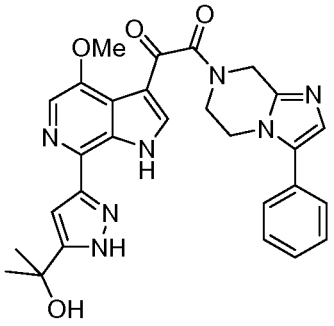
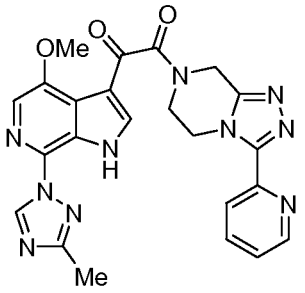
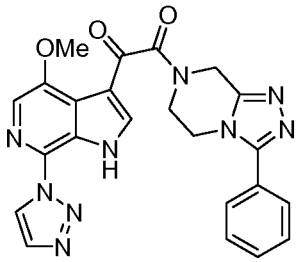
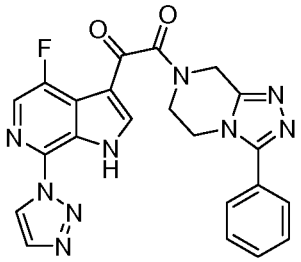
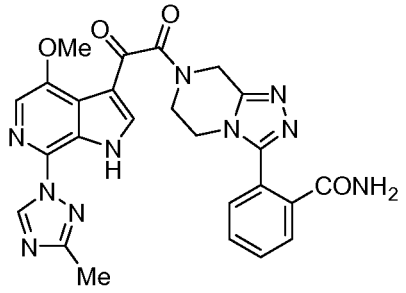
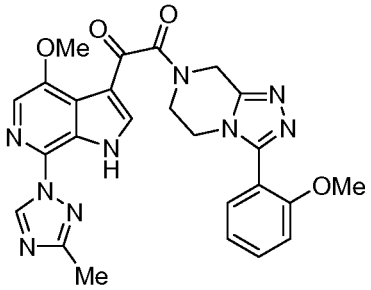
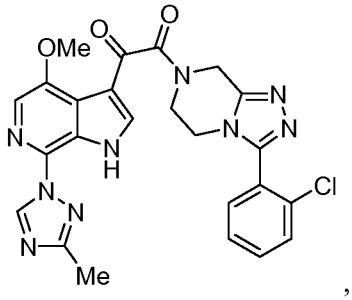
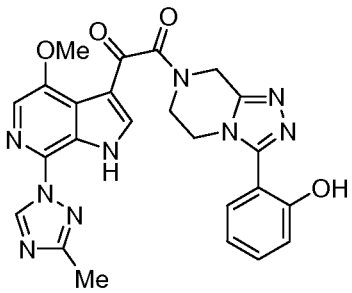
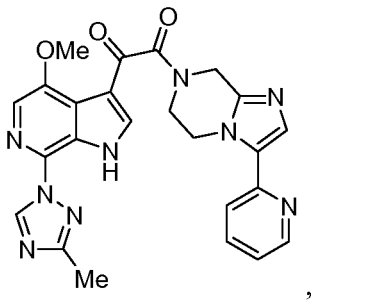
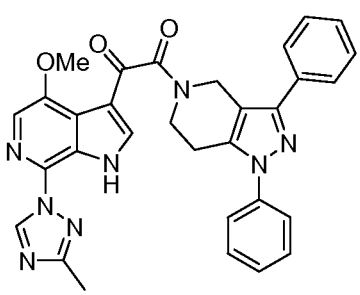
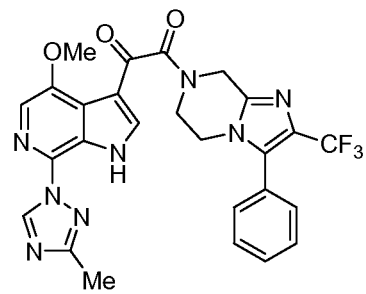


