(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 February 2020 (20.02.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/035880 A1

(51) International Patent Classification:
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/IN2019/050594

(22) International Filing Date:
13 August 2019 (13.08.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201841005491 13 August 2018 (13.08.2018) IN

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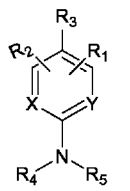
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

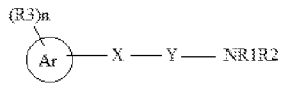
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR,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

Declarations under Rule 4.17:
— *of inventorship (Rule 4.17(iv))*

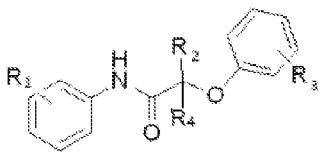
(54) Title: INHIBITORS TO TARGET HIV-1 NEF-CD80/CD86 INTERACTIONS FOR THERAPEUTIC INTERVENTION



Formula I



Formula II



Formula III

(57) Abstract: The compounds of Formula I, II, and III along with their stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof are described in the present disclosure. The said compounds restore immune activation in case of infections or a disease associated with an HIV infection in a subject in need thereof.

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Published:

— *with international search report (Art. 21(3))*

— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

INHIBITORS TO TARGET HIV-1 *NEF*-CD80/CD86 INTERACTIONS FOR THERAPEUTIC INTERVENTION

FIELD OF INVENTION

[0001] The present disclosure relates to prevention/ treatment of immune evasion by human immunodeficiency virus (HIV) related infections. The compounds of the present disclosure are useful as medicaments and their use in the manufacture of medicaments for treatment, prevention or suppression of diseases, and conditions mediated by HIV.

BACKGROUND

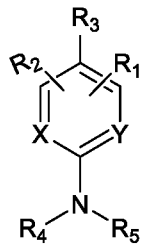
[0002] In recent years, there has been considerable progress in the treatment of HIV-related illness through different approaches. One of them being use of highly active antiretroviral therapy (HAART), which involves the use of different kinds of anti-retroviral agents that act on different stages of the HIV life cycle. The anti-retro viral drugs have different mechanism of action, such as nucleoside/nucleotide reverse transcriptase inhibitors, non- nucleoside retroviral treatment, maturation and cellular inhibitors, integrase inhibitors, protease inhibitors and immune-based therapy. Despite the rapid development of the HIV therapy, the key issue for eradication of virus reservoir composed of latently infected memory CD4+ T cells carrying integrated pro-virus remains. The resting memory CD4+ T cells can persist for months to years carrying replication competent viral genome thus posing problems for patients on HAART. The current therapy does not eradicate the provirus and needs more research to address this issue.

[0003] *Nef* protein, a HIV-1 auxiliary protein, and inhibition of its interaction and complexes comprising *Nef*, with other cellular components have been studied in detail. *Nef* interaction with Src protein-tyrosine kinase family (series of signaling molecules) is required for the onset and progression of AIDS in HIV-1-infected persons. (Lugari et. al, Bioorganic & Medicinal Chemistry 19 (2011) 7401–7406; Emert-Sedlak et al., ACS Chem Biol. 2009 4(11), 939-947; US 8541415).

[0004] Interestingly, the virus uses the *Nef* protein to evade killing of its host cell by cytotoxic T-lymphocytes. Inhibiting *Nef*-mediated functions thus presents a different strategy for increasing CTL activity against HIV infected cells by making the latter more visible to the immune system.

SUMMARY

[0005] The present disclosure relates to compounds of Formula I, II, and III that restore immune activation in case of infections. The present disclosure specifically relates to a method for the prevention or treatment of an HIV infection or a disease associated with an HIV infection in a subject in need thereof, comprising: administering to a HIV infected subject a therapeutic dose of a compound selected from the group consisting of Formula I,



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

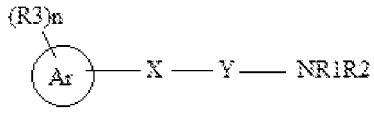
R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein N=CHC$_6$ aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl, is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;

Formula II,



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

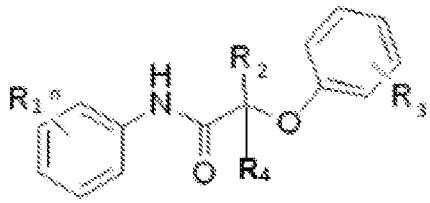
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

$R_3$is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-(Cl)$_2$ or CONHNHSO$_2$Ph-Me; and

n is selected from 0-5; and

Formula III



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and n is selected from 1 to 5.

[0006] The present disclosure further relates to a compound selected from the group consisting of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, for prophylaxis and/or treatment of an HIV infection or a disease associated with an HIV infection

[0007] The present disclosure further relates to use of a compound selected from the group consisting of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, towards restoration of immune signaling via T cell activation through inhibiting *Nef*-CD80/86 interactions.

[0008] The present disclosure further relates to a compound selected from the group consisting of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof,

for use in treating a disease or condition in a patient wherein said disease or condition is caused by cancers including chronic lymphocytic leukemia, colon carcinoma, multiple myeloma or viral infections including HIV, HPV, herpes and the like.

[0009] The present disclosure further relates to use of a compound selected from the group consisting of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, in treating disease or condition in a subject, wherein said disease or condition is caused by HIV. The subject may be a mammal including humans. These and other features, aspects, and advantages of the present subject matter will become better understood with reference to the following description. This summary is provided to introduce a selection of concepts in a simplified form. This summary is not intended to identify key features or essential features of the disclosure, nor is it intended to be used to limit the scope of the subject matter.

BRIEF DESCRIPTION OF DRAWINGS

[00010] Figure 1 illustrates the biochemical screening of the compounds in accordance with an implementation of the present disclosure.

[00011] Figure 2 illustrates the schematic representation of the cell-based assay, in accordance with an implementation of the present disclosure.

[00012] Figure 3 illustrates the inhibition of *Nef* mediated internalization of surface CD80/86 as measured by flow cytometry by compounds from Formula I, II and III in accordance with an implementation of the present disclosure.

[00013] Figure 4 illustrates the schematic representation of the cell-based T cell activation assay in accordance with an implementation of the present disclosure.

[00014] Figure 5 illustrates the inhibition of *Nef* mediated T cell inactivation in an APC in accordance with an implementation of the present disclosure.

DETAILED DESCRIPTION

[00015] Those skilled in the art will be aware that the present disclosure is subject to variations and modifications other than those specifically described. It is to be

understood that the present disclosure includes all such variations and modifications. The disclosure also includes all such steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any or more of such steps or features.

Definitions

[00016] For convenience, before further description of the present disclosure, certain terms employed in the specification, and examples are collected here. These definitions should be read in the light of the remainder of the disclosure and understood as by a person of skill in the art. The terms used herein have the meanings recognized and known to those of skill in the art, however, for convenience and completeness, particular terms and their meanings are set forth below.

[00017] The articles "a", "an" and "the" are used to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article.

[00018] The terms "comprise" and "comprising" are used in the inclusive, open sense, meaning that additional elements may be included. Throughout this specification, unless the context requires otherwise the word "comprise", and variations, such as "comprises" and "comprising", will be understood to imply the inclusion of a stated element or step or group of element or steps but not the exclusion of any other element or step or group of element or steps.

[00019] The term "including" is used to mean "including but not limited to". "Including" and "including but not limited to" are used interchangeably.

[00020] In the structural formulae given herein and throughout the present disclosure, the following terms have been indicated meaning, unless specifically stated otherwise.

[00021] The term "therapeutic dose" refers to providing any compound of the present disclosure (drug) in a dose per unit time over an extended time to a subject in need thereof. The therapeutic dose according to the present disclosure may be in a range of 50 µM to 1000 µM.

[00022] The term “relevant dose” refers to providing any compound of the present disclosure (drug) in a dose per unit time over an extended time to a subject for preventing HIV.

[00023] The term “low levels of CD80/86 receptors” can be defined as any condition which leads to a decrease in levels of CD80/86 receptors on the T cells.

[00024] The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 10 carbon atoms. This term is exemplified by groups such as n-butyl, iso-butyl, t-butyl, n-hexyl, n-decyl, and the like. The groups may be optionally substituted.

[00025] The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 4, 5, 6, 7, 8, 9, or 10 carbon atoms and having 1, 2, 3, 4, 5 or 6 double bond (vinyl), preferably 1 double bond. The groups may be optionally substituted.

[00026] The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon, preferably having from 4, 5, 6, 7, 8, 9, or 10carbon atoms and having 1, 2, 3, 4, 5 or 6 sites of acetylene (triple bond) unsaturation, preferably 1 triple bond. The groups may be optionally substituted.

[00027] “Halo” or “Halogen”, alone or in combination with any other term means halogens such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

[00028] The term "aryl" refers to an aromatic carbocyclic group of 5 to 18 carbon atoms having a single ring (e.g. phenyl) or multiple rings (e.g. biphenyl), or multiple condensed (fused) rings (e.g. naphthyl or anthranyl). Preferred aryls include phenyl, naphthyl and the like. The groups may be optionally substituted.

[00029] The term "heteroaryl" refers to a heteroaromatic carbocyclic group of 2 to 10 carbon atoms having a single ring or multiple rings, or multiple condensed rings. Preferred heteroaryls include pyrazole, thiazole,oxazole, benzoxazole, pyridine and the like. The groups may be optionally substituted.

[00030] The term "cycloalkyl" refers to carbocyclic groups of from 3 to 12 carbon atoms having a single cyclic ring or multiple condensed rings, which may be partially

unsaturated. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclohexyl, cyclohexenyl, and the like, or multiple ring structures or carbocyclic groups to which is fused an aryl group. The groups may be optionally substituted.

[00031] The term "heterocyclyl" refers to a saturated or partially unsaturated group or unsaturated group having a single ring or multiple condensed rings, having from 2 to 10 carbon atoms and from 1 to 10 hetero atoms, preferably 1, 2, or 3 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Preferred heterocyclyls include morpholine, piperidine, and the like. The groups may be optionally substituted.

[00032] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds.

[00033] The term "effective amount" means an amount of a compound or composition, which is sufficient enough to significantly and positively modify the symptoms and/or conditions to be treated. The effective amount will vary depending on various conditions and is within the knowledge and expertise of the attending physician.

[00034] The compounds described herein may contain one or more chiral centers and/or double bonds and therefore, may exist as stereoisomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated or identified compounds including the stereoisomerically pure form and enantiomeric and stereoisomeric mixtures. The compounds may also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated or identified compounds.

[00035] The term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms, which are suitable for use in contact with the tissues of human beings and animals and is understood by a person skilled in the art.

[00036] "Pharmaceutically acceptable salt" embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, and organic bases.

[00037] The term "polymorphs" refers to crystal forms of the same molecule, and different polymorphs may have different physical properties.

[00038] The term "solvate", as used herein, refers to a crystal form of a substance, which contains solvent.

[00039] The term "hydrate" refers to a solvate wherein the solvent is water.Ratios, concentrations, amounts, and other numerical data may be presented herein in a range format. It is to be understood that such range format is used merely for convenience and brevity and should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited. For example, a concentration range of about 50 to 1000 µM should be interpreted to include not only the explicitly recited limits of about 50 µM to about 1000 µM, but also to include sub-ranges, such as 75-875 µM, 80-500 µM, and so forth, as well as individual amounts, including fractional amounts, within the specified ranges, such as 100 µM, and 155 µM, for example.

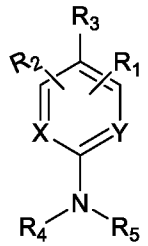
[00040] The present disclosure relates to compounds for treatment of HIV infection. The target is novel interaction of *Nef* protein from the HIV-1 virus with the host immune receptors CD80/CD86 responsible for T cell stimulation.

[00041] An indispensable factor for HIV pathogenicity is the *Nef* protein. It allows HIV to evade the immune response, maintain high viral load and is needed for replication and dissemination, down-regulate cell surface receptors involved in the generation of immune response, including MHC-1 and MHC-2. It has been surprising found that in addition to relocation of MHC, *Nef* also down-regulates surface expression of the B-7 family of co-stimulatory proteins, namely CD80 and CD86 expressed on antigen presenting cells, leading to impaired T cell stimulation *in vitro*. *Nef* binds directly to the cytoplasmic tails of CD80 and CD86 and prone to reversal by introduction of peptides,

making it a suitable target for therapeutic intervention. Targeting *Nef*-CD80/86 interactions has a unique mechanism of action: prevention of immune evasion of infected cells. The disclosure revolves around the inhibition of *Nef*-mediated functions, which is a distinct strategy since it targets a key function of *Nef* in its ability to directly modulate infected immune cell (macrophage) capacity to generate HIV-specific T cells from naïve T cell, potentially bringing forth a different class of drugs. The disclosure presents a new line of antiviral therapy through immune signaling restoration.

[00042] The host-virus interface is also less amenable to drug resistance than purely viral targets. The present disclosure discloses a method for preventing/ treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of Formula I. Formula II, and Formula III as described herein, wherein the therapeutic dose of the compound is in a range of 50 to 1000 µM. The present disclosure is intended to cover all the sub-ranges and individual values. The range can be 50 to 100 µM, or 100 to 1000 µM, or 150 to 900 µM, or 125 to 500 µM, or 500 to 900 µM, or 750 to 950 µM, or 75 to 150 µM, or 100 to 200 µM.

[00043] In an embodiment, the present disclosure provides a method for preventing/ treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of Formula I,



Formula I

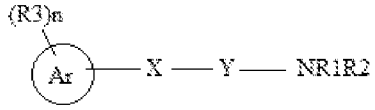
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{5-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

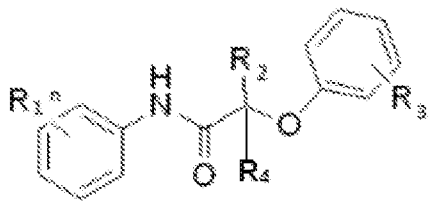
X is selected from O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh\text{-}Me$, $NHCONHPh\text{-}(Cl)_2$ or $CONHNHSO_2Ph\text{-}Me$; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

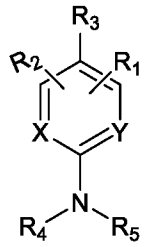
R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5. In another embodiment of the present disclosure, the therapeutic dose of the compound is in a range of 50 to 1000 µM. In yet another embodiment of the present disclosure, the therapeutic dose of the compound is in a range of 50 to 100 µM. In an alternate embodiment of the present disclosure, the therapeutic dose of the compound is in a range of 100 to 1000 µM. In one another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 150 to 900 µM. In an alternate embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 125 to 500 µM. In another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 500 to 900 µM. In another embodiment of the

present disclosure, the therapeutic dose of the compound is in the range of 750 to 950 µM. In another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 75 to 150 µM. In another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 100 to 200 µM.

[00044] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula I,



Formula I

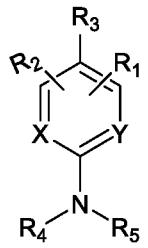
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, and amino, wherein C_{1-10} alkyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00045] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula I,



Formula I

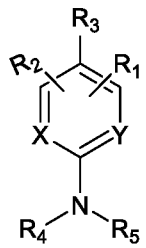
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, and C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, and C_{1-10} alkoxy;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00046] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula I,



Formula I

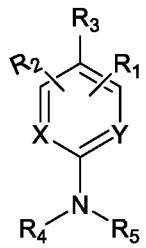
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and C_{1-5} alkyl, wherein C_{1-5} alkyl, and C_6 aryl are optionally substituted with one to four substituents independently selected from hydroxyl, fluorine, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkoxy, nitro, halogen or C_{1-5} alkyl, wherein C_{1-5} alkyl and C_{1-5} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-5} alkyl, C_{1-5} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00047] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula I,



Formula I

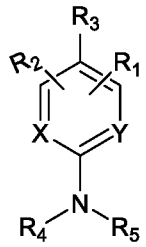
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and CF_3, wherein C_6 aryl are optionally substituted with one to four substituents independently selected from hydroxyl, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from $-OCH_3$, $-OCF_3$, nitro, fluorine, CF_3;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and $-N=CHC_6$ aryl, wherein $N=CHC_6$ aryl is further substituted with one to four substituents selected from fluorine and bromine; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00048] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula I,



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

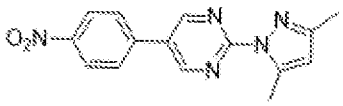
R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents

independently selected from hydroxyl, halogen, C_{1-10} alkyl or C_{1-10} alkoxy, C_{2-10} heterocyclyl;

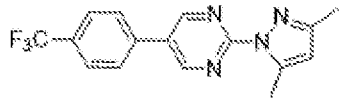
R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

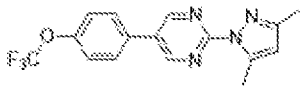
[00049] In an embodiment, the present disclosure provides a compound of Formula I or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, which is selected from a group consisting of:



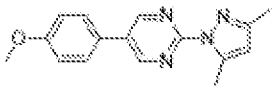
I_1a



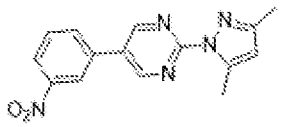
I_1b



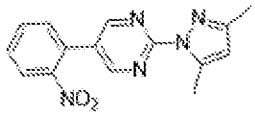
I_1c



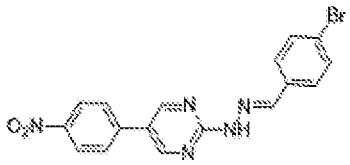
I_1d



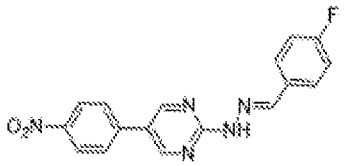
I_1e



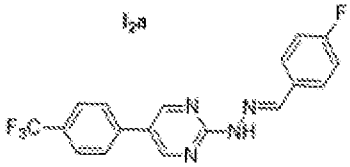
I_1f



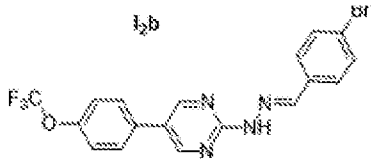
I_2a



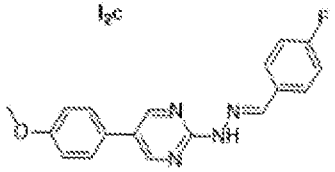
I_2b



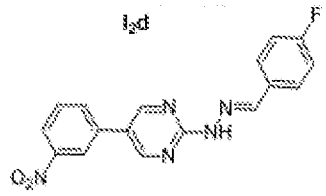
I_2c



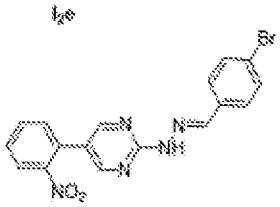
I_2d



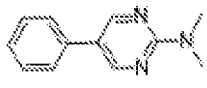
I_2e



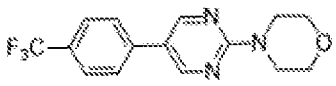
I_2f



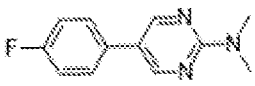
I_2g



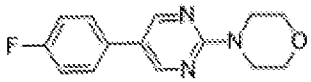
I_3a



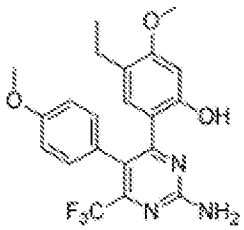
I_3b



I_3c

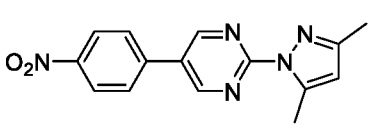


I_3d

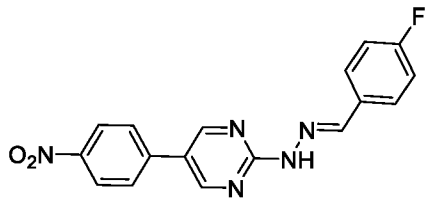


I_4

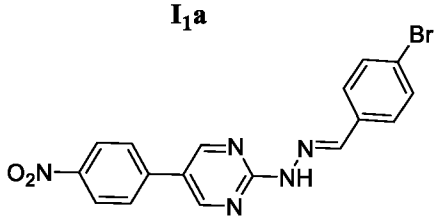
[00050] In an embodiment, the present disclosure provides a compound of Formula I or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, which is selected from a group consisting of:



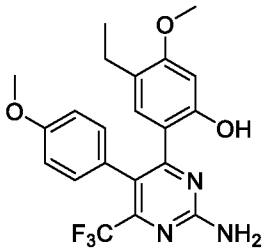
I_1a



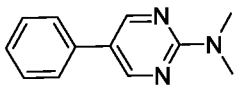
I_2b



I_2a

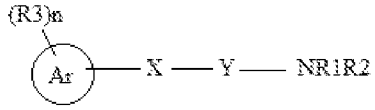


I_4



I_3a

[00051] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

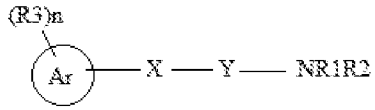
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5.

