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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2012 (15.11.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/154880 A1

(51) International Patent Classification:
A01N 43/90 (2006.01)

(21) International Application Number:
PCT/US2012/037159

(22) International Filing Date:
9 May 2012 (09.05.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/484,065 9 May 2011 (09.05.2011) US

(71) Applicant *(for all designated States except US)*: **PROTEOSTASIS THERAPEUTICS, INC.** [US/US]; 200 Technology Square, Suite 402, Cambridge, MA 02139 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **TAIT, Bradley** [US/US]; 22 Bartlett Street, Malden, MA 02148 (US). **POWELL, Noel, A.** [US/US]; 28 Carlisle Road, Westford, MA 01886 (US). **CULLEN, Matthew** [US/US]; 550 Liberty Street, #1803, Braintree, MA 02184 (US).

(74) Agents: **HARLAN, Edgar, W.** et al.; Elmore Patent Law Group, 484 Groton Road, Westford, MA 01886 (US).

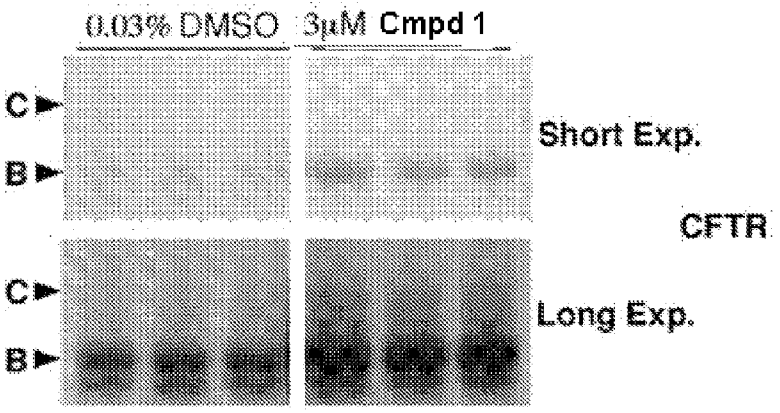
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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, 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, ML, MR, NE, SN, TD, TG).

Published:

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

(54) **Title**: PROTEOSTASIS REGULATORS FOR TREATING CYSTIC FIBROSIS AND OTHER PROTEIN MISFOLDING DISEASES



THE FIGURE

(57) **Abstract**: The present invention is directed to compounds of Formulae (Ia-Ib), (IIa-IId), (IIIa- IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb), pharmaceutical compositions thereof and methods of use thereof in the treatment of conditions associated with a dysfunction in proteostasis.

WO 2012/154880 A1

PROTEOSTASIS REGULATORS FOR TREATING CYSTIC FIBROSIS AND OTHER PROTEIN MISFOLDING DISEASES

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 61/484,065 filed May 9, 2011. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Cells normally maintain a balance between protein synthesis, folding, trafficking, aggregation, and degradation, referred to as protein homeostasis, utilizing sensors and networks of pathways [Sitia et al., *Nature* **426:** 891-894, 2003; Ron et al., *Nat Rev Mol Cell Biol* **8:** 519-529, 2007]. The cellular maintenance of protein homeostasis, or proteostasis, refers to controlling the conformation, binding interactions, location and concentration of individual proteins making up the proteome. Protein folding *in vivo* is accomplished through interactions between the folding polypeptide chain and macromolecular cellular components, including multiple classes of chaperones and folding enzymes, which minimize aggregation [Wiseman et al., *Cell* **131:** 809-821, 2007]. Whether a given protein folds in a certain cell type depends on the distribution, concentration, and subcellular localization of chaperones, folding enzymes, metabolites and the like [Wiseman et al.]. Human loss of function diseases are often the result of a disruption of normal protein homeostasis, typically caused by a mutation in a given protein that compromises its cellular folding, leading to efficient degradation [Cohen et al., *Nature* **426:** 905-909, 2003]. Human gain of function diseases are similarly the result of a disruption in protein homeostasis leading to protein aggregation [Balch et al. (2008), *Science* 319: 916-919].

Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene[1] which encodes a multi-membrane spanning epithelial chloride channel. Ninety percent of patients have a deletion of phenylalanine (Phe) 508 (ΔF508) on at least one allele. This mutation results in disruption of the energetics of the protein fold[2] leading to efficient degradation of CFTR in the endoplasmic reticulum (ER). The loss of a functional CFTR channel at the plasma membrane disrupts ionic homeostasis (Cl^-, Na^+, HCO_3^-) and airway surface hydration leading to reduced lung function[1].

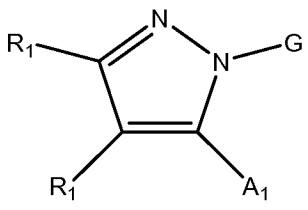
Reduced periciliary liquid volume and increased mucus viscosity impede mucociliary clearance resulting in chronic infection and inflammation, phenotypic hallmarks of CF disease[3]. In addition to respiratory dysfunction, ΔF508 also impacts the normal function of additional organs (pancreas, intestine, gall bladder), suggesting that the loss-of-function impacts multiple downstream pathways that will require correction.

CF and other maladies of protein misfolding, including lysosomal storage diseases, type II diabetes, and cardiovascular and neurological diseases, arise as a result of an imbalance in the capacity of the protein homeostasis (proteostasis) environment to handle the reduced energetic stability of misfolded, mutated proteins that are critical for normal physiology[4-6]. The cellular proteomic and metabolic environment is highly adaptable, and responds to stress and disease through numerous signaling pathways that include, among others, the unfolded protein response (UPR) and heat shock response (HSR). The latter respond to misfolding and/or aggregation of proteins by altering the transcriptional and post-translational regulation of synthesis, folding and trafficking components to restore function to the protein fold as well as cell, tissue and host physiology[4,7]. There remains a need in the art for compounds and pharmaceutical compositions to treat conditions associated with proteostasis dysfunction.

SUMMARY OF THE INVENTION

The present invention is directed to compounds having the Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb), compositions thereof and methods for the treatment of a condition associated with a dysfunction in proteostasis comprising an effective amount of these compounds.

In one embodiment, the invention is a compound having the Formula (Ia):



(Ia);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G is a 3- to 7-membered optionally substituted heterocyclic or an optionally substituted heteroaryl;

A_1 is $N(R_a)_2$;

Each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally

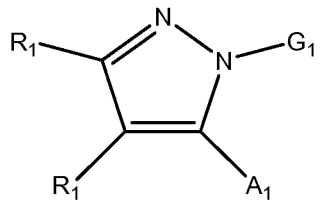
substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In another embodiment, the invention is directed to a compound having the Formula (Ib):



(Ib);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_1 is optionally substituted pyridyl or optionally substituted pyrimidyl;

A_1 is $N(R_a)_2$;

Each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)N(R_b)_2$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$, and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

The invention additionally encompasses a method of treating cancer or a tumor comprising administering to a patient in need thereof an effective amount of a compound having the Formula (Ia-Ib), (IIa-IId), (III), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, solvate, clathrate or prodrug of any of thereof.

BRIEF DESCRIPTION OF THE DRAWING

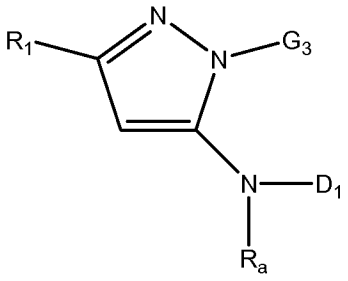
The Figure is an immunoblot analysis showing enhanced levels of bands B and C when CFBE41o- lung cells were cultured in the presence and absence of DMSO (lane 1) and compound 1 (lane 2) in the assay described below in the Exemplification section.