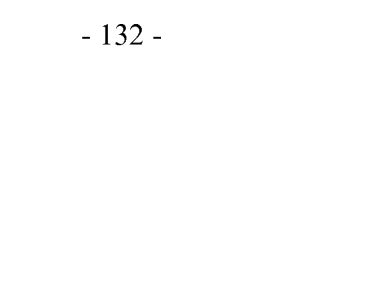
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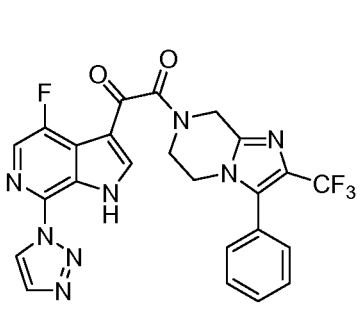
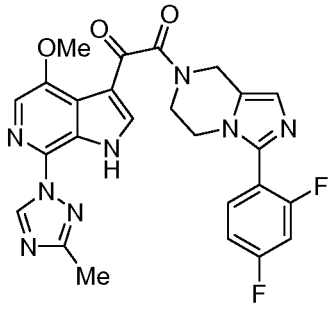
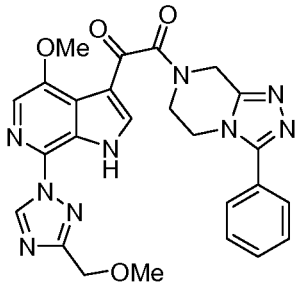
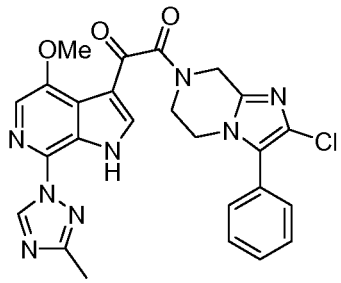
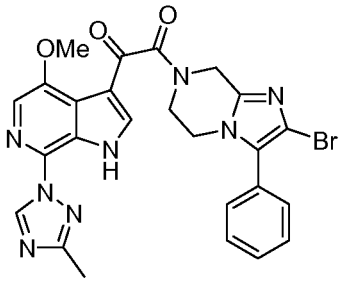
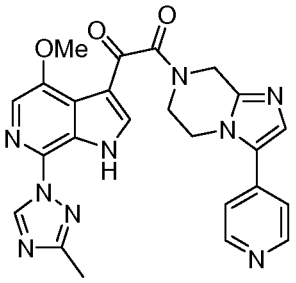
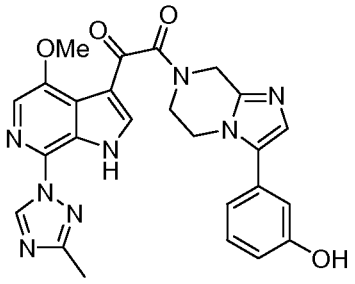
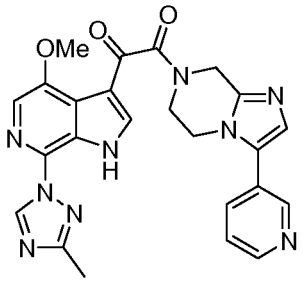
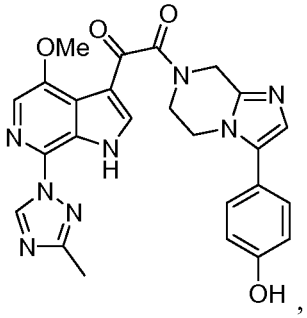
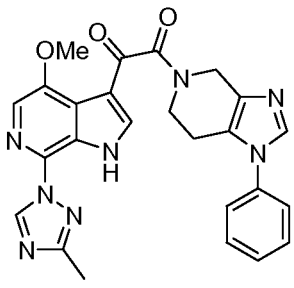
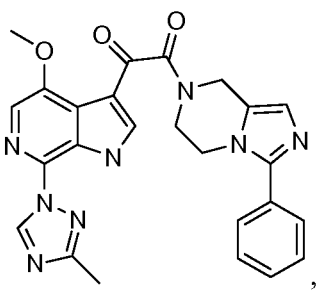