[00052] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or $R_1$and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

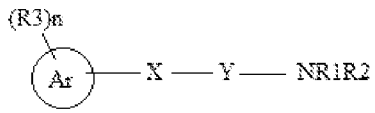
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$or CONHNHSO_2Ph-Me; and

n is selected from 0-5.

[00053] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

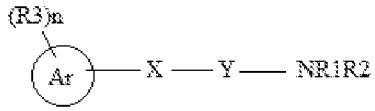
Y is C=O;

Ar is selected from C_{5-10}aryl or C_{2-10}heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$or CONHNHSO_2Ph-Me; and

n is selected from 0-5.

[00054] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or

R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

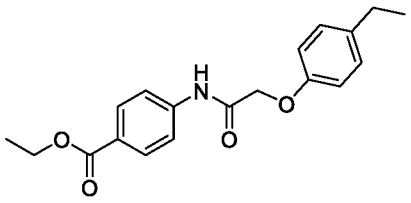
Y is C=O;

Ar is C_{5-10} aryl;

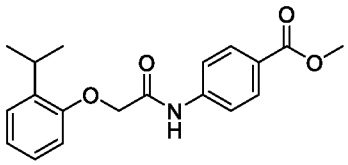
R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$or CONHNHSO_2Ph-Me; and

n is selected from 0-5.

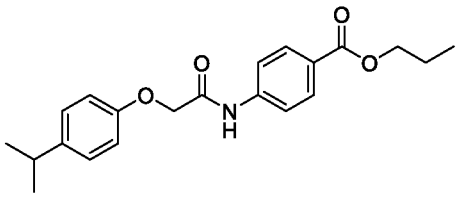
[00055] In an embodiment, the present disclosure provides a compound of Formula II or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, which is selected from a group consisting of:



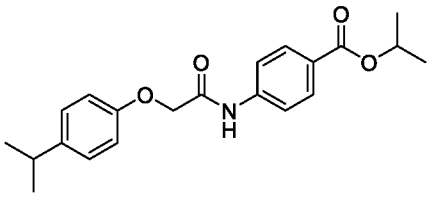
II_1a



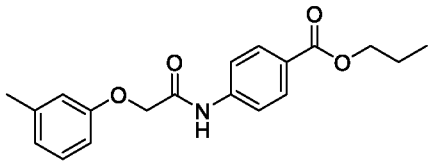
II_1b



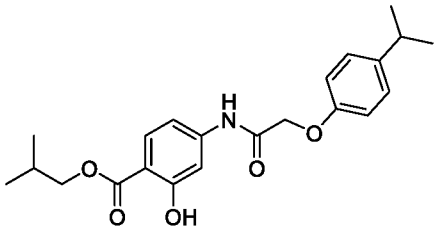
II_1c



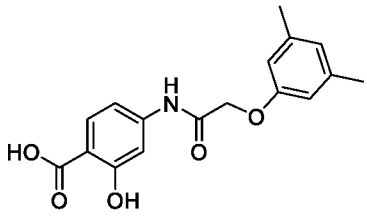
II_1d



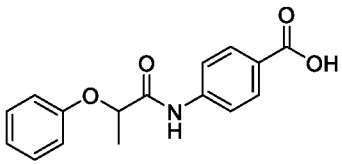
II_1e



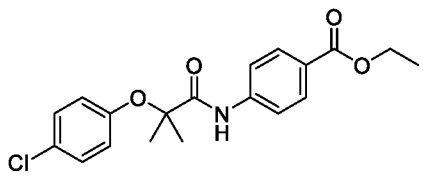
II_1f



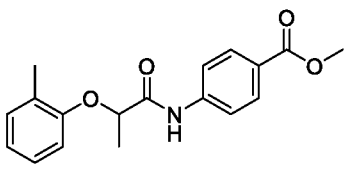
II_2a



II_2b

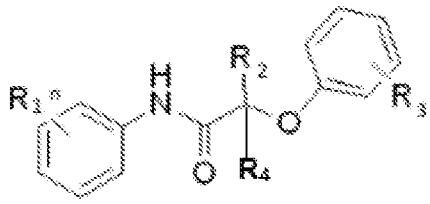


II_2c



II_2d

[00056] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula III



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

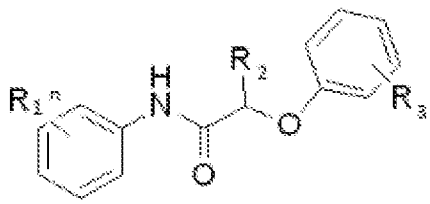
R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5.

[00057] In an embodiment, the present disclosure provides a method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound of Formula III



Formula III

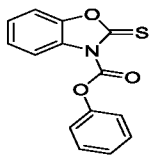
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-5}alkyl;

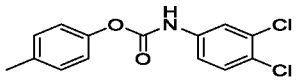
R_2 and R_4 is independently selected from hydrogen or C_{1-5} alkyl;

R_3 is selected from C_{1-5}alkyl or chlorine; and n is selected from 1 to 2.

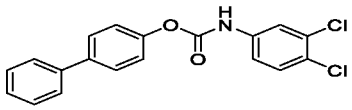
[00058] In an embodiment, the present disclosure provides a compound of Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, which is selected from a group consisting of:



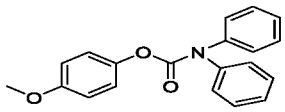
III_1



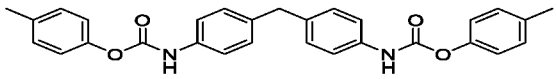
III_2a



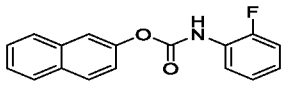
III_2b



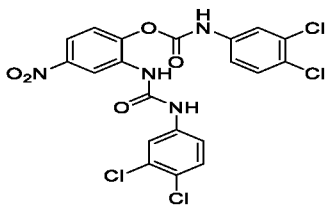
III_2c



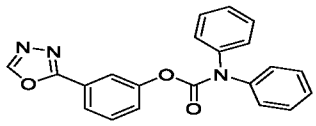
III_2d



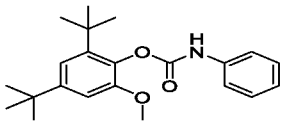
III_3



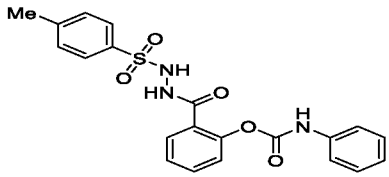
III_4



III_5

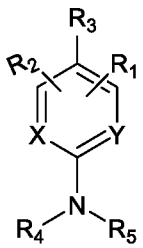


III_6



III_7

[00059] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



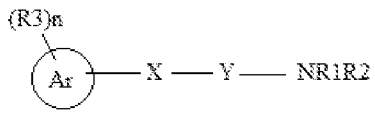
Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy, C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10}heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

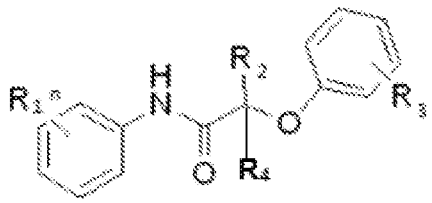
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, NHCONHPh-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

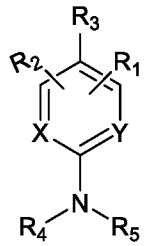
R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from1 to 5. In another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 50 to 1000 µM. In yet another embodiment of the

present disclosure, the therapeutic dose of the compound is in the range of 50 to 100 µM. In an another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 100 to 1000 µM. In an alternate embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 150 to 900 µM. In one another embodiment of the present disclosure, the therapeutic dose of the compound is in the range of 125 to 500 µM. In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, $C_{6\text{-}10}$ aryl, $C_{1\text{-}10}$ alkyl, and amino, wherein $C_{1\text{-}10}$ alkyl, and $C_{6\text{-}10}$ aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy or $C_{2\text{-}10}$ heterocyclyl;

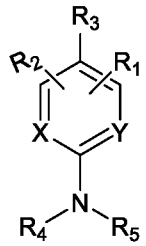
R_3 is $C_{6\text{-}10}$ aryl, wherein $C_{6\text{-}10}$ aryl is optionally substituted with one to four substituents independently selected from $C_{1\text{-}10}$ alkoxy, nitro, halogen or $C_{1\text{-}10}$ alkyl, wherein $C_{1\text{-}10}$ alkyl and $C_{1\text{-}10}$ alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy or $C_{2\text{-}10}$ heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, $C_{1\text{-}10}$ alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen;

or R_4 and R_5 are joined to form a $C_{2\text{-}10}$ heterocyclyl or a $C_{2\text{-}10}$ heteroaryl, wherein $C_{2\text{-}10}$

heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00060] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

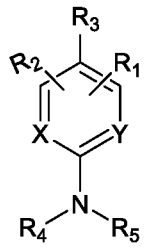
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, and C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl or C_{1-10} alkoxy;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen, C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen, or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00061] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

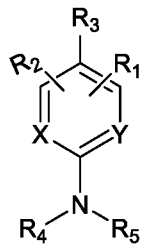
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and C_{1-5} alkyl, wherein C_{1-5} alkyl, and C_6 aryl are optionally substituted with one to four substituents independently selected from hydroxyl, fluorine, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from C_{1-5}alkoxy, nitro, halogen, C_{1-5} alkyl, wherein C_{1-5} alkyl and C_{1-5} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-5} alkyl, C_{1-5} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00062] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

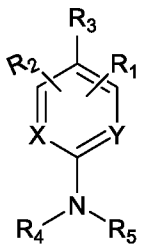
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and CF_3, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from hydroxyl, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from $-OCH_3$, $-OCF_3$, nitro, fluorine or CF_3;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and $-N=CHC_6$ aryl, wherein $-N=CHC_6$ aryl is further substituted with one to four substituents selected from fluorine and bromine; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00063] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

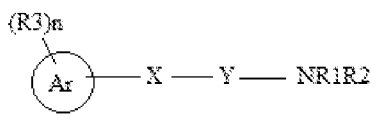
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen, or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00064] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

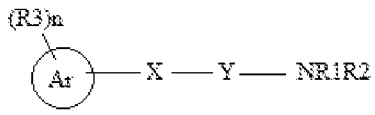
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, NHCONHPh-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5.

[00065] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

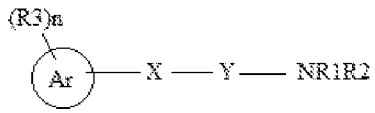
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

$R_3$is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$ or CONHNHSO_2Ph-Me; and

n is selected from 0-5.

[00066] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring,

wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

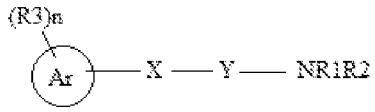
Y is C=O;

Ar is selected from C_{5-10} aryl or C_{2-10} heteroaryl;

$R_3$is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5.

[00067] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

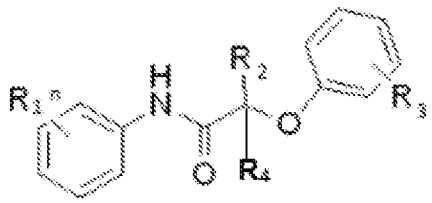
Y is C=O;

Ar is C_{5-10} aryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5.

[00068] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula III



Formula III

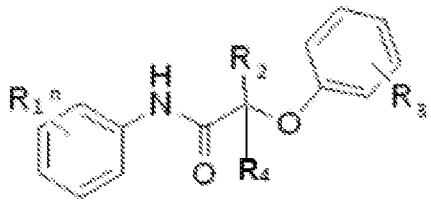
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and n is selected from 1 to 5.

[00069] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula III



Formula III

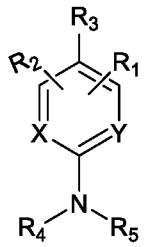
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-5} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-5} alkyl;

R_3 is selected from C_{1-5} alkyl or chlorine; and n is selected from 1 to 2.

[00070] In an embodiment, the present disclosure provides a method for treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

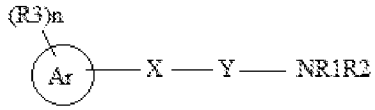
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10}alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

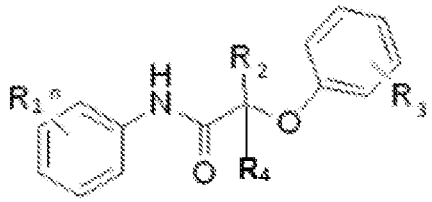
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

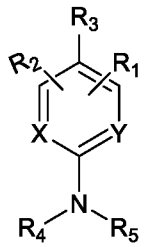
R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5.

[00071] In an embodiment, the present disclosure provides a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

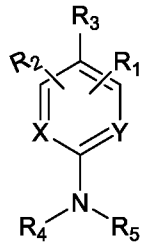
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, and amino, wherein C_{1-10} alkyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10}alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00072] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



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Formula I

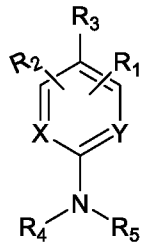
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, and C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl or C_{1-10} alkoxy;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC$_6$ aryl, wherein -N=CHC$_6$ aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00073] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

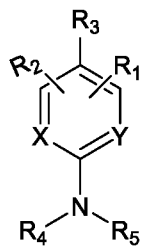
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and C_{1-5} alkyl, wherein C_{1-5} alkyl, and C_6 aryl are optionally substituted with one to four substituents independently selected from hydroxyl, fluorine, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkoxy, nitro, halogen or C_{1-5} alkyl, wherein C_{1-5} alkyl and C_{1-5} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-5} alkyl, C_{1-5} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00074] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

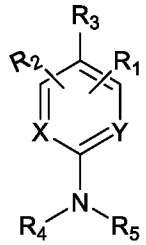
R_1 and R_2 are independently selected from the group consisting of hydrogen, C_6 aryl, and CF_3, wherein C_6 aryl are optionally substituted with one to four substituents independently selected from hydroxyl, C_{1-5} alkyl or C_{1-5} alkoxy;

R_3 is C_6 aryl, wherein C_6 aryl is optionally substituted with one to four substituents independently selected from -OCH_3, -OCF_3, nitro, fluorine or CF_3;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-5} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four

substituents selected from fluorine and bromine; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-5} alkyl; and X and Y are N.

[00075] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

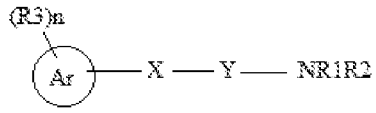
R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro or C_{1-10} alkyl, wherein C_{1-10} alkyl and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10}

heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and X and Y are N.

[00076] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

X is O;

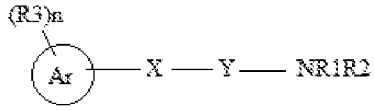
Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

$R_3$is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$ or CONHNHSO_2Ph-Me; and n is selected from 0-5.

[00077] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of

CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

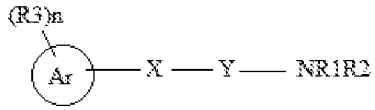
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, NHCONHPh-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and n is selected from 0-5.

[00078] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

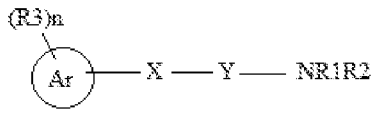
X is O;

Y is C=O;

Ar is selected from C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, NHCONHPh-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and n is selected from 0-5.

[00079] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula II



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

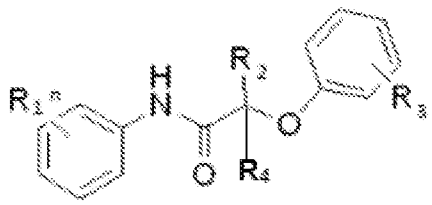
X is O;

Y is C=O;

Ar is C_{5-10} aryl;

$R_3$is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, CH_2PhNHCOOPh-Me, NHCONHPh-$(Cl)_2$ or CONHNHSO_2Ph-Me; and n is selected from 0-5.

[00080] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by qf CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula III



Formula III

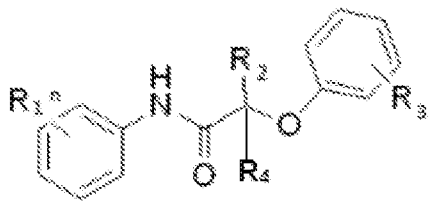
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and n is selected from 1 to 5.

[00081] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula III



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-5} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-5} alkyl;

R_3 is selected from C_{1-5} alkyl or chlorine; and n is selected from 1 to 2.