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

As used herein, the words "a" and "an" are meant to include one or more unless otherwise specified. For example, the term "a cell" encompasses both a single cell and a combination of two or more cells.

In one embodiment, the invention provides compounds having the Formula (IIa):



(IIa);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 8-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

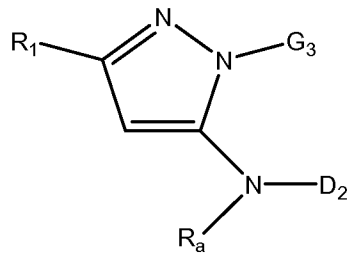
D_1 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In an additional embodiment, the invention is a compound having the Formula (IIb):



(IIb);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

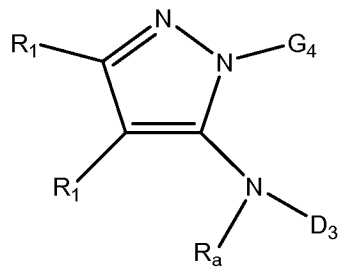
Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

D_2 is selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted benzyl, optionally substituted heteroaryl, and $C(R_5)_3$;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_5 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; alternatively, two R_5 groups can be taken together with the carbon to which they are attached to form a spiro C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and n is 0, 1 or 2.

The invention is additionally directed to a compound having the Formula (IIc):



(IIc);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_4 is a 6-membered heteroaryl containing one or more ring nitrogen atoms;

D_3 is optionally substituted aryl or optionally substituted heteroaryl;

Each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$,

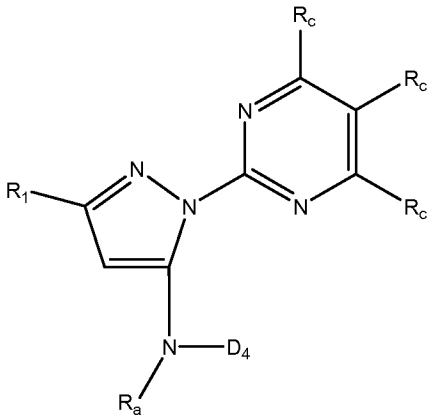
$NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In yet an additional aspect, the invention is a compound having Formula (IId):



(IId);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein;

D_4 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted

heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

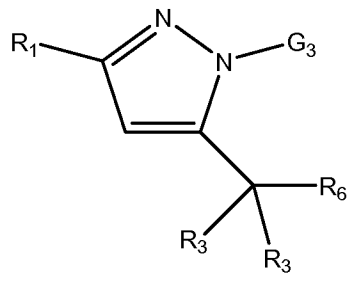
Each R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

Each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In a further aspect, the invention is a compound having the Formula (IIIa):



(IIIa);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, the two R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl;

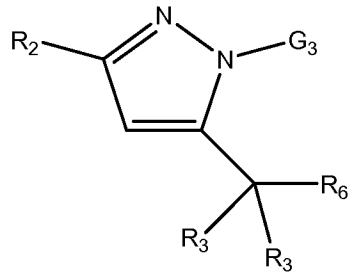
R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)NR_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;or two R_b groups are taken together with the atom which they are

attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In yet another embodiment, the invention is a compound having the Formula (IIIb):



(IIIb);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_2 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, and optionally substituted C_3-C_{12} cycloalkenyl;

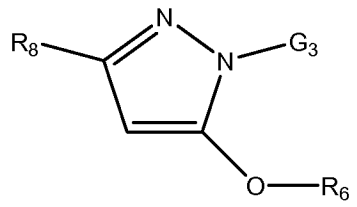
Each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; alternatively, the two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl, or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In an additional aspect, the invention is a compound having the Formula (IV):



(IV);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, an aryl, or a heteroaryl, each optionally substituted;

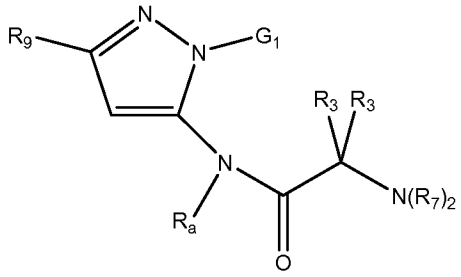
R_8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl, wherein the two R_b groups can be taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

n is 0, 1 or 2.

In another embodiment, the invention is a compound having the Formula (V):



(V);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_1 is an optionally pyridyl or an optionally substituted pyrimidyl;

R_9 is selected from the group consisting of substituted methyl, optionally substituted C_2-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; alternatively, the two R_3 groups can be taken together with

the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl;

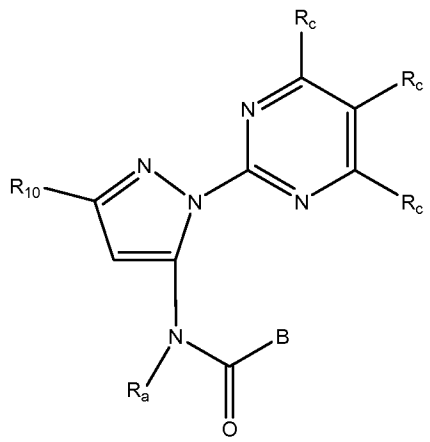
Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

Each R_7 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; alternatively, the two R_7 are taken together with the nitrogen atom to which they are attached to form a 3- to 7- membered heterocyclic or heteroaryl;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In an additional embodiment, the invention is a compound having the Formula (VI):



(VI);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

B is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl;

R_{10} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

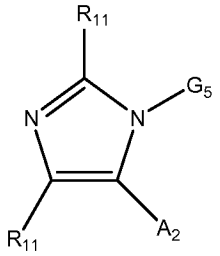
Each R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

Each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

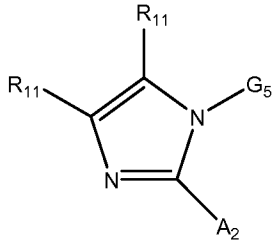
Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl, or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

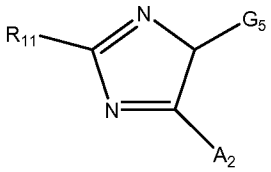
In a further embodiment, the invention is a compound having the Formula (VIIa), (VIIb) or (VIIc):



(VIIa)



(VIIb)



(VIIc);

or a pharmaceutically acceptable salt, prodrug or solvate thereof wherein:

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

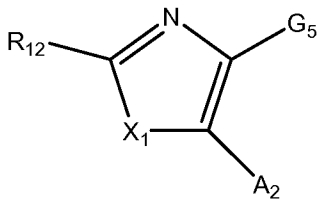
R_{11} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

In yet another embodiment, the invention is a compound having the Formula (VIII):



(VIII);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

X_1 is selected from the group consisting of O and S;

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

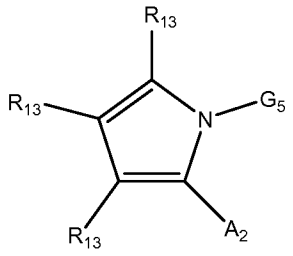
R_{12} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

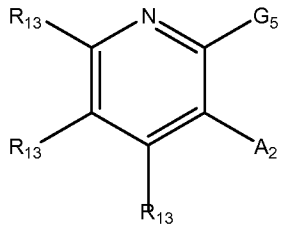
Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2;

In yet a further aspect, the invention is a compound having the Formula (IXa) or (IXb):



(IXa)



(IXb)