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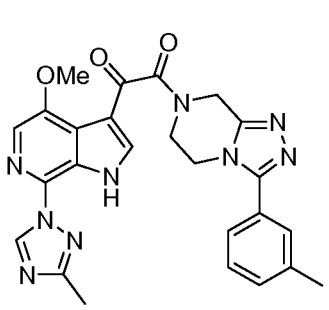
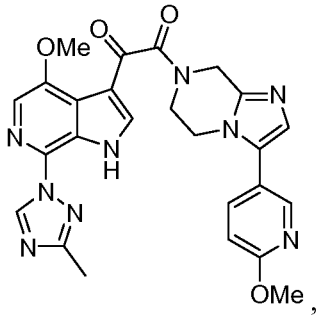
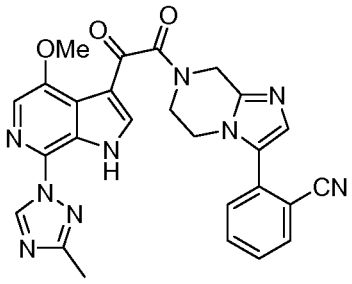
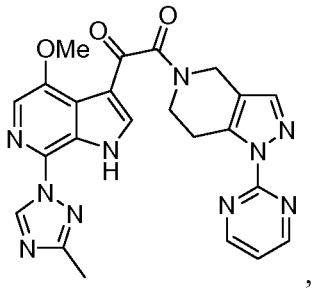
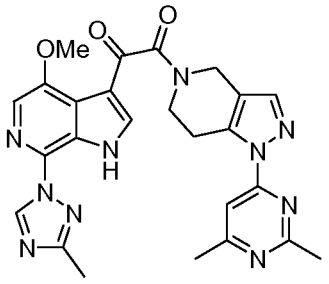
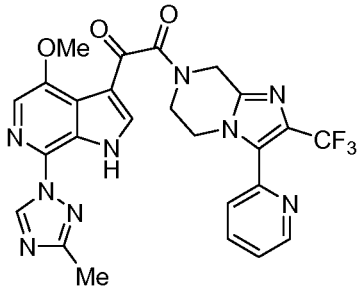
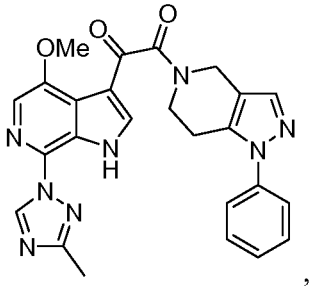
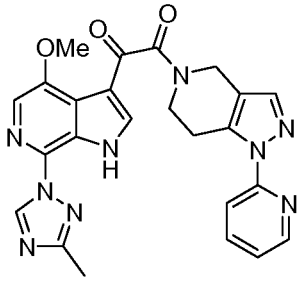
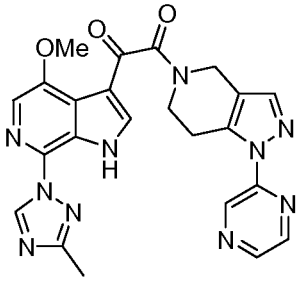
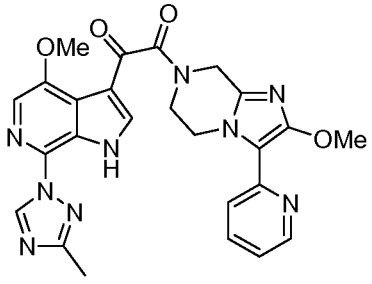
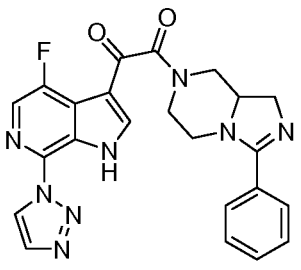
5. A compound which is selected from the group consisting of:

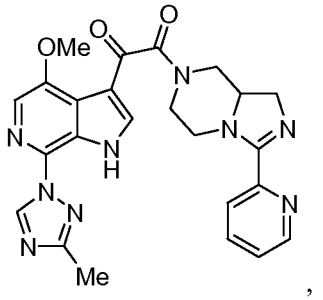
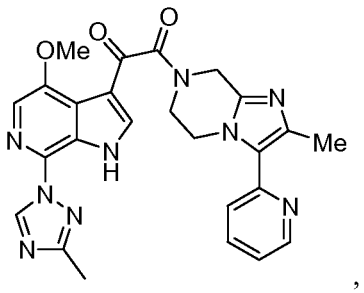
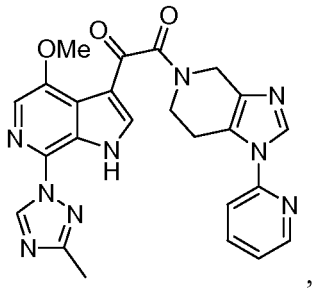
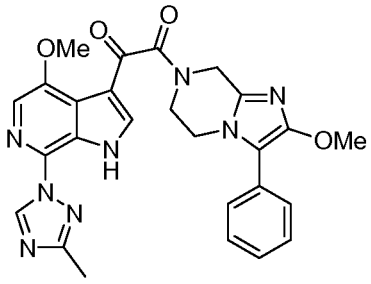
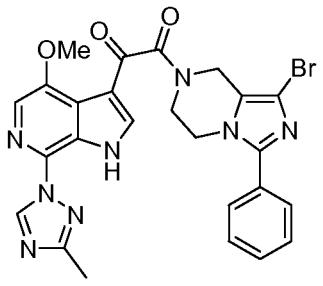
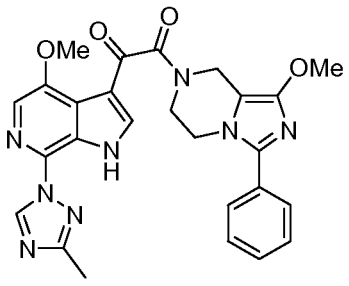

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6. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 1, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

7. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 2, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

8. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 3, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

9. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 4, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

10. A pharmaceutical composition which comprises an antiviral effective amount of one or more of the compounds of Formula I as claimed in claim 5, together with one or more pharmaceutically acceptable carriers, excipients or diluents.