[00082] In an embodiment, the present disclosure provides a compound of Formula I, II, or III or its or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, which is selected from a group consisting of

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(4-nitrophenyl)pyrimidine (I_1a),

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-[4-(trifluoromethyl)phenyl]pyrimidine(I_1b),

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-[4-(trifluoromethoxy)phenyl]pyrimidine (I_1c),

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(4-methoxyphenyl)pyrimidine (I_1d),

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(3-nitrophenyl)pyrimidine (I_1e),

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(2-nitrophenyl)pyrimidine (I_1f),

2-[2-(4-Bromobenzylidene)hydrazinyl)-5-(4-nitrophenyl)]pyrimidine (I_2a),
2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-nitrophenyl)pyrimidine (I_2b),
(*E*)-2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-(trifluoromethyl)phenyl)pyrimidine (I_2c),
(*E*)-2-[2-(4-Bromobenzylidene)hydrazinyl)-5-(4-(trifluoromethoxy)phenyl]pyrimidine (I_2d),
(*E*)-2-[2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-methoxyphenyl]pyrimidine (I_2e),
(*E*)-2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(3-nitrophenyl)pyrimidine (I_2f),
(*E*)-2-[(2-(4-Bromobenzylidene)hydrazinyl)-5-(2-nitrophenyl)]pyrimidine (I_2g),
N,*N*-Dimethyl-5-phenylpyrimidin-2-amine (I_3a),
4-(5-(4-(Trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b),
5-(4-Fluorophenyl)-N,N-dimethylpyrimidin-2-amine (I_3c),
4-(5-(4-Fluorophenyl)pyrimidin-2-yl)morpholine (I_3d),
2-(2-amino-5-(4-methoxyphenyl)-6-(trifluoromethyl)pyrimidin-4-yl)-4-ethyl-5-methoxyphenol (I_4),
Phenyl 2-thioxobenzo[d]oxazole-3(2*H*)-carboxylate (II_1),
p-Tolyl (3,4-dichlorophenyl)carbamate (II_2a),
[1,1'-biphenyl]-4-yl (3,4-dichlorophenyl)carbamate (II_2b),
4-Methoxyphenyl diphenylcarbamate (II_2c),
Di-*p*-tolyl [methylenebis(4,1-phenylene)]dicarbamate (II_2d),
Naphthalen-2-yl (2-fluorophenyl)carbamate (II_3),
2-[3-(3,4-dichlorophenyl)ureido]-4-nitrophenyl (3,4-dichlorophenyl)carbamate (II_4),
3-[(1,3,4-oxadiazol-2-yl)phenyl] diphenylcarbamate (II_5),
2,4-di-tert-butyl-6-methoxyphenyl phenylcarbamate (II_6),
2-[(2-Tosylhydrazine-1-carbonyl)phenyl] phenylcarbamate (II_7),
Ethyl 4-[2-(4-ethylphenoxy)acetamido]benzoate (III_1a),
Methyl 4-[2-(2-isopropylphenoxy)acetamido]benzoate (III_1b),
Propyl 4-[2-(4-isopropylphenoxy)acetamido]benzoate (III_1c),
Isopropyl 4-[2-(4-isopropylphenoxy)acetamido]benzoate (III_1d),

Propyl 4-[2-(m-tolyloxy)acetamido]benzoate (III_1e),

Isobutyl 2-hydroxy-4-[2-(4-isopropylphenoxy)acetamido]benzoate(III_1f),

4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a),

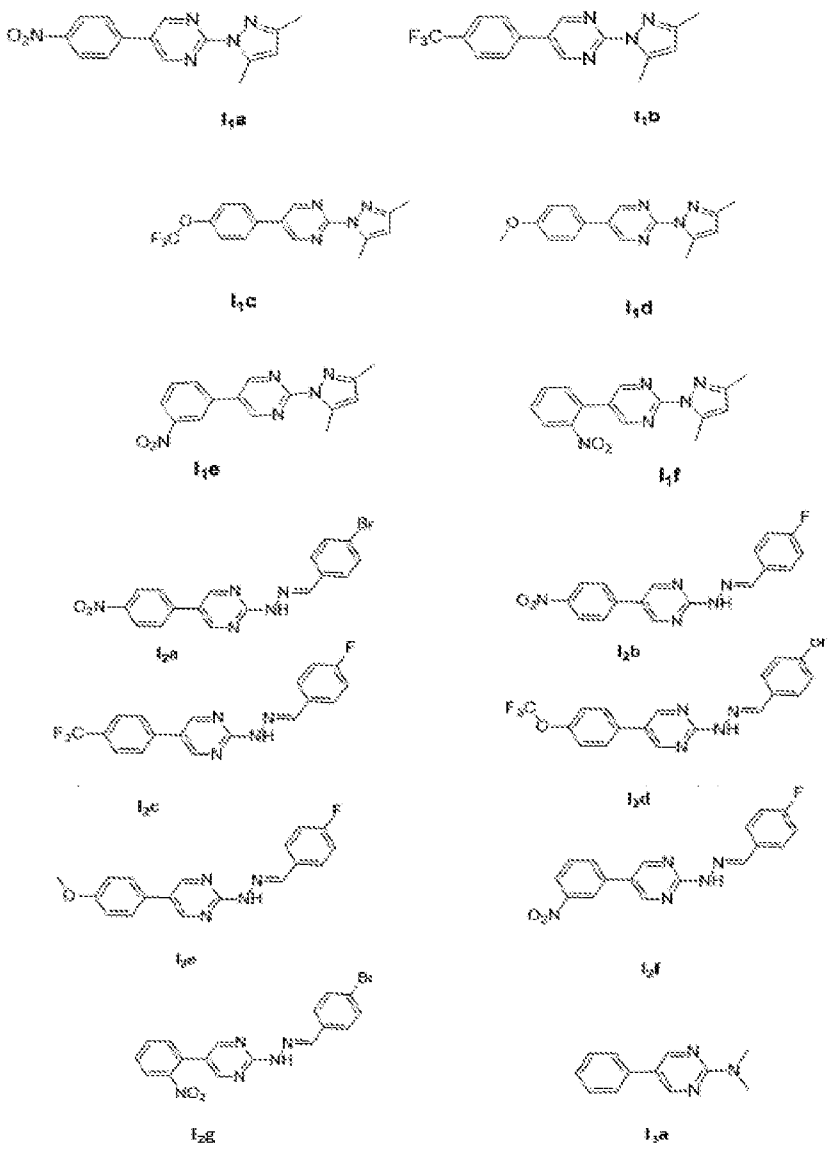
4-(2-Phenoxypropanamido)benzoic acid (III_2b),

Ethyl 4-[2-(4-chlorophenoxy)-2-methylpropanamido]benzoate (III_2c), and

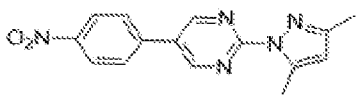
Methyl 4-[2-(o-tolyloxy)propanamido]benzoate (III_2d).

[00083] The compounds for Formula I, II, or III causes restoration of immune signaling via T cell activation through inhibiting *Nef*-CD80/86 interactions.

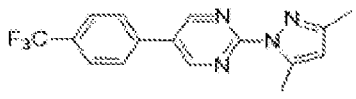
[00084] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of Formula I, wherein compound of Formula I is selected from a group consisting of:



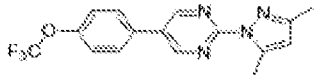
[00085] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I, wherein compound of Formula I is selected from a group consisting of:



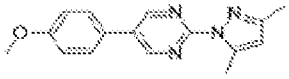
I_1a



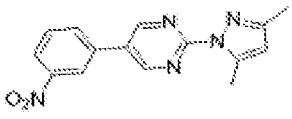
I_1b



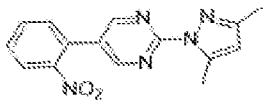
I_1c



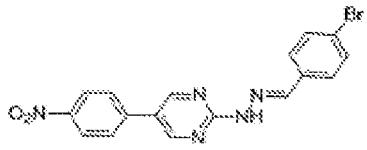
I_1d



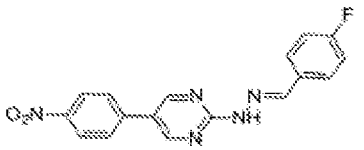
I_1e



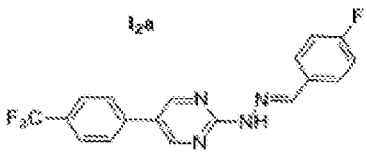
I_1f



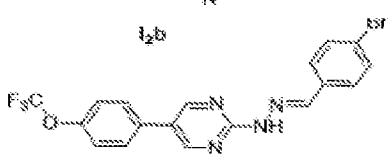
I_2a



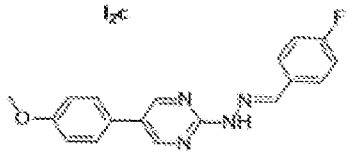
I_2b



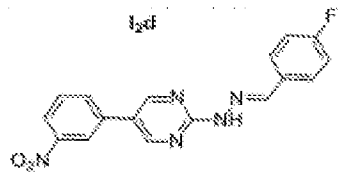
I_2c



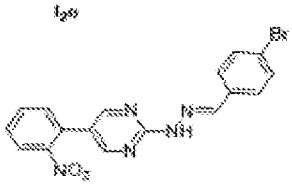
I_2d



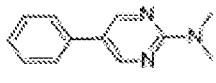
I_2e



I_2f



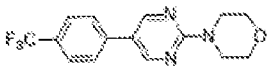
I_2g



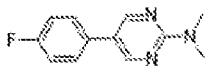
I_3a

[00086] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject comprising: administering to a HIV

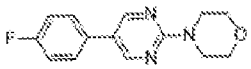
infected subject a therapeutic dose of a compound selected the group consisting of Formula I, wherein compound of Formula I is selected from a group consisting of:



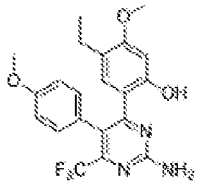
I_{3b}



I_{3c}

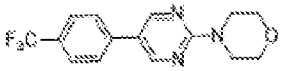


I_{3d}

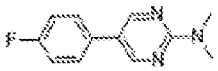


I_4

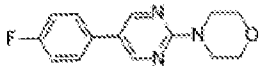
[00087] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I, wherein compound of Formula I is selected from a group consisting of:



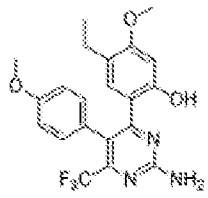
I_{3b}



I_{3c}



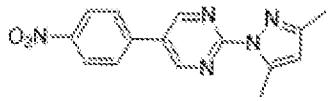
I_{3d}



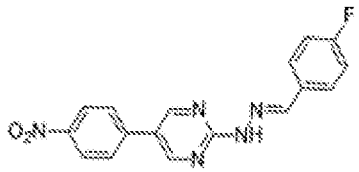
I_4

[00088] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of

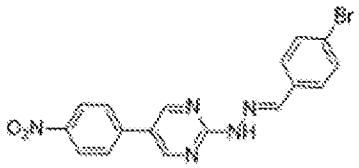
Formula I, wherein compound of Formula I is selected from a group consisting of:



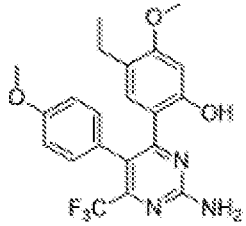
I_{1a}



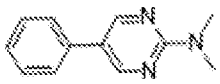
I_{2b}



I_{2a}

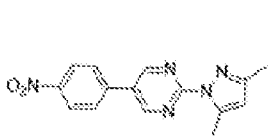


I_4

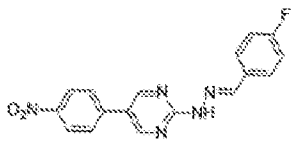


I_{3a}

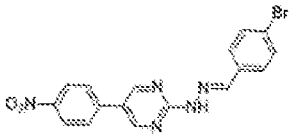
[00089] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of Formula I, wherein compound of Formula I is selected from a group consisting of:



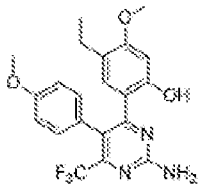
I_{1a}



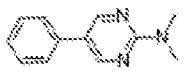
I_{2b}



I_{2a}

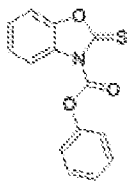


I_4

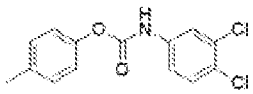


I_{3a}

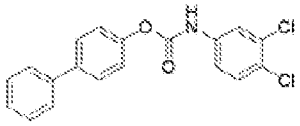
[00090] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of Formula II, wherein compound of Formula II is selected from a group consisting of:



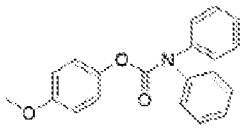
II_1



II_2a

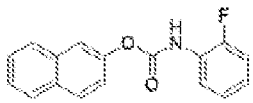


II_2b

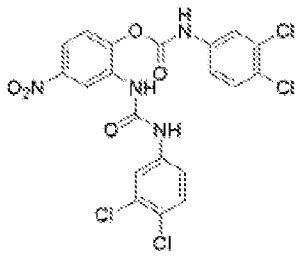


II_2c

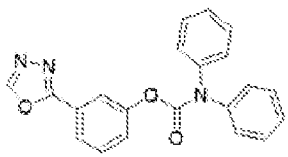
II_2d



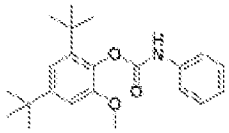
II_3



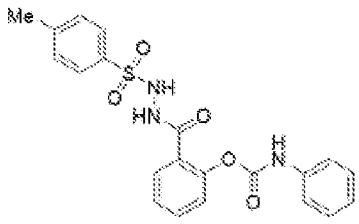
II_4



II_5



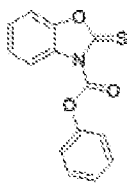
II_6



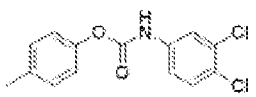
II_7

[00091] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the

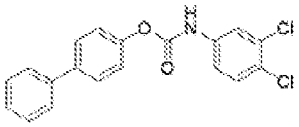
group consisting of Formula II, wherein compound of Formula II is selected from a group consisting of:



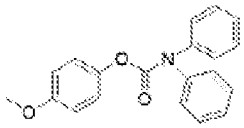
II_1



II_2a

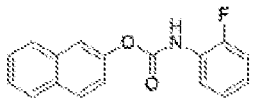


II_2b

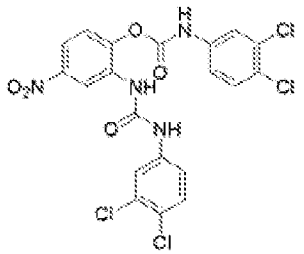


II_2c

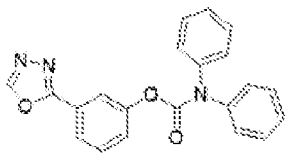
II_2d



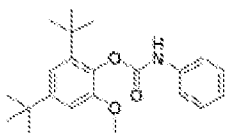
II_3



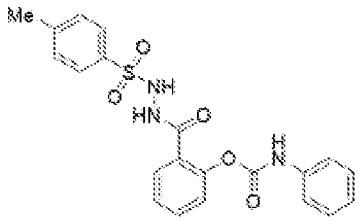
II_4



II_5

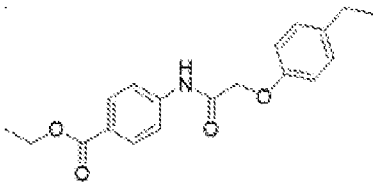


II_6

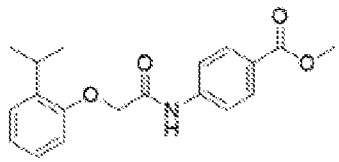


II_7

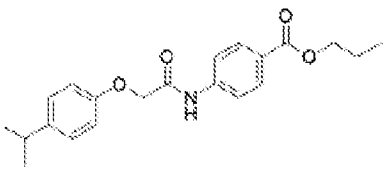
[00092] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected the group consisting of Formula III, wherein compound of Formula III is selected from a group consisting of:



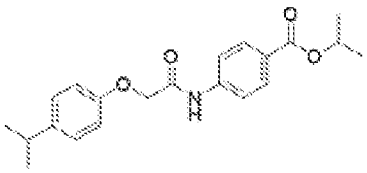
III_{1a}



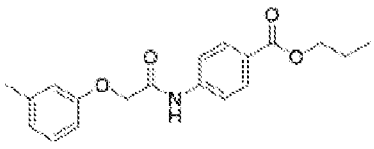
III_{1b}



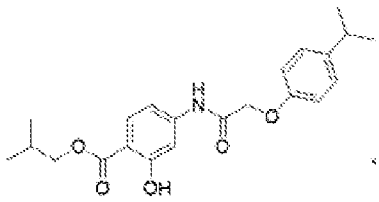
III_{1c}



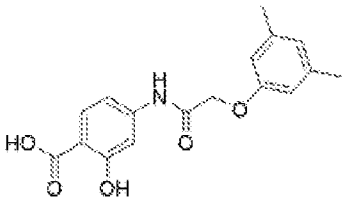
III_{1d}



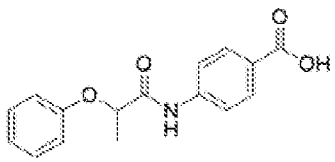
III_{1e}



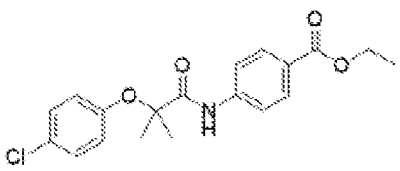
III_{1f}



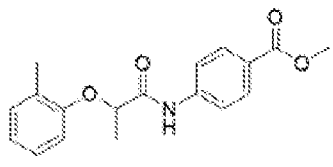
III_{1a}



III_{2b}



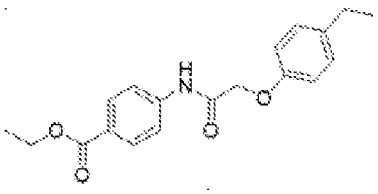
III_{2c}



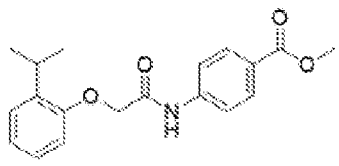
III_{2d}

[00093] In an embodiment, the present disclosure provides a method of treating or preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the

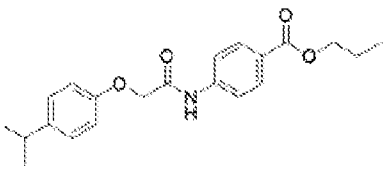
group consisting of Formula III, wherein compound of Formula III is selected from a group consisting of:



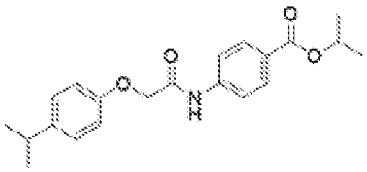
III_{3a}



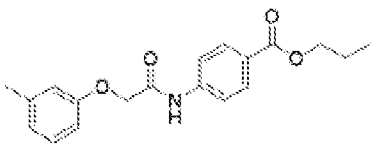
III_{3b}



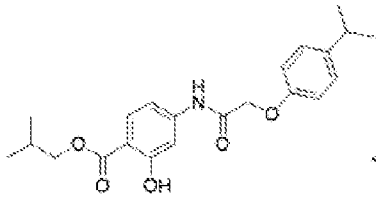
III_{3c}



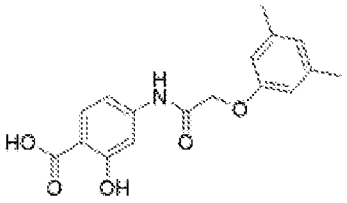
III_{3d}



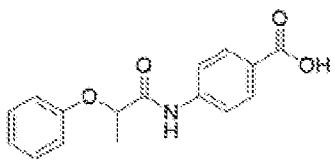
III_{3e}



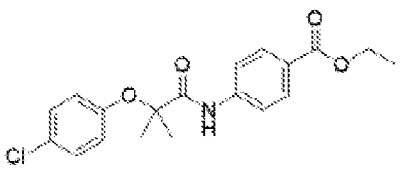
III_{3f}



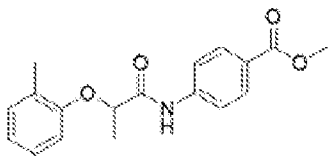
III_{3g}



III_{3h}

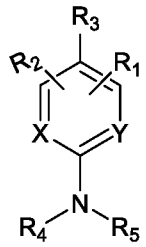


III_{3i}



III_{3j}

[00094] In an embodiment, the present disclosure provides a method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from the group consisting of Formula I,



Formula I

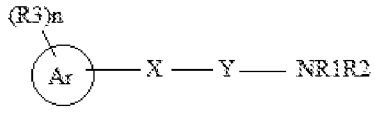
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{5-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy, and C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein -N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, and halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

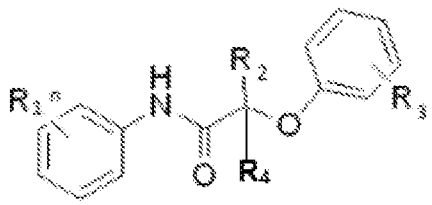
X is selected from O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl;

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5. In another embodiment of the present disclosure, the relevant dose is in the range of 50 to 1000 µM.