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

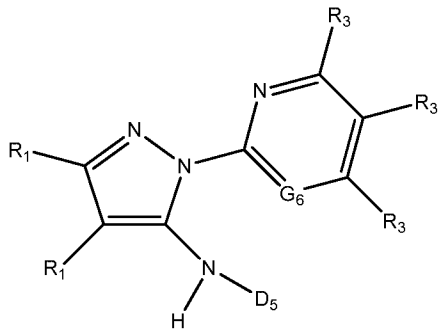
Each R_{13} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$, or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

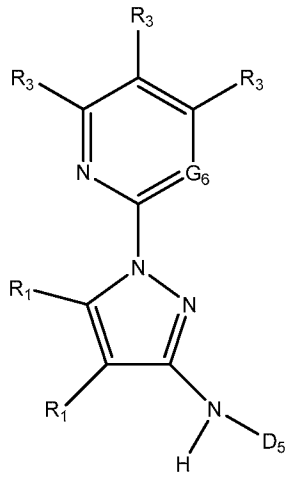
Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

The invention is additionally directed to a compound having the Formula (Xa) or (Xb):



(Xa)



(Xb)

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_6 is nitrogen or C-H;

D_5 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)NR_bR_b$, and $S(O)_nR_b$;

Each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Both R_1 can join with the carbon atoms to which they are attached to form an optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

Each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

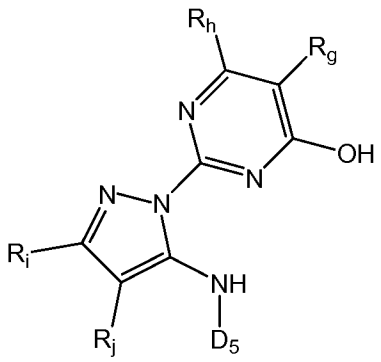
C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

Any two R_3 can join to form an optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

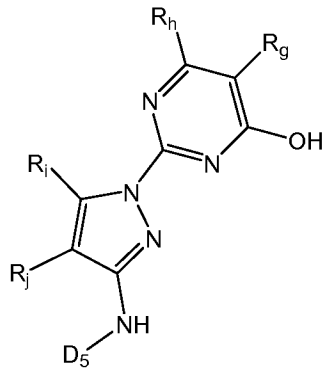
Each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

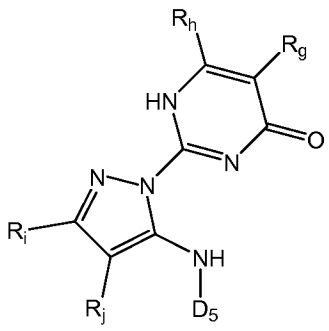
Preferred compounds of Formula (Xa) and (Xb) are represented by Formulas (XIa) and (XIb), respectively, which include all tautomeric forms, including those represented by Formulas (XIIa) and (XIIb), respectively.



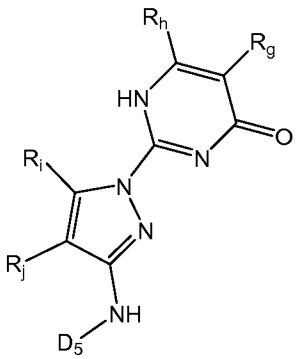
(XIa)



(XIb)



(XIIa)



(XIIb)

where in each of Formulas (XIa), (XIb), (XIIa) and (XIIb), R_g and R_h independently have the meanings given for R_3 in Formulas (Xa) and (Xb); R_i and R_j independently have the meanings given for R_1 in Formulas (Xa) and (Xb) and D_5 has the meaning given for this variable in Formulas (Xa) and (Xb). Preferably, R_g and R_h are each independently hydrogen or C_1-C_6-alkyl, or R_g and R_h are taken with the carbon atoms to which they are attached to form an optionally substituted benzo ring. Preferably, R_g and R_h are each independently hydrogen or methyl. In particularly preferred ambodiments, R_g and R_h are both hydrogen, R_g and R_h are both methyl, or R_h is methyl and R_g is hydrogen. Preferably, R_i and R_j are each independently selected from hydrogen and C_1-C_6-alkyl. In certain embosiments, R_j is hydrogen and R_i is C_1-C_6-alkyl, such as methyl. D_5 is preferably C_1-C_6-alkyl, C_5-C_8-cycloalkyl, aryl-C_1-C_6-alkyl, such as benzyl, or optionally substituted phenyl, such as phenyl substituted with up to three substituents independently selected from halogen, C_1-C_6-alkyl and C_1-C_6-alkoxy, such as methoxy. In preferred ambodiments, phenyl is unsubstituted or non-substituted, for example with chloro, CN, C_1-C_4-alkyl or methoxy.

In one aspect, the pharmaceutical composition comprises a compound of Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

The invention also includes a method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering an effective amount of a compound of Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

The invention further includes a method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering to said patient an effective amount of a compound of Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

In yet a further aspect, the invention is a method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering to said patient an effective amount of a compound having the Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, prodrug or solvate thereof.

In an additional aspect, the invention is directed to a pharmaceutical composition comprising:

a pharmaceutically acceptable carrier or excipient;

an effective amount of a compound having the Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, solvate, clathrate or prodrug of any of thereof; and

an effective amount of a second agent selected from the group consisting of a proteostasis regulator and a pharmacologic chaperone.

As discussed above, the present invention is directed to compounds of Formulae (Ia-Ib), (IIa-IId), (III), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb), and pharmaceutically acceptable salts, prodrugs or solvates thereof, pharmaceutical compositions thereof and methods of use thereof in the treatment of conditions associated with a dysfunction in proteostasis.

In some embodiments, the invention is directed to a compound of Formula (Ia), pharmaceutical compositions thereof or methods of use thereof.

In certain additional aspects, the invention is a compound of Formula (Ib), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In some embodiments, the compound has the Formula (Ib), wherein G_1 is an optionally substituted pyrimidyl.

In yet an additional embodiment, the invention is directed to a compound of Formula (IIa), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In one embodiment, the compound has the Formula (IIa), wherein G_3 is a 3- to 8-membered heterocyclic or a heteroaryl, each optionally substituted.

In some embodiments, the compound has the Formula (IIa), wherein D_1 is phenyl substituted in its para position with a substituent selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bNR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$, and wherein the phenyl ring can optionally be further substituted. In further aspects, the compound has the Formula (IIa), wherein D_1 is phenyl substituted with a group selected from optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, and optionally substituted C_2-C_{10} alkynyl. In yet additional embodiments, D_1 is

phenyl substituted at its para position with a group selected from optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, and optionally substituted C_2-C_{10} alkynyl.

In certain embodiments, the compound has the Formula (IIa), wherein R_1 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bNR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$. In certain additional embodiments, R_1 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl.

In yet additional aspects, the compound has the Formula (IIa), wherein R_a is selected from the group consisting hydrogen, and optionally substituted C_1-C_{10} alkyl.

In a further embodiment, the compound has the Formula (IIa), wherein G_3 is selected from the group consisting of, azetidinyl, azolidinyl, oxolanyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, piperidinyl, pyridyl, pyrimidyl, diazinyl, triazinyl, and tetrahydropyranyl, each optionally substituted. In yet an additional embodiment, the compound has the Formula (IIa), wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

The invention additionally encompasses compounds having the Formula (IIb), pharmaceutically acceptable salts, prodrugs or solvates thereof. In some embodiments, the compound has the Formula (IIb), wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$. In a further aspect, R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

In an additional aspect, the compound has the Formula (IIb), wherein D_2 is selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted benzyl, and optionally substituted heteroaryl. In yet additional aspects, the compound has the Formula (IIb), wherein D_2 is $C(R_5)_3$ and each R_5 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl.