11. The pharmaceutical composition of claim 6, useful for treating infection by HIV, which additionally comprises an antiviral effective amount of an AIDS treatment agent selected from the group consisting of:

(a) an AIDS antiviral agent;

(b) an anti-infective agent;

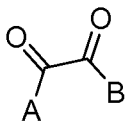
(c) an immunomodulator; and

(d) another HIV entry inhibitor.

12. A method for treating a mammal infected with the HIV virus comprising administering to said mammal an antiviral effective amount of a compound of Formula I as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients or diluents.

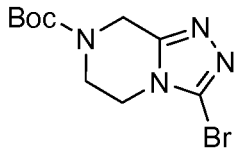
13. The method of claim 10, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of an AIDS antiviral agent; an anti-infective agent; an immunomodulator; and another HIV entry inhibitor.

14. A method of making the compound of Formula I of claim 1:

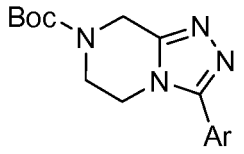


I

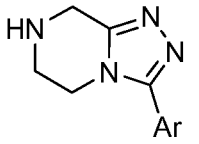
which comprises reacting the compound



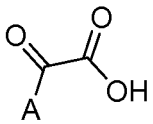
with a reagent selected from the group of Ar-$B(OH)_2$ and Ar-$SnBu_3$ in the presence of a catalyst to yield



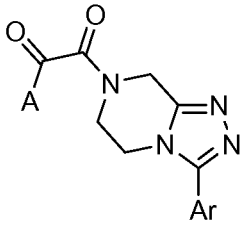
and thereafter acidifying said compound in the presence of H+ to yield



and thereafter reacting said compound with

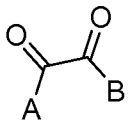


in the presence of TBTU , DEBPT or BOP to yield



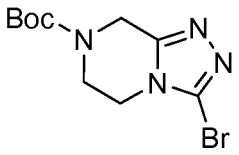
15. The method of claim 14, wherein said catalyst is palladium.

16. A method of making the compound of Formula I of claim 1:

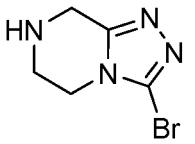


I

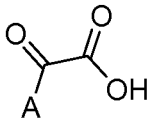
which comprises acidifying the compound



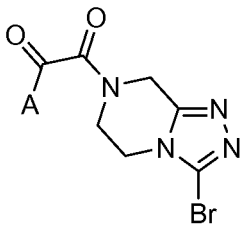
in the presence of H^+ to yield



and thereafter reacting said acidified compound with

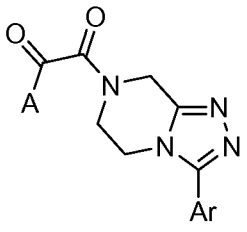


in the presence of TBTU, DEBPT or BOP to yield



,

and thereafter reacting this compound with a reagent selected from the group of Ar-$B(OH)_2$ and Ar-$SnBu_3$ in presence of a catalyst to yield



.

17. The method of claim 16, wherein said catalyst is palladium.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2009/048427

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D487/00 C07D519/00 A61K31/437 A61K31/4985
A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7 348 337 B2 (WANG TAO [US] ET AL) 25 March 2008 (2008-03-25) cited in the application claims 1,53-58; table 2	1-17
A	WO 2007/127635 A (SQUIBB BRISTOL MYERS CO [US]; WANG TAO [US]; KADOW JOHN F [US]; ZHANG) 8 November 2007 (2007-11-08) claims 1,35-41	1-17
A	WO 2005/117868 A (SQUIBB BRISTOL MYERS CO [US]; RUEDIGER EDWARD H [CA]; DEON DANIEL H [C) 15 December 2005 (2005-12-15) claims 1,11,12	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2009	26/10/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2009/048427

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 2004063744 A1	01-04-2004
		US 2004186292 A1	23-09-2004
WO 2007127635 A	08-11-2007	AR 060658 A1	02-07-2008
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		CA 2650382 A1	08-11-2007
		EA 200802203 A1	28-04-2009
		EP 2010525 A2	07-01-2009
		KR 20090005393 A	13-01-2009
		US 2007249579 A1	25-10-2007
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WO 2005117868 A	15-12-2005	US 2005267130 A1	01-12-2005