[00095] In an embodiment, the present disclosure provides a method of treating or preventing or treating HIV infection in a subject by immune evasion as described herein, wherein the compounds causes restoration of immune signaling *via* T cell activation through inhibiting *Nef*-CD80/86 interactions.

[00096] In an embodiment, the present disclosure provides a method for treating/preventing infections which have low levels of CD80/86 receptors compared to non-infected state, selected from the including chronic lymphocytic leukemia, colon carcinoma, multiple myeloma, viral infections including HIV, HPV, herpes.

[00097] In an embodiment, the present disclosure relates to a method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from the group consisting of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), and 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a). In another embodiment of the present disclosure, the relevant dose is in the range of 50 to 1000 µM.

[00098] In an embodiment, the present disclosure relates to a method for preventing HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected from a group consisting of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a). and combinations thereof. In another embodiment of the present disclosure,

the therapeutic dose is in the range of 50 to 1000 µM. In yet another embodiment, the compound is a combination of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a).

[00099] In an embodiment, the present disclosure relates to method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected from a group consisting of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), and 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a). In another embodiment of the present disclosure, the relevant dose is in the range of 50 to 1000 µM.

[000100] In an embodiment, the present disclosure relates to method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected from a group consisting of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a), and combinations thereof. In another embodiment of the present disclosure, the therapeutic dose is in the range of 50 to 1000 µM. In yet another embodiment, the compound is a combination of 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a).

[000101] In an embodiment, the present disclosure relates to a method for preventing or treating HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising: administering to a subject a relevant dose of a compound selected from 4-(5-(4-(trifluoromethyl)phenyl)pyrimidin-2-yl)morpholine (I_3b), naphthalen-2-yl (2-fluorophenyl)carbamate (II_3), or 4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III_2a). In another embodiment of the present disclosure, the relevant dose is in the range of 50 to 1000 µM.

[000102] In an embodiment, the present disclosure relates to a method for treating/preventing infections which have low levels of CD80/86 receptors compared to non-infected state, selected from the including cancers like chronic lymphocytic leukemia, colon carcinoma, multiple myeloma, viral infections including HIV, HPV, herpes using the compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof.

[000103] The infections in bovine, feline, simian that act through *Nef* superfamily pathways.

[000104] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, for use in killing or inhibiting the growth virus.

[000105] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, for use in killing or inhibiting the growth of HIV.

[000106] In an embodiment, the present disclosure relates to use of a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, in killing or inhibiting the growth of HIV.

[000107] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically

active forms and pharmaceutically active derivative thereof, for use in treating a disease or condition in a patient wherein said disease or condition is caused by HIV.

[000108] In an embodiment, the present disclosure relates to use of a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, in treating disease or condition in a patient, wherein said disease or condition is caused by HIV. The patient is a typically a mammal, preferably a human.

[000109] In an embodiment, the present disclosure relates toa method of treating a disease or condition in a patent, said method comprising administering to a patient a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, wherein said disease or condition is caused by HIV.

[000110] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, for useas a medicament.

[000111] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, for usein the preparation of medicaments for inhibiting viral growth.

[000112] In an embodiment, the present disclosure relates to medicaments that include a compound of Formula I, Formula II, and Formula III, or an addition salt of the compound of Formula I, Formula II, and Formula III with a pharmaceutically acceptable acid or base. These medicaments find their use in therapeutics, especially in the treatment of viral infection caused by HIV.

[000113] In an embodiment, the present disclosure relates to the use of a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, in the manufacture of a medicament for the production of an antiviral effect in a warm-blooded animal such as man.

[000114] In an embodiment, the present disclosure relates to a method for producing an antiviral effect in a warm-blooded animal such as man, said method including administering to said animal an effective amount of a compound of Formula I, Formula II, and Formula III or a pharmaceutically acceptable salt thereof.

[000115] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or a pharmaceutically acceptable salt thereof, for use in the treatment and/or prophylaxis of viral infections in a warm-blooded animal, such as man.

[000116] In an embodiment, the present disclosure relates to a compound of Formula I, Formula II, and Formula III or a pharmaceutically acceptable salt thereof, for the therapeutic and prophylactic treatment of mammals including humans, in particular in treating viral infections caused by HIV, is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

[000117] In an embodiment, the present disclosure relates to a pharmaceutical composition including a compound of Formula I, Formula II, and Formula III or its stereoisomers, pharmaceutically acceptable salts, complexes, hydrates, solvates, tautomers, polymorphs, racemic mixtures, optically active forms and pharmaceutically active derivative thereof, and at least one pharmaceutically acceptable carrier, diluent, or excipient.

[000118] The term, “pharmaceutically acceptable” includes compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals

without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[000119] The compounds of Formula I, Formula II, and Formula III may form stable pharmaceutically acceptable acid or base salts, and in such cases administration of a compound as a salt may be appropriate. The salts may be formed by conventional means.The compositions of the disclosure may be in a form suitable for oral use, for topical use, for administration by inhalation, for administration by insufflation or for parenteral administration.

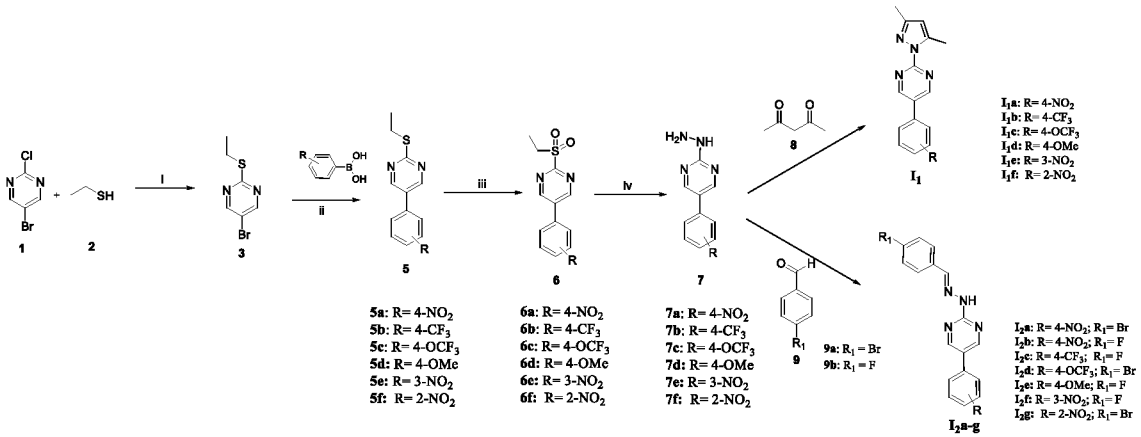
[000120] The compositions of the present disclosure may be obtained by conventional procedures using conventional pharmaceutical excipients well known in the art.

[000121] The compounds disclosed herein may be applied as a sole therapy or may involve, in addition to a compound of the disclosure, one or more other substances and/or treatments.

PROCESS AND CHARACTERIZATION DATA

[000122] There is also provided a process as shown in the following Schemes 1-7, for the preparation of compounds of the Formula I, Formula II, and Formula III, wherein all the groups are as defined earlier. The examples given below are provided by the way of illustration only and therefore should not be construed to limit the scope of the invention.

Scheme-1

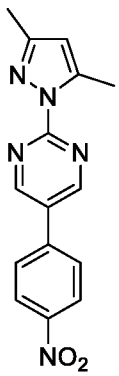


Reagents and conditions: i) NaH, benzene, 0 °C, rt, 12 h; ii) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 110 °C, 6h; iii) m-CPBA, DCM, 0 °C, rt, 12 h; iv) hydrazinehydrate, 0 °C, rt, 12 h, v) Methanol, rt, 12 h.

General procedure for the synthesis of I_{1a-f} of Scheme- 1

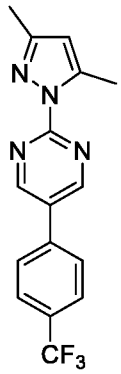
[000123] To a solution of compound **7** (3.4 mmol) in methanol was added acetyl acetone **8** (5.19 mmol) and catalytic amounts of acetic acid. The resulting mixture was stirred at 60° C- 70° C for 5 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **I_{1a-f}**.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(4-nitrophenyl)pyrimidine (I_{1a}, Scheme 1):



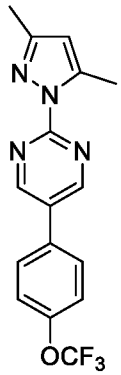
[000124] ^1H NMR (400 MHz, $CDCl_3$) δ 9.28 (m, 2H), 8.38 – 8.24 (m, 2H), 7.94 – 7.80 (m, 2H), 6.14 (s, 1H), 2.38 (s, 6H); HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_5O_2[M+H]^+$ 296.1147, found 296.1147.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-[4-(trifluoromethyl)phenyl]pyrimidine(I_1b, Scheme 1):



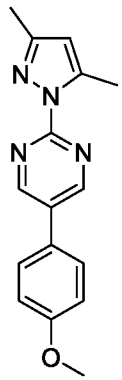
[000125] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.24 (s, 2H), 7.70 – 7.67 (m, 2H), 7.61 – 7.58 (m, 2H), 6.13 (s, 1H), 2.36 (m, 6H); HRMS (ESI-TOF) calcd for $C_{16}H_{13}F_3N_4$ $[M+H]^+$ 318.1092, found 318.1083.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-[4-(trifluoromethoxy)phenyl]pyrimidine (I_1c, Scheme 1):



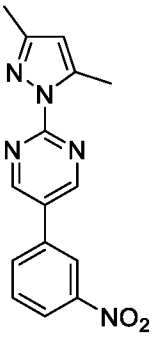
[000126] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36 (s, 2H), 7.68 – 7.48 (m, 2H), 7.19 – 6.96 (m, 2H), 6.12 (s, 1H), 2.44 – 2.25 (m, 6H).; HRMS (ESI-TOF) calcd for $C_{16}H_{13}F_3N_4O$ $[M+H]^+$ 334.1041, found 334.1062.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(4-methoxyphenyl)pyrimidine (I_1d, Scheme 1):



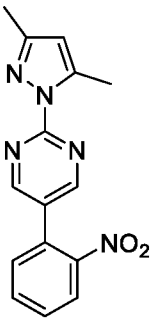
[000127] ^{1}H NMR (500 MHz, CDCl3) δ 9.21 (s, 2H), 7.63 – 7.55 (m, 2H), 7.12 – 6.96 (m, 2H), 6.12 (s, 1H), 3.81 (s, 3H), 2.36 (s, 6H); HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_4O$ $[M+H]^+$ 280.1324, found 280.1348.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(3-nitrophenyl)pyrimidine (I$_1$e, Scheme 1):



[000128] ^{1}H NMR (500 MHz, CDCl3) δ 9.26 (s, 2H), 8.56 (s, 1H), 8.22-8.19 (m, 1H), 7.99-7.91 (m, 1H), 7.68-7.59 (m, 1H), 6.13 (s, 1H), 2.37 (s, 6H); HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_5O_2$ $[M+H]^+$ 295.1069, found 295.1054.

2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-5-(2-nitrophenyl)pyrimidine (I$_1$f, Scheme 1):

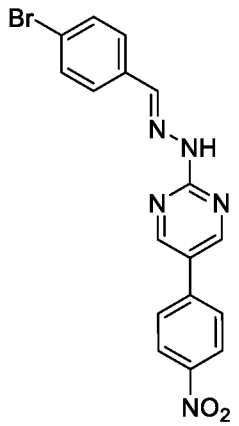


[000129] ^{1}H NMR (500 MHz, CDCl3) δ 9.12 (s, 2H), 8.29-8.27 (m, 1H), 7.82-7.79 (d, *J* = 29.8 Hz, 1H), 7.60 (s, 1H), 6.13 (s, 1H), 2.36 (m, 6H); HRMS (ESI-TOF) calcd for $C_{15}H_{13}N_5O_2$ $[M+H]^+$ 295.1069, found 295.1047.

General procedure for the synthesis of I2a-g of Scheme 1:

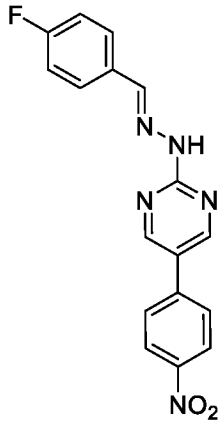
[000130] To a solution of compound **7** (0.4 mmol) in methanol/ethanol was added substituted benzaldehyde **9** (0.51 mmol) and catalytic amounts of acetic acid. The resulting mixture was stirred at room temperature for 5 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **I2a-g**.

2-[2-(4-Bromobenzylidene)hydrazinyl)-5-(4-nitrophenyl)]pyrimidine (I2a, Scheme 1):



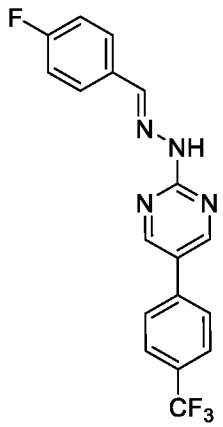
[000131] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.71 (s, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 7.86 (s, 1H), 7.61 (dd, *J* = 15.3, 8.6 Hz, 5H), 7.48 (d, *J* = 8.5 Hz, 3H); HRMS (ESI-TOF) calcd for $C_{17}H_{13}BrN_5O_2$: [M+H] 399.2280 found 399.2282.

2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-nitrophenyl)pyrimidine (I2b, Scheme 1):



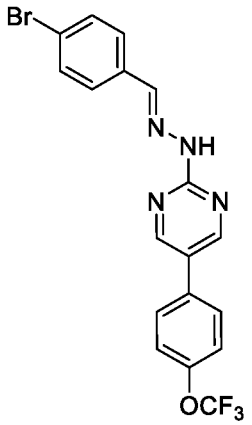
[000132] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.71 (s, 2H), 8.28 (d, *J* = 8.8 Hz, 2H), 7.86 (s, 1H), 7.61 (dd, *J* = 15.3, 8.6 Hz, 5H), 7.48 (d, *J* = 8.5 Hz, 3H); HRMS (ESI-TOF) calcd for $C_{17}H_{13}FN_5O_2$: [M+H] 338.1053 found 338.1055.

(*E*)-2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-(trifluoromethyl)phenyl)pyrimidine (I2c, Scheme 1):



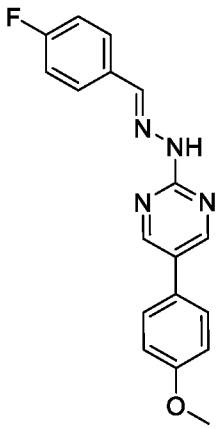
[000133] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.86 (m, 2H), 7.69 – 7.64 (m, 2H), 7.63 – 7.58 (m, 2H), 7.56 (s, 1H), 7.54 – 7.48 (m, 2H), 7.30 – 7.23 (m, 2H); HRMS (ESI-TOF) calcd for $C_{18}H_{12}F_4N_4$: [M+H] 360.0998 found 360.0986.

(*E*)-2-[2-(4-Bromobenzylidene) hydrazinyl)-5-(4--(trifluoromethoxy) phenyl] pyrimidine (I2d, Scheme 1):



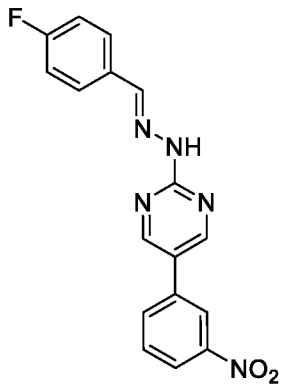
[000134] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.87 (s, 2H), 7.67 – 7.57 (m, 4H), 7.32 – 7.24 (m, 2H), 7.15 – 7.09 (m, 2H), 7.00 (s, 1H); HRMS (ESI-TOF) calcd for $C_{18}H_{12}BrF_3N_4O$: [M+H] 436.0147 found 436.0126.

(*E*)-2-[2-(4-Fluorobenzylidene)hydrazinyl)-5-(4-methoxyphenyl]pyrimidine (I2e, Scheme 1):



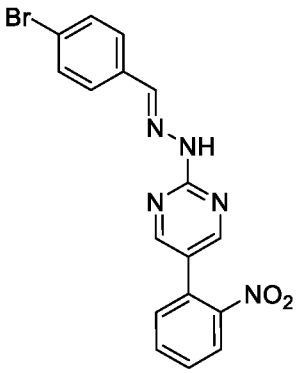
[000135] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.84 – 8.77 (m, 2H), 7.63 – 7.59 (m, 2H), 7.56 (s, 1H), 7.54 – 7.49 (m, 2H), 7.29 – 7.25 (m, 2H), 7.08 – 7.04 (m, 2H), 3.91 – 3.72 (m, 3H); HRMS (ESI-TOF) calcd for $C_{18}H_{15}FN_4O$: [M+H] 322.1230 found 322.1242.

(*E*)-2-(2-(4-Fluorobenzylidene)hydrazinyl)-5-(3-nitrophenyl)pyrimidine (I2f, Scheme 1):



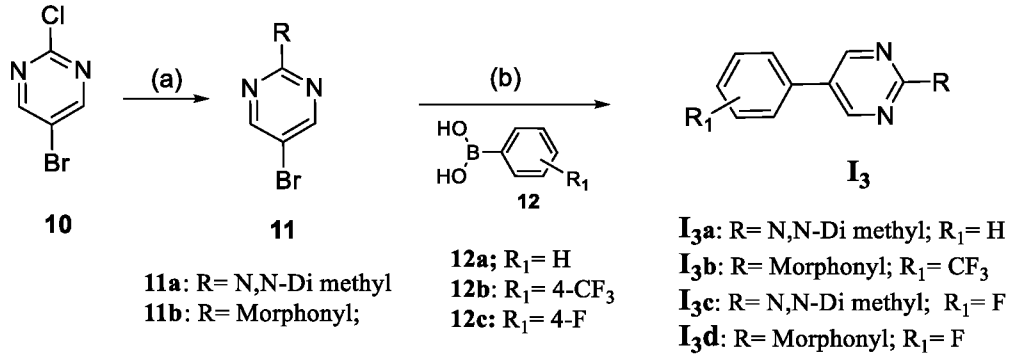
[000136] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.89 – 8.83 (m, 2H), 8.59 (s, 1H), 8.25 (s, 1H), 8.01 (s, 1H), 7.71 (s, 1H), 7.57 (s, 1H), 7.54 – 7.48 (m, 2H), 7.32 – 7.23 (m, 2H); HRMS (ESI-TOF) calcd for $C_{17}H_{12}FN_5O_2$: [M+H] 337.0975 found 337.0954.

(*E*)-2-[(2-(4-Bromobenzylidene)hydrazinyl)-5-(2-nitrophenyl)]pyrimidine (I2g, Scheme 1):



[000137] ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.60 – 8.55 (m, 2H), 8.30 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 7.61 (s, 1H), 7.60 – 7.55 (m, 2H), 7.53 (s, 1H), 7.40 – 7.34 (m, 2H); HRMS (ESI-TOF) calcd for $C_{17}H_{12}FN_5O_2$: [M+H] 337.0975 found 337.0968.

Scheme-2

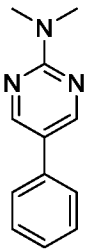


Reagents and conditions: (a) 2° amines, K_2CO_3, MeOH, rt, 12 h; (b) $Pd(PPh_3)_4$, K_2CO_3, dioxane, 110 °C, 6h.

General procedure for the synthesis of I3a-d of Scheme 2:

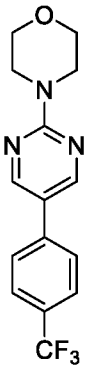
[000138] To a solution of **11** (8.2 mmol) in dioxane (3 mL) under nitrogen atmosphere were added tetrakis(triphenylphosphine)palladium (0.047 g, 0.41 mmol), substituted phenylboronic acid **12** (0.98 mmol), and K_2CO_3 dissolved in 2 mL of water. The mixture was stirred under reflux for 6 h. The reaction mixture was diluted with EtOAc, filtered through celite, and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **I3a-d**.