In certain additional embodiments, the compound has the Formula (IIb), wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl, such as optionally substituted pyridyl and optionally substituted pyrimidyl. In one embodiment, the compound has the Formula (IIb), wherein G_3 is optionally substituted pyrimidyl.

The invention also encompasses compounds having the Formula (IIc), and pharmaceutically acceptable salts, prodrugs and solvates thereof. In one embodiment, the compound has the Formula (IIc), wherein each R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In some embodiments, each R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

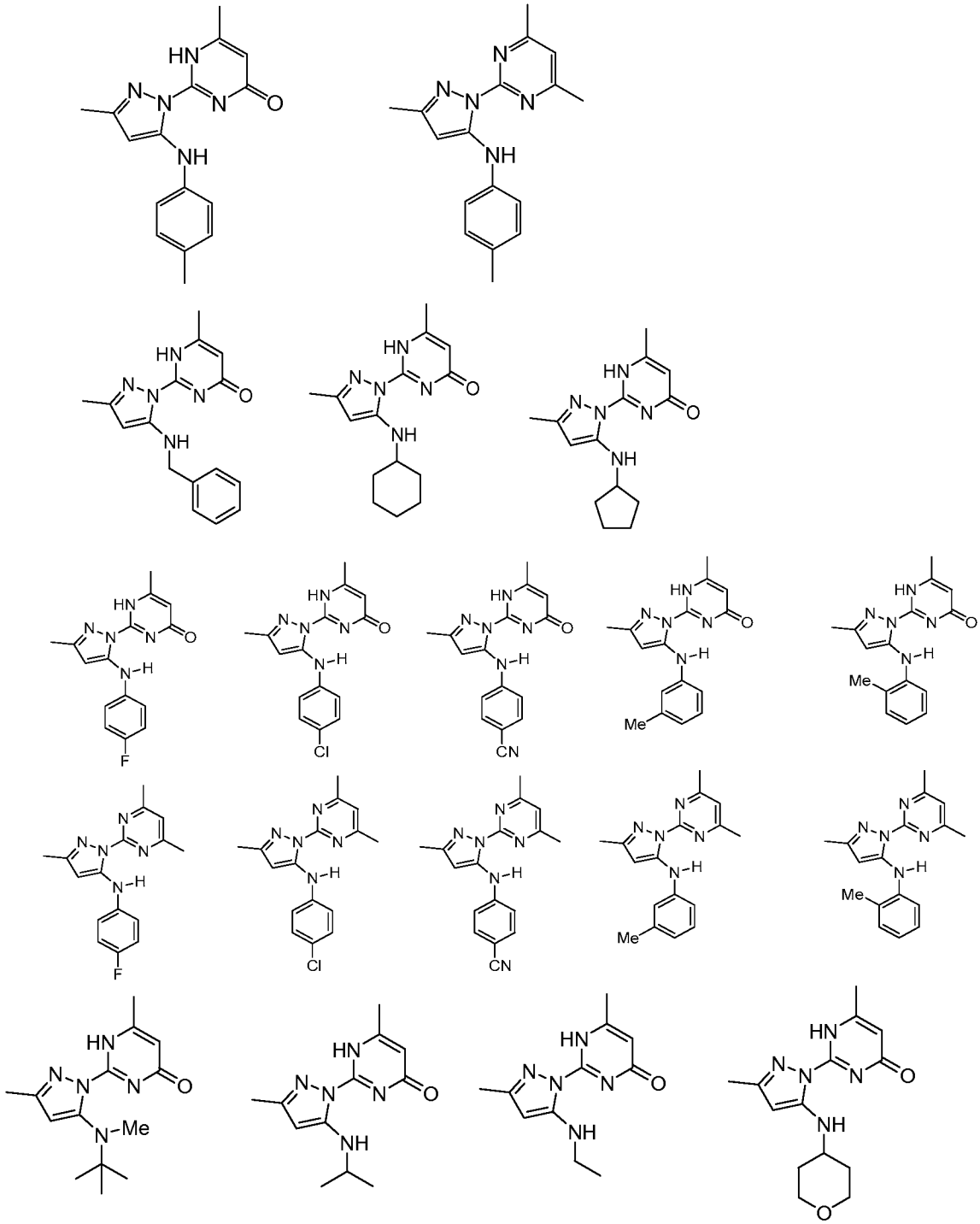
In a further embodiment, the compound has the Formula (IIc), wherein G_4 is selected from the group consisting of optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted diazinyl, and optionally substituted traizinyl. In an additional embodiment, G_4 is optionally substituted pyrimidyl.

In another aspect, the compound has the Formula (IIc), wherein D_3 is optionally substituted phenyl. In some embodiments, D_3 is phenyl substituted with one or more optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

In an additional embodiment, the compound of the invention has the Formula (IId), or is a pharmaceutically acceptable salt, prodrug or solvate thereof. In some embodiments, the compound has the Formula (IId), wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In some embodiments, R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

In an additional aspect, the invention is a compound having the Formula (IId), wherein each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl and OR_b. In an additional aspect, R_c is OH or O-C_1-C_4 alkyl, wherein the C_1-C_4 alkyl is optionally substituted.

Non-limiting examples of compounds encompassed by Formulae (IIa-IId) are shown below:



In some embodiments, the invention is directed to a compound having the Formula (IIIa). In some embodiments, the compound has the Formula (IIIa), wherein R_6 is phenyl substituted in its para position with a substituent selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl,

optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$, and wherein the phenyl ring can optionally be further substituted.

In certain embodiments, the compound has the Formula (IIIa), wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In additional aspects, the invention has the Formula (IIIa), wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

In another embodiment, the compound has the Formula (IIIa), wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl. In another embodiment, G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl. In a further aspect, the compound has the Formula (IIIa), wherein G_3 is optionally substituted pyrimidyl.

In yet another embodiment, the compound of the invention has the Formula (IIIb). In one aspect, the compound has the Formula (IIIb), wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl. In an additional embodiment, G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl. In certain embodiments, the compound has the Formula (IIIb) wherein G_3 is optionally substituted pyrimidyl.

In a further aspect, the invention is directed to a compound of Formula (IV), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In some embodiments, the compound has the Formula (IV), wherein R_6 is phenyl substituted in its para position with a substituent selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally

substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$, and wherein the phenyl ring can optionally be further substituted.

In some embodiments, the compound has the Formula (IV), wherein R_8 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl.

In certain embodiments, the compound has the Formula (IV), wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl. For example, G_3 can be optionally substituted pyridyl or optionally substituted pyrimidyl.

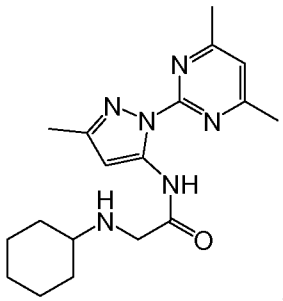
In an additional embodiment, the invention is directed to a compound of Formula (V), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In one embodiment, the compound has the Formula (V), wherein R_9 is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In yet another aspect, R_9 is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

The invention also encompasses a compound having the Formula (V), or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein at least one R_3 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$,

$NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

In additional embodiments, the invention is directed to a compound havin the Formula (V), wherein G_1 is optionally substituted pyrimidyl.

A non-limiting example of a compound having the Formula (V) is:



.