***N,N*-Dimethyl-5-phenylpyrimidin-2-amine (I3a, Scheme 2):**



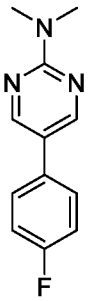
[000139] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 2H), 7.38 (dt, *J* = 15.2, 7.5 Hz, 4H), 7.26 (t, *J* = 7.1 Hz, 1H), 3.17 (s, 6H); HRMS (ESI-TOF) calcd for $C_{12}H_{14}N_3$: [M+H] 200.1188 found 200.1187.

4-[5-(4-(Trifluoromethyl)phenyl)pyrimidin-2-yl]morpholine (I3b, Scheme 2):



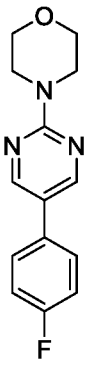
[000140] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8. Hz, 2H), 3.87 (m, 4H), 3.83 – 3.77 (m, 4H); HRMS (ESI-TOF) calcd for $C_{15}H_{15}F_3N_3O$: $[M+H]^+$ 310.1167 found 310.1170.

5-(4-Fluorophenyl)-N,N-dimethylpyrimidin-2-amine (I3c, Scheme 2):



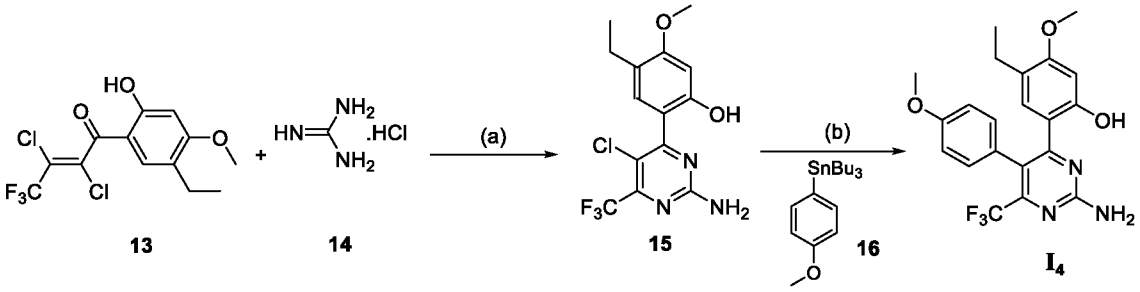
[000141] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 2H), 7.68 – 7.51 (m, 2H), 7.29 – 7.12 (m, 2H), 2.97 (s, 6H); HRMS (ESI-TOF) calcd for $C_{15}H_{12}FN_3$: $[M+H]^+$ 217.1015 found 217.1036.

4-[5-(4-Fluorophenyl)pyrimidin-2-yl]morpholine (I3d, Scheme 2):



[000142] ^{1}H NMR (400 MHz, $CDCl_3$) δ8.74 (m, 2H), 7.64 – 7.58 (m, 2H), 7.23 – 7.14 (m, 2H), 3.80 – 3.75 (m, 2H), 3.52 – 3.47 (m, 4H), 3.43 – 3.38 (m, 4H); HRMS (ESI-TOF) calcd for $C_{14}H_{14}FN_3O$: $[M+H]^+$ 259.1121 found 259.1158.

Scheme-3

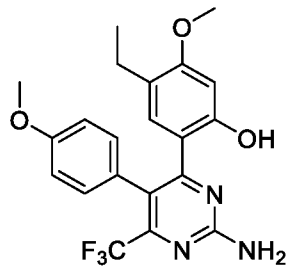


Reagents and conditions: (a) K_2CO_3, 1,4-dioxane, reflux, 12 h; (b) $Pd(PPh_3)_4$, CH_3CN, microwave 180 °C, 1h.

General procedure for the synthesis of I_4 of Scheme 3

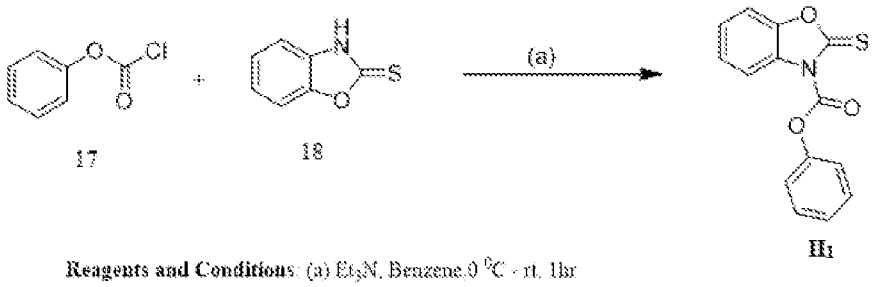
[000143] To a solution of **13** (8.2 mmol) and **14** in dioxane (3 mL) were refluxed for 12 h. The reaction mixture was diluted with EtOAc, filtered through celite, and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was further used without any purification. The compound **15** (8.2 mmol) was dissolved in acetonitrile (3 mL) under nitrogen atmosphere and then added tetrakis(triphenylphosphine)palladium (0.41 mmol), substituted compound **16** (0.98 mmol), and K_2CO_3 solution (dissolved in 2 mL of water). The mixture was heated 180 °C on microwave for 1h. The reaction mixture was diluted with EtOAc, filtered through celite, and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **I_4** as a white solid.

2-[2-amino-5-(4-methoxyphenyl)-6-(trifluoromethyl)pyrimidin-4-yl]-4-ethyl-5-methoxyphenol (I_4, Scheme 3):



[000144] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.55 (d, 2H), 7.31 (s, 1H), 7.07 – 7.04 (d, 2H), 6.61 (s, 1H), 6.55 (s, 1H), 3.86 – 3.79 (m, 6H), 2.61 – 2.52 (q, 2H), 1.68 (s, 2H), 1.31 – 1.25 (t, 3H); HRMS (ESI-TOF) calcd for $C_{21}H_{20}F_3N_3O_3$: [M+H] 419.1457 found 419. 1479.

Scheme-4



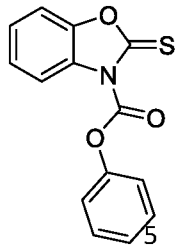
17 18 II_1

Reagents and Conditions: (a) Et_3N, Benzene,0 ^{0}C - rt, 1hr

General procedure for the synthesis of II_1 of Scheme 4:

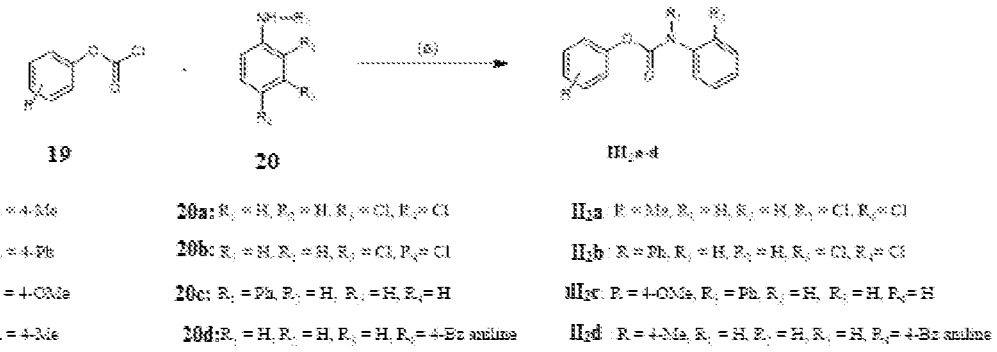
[000145] To a solution of benzo[d]oxazole-2(3*H*)-thione **18** (2.6 mmol) in ethylacetate was added phenyl chloroformate **17** slowly at 0 ^{0}C (4.00 mmol) and catalytic amounts of pyridine. The resulting mixture was stirred at rt for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II_1**.

Phenyl 2-thioxobenzo[d]oxazole-3(2*H*)-carboxylate (II_1, Scheme 4):



[000146] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 1H), 7.45 – 7.37 (m, 2H), 7.33 – 7.25 (m, 6H). LC-MS (ESI+): *m\z* 272.0303[M + H]$^+$.

Scheme 5

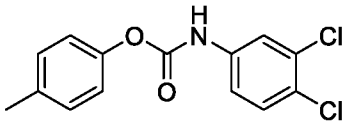


Reagents and Conditions: (a) Pyridine, Ethylacetate, 0 °C - rt, 1hr

General procedure for the synthesis of II2a-d of Scheme 5:

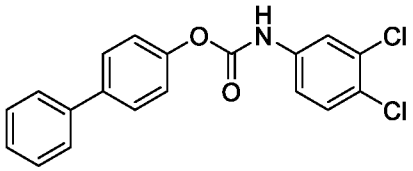
[000147] To a solution of substituted anilines **20** (2.6 mmol) in ethylacetate was added substituted phenyl chloroformate **19** slowly at 0 ^{0}C (4.00 mmol) and catalytic amounts of pyridine. The resulting mixture was stirred at rt for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II2a-d**.

***p*-Tolyl (3,4-dichlorophenyl)carbamate (II2a, Scheme 5):**



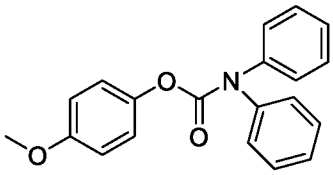
[000148] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11(s, 1H), 7.60 (s, 1H), 7.35 (d, *J* = 2.2 Hz, 2H), 7.15 – 7.03 (m, 2H), 7.03 – 6.90 (m, 2H), 2.41 – 2.18 (m, 3H). LC-MS (ESI+): *m\z* 296.0240[M + H]$^+$.

[1,1'-biphenyl]-4-yl (3,4-dichlorophenyl)carbamate (II$_2$b, Scheme 5):



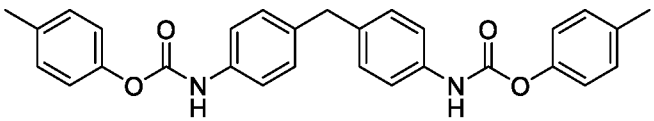
[000149] ^{1}H NMR (400 MHz, $CDCl_3$) δ10.11 (s, 1H), 7.83 (s, 1H), 7.76 – 7.47 (m, 4H), 7.47 – 7.41 (m, 2H), 7.35 (d, *J* = 3.4 Hz, 2H), 7.26 – 7.04 (m, 3H). LC-MS (ESI+): *m\z* 358.0396[M + H]$^+$.

4-Methoxyphenyl diphenylcarbamate (II$_2$c, Scheme 5):



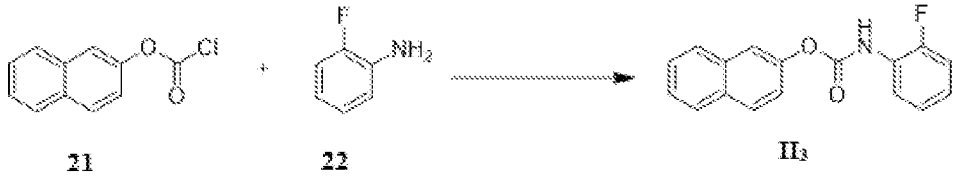
[000150] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.23 (m, 1H), 7.15 – 7.07 (m, 1H), 7.03 – 6.95 (m, 1H), 6.88 – 6.81 (m, 1H), 6.81 – 6.75 (m, 1H), 6.75 – 6.67 (m, 1H), 3.74 (s, 1H). LC-MS (ESI+): *m\z* 320.1281[M + H]$^+$.

Di-*p*-tolyl [methylenebis(4,1-phenylene)]dicarbamate (II$_2$d, Scheme 5):



[000151] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 2H), 7.52 – 7.38 (m, 4H), 7.38 – 7.29 (m, 4H), 7.19 – 7.07 (m, 4H), 7.04 – 6.95 (m, 4H), 3.91 – 3.57 (s, 2H), 2.50 – 2.17 (s, 6H). LC-MS (ESI+): *m\z* 467.1965[M + H]$^+$.

Scheme 6



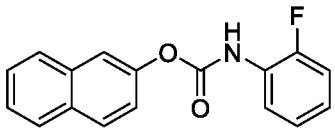
21 22 II_3

Reagents and Conditions: (a) Pyridine, Ethylacetate ,0 ^{0}C - rt, 1hr

General procedure for the synthesis of II_3 of Scheme 6:

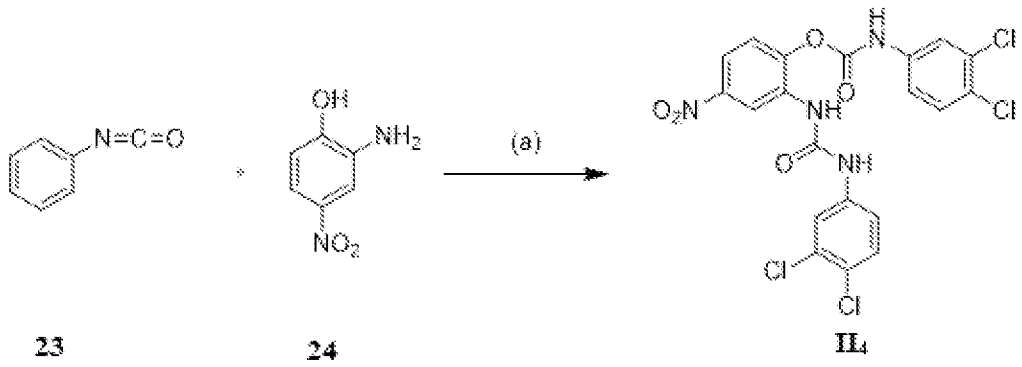
[000152] To a solution of substituted aniline **22** (2.6 mmol) in ethylacetate was added substituted phenyl chloroformate **21** slowly at 0 ^{0}C (4.00 mmol) and catalytic amounts of pyridine. The resulting mixture was stirred at rt for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II_3**.

Naphthalen-2-yl (2-fluorophenyl)carbamate (II_3, Scheme 6):



[000153] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.78 – 7.68 (m, 1H), 7.52 (s, 1H), 7.34 (t, *J* = 5.1 Hz, 1H), 7.10 (dd, *J* = 15.8, 3.3 Hz, 1H). LC-MS (ESI+): *m\z* 282.0295[M + H]$^+$.

Scheme 7



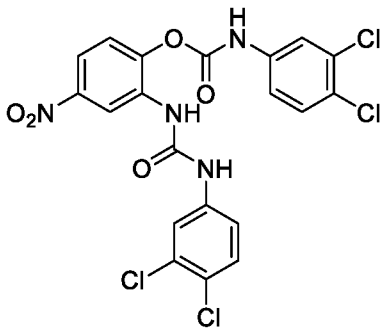
23 24 II_4

Reagents and conditions: (a) t-BuOK, Benzene, 45-50 ^{0}C, 1hr

General procedure for the synthesis of II_4 of Scheme 7:

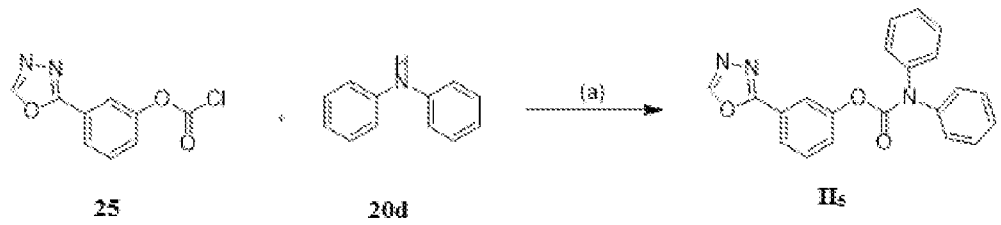
[000154] To a solution of phenylisocyante **23**(4.2mmol) in benzene was added potassium tert-butoxide (10mol %) slowly and then 2-amino-4-nitrophenol **24** (4.2mmol) was added. The resulting mixture was stirred at 45-50 ^{0}C for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II_4**.

2-[3-(3,4-dichlorophenyl)ureido]-4-nitrophenyl (3,4-dichlorophenyl)carbamate (II_4, Scheme 7):



[000155] ^{1}H NMR (400MHz, DMSO-d_6) δ 9.23 (s, 1H), 8.59 (s, 1H), 8.41 (s, 1H), 8.05 (s, 1H), 7.81 (s, 1H), 7.55 (d, J = 34.9 Hz, 2H), 7.46 – 7.32 (m, 3H), 7.28 (s, 1H), 7.01 (s, 1H). LC-MS (ESI+): $m\backslash z$ 528.9635[M + H]$^+$.

Scheme 8



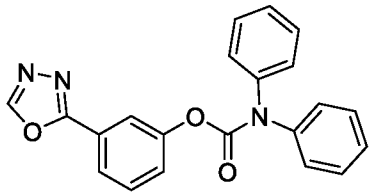
25 20d II_5

Reagents and conditions: Pyridine, Ethylacetate, 0 ^{0}C -rt, 1hr

General procedure for the synthesis of II_5 of Scheme 8:

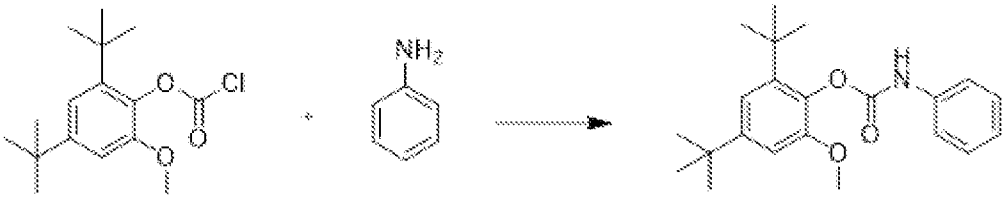
[000156] To a solution of substituted aniline **20d** (2.6 mmol) in ethylacetate was added substituted phenyl chloroformate **25** slowly at 0 ^{0}C (4.00 mmol)and catalytic amounts of pyridine. The resulting mixture was stirred at rt for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II_5**.

3-[(1,3,4-oxadiazol-2-yl)phenyl] diphenylcarbamate (II_5, Scheme 8):



[000157] ^{1}H NMR (400 MHz, DMSO) δ 9.45 (s, 1H), 7.82 (s, 1H), 7.51 (s, 1H), 7.42 – 7.26 (m, 10H), 7.18 (m, 1H), 7.14 – 7.03 (m, 2H).). LC-MS (ESI+): $m\backslash z$ 358.1186[M + H]$^+$.

Scheme 9



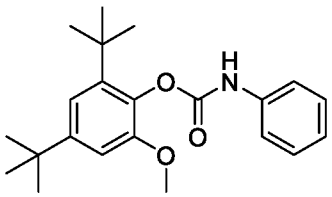
26 27 II_6

Reagents and conditions:(a) Pyridine, Ethylacetate ,0 ^{0}C - rt, 1hr

General procedure for the synthesis of II_6 of Scheme 9:

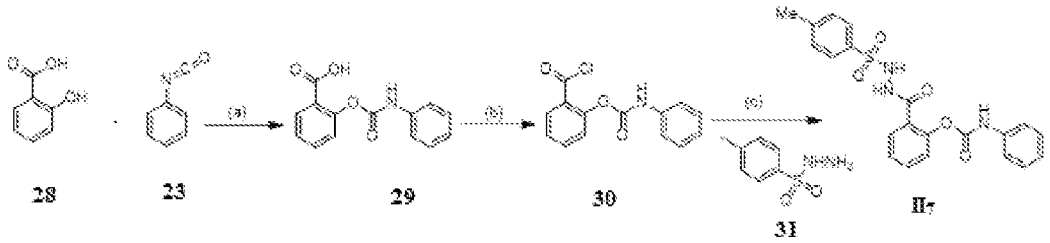
[000158] To a solution of substituted aniline **27** (2.6 mmol) in ethyl acetate was added substituted phenyl chloroformate **26** slowly at 0 ^{0}C (4.00 mmol) and catalytic amounts of pyridine. The resulting mixture was stirred at rt for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **II_6**.

2,4-di-tert-butyl-6-methoxyphenyl phenylcarbamate (II_6, Scheme 9):



[000159] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86(s, 1H), 7.60 – 7.34 (m, 4H), 7.16 (m, 1H), 7.03 (s, 1H), 6.79 (s, 1H), 3.81 – 3.74 (m, 3H), 1.43 – 1.36 (m, 9H), 1.35 – 1.29 (m, 9H); LC-MS (ESI+): *m\z* 356.2220[M + H]$^+$.

Scheme 10

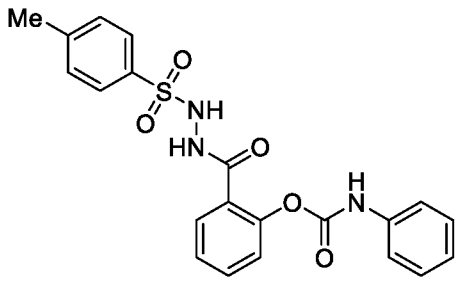


Reagents and conditions: (a) t-BuOk, benzene, 45-50 °C, 1hr; (b) $SOCl_2$, benzene, reflux, 2hr; (d) THF, N_2, reflux, 2hr

General procedure for the synthesis of II_7 of Scheme 10):

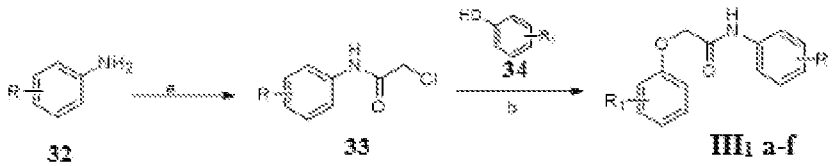
[000160] To a solution of acid **29** (2 mmol) in benzene (5 mL) was added thionyl chloride (6 mmol). The reaction mixture was stirred under reflux for 2 hrs and concentrated to give the crude acid chlorides **30** as yellow liquids. This liquid was dissolved in dry THF (5 ml) added drop wise to *p*-tosylhydrazine **31** (1 mmol). After being refluxed for 2-4 hrs the reaction mixture was concentrated. Reaction completion monitored by TLC. The resulting mixture was partition between ethyl acetate and water and the organic layer was separated and finally washed with brine, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography by using gradient mixture of ethyl acetate and hexane to afford compounds II_7.

2-[(2-Tosylhydrazine-1-carbonyl)phenyl] phenylcarbamate (II_7, Scheme 10):



[000161] ^{1}H NMR (400 MHz, DMSO) δ 8.99 (s, 1H), 8.12 – 7.99 (m, 1H), 7.85 (s, 2H), 7.69 – 7.46 (m, 4H), 7.46 – 7.33 (m, 5H), 7.30 (s, 1H), 7.11 (s, 1H), 4.56 (s, 1H), 2.41 – 2.35 (m, 3H); LC-MS (ESI+): *m\z* 426.1118[M + H]$^+$.

Scheme 11



32a: R= COOEt;
32b: R= COOMe;
32c: R= COOPr;
32d: R= COO*iso*-Pr;
32e: R= COOPr;
32f: R= 3-OH, 4-COO*iso*-Bu

33a: R_1= 4-Et
33b: R_1= 2-*iso*-Pr
33c: R_1= 4-*iso*-Pr
33d: R_1= 4-*iso*-Pr
33e: R_1= 3-Me
33f: R_1= 4-*iso*-Pr

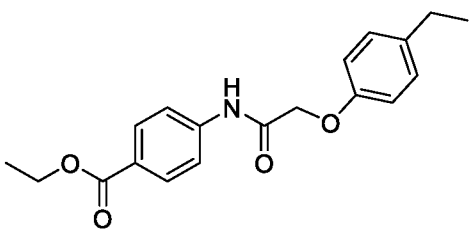
III1a: R= COOEt; R_1= 4-Et
III1b: R= COOMe; R_1= 2-*iso*-Pr
III1c: R= COOPr; R_1= 4-*iso*-Pr
III1d: R= COO*iso*-Pr; R_1= 4-*iso*-Pr
III1e: R= COOPr; R_1= 3-Me
III1f: R= 3-OH, 4-COO*iso*-Bu; R_1= 4-*iso*-Pr

Reagents and conditions: a) Chloroacetyl chloride, Et_3N, DCM, rt, 6h, 75-85%, b) K_2CO_3, DMF, rt, 12h, 80-90%.

General procedure for the synthesis of III1a-g of Scheme 11:

[000162] To a solution of substituted anilines **32** (5 mmol) in DCM (5ml) and triethylamine (10 mmol) was added chloroacetyl chloride (7.5 mmol). The reaction was stirred at room temperature for 6 hours then diluted with water and extract with DCM, the organic layer was separated and washed with brine, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated to give the crude 2-chloro amides **33** as a yellow liquid. This yellow liquid was dissolved in dimethyl formamide (5 ml) was added K_2CO_3 (15 mmol) and corresponding substituted phenols **34** at room temperature. After being stirred at room temperature for 12h, the reaction mixture was diluted with ice water and extract with ethyl acetate, the organic layer was separated and washed with brine, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/Hexane as eluents to get compounds **III1a-f**.

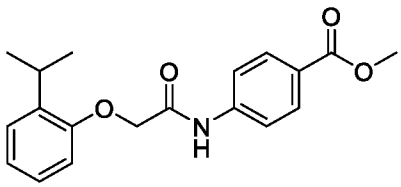
Ethyl 4-[2-(4-ethylphenoxy)acetamido]benzoate (III1a, Scheme 11):



[000163] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 4.60 (s, 2H), 4.37

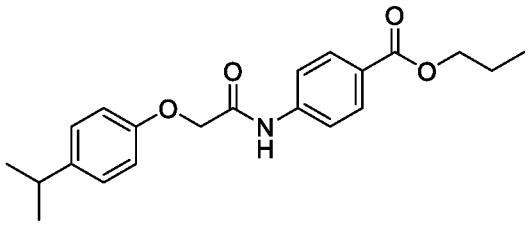
(q, J = 7.1 Hz, 2H), 2.62 (q, J = 7.6 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.6 Hz, 3H);HRMS (ESI-TOF) calcd for $C_{19}H_{21}NO_4$ $[M + H]^+$ 328.1549, found 328.1567.

Methyl 4-[2-(2-isopropylphenoxy)acetamido]benzoate (III_1b, Scheme 11):



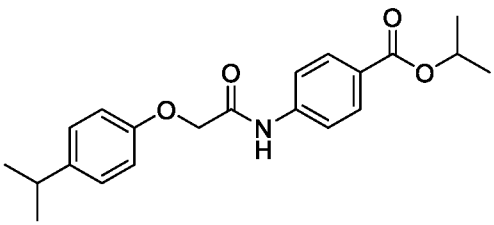
[000164] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.03 (d, J = 8.65 Hz, 2H), 7.64 (d, J = 8.65 Hz, 2H), 7.24 (d, J = 7.4 Hz, 1H), 7.19 (t, J = 8.02 Hz, 1H), 7.06 (t, J = 7.38 Hz, 1H), 6.84(d, J = 8.03Hz, 1H), 4.64 (s, 2H), 3.91 (s, 3H), 3.34 – 3.28 (m, 1H), 1.32 (d, J = 7.38 Hz, 6H); ; HRMS (ESI-TOF) calcd for $C_{19}H_{21}NO_4$ $[M + H]^+$ 328.1549, found 328.1565.

Propyl 4-[2-(4-isopropylphenoxy)acetamido]benzoate (III_1c, Scheme 11):



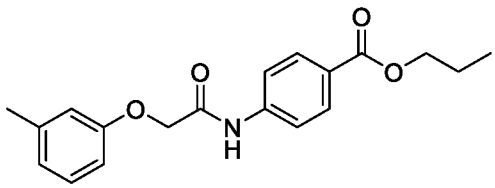
[000165] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.07 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 4.63 (s, 2H), 4.30 (t, J = 6.7 Hz, 2H), 2.95 – 2.88 (m, 1H), 1.88 – 1.76(m, 2H), 1.26 (d, J = 6.9 Hz, 6H), 1.05 (t, J = 7.4 Hz, 3H);;HRMS (ESI-TOF) calcd for $C_{21}H_{25}NO_4$ $[M + Na]^+$ 378.1682, found 378.1681.

Isopropyl 4-[2-(4-isopropylphenoxy)acetamido]benzoate (III_1d, Scheme 11):



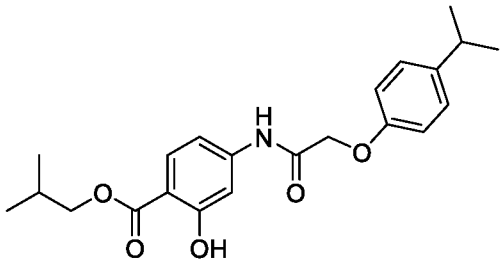
[000166] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.06 (d, *J* = 8.7 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 5.30 – 5.23(m, 1H), 4.63 (s, 2H), 2.95 – 2.88 (m, 1H), 1.39 (d, *J* = 6.3 Hz, 6H), 1.26 (d, *J* = 6.9 Hz, 6H); HRMS (ESI-TOF) calcd for $C_{21}H_{25}NO_4$ $[M + Na]^+$ 378.1682, found 378.1645.

Propyl 4-[2-(m-tolyloxy)acetamido]benzoate (III$_1$e, Scheme 11):



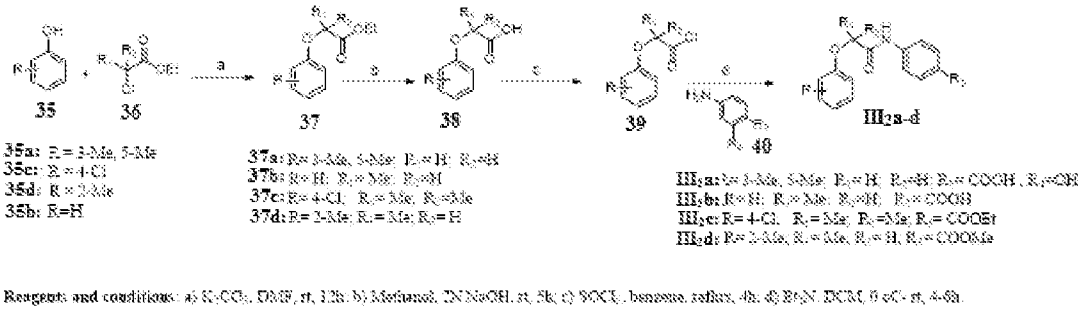
[000167] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.69 (d, *J* = 8.7 Hz, 2H), 7.23 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.84 – 6.77 (m, 2H), 4.62 (s, 2H), 4.27 (t, *J* = 6.7 Hz, 2H), 2.37 (s, 3H), 1.85 – 1.74 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); HRMS (ESI-TOF) calcd for $C_{19}H_{21}NO_4$ $[M + H]^+$ 328.1549, found 328.1541.

Isobutyl 2-hydroxy-4-[2-(4-isopropylphenoxy)acetamido]benzoate(III$_1$f, Scheme 11):



[000168] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 4H), 7.36 – 7.15 (m, 8H), 7.12 (s, 4H), 7.04 (s, 4H), 7.01 – 6.90 (m, 12H), 4.93 – 4.87 (m, 8H), 4.37 (s, 4H), 4.28 – 4.03 (m, 8H), 3.03 (s, 3H), 2.27 (s, 3H), 1.42 – 1.20 (m, 24H), 1.13 – 0.90 (m, 24H). LC-MS (ESI+): *m\z* 386.1962 $[M + H]^+$.

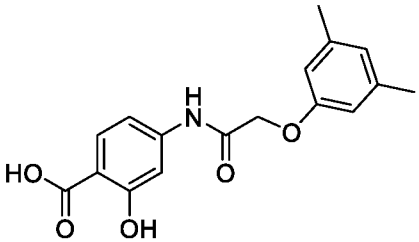
Scheme 12



General procedure for the synthesis of III2a-d, Scheme 12):

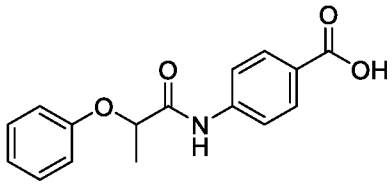
[000169] To a suspension of substituted phenoxyalkyl acids **38** (2 mmol) in benzene (5 mL) was added thionyl chloride (6 mmol). The reaction mixture was stirred under reflux for 5 h and concentrated to give the crude acid chlorides **39** as yellow liquids. This liquid was dissolved in dry DCM (5 ml) added drop wise to the substituted anilines **40** (1 mmol) in triethylamine (3 mmol) and DCM (5 ml) at 0°C. After being stirred at room temperature for 4h the reaction mixture was concentrated. The resulting mixture was partition between ethyl acetate and water and the organic layer was separated. The organic layer washed with saturated bicarbonate solution and washed with 2N HCl and finally washed with brine, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography by using gradient mixture of ethyl acetate and hexane to afford compounds **III2a-d**.

4-[2-(3,5-dimethylphenoxy)acetamido]-2-hydroxybenzoic acid (III2a, Scheme 12):



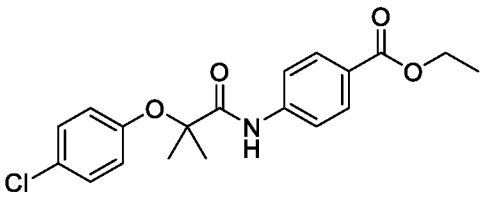
[000170] ^{1}H NMR (400 MHz, DMSO) δ 9.88 (s, 1H), 8.05 (s, 1H), 7.49 (s, 1H), 7.10 (s, 1H), 6.78 – 6.68 (m, 3H), 4.84 – 4.78 (m, 2H), 2.38 – 2.32 (m, 6H). LC-MS (ESI+): *m\z* 316.1179[M + H]$^+$.

4-(2-Phenoxypropanamido)benzoic acid (III2b, Scheme 12):



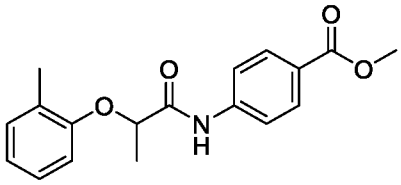
[000171] ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.72 (s, 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.7 Hz, 2H), 7.36– 7.27 (m, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 4.92 (q, *J* = 6.7 Hz, 1H), 1.63 (d, *J* = 6.7 Hz, 3H);HRMS (ESI-TOF) calcd for $C_{16}H_{15}NO_4$ $[M + H]^+$ 286.1079, found 286.1074.

Ethyl 4-[2-(4-chlorophenoxy)-2-methylpropanamido]benzoate (III$_2$c, Scheme 12):



[000172] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.59 (s, 6H), 1.41 (t, *J* = 7.1 Hz, 3H); HRMS (ESI-TOF) calcd for $C_{18}H_{18}ClNO_4$ $[M + H]^+$ 348.1002, found 348.0999.

Methyl 4-[2-(o-tolyloxy)propanamido]benzoate (III$_2$d, Scheme 12):



[000173] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H), 7.27 – 7.16 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.82 (q, *J* = 6.7 Hz, 1H), 3.92 (s, 3H), 2.38 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 3H); HRMS (ESI-TOF) calcd for $C_{18}H_{19}NO_4$ $[M + H]^+$ 314.1392, found 314.1428.

<u>Synthesis of the Intermediates</u>

General procedure for the synthesis of intermediate 3 of I$_1$a-f (Scheme 1):

[000174] To a solution of compound **1** (1.93 mg, 10 mmol) in dry benzene at 0°C was added ethane thiol **2** (0.93 g, 1.5 mmol), followed by NaH (0.36 mg, 1.5 mmol) in

portion wise. The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, it was quenched with ice-cold water and extracted with ethylacetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to give compound **3** as a white liquid (1.9 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 – 8.73 (s, 2H), 3.16 – 3.00 (q, 2H), 1.41 – 1.23 (t, 3H); Mass (ESI+) 217.9513 [M+H].

General procedure for the synthesis of intermediate 5a-f of I_1a-f (Scheme 1)

[000175] To a solution of **3** (8.7 mmol) in dioxane (4 mL) under nitrogen atmosphere were added tetrakis(triphenylphosphine)palladium (0.44 mmol), substituted phenylboronic acid **4** (10.5 mmol), and K_2CO_3 (8 mmol), dissolved in 4 mL of water. The mixture was stirred under reflux for 6 h. The reaction mixture was diluted with EtOAc, filtered through celite, and washed with water. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to furnish compound **5**.

2-(Ethylthio)-5-(4-nitrophenyl)pyrimidine 5a of I_1 (Scheme 1)

[000176] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 – 8.58 (s, 2H), 8.46 – 8.20 (d, 2H), 7.93 – 7.64 (d, 2H), 3.18 – 3.05 (q, 2H), 1.38 – 1.29 (t, 3H); Mass (ESI+) 261.05 [M+H].

2-(Ethylthio)-5-(4-trifluoromethylphenyl)pyrimidine 5b of I_1 (Scheme 1):

[000177] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 – 8.45 (s, 2H), 8.21 – 8.13 (d, 2H), 7.73 – 7.54 (d, 2H), 3.03 – 2.96 (q, 2H), 1.31 – 1.22 (t, 3H); Mass (ESI+) 255.09 [M+H].

2-(Ethylthio)-5-(4-trifluoromethoxyphenyl)pyrimidine 5c of I_1 (Scheme 1):

[000178] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 – 8.49 (s, 2H), 8.21 – 8.17 (d, 2H), 7.29 – 7.13 (d, 2H), 3.03 – 2.96 (q, 2H), 1.31 – 1.22 (t, 3H); Mass (ESI+) 271.16 [M+H].

2-(Ethylthio)-5-(4-methoxyphenyl)pyrimidine 5d of I_1 (Scheme 1):

[000179] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 – 8.45 (s, 2H), 8.19 – 8.14 (d, 2H), 7.09 – 6.94 (d, 2H), 3.21 (s, 3H), 3.03 – 2.96 (q, 2H), 1.31 – 1.22 (t, 3H); Mass (ESI+) 217.12 [M+H].

2-(Ethylthio)-5-(3-nitrophenyl)pyrimidine 5e of I_1 (Scheme 1):

[000180] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 – 8.58 (s, 2H), 8.48 – 8.23 (m, 4H), 3.18 – 3.05 (q, 2H), 1.38 – 1.29 (t, 3H); Mass (ESI+) 261.05 [M+H].

2-(Ethylthio)-5-(2-nitrophenyl)pyrimidine 5f of I_1 (Scheme 1):

[000181] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 – 8.58 (s, 2H), 8.46 – 8.10 (m, 4H), 3.18 – 3.05 (q, 2H), 1.38 – 1.29 (t, 3H); Mass (ESI+) 261.05 [M+H].

General procedure for the synthesis of intermediate 6a-f of I_1 (Scheme 1)

[000182] To a solution of compound **5** (7.6 mmol) in DCM at 0° C was added 3-chloroperbenzoic acid (15.3 mmol) in portion wise. The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, saturated bicarbonate solution (10 mL) was added, and the reaction mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound **6**. The crude products were further used without any purification.