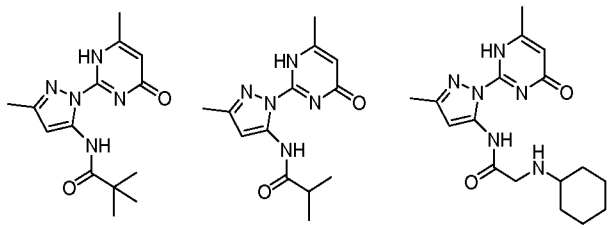
In additional embodiments, the invention is directed to a compound having the Formula (VI). In some embodiments, the compounds has the Formula (VI), R_{10} is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_4-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cyloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally sustituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $CO)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In yet an additional aspect, R_{10} is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_4-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bNR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

In additional aspects, the compound has the Formula (VI), wherein B is $C(R_3)_2N(R_f)_2$: wherein each R_3 is as previously defined and each R_f is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$,

$NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

In another aspect, the compound has the Formula (VI), wherein each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl and OR_b. In yet another embodiment, the compound has the Formula (VI), wherein R_c is selected from the group consisting of hydroxyl and optionally substituted O-C_1-C_4 alkyl.

Non-limiting examples of compounds having the Formula (VI) are selected from the group consisting of:



.

In an additional embodiment, the invention is a compound having the Formula (VIIa), (VIIb), or (VIIc), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In some embodiments, the invention is a compound having the Formula (VIIa), (VIIb) or (VIIc), wherein R_{11} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In one embodiment, R_{11} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

In certain aspects, the compound has the Formula (VIIa), (VIIb) or (VIIc), wherein A_2 is NR_aR_g, wherein R_g is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, and

$C(O)C(O)R_b$. In certain embodiments, R_g is optionally substituted aryl or optionally substituted heteroaryl.

The invention also encompasses compounds having the Formula (VIII), and pharmaceutically acceptable salts, prodrugs and solvates thereof. In some embodiments, the compound has the Formula (VIII), wherein R_{12} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In some embodiments, R_{12} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

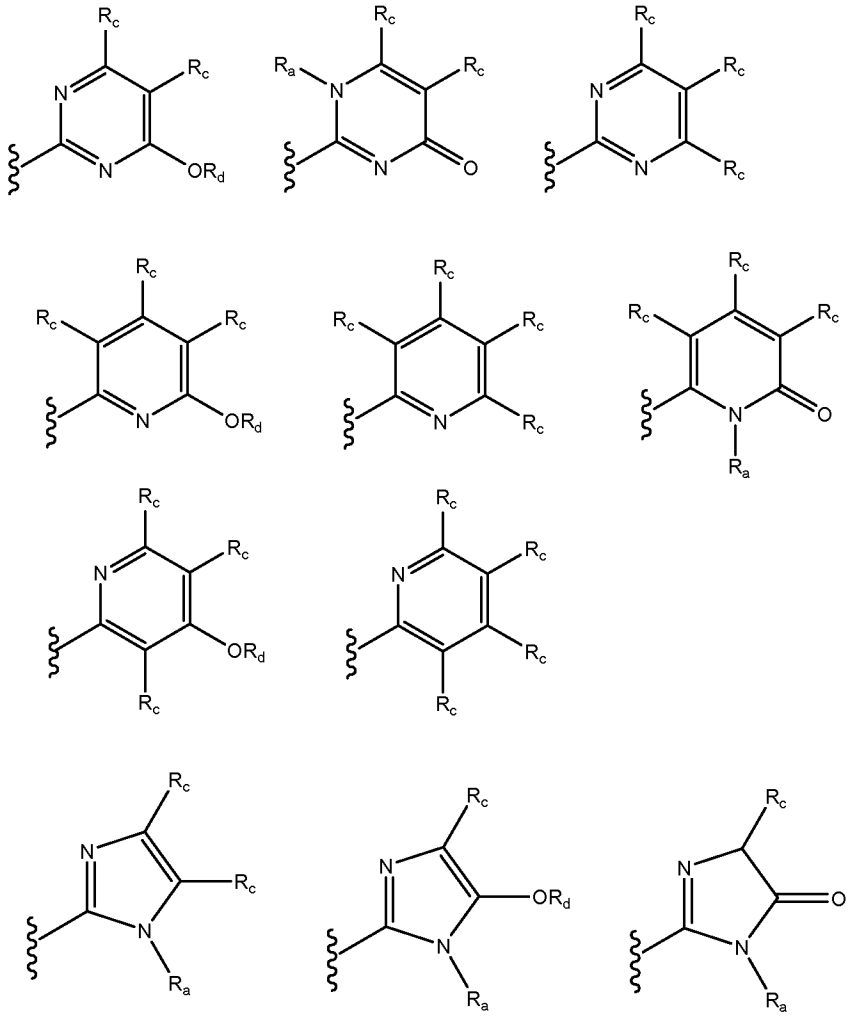
In an additional embodiment, the compound has the Formula (VIII), wherein X_1 is O. In a further aspect, the compound has the Formula (VIII), wherein X_1 is S.

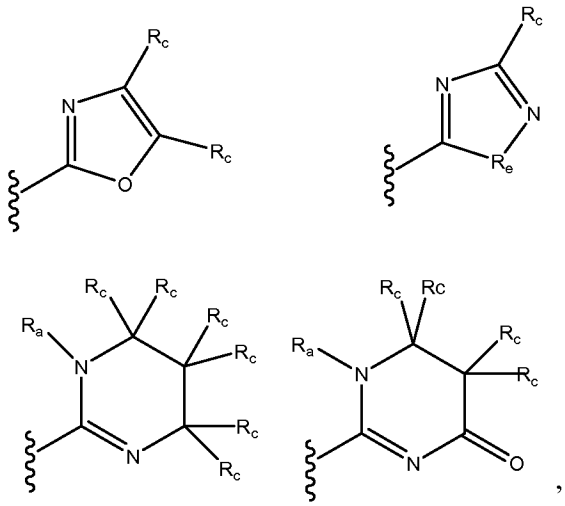
The invention is also directed to compounds having the Formula (IXa) or (IXb), or a pharmaceutically acceptable salt, prodrug or solvate thereof. In one embodiment, the compound has the Formula (IXa) or (IXb), wherein at least one R_{13} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$. In some embodiments, at least one R_{13} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

In a further aspect, the compound has the Formula (IXa) or (IXb), wherein A_2 is NR_aR_g, wherein R_g is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10}

alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, and $C(O)C(O)R_b$.

In certain additional aspects, the invention is directed to a compound of Formula (IIa), (IIb), (IIIa), (IIIb) or (IV), wherein G_3 is selected from the group consisting of:





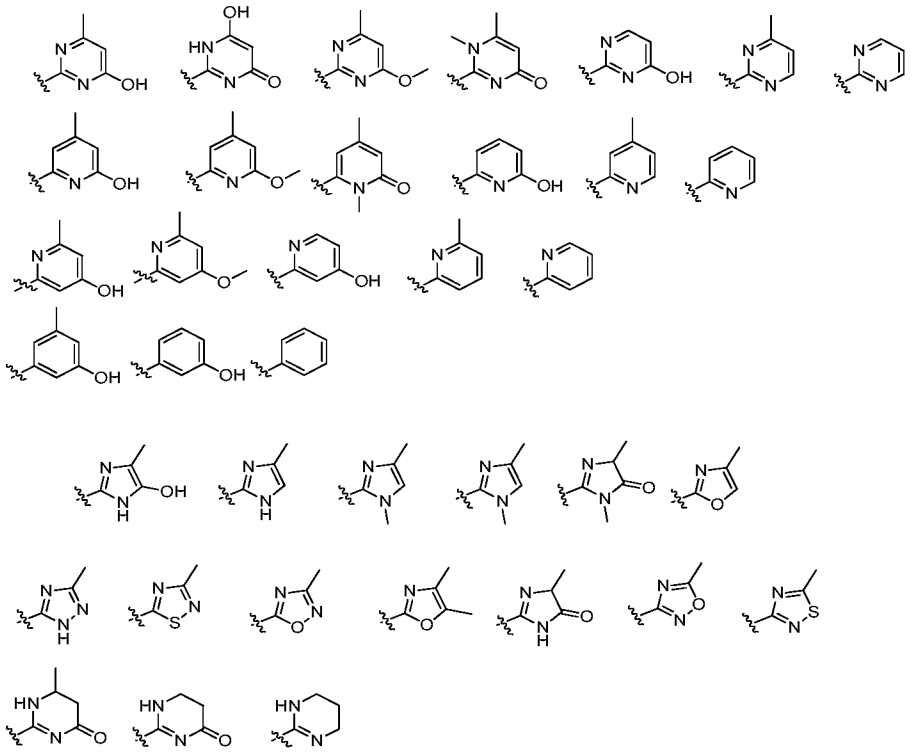
wherein:

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

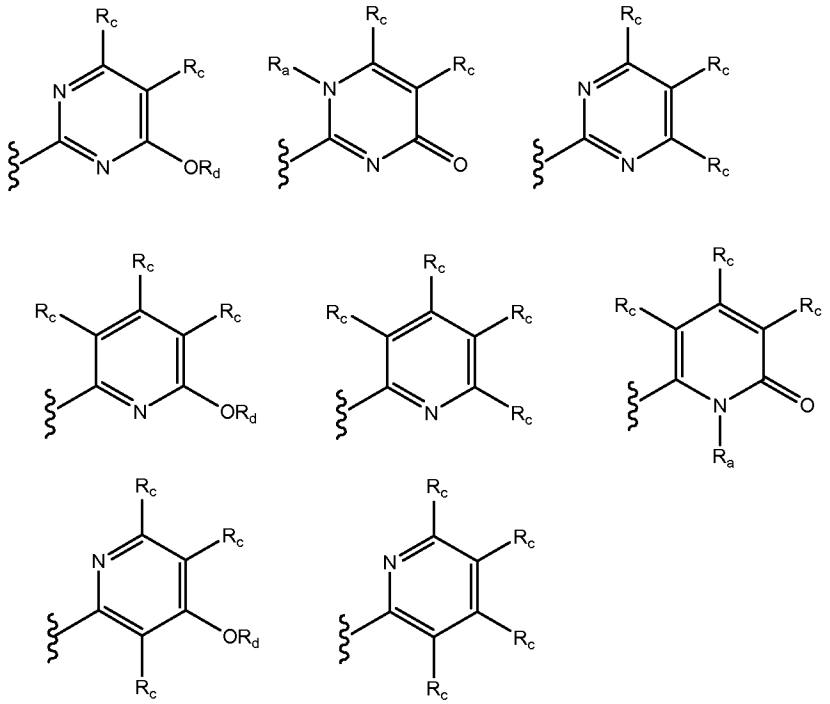
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; and

R_e is $N(R_a)$, O, or S.

In yet an additional aspect, the compound has the Formula (IIa), (IIb), (III), or (IV) wherein G_3 is selected from the group consisting of:



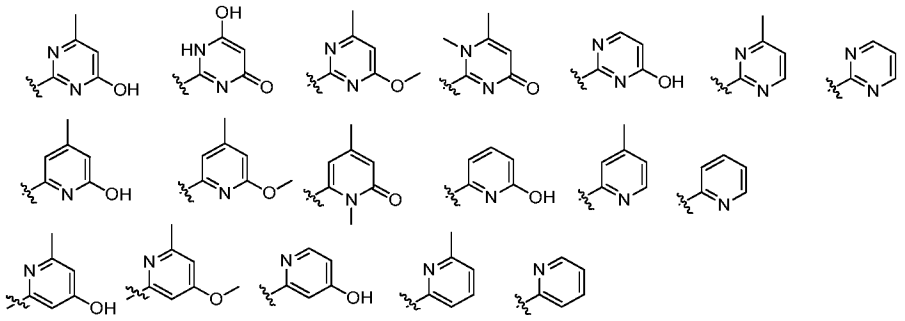
In some embodiments, the invention is directed to a compound of Formula (V), wherein G_1 is selected from the group consisting of:



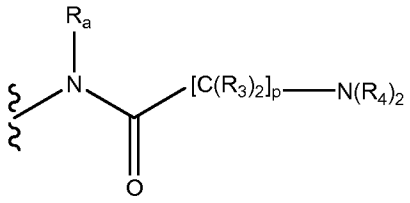
wherein:

each R_a, R_c and R_d are as defined above.

In another embodiment, the invention is a compound having the Formula (V), wherein G_1 is selected from the group consisting of:



In one embodiment, the invention is a compound of Formula (Ia), (Ib), (VIIa-VIIc), (VIII), or (IXa-Ixb), wherein each of A_1 or A_2 is independently:



;

wherein p is 0, 1, 2 or 3;

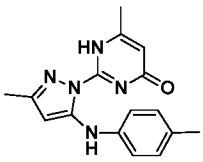
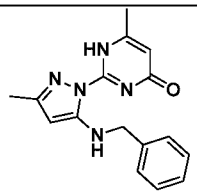
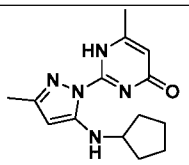
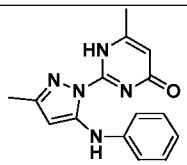
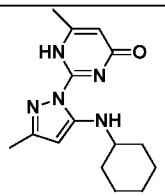
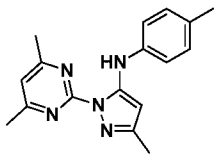
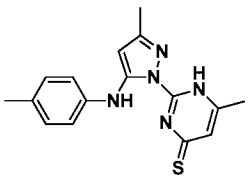
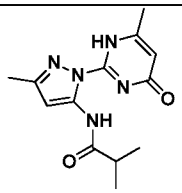
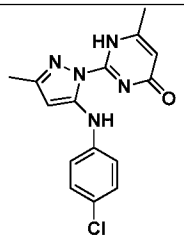
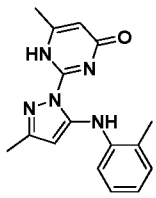
Each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C3-C8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; or yet alternatively, two vicinal R_3 groups can be taken together with the atoms to which they are attached to form a C_3-C_8 cycloalkyl, C3-C8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

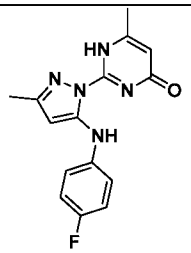
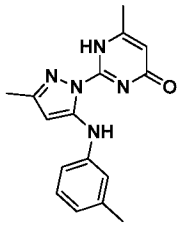
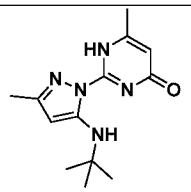
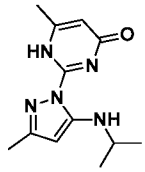
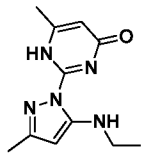
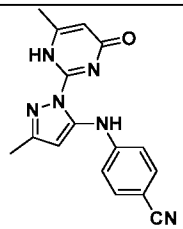
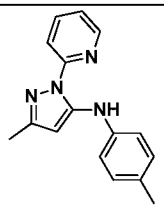
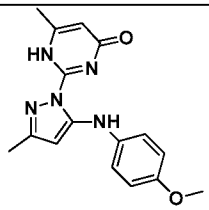
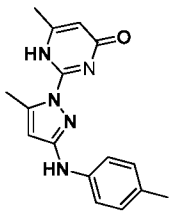
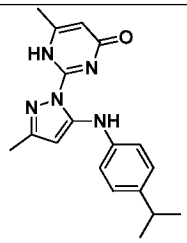
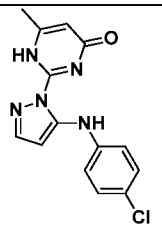
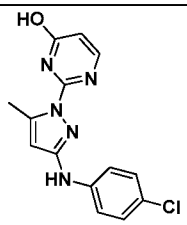
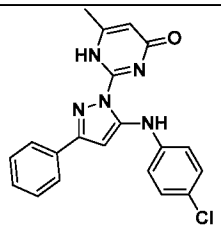
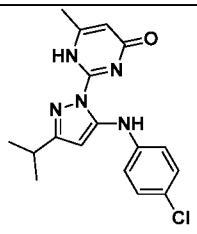
Each R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl,