General procedure for the synthesis of intermediate 7a-f of I_1 (Scheme 1)

[000183] To a solution of compound **6** (5.1 mmol) in THF was added hydrazine hydrate (0.5 g, 10.2 mmol). The resulting mixture was stirred at 60° C- 70° C for 3 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the reaction mixture was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give compound **7**. The crude products were further used without any purification.

General procedure for the synthesis of intermediate 11a-b of I_3a-d (Scheme 2)

[000184] To a solution of compound **10** (1 mmol) in methanol was added 2° amine (1.5 mmol), and K_2CO_3 (1 mmol). The resulting mixture was stirred at room temperature for 1 h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to get compound **11**.

General procedure for the synthesis of intermediate 29 of II_7 (Scheme 10):

[000185] To a solution of phenylisocyante **23** (4.2mmol) in benzene was added potassium *tert*-butoxide (10mol %) slowly and then salicylic acid **28** (4.2mmol) was added. The resulting mixture was stirred at 45-50 ^{0}C for 1h. After completion of the reaction (reaction monitored by TLC) the solvent was removed under vacuum, and the compound was extracted with EtOAc. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were purified on a silica gel column using hexane/EtOAc to afford compound **29**.

General procedure for the synthesis of intermediate 38a-d of III_{2a-d} (Scheme 12):

[000186] To a solution of substituted phenols **35** (10 mmol) in DMF (10 ml) was added K_2CO_3 (20 mmol) and substituted 2-chloroethylacetate **36** (12 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h, and then the reaction mixture was poured in ice water, extracted with ethyl acetate twice. Combined the organic layers washed with brine solution and dried over anhydrous Na_2SO_4, and concentrated to get the crude compounds **37**. These crude compounds **37** were dissolved in methanol (10 ml) was added 2N NaOH (6 ml) at room temperature and stirred for 12h. Solvent was evaporated under vaccum and the resulting mixture was acidified with 2N HCl and then solids were filtered off. The solids were washed with water and hexane and dried for some time under vaccum to get the pure substituted 2-phenoxyacetic acids **38a-d** in 80-90%.

2-(3,5-Dimethylphenoxy)acetic acid (38a, Scheme 12):

[000187] ^{1}H NMR (400 MHz, CD_3OD) δ 7.01 (s, 1H), 6.77 – 6.67 (m, 2H), 4.94 – 4.87 (s, 2H), 2.39 – 2.32 (m, 6H); LC-MS (ESI+): *m\z* 386.1962 $[M + H]^+$.

2-Phenoxypropanoic acid (38b, Scheme 12):

[000188] ^{1}H NMR (400 MHz, CD_3OD) δ 7.34 (t, *J* = 8.0 Hz, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 2H), 4.75 (q, *J* = 6.75 Hz, 1H),1.64 (d, *J* = 6.75 Hz, 3H); LC-MS (ESI+): *m\z* 167.08 $[M + H]^+$.

2-(4-Chlorophenoxy)-2-methylpropanoic acid (38c, Scheme 12):

[000189] ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 2H), 1.59 (s, 6H);LC-MS (ESI+): m\z 215.12$[M + H]^+$.

2-(*o*-Tolyloxy)propanoic acid (38d, Scheme 12):

^{1}H NMR (400 MHz, CD_3OD) δ 7.28 – 7.15 (m, 2H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.82 (q, *J* = 6.7 Hz, 1H), 1.69 (d, *J* = 6.8 Hz, 3H); LC-MS (ESI+): *m\z* 181.09$[M + H]^+$.

EXAMPLES

[000190] The following examples provide the details about the, applications of the compounds of the present disclosure. It should be understood the following is representative only, and that the invention is not limited by the details set forth in these examples.

Example 1

Biological Activity/Assay

[000191] Through an *in vitro* biochemistry screen, small molecules were identified which can target *Nef* interaction with CD80 and CD86. Out of the 1061 compounds, three scaffolds were identified. Compounds from these scaffolds (Formula I, Formula II, and Formula III) were validated in (a.) Primary biochemistry screen; and (b.) Cell-based screen.

Validation of compounds in Primary Screen

[000192] Standard ELISA assay was used to validate the compounds as a primary screen. The basic steps of the assay are outlined in Figure 1. The cytosolic peptides CD80, CD86 and CD74 are coated on a microplate, while CD80 and CD86 has higher binding capacity with the Nef protein, CD74 is non-specific peptide and is a peptide negative control for Nef binding. The coated plates are incubated overnight at 4 ^oC. The plates were washed 5 times with PBS (0.02 %Tween-20) before every step. After washing, the wells were blocked with 5% blotto and incubated at RT with shaking (650 rpm). The plates were washed 5 times with PBS (0.02 % -tween20) after every step. Primary antibody mouse anti-Nef raised in rabbit dissolved in 2.5% blotto (1:1000) were added and incubated on shaker for 1 hour at RT. Plate was washed and 100µL anti rabbit

raised in donkey dissolved in 2.5% blotto (1:11000) was added and incubated at RT for 45 min. Plate was washed with PBS and TMB substrate solution was added and incubated in dark for 5-10 min. The reaction was stopped with 1N H_2SO_4 and the absorbance was measured at 450 nm. Positive control (Nef) and Negative control (No peptide with Nef) were analysed for highest binding of Nef with peptide. The absorbance of the plates was measured at 450 nm.

[000193] A throughput screen was performed to pull out the actives. Standard quality control metrics like Z' were used to qualify plates and Z' scores were used to identify actives. The IC_{50} value of the compounds were further determined to evaluate the efficacy of the test compounds.

[000194] The IC_{50} values of the compounds have been illustrated in Table 1. Eighteen compounds were found to show HIV inhibiting activity and increasing the expression of CD80 and CD86 proteins. Actives predominantly belong to compounds from Formula I, II and III with IC_{50}s in nano or subnanomolar ranges were selected. Selected compounds were then screened in the cell-based assays systems.

Table 1*:* pIC_{50} values of representative actives from Primary Screen

Sl No	Formula	Compound ID	CD80 pIC50 value	CD86 pIC50 value
1	Formula I	I_1a	11.63	
2		I_2a	15.04	
3		I_2b	15.52	
4		I_3a	10.96	
5		I_3b	9.89	8.79

6	**Formula II**	**II_1**	**10.04**	
7		**II_3**		**10.9**
8		**II_4**	**10.56**	**9.56**
9		**II_5**	**11.56**	
10		**II_6**	**12.46**	
11		**II_7**	**10.06**	
12		**II_{2a}**	**14.7**	
13		**II_{2c}**	**12.71**	
14		**II_{2d}**	**7.98**	**6.29**
15	**Formula III**	**III_{1e}**	**8.63**	
16		**III_{1a}**	**17.03**	
17		**III_{2a}**	**11.35**	
18		**III_{2b}**	**8.95**	
19		**III_{2c}**	**8.82**	

[000195] Table 1 illustrates the efficacy of individual compounds in inhibiting the *Nef* mediated downregulation of CD80 and CD86 proteins. Out of the total 19 compounds of Formula I, II, and III, the compounds which were found effective in inhibiting *Nef*-CD80 binding, in terms of higher pIC_{50} values (IC_{50}s in nano or

subnanomolar ranges), were compounds $I_{1}a$ (pIC_{50}=11.63), $I_{2}a$ (pIC_{50}=15.04), $I_{2}b$ (pIC_{50}=15.52), $I_{3}a$ (pIC_{50}=10.96), $I_{3}b$ (pIC_{50}=9.89) of Formula I, compounds II_{1} (pIC_{50}=10.04), II_{4} (pIC_{50}=10.56), II_{6} (pIC_{50}=12.46), II_{5} (pIC_{50}=11.52), $II_{2}c$ (pIC_{50}=12.71), II_{7} (pIC_{50}=10.06),$II_{2}d$ (pIC_{50}=7.98), $II_{2}a$ (pIC_{50}=14.70) of Formula II, and $III_{2}b$ (pIC_{50}=8.95), $III_{2}a$ (pIC_{50}=11.35), $III_{1}e$ (pIC_{50}=8.63), $III_{1}a$ (pIC_{50}=17.03), $III_{2}c$(pIC_{50}=8.82) of Formula III respectively. Some of the effective compounds in terms of higher pIC_{50} values were $I_{2}a$ (pIC_{50}=15.04), $I_{2}b$ (pIC_{50}=15.52), $III_{1}a$ (pIC_{50}=17.03), and $II_{2}a$ (pIC_{50}=14.70) respectively. On the other hand, the compounds which were found effective in inhibiting *Nef*-CD86 binding were $I_{3}b$ (pIC_{50}=8.79) of Formula I and II_{4} (pIC_{50}=9.56), II_{3} (pIC_{50}=10.90) and $II_{2}d$ (pIC_{50}=6.29) of Formula II. Thus, the compound which were active in inhibiting interactions of Nef protein with both CD80 and CD86 proteins were $I_{2}b$, II_{4} and $II_{2}d$ respectively.

Example 2

Cell-Based Screen: Phenotypic screen for downregulation

[000196] The schematic of the cell-based assay is as shown in the Figure 2. CD80 and CD86 are two major co-stimulatory cell surface proteins that are present on antigen presenting cells (APCs) and provide a co-stimulatory signal necessary for activation and survival of the naïve T cells. Both these proteins get down regulated during HIV infection *via* a *Nef* mediated pathway. It has been speculated that *Nef* ability to reduce CD80 and CD86 surface expression in infected cells can prevent the activation of naive T cells, necessary for an efficient recognition and elimination of the target cells. Figure 2 illustrates that in the presence of the compounds of Formula I, Formula II or Formula III, the binding of *Nef* with CD80 and CD86 is inhibited thus increasing their expression. The increased expression would activate naïve T cells and aid in eliminating the infection.

[000197] Briefly monocyte / B cell lines were either delivered with *Nef* protein or exposed to replication deficient retrovirus and the levels of surface CD80/86 was evaluated by flow cytometry with/without compound treatment. The compounds were qualified based on the ability to reverse the down regulation of CD80/86 caused by the *Nef* protein. Similar quality checks were used in the secondary screen as in primary

screen. Results from representative compounds were tested in the phenotypic assay for downregulation is presented in the Figure 3. Briefly, B/ monocyte cells were preexposed to 100 µM of the 4 compounds for 2 hrs and then infected with non-replicative reterovirus containing NEF. The internalization of surface receptors were measured by flow cytometry after optimal infection (48-72 hrs). Representative compounds from each scaffold (I_3b, II_3 and III_2a) showed reversal of *Nef* mediated internalization of CD80/86.

Example 3

Efficacy assay system to test T cell activation:

[000198] The appropriate cell system was designed to mimic the biology of the said interactions. The schematic representation of the cell-based T cell activation assay is as shown in Figure 4. Figure 4 (A) represents the principle behind the activation of naïve T cells by the antigen presenting cells (APC), including dendritic cells, B cells, monocytes, macrophages. The activation is based on CD80/86 co-stimulation along with CD3 activation by major histocompatibility complex (MHC) as evidenced by an increase in IL-2 release from the activated T cells.

[000199] Figure 4(B) is a schematic representation that displays the addition of *Nef* in the APC causes down regulation of the CD80/86 and hence loss of T cell activation, which leads to a reduction in IL-2 release.

[000200] Figure 4(C) displays the rescue of internalization of CD80/86 back to the surface of the APC by means of inhibitiors to the *Nef* protein delivered to the APC cell line, which restores CD80/86 co-stimulation and hence results in IL-2 release from the T cells.

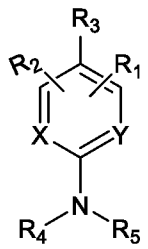
[000201] Representative compounds from the Formula I, II and III were tested in the functional T cell assay and the results are as presented in Figure 5. B-cell line was pre-exposed to 100 µM of the 4 compounds for 1 hr. The cells were washed and then Nef was introduced via protein delivery agent. The cells were washed again and co-cultured with T cell line. The IL-2 release (as an indicator of activation) was measured by ELISA after 3 hrs. Addition of Nef reduced the T cell activation by more than 50%. Addition of compounds (I_3b, II_3 and III_2a) reversed the Nef mediated inactivation.

ADVANTAGE

[000202] The method of treatment of HIV infection by targeting *Nef*-CD80/86 interactions has a very distinct and unique mechanism of action: prevention of immune evasion of infected cells. None of the potential or existing therapy has targeted the viral strategy of immune evasion and the present disclosure presents a new class of drugs. Also, targeting host-virus interface is also less amenable to drug resistance than pure viral targets. This, hence, would provide hope to class of people where existing retroviral treatments have failed and also a profound impact on pre-exposure prophylaxis to the hot-spot population.

I/We claim:

1. A method for treating HIV subtypes causing disease in a subject comprising: administering to a HIV infected subject a therapeutic dose of a compound selected from a group consisting of Formula I,



Formula I

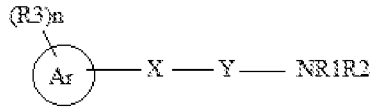
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro, halogen or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen, hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

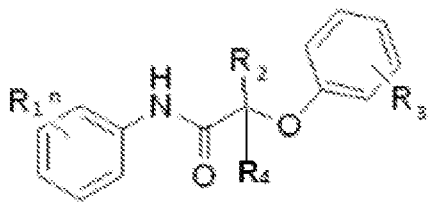
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl,

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

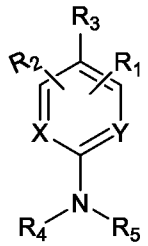
R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10}alkyl or halogen; and

n is selected from 1 to 5.

2. A method for preventing HIV subtypes causing disease in a subject in need thereof comprising: administering to a HIV high risk subject a relevant dose of a compound selected from a group consisting of



Formula I

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

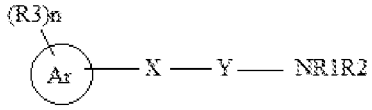
R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen; hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein N=CHC_6 aryl is further substituted with one to four halogen;

or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10}

heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

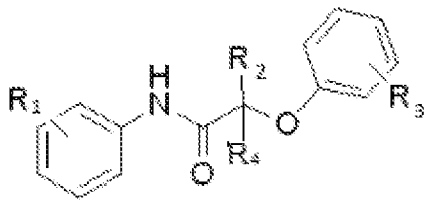
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl,

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

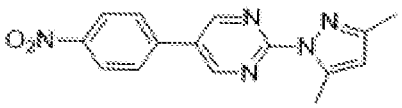
R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

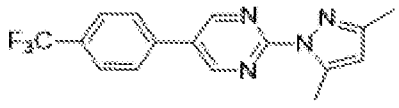
R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5.

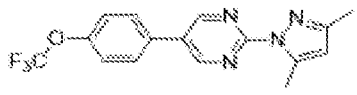
3. The method according to claim 1 or 2, wherein compound of Formula I is selected from a group consisting of:



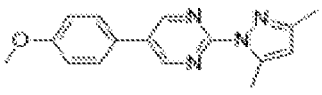
I_1a



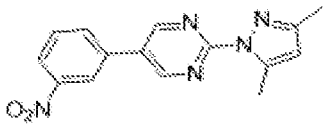
I_1b



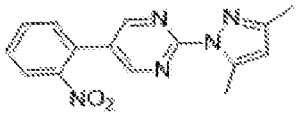
I_1c



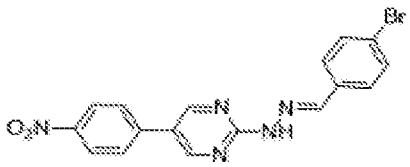
I_1d



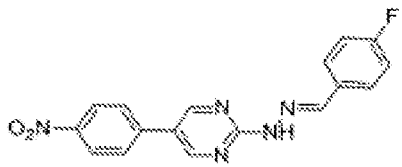
I_1e



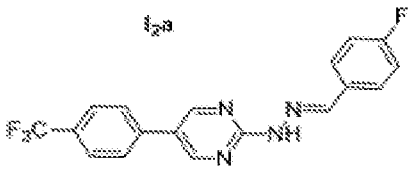
I_1f



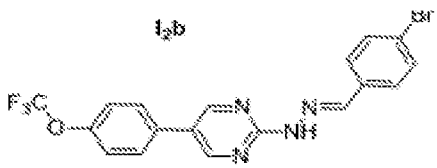
I_2a



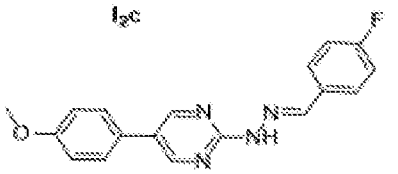
I_2b



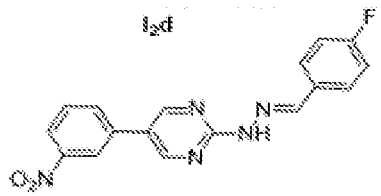
I_2c



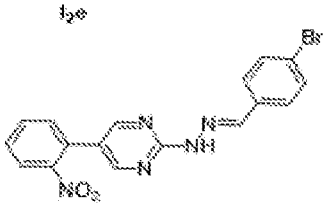
I_2d



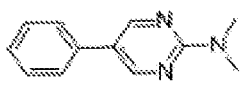
I_2e



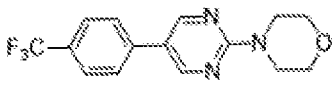
I_2f



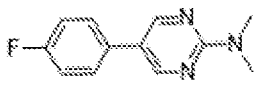
I_2g



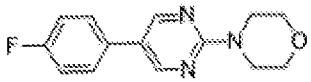
I_3a



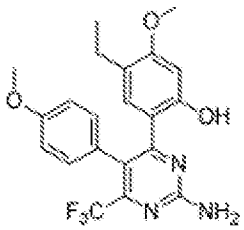
I_3b



I_3c

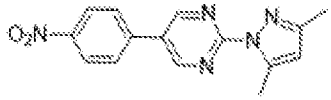


I_3d

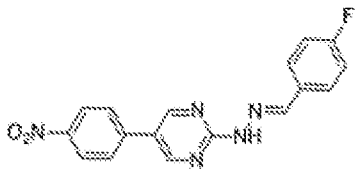


I_4

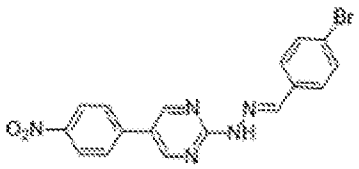
4. The method according to claim 1 or 2, wherein compound of Formula I is selected from a group consisting of:



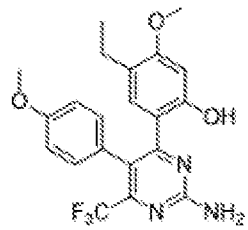
I_{3a}



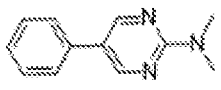
I_{2b}



I_{2a}

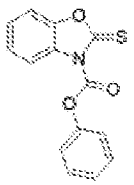


I_4

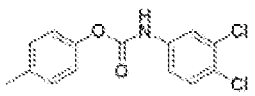


I_{3a}

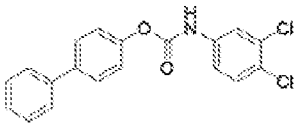
5. The method according to claims 1 or 2, wherein compound of Formula II is selected from a group consisting of:



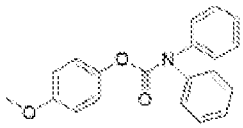
II_1



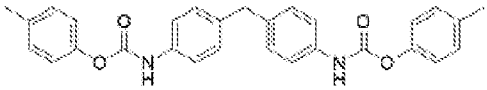
II_2a



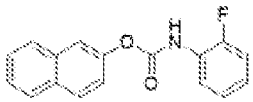
II_2b



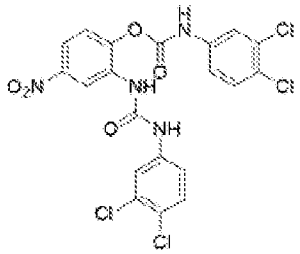
II_2c



II_2d



II_3



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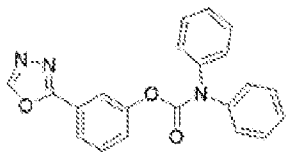
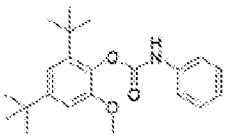
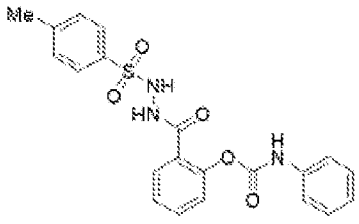