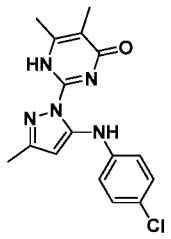
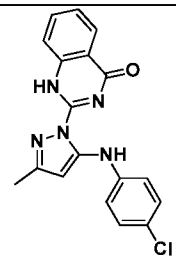
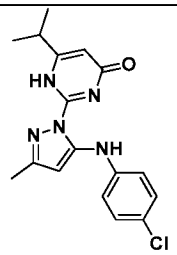
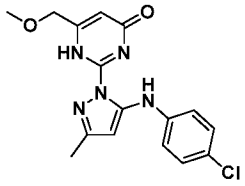
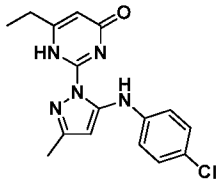
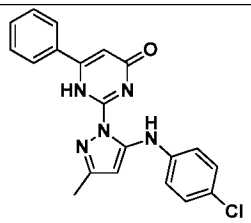
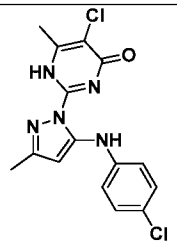
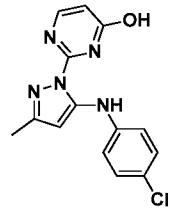
optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or alternatively, the two R_4 groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl.

In additional embodiment, the compound is selected from those shown below in Table 1:

TABLE 1

Compound Number	Compound	Compound Number	Compound
1		2	
3		4	
5		6	
7		8	
9		10	

11		12	
13		14	
15		16	
17		18	
19		20	
21		22	
23		24	

25		26	
27		28	
29		30	
31		32	

As discussed above, the invention additionally encompasses pharmaceutical compositions. For example, pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound of Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xa), (XIa-XIb) or (XIIa-XIIb) are encompassed by the invention.

In an additional embodiment, the pharmaceutical composition comprises an effective amount of a compound shown above in Table 1.

It is to be understood that the specific embodiments described herein can be taken in combination with other specific embodiments delineated herein. For example, for compounds of Formula (IIa), R_1 was defined as optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl and optionally substituted C_2-C_{10} alkynyl and G_3 was defined as optionally substituted pyrimidyl in an additional embodiment above. The invention thus, for example, encompasses compounds of Formula (IIa), wherein R_1 is

optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl and optionally substituted C_2-C_{10} alkynyl and G_3 is optionally substituted pyrimidyl.

The term "alkyl", as used herein, unless otherwise indicated, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; for example, "C_1-C_{10} alkyl" denotes alkyl having 1 to 10 carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, n-hexyl, 2-methylbutyl, 2-methylpentyl, 2-ethylbutyl, 3-methylpentyl, and 4-methylpentyl.

The term, "alkenyl", as used herein, refers to both straight and branched-chain moieties having the specified number of carbon atoms and having at least one carbon-carbon double bond.

The term, "alkynyl", as used herein, refers to both straight and branched-chain moieties having the specified number or carbon atoms and having at least one carbon-carbon triple bond.

The term "cycloalkyl," as used herein, refers to cyclic alkyl moieties having 3 or more carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl.

The term "cycloalkenyl," as used herein, refers to cyclic alkenyl moieties having 3 or more carbon atoms.

The term "cycloalkynyl," as used herein, refers to cyclic alkynyl moieties having 5 or more carbon atoms.

The term "heterocyclic" encompasses heterocycloalkyl, heterocycloalkenyl, heterobicycloalkyl, heterobicycloalkenyl, heteropolycycloalkyl, heteropolycycloalkenyl and the like. Heterocycloalkyl refers to cycloalkyl groups containing one or more heteroatoms (O, S, or N) within the ring. Heterocycloalkenyl as used herein refers to cycloalkenyl groups containing one or more heteroatoms (O, S or N) within the ring. Heterobicycloalkyl refers to bicycloalkyl groups containing one or more heteroatoms (O, S or N) within a ring. Heterobicycloalkenyl as used herein refers to bicycloalkenyl groups containing one or more heteroatoms (O, S or N) within a ring.

Cycloalkyl, cycloalkenyl, heterocyclic, groups also include groups similar to those described above for each of these respective categories, but which are substituted with one or more oxo moieties.

The term "aryl", as used herein, refers to mono- or polycyclic aromatic carbocyclic ring systems. A polycyclic aryl is a polycyclic ring system that comprises at least one

aromatic ring. Polycyclic aryls can comprise fused rings, covalently attached rings or a combination thereof. The term "aryl" embraces aromatic radicals, such as, phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl. An aryl group may be substituted or unsubstituted. In some embodiments, the aryl is a C_4-C_{10} aryl.

The term "heteroaryl", as used herein, refers to aromatic carbocyclic groups containing one or more heteroatoms (O, S, or N) within a ring. A heteroaryl group can be monocyclic or polycyclic. A heteroaryl group may additionally be substituted or unsubstituted. The heteroaryl groups of this invention can also include ring systems substituted with one or more oxo moieties. A polycyclic heteroaryl can comprise fused rings, covalently attached rings or a combination thereof. Examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl, phthalazinyl, triazinyl, isoindolyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinolyl, tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, thiazolopyridinyl, oxazolopyridinyl and azaindolyl. The foregoing heteroaryl groups may be C-attached or heteroatom-attached (where such is possible). For instance, a group derived from pyrrole may be pyrrol-1-yl (N-attached) or pyrrol-3-yl (C-attached). In some embodiments, the heteroaryl is 4- to 10-membered heteroaryl.

The term “substituted” refers to substitution by independent replacement of one, two, or three or more of the hydrogen atoms with substituents including, but not limited to, -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -C_3-C_{12} cycloalkenyl, C_3-C_{12} cycloalkynyl, -heterocyclic, -F, -Cl, -Br, -I, -OH, -NO_2, -N_3, -CN, -NH_2, oxo, thioxo, -NHR_x, -NR_xR_x, dialkylamino, -diarylamino, -diheteroarylamino, -OR_x, -$C(O)R_y$, -$C(O)C(O)R_y$, -OCO_2R_y, -$OC(O)R_y$, $OC(O)C(O)R_y$, -$NHC(O)R_y$, -$NHCO_2R_y$, -$NHC(O)C(O)R_y$, $NHC(S)NH_2$, -$NHC(S)NHR_x$, -$NHC(NH)NH_2$, -$NHC(NH)NHR_x$, -$NHC(NH)R_x$, -$C(NH)NHR_x$, and $(C=NR_x)R_x$; -NRx$C(O)R_x$, -$NR_xC(O)N(R_x)_2$, -NRxCO_2R_y, -NRx$C(O)C(O)R_y$, -$NR_xC(S)NH_2$, -$NR_xC(S)NHR_x$, -$NR_xC(NH)NH_2$, -$NR_xC(NH)NHR_x$, -NRx$C(NH)R_x$, -$C(NRx)NHR_x$ -$S(O)R_y$, -$NHSO_2R_x$, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, -polyalkoxyalkyl, -polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-R_x, or -methylthiomethyl, wherein R_x is selected from the group consisting of -C_1-C_{12}

alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -aryl, -heteroaryl and -heterocyclic and -R_y is selected from the group consisting of -C_1-C_{12} alkyl, -C_2-C_{12} alkenyl, -C_2-C_{12} alkynyl, -C_3-C_{12} cycloalkyl, -aryl, -heteroaryl, -heterocyclic, -NH_2, -NH-C_1-C_{12} alkyl, -NH-C_2-C_{12} alkenyl, -NH-C_2-C_{12}-alkynyl, -NH-C_3-C_{12} cycloalkyl, -NH-aryl, -NH-heteroaryl and -NH-heterocyclic. It is understood that the aryls, heteroaryls, alkyls, and the like can be further substituted.