II_5

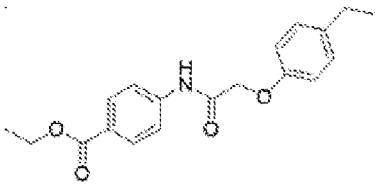


II_6

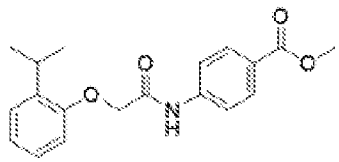


II_7

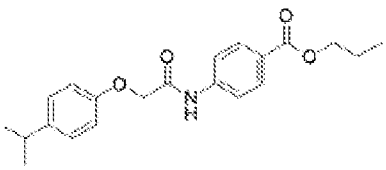
6. The method according to claims 1 or 2, wherein compound of Formula III is selected from a group consisting of:



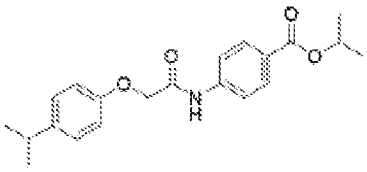
III_{1a}



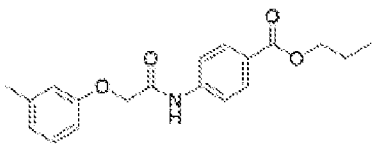
III_{1b}



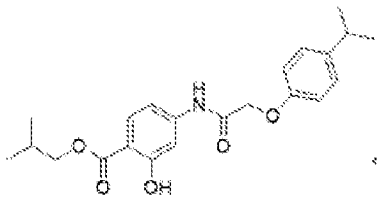
III_{1c}



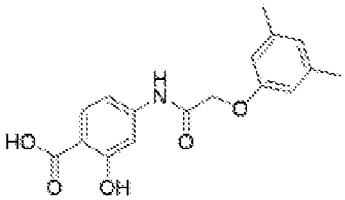
III_{1d}



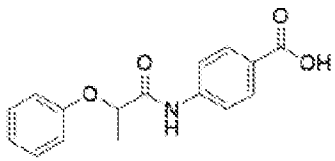
III_{1e}



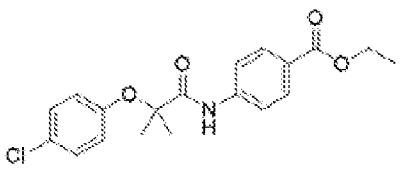
III_{1f}



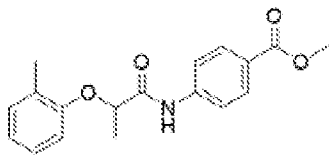
III_{2a}



III_{2b}



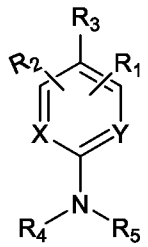
III_{2c}



III_{2d}

7. A method of treating or preventing HIV infection in a subject by immune evasion mediated by internalization of CD80/86 receptors by its *Nef* protein comprising:

administering to a subject a relevant dose of a compound selected from a group consisting of



Formula I

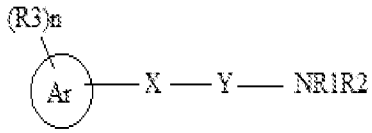
or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein

R_1 and R_2 are independently selected from the group consisting of hydrogen, C_{6-10} aryl, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and amino, wherein C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, and C_{6-10} aryl are optionally substituted with one to four substituents independently selected from hydroxyl, halogen, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_3 is C_{6-10} aryl, wherein C_{6-10} aryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkoxy, nitro or C_{1-10} alkyl, wherein C_{1-10} alkyl, and C_{1-10} alkoxy is optionally substituted with one to four substituents selected from halogen; hydrogen, hydroxyl, C_{1-10} alkyl, C_{1-10} alkoxy or C_{2-10} heterocyclyl;

R_4 and R_5 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and -N=CHC_6 aryl, wherein N=CHC_6 aryl is further substituted with one to four halogen; or R_4 and R_5 are joined to form a C_{2-10} heterocyclyl or a C_{2-10} heteroaryl, wherein C_{2-10} heterocyclyl or C_{2-10} heteroaryl is optionally substituted with one to four substituents independently selected from C_{1-10} alkyl; and

X and Y are N;



Formula II

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1, and R_2 are independently selected from the group consisting of hydrogen, C_{1-10} alkyl, hydroxy, thio, amino, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl, acyl, amido, imido, sulfinyl, sulfonyl, carboxaldehyde, cyano, isocyano, azido, hydrazino, nitro, halo; or R_1 and R_2 are joined to form an optionally substituted monocyclic or a bicyclic ring, wherein C_{1-10} alkyl, C_{2-10} heterocyclyl, C_{5-10} aryl, C_{2-10} heteroaryl or monocyclic or a bicyclic ring are optionally substituted with one four substituents independently selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, cyano, thio, and -CH_2-Ph-NH-COO-Ph-Me;

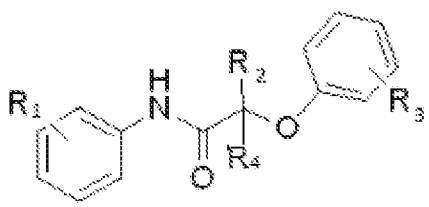
X is O;

Y is C=O;

Ar is selected from C_{1-10} alkyl, C_{5-10} aryl or C_{2-10} heteroaryl,

R_3 is absent or is selected from hydroxy, C_{1-10} alkyl, C_{5-10} aryl, C_{2-10} heteroaryl, C_{2-10} heterocyclyl, C_{1-10} alkoxy, halogen, haloalkyl, perhaloalkyl, nitro, cyano, $CH_2PhNHCOOPh$-Me, $NHCONHPh$-$(Cl)_2$ or $CONHNHSO_2Ph$-Me; and

n is selected from 0-5; and



Formula III

or its stereoisomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, wherein,

R_1 is independently selected from the group consisting of OH, COOH, and COORa, wherein Ra is C_{1-10} alkyl;

R_2 and R_4 is independently selected from hydrogen or C_{1-10} alkyl;

R_3 is selected from C_{1-10} alkyl or halogen; and

n is selected from 1 to 5.

8. The method as claimed in claim 7, wherein the compounds causes restoration of immune signaling *via* T cell activation through inhibiting *Nef*-CD80/86 interactions.

9. A method for treating/preventing infections characterized by low levels of CD80/86 receptors compared to non-infected state, including chronic lymphocytic leukemia, colon carcinoma, multiple myeloma, viral infections including HIV, HPV, herpes.

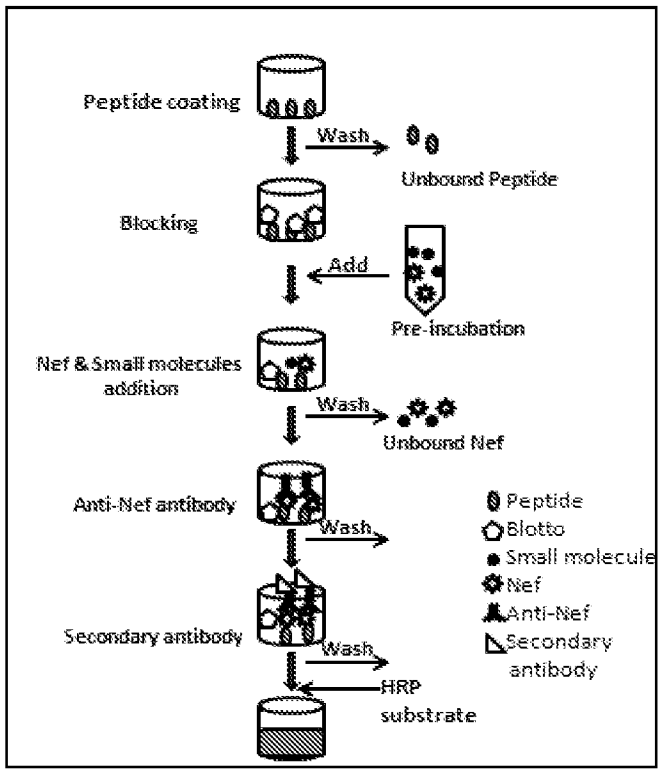


Figure 1

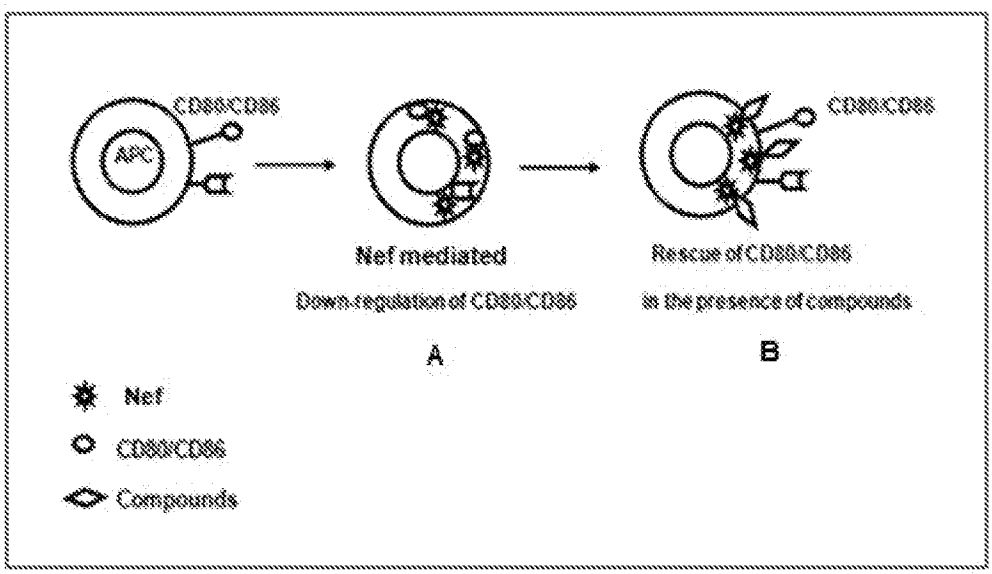
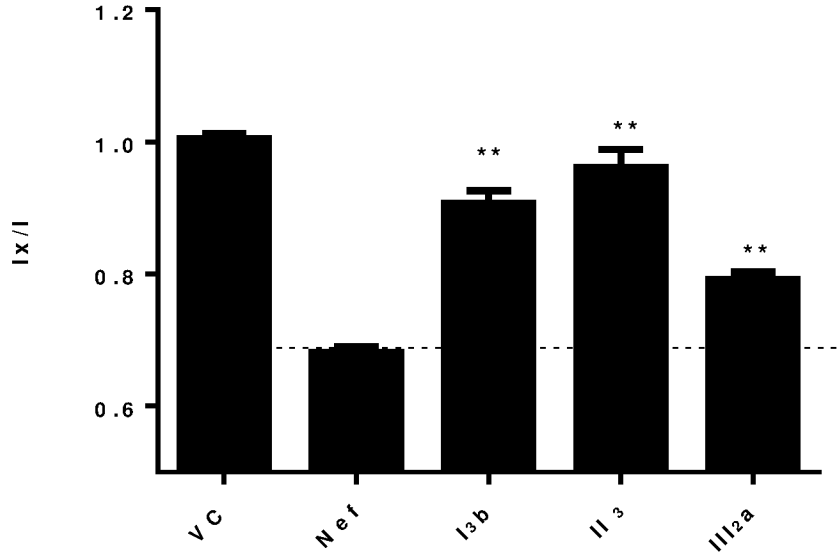


Figure 2

A


1.2
1.0
0.8
0.6
Ix/I
**
**
**
VC
Nef
I3b
II3
III2a

B

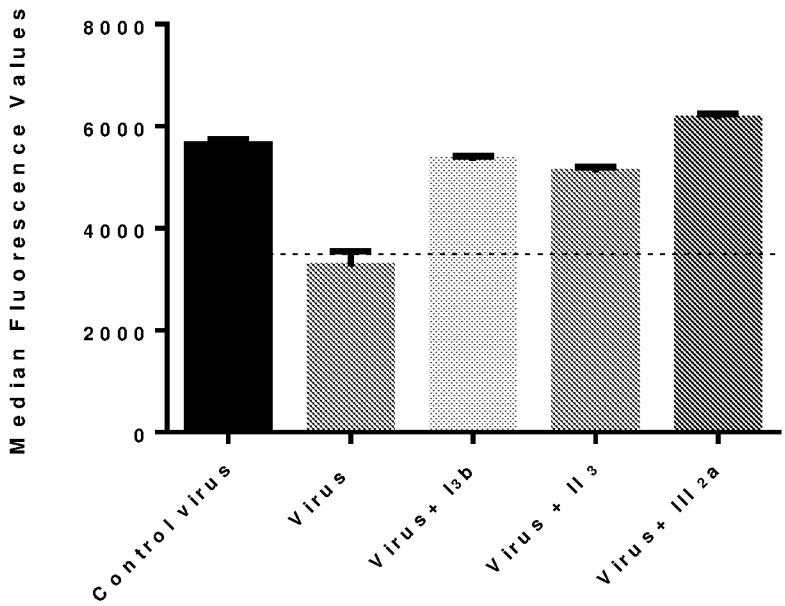

Median Fluorescence Values
8000
6000
4000
2000
0
Control virus
Virus
Virus+ I3b
Virus + II3
Virus+ III2a

Figure 3

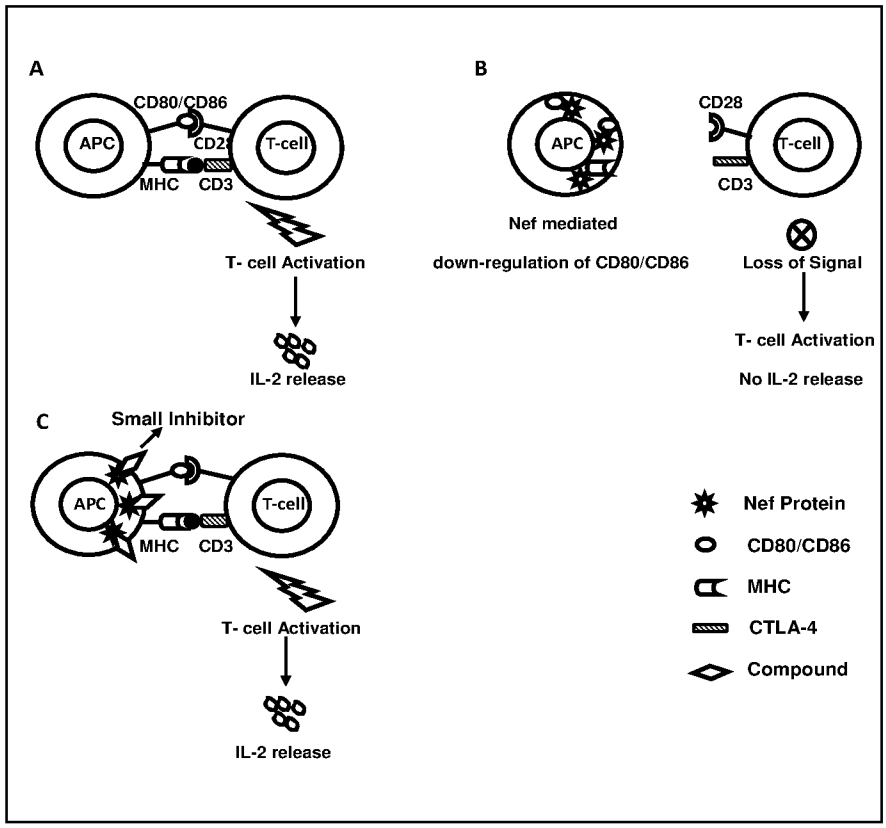


Figure 4

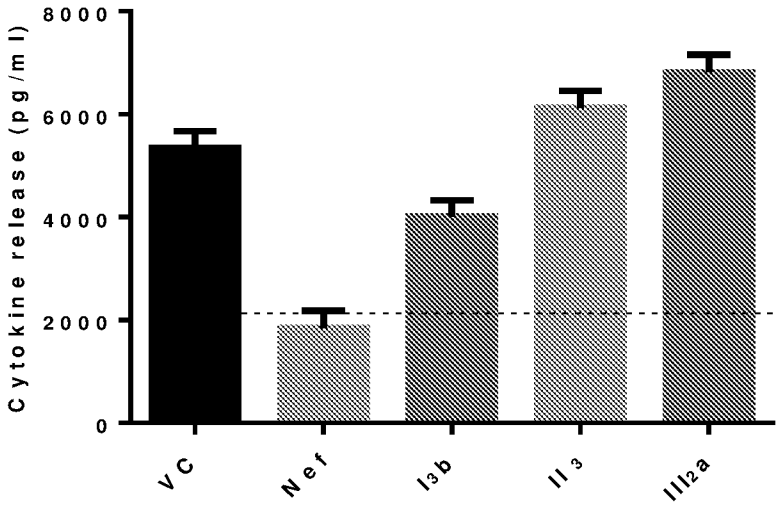


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050594

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/519 Version=2019.01

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)

A61K

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 practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	A. Lugari et. al., A specific protein disorder catalyzer of HIV-1 Nef, Bioorganic & medicinal chemistry, 2011 Dec 15;19(24):7401-7406, DOI: 10.1016/j.bmc.2011.10.051 Abstract, Figure 2, Pages 7401, 7404	1-8
Y	S. Betzi et. al., Protein-protein interaction inhibition (2P2I) combining high throughput and virtual screening: application to the HIV-1 Nef protein, Proceedings of the National Academy of Sciences, 2007 Dec 4; 104(49):19256-19261, DOI: 10.1073/pnas.0707130104 Abstract, Table 1, Page 19259	1-8
Y	US 8975254 (B2) WOHLFAHRT GERD[FI] ET AL 10-03-2015 (10 MARCH 2015) Abstract, col 2, lines 15-30, col 3-8, col 11-18, claims	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"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
20-11-2019	20-11-2019
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Dr. Dasari Ayodhya Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2019/050594

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
The subject matter of claim 9 relates to a method for treatment of the
human or animal body, which does not require an international search by this authority in accordance with PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
The present application is found to contravene the requirements of unity of invention according to Art. 3(4)(iii) PCT, Art. 34 (3)(a) PCT and Rule 13 PCT for the following reasons: The following features have been identified which possibly lead to the following inventions/groups of inventions:

Invention 1: Claims 1-2 (partially), 3-4, and 7-9 (partially) relate to the various compounds of the compound formula (I), its use as a method for treating HIV subtypes causing disease.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/IN2019/050594

Continuation of Observations where unity of invention is lacking(Box III)

Invention 2: Claims 1-2 (partially), 5, and 7-9 (partially), relates to the compound of formula (II), its use as a method for treating HIV subtypes causing disease.

Invention 3: Claims 1-2 (partially), 6, and 7-9 (partially), relates to the compound of formula (III), its use as a method for treating HIV subtypes causing disease.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2019/050594

Citation	Pub.Date	Family	Pub.Date
US 8975254 B2	10-03-2015	AU 2010311299 A1	12-04-2012
		EP 2493858 A1	05-09-2012
		CN 102596910 A	18-07-2012