The term "haloalkyl" as used herein refers to an alkyl group having 1 to (2n+1) subsistent(s) independently selected from F, Cl, Br or I, where n is the maximum number of carbon atoms in the alkyl group.

As will be understood by the skilled artisan, “H” is the symbol for hydrogen, “N” is the symbol for nitrogen, “S” is the symbol for sulfur, “O” is the symbol for oxygen.

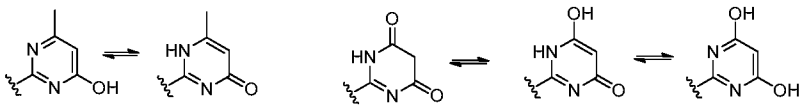
“Me” is an abbreviation for methyl.

Non-limiting examples of optionally substituted aryl are phenyl, substituted phenyl, napthyl and substituted naphthyl.

Certain of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (R)- and (S)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R--S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

Where a particular stereochemistry is described or depicted it is intended to mean that a particular enantiomer is present in excess relative to the other enantiomer. A compound has an R-configuration at a specific position when it is present in excess compared to the compound having an S-configuration at that position. A compound has an S-configuration at a specific position when it is present in excess compared to the compound having an R-configuration at that position.

Likewise, all tautomeric forms are also intended to be included.Where a particular compound is described or depicted it is intended to encompass that chemical structure as well as tautomers of that structure. For example the structures below are exemplary, but in no way limiting, of potential tautomers.



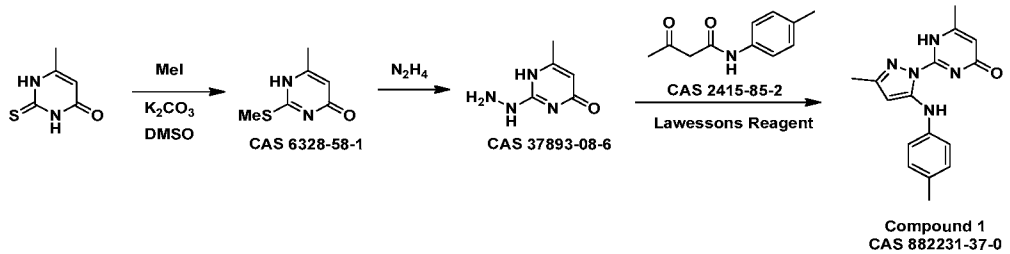
It is to be understood that atoms making up the compounds of the present invention are intended to include isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. Isotopes of hydrogen include, for example, tritium and deuterium, and isotopes of carbon include, for example, ^{13}C and ^{14}C. The invention therefore encompasses embodiments in which one or more of the hydrogen atoms in Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb) are replaced with deuterium. The invention also encompasses embodiments wherein one or more of the carbon atoms in Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb) is replaced with silicon atoms.

The invention additionally encompasses embodiment wherein one or more of the nitrogen atoms in Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb) are oxidized to N-oxide.

Exemplary synthetic routes for the preparation of compounds of the invention are shown below as Schemes 1-4 below. Methods for the synthesis that can be used to synthesize compounds of the invention have also been discussed in the literature, for example, in some of the references listed below. As will be understood by the skilled artisan, diastereomers can be separated from the reaction mixture using column chromatography.

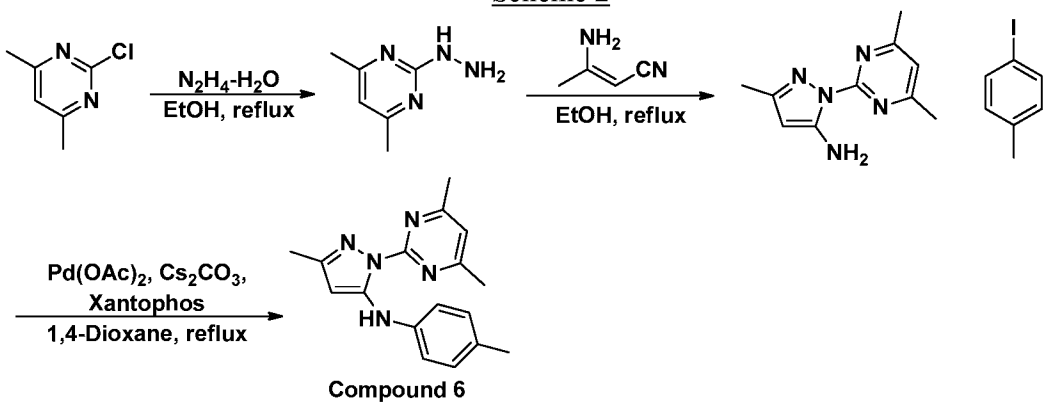
The synthesis of Compound 1 was carried out by converting 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one to Compound 1. Commercially 6-methyl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one is treated with methyl iodide and potassium carbonate, in dimethyl sulfoxide, to afford 6-methyl-2-(methylthio)prymidin-4(1*H*)-one (CAS: 6328-58-1).[19] The resulting 6-methyl-2-(methylthio)prymidin-4(1*H*)-one was treated with hydrazine and potassium carbonate in 2-propanol, at reflux, to afford 2-hydrazinyl-6-methylpryimidin-4(1*H*)-one (CAS: 37893-08-6).[20] Treating a mixture of 2-hydrazinyl-6-methylpryimidin-4(1*H*)-one and 3-oxo-*N*-(*p*-tolyl)butanamide (CAS: 2415-85-2) in 1,4-dioxane with Lawesson's reagent and a sub-stoichiometric amount of pyridine affords the desired pyrazole (Compound **1**).[21] The starting β-ketoamides can be purchased or synthesized as described in the literature.[22] Compound 1 can be isolated as a free base or as a hydrochloride salt.

Scheme 1



Scheme 2 depicts another potential method for the synthesis of compounds described in the invention from a substituted 2-chloropyrimidine. The preparation of Compound 6 from 2-chloro-4,6-dimethylpyrimidine is shown as an example. A solution of 2-chloro-4,6-dimethylpyrimidine in ethanol was treated with hydrazine hydrate and then heated at reflux to afford 2-hydrazinyl-4,6-dimethylpyrimidine. The 2-hydrazinyl-4,6-dimethylpyrimidine and (*Z*)-3-aminobut-2-enenitrile, in ethanol, were heated to reflux. The resulting 1-(4,6-dimethylpyrimidin-2-yl)-3-methyl-1*H*-pyrazol-5-amine, in 1,4-dioxane, was heated to reflux in the presence of palladium(II) diacetate, cesium carbonate, 1-iodo-4-methylbenzene, and Xantophos to afford compound 6. Reagents and aryl halides can be purchased or prepared as described in the literature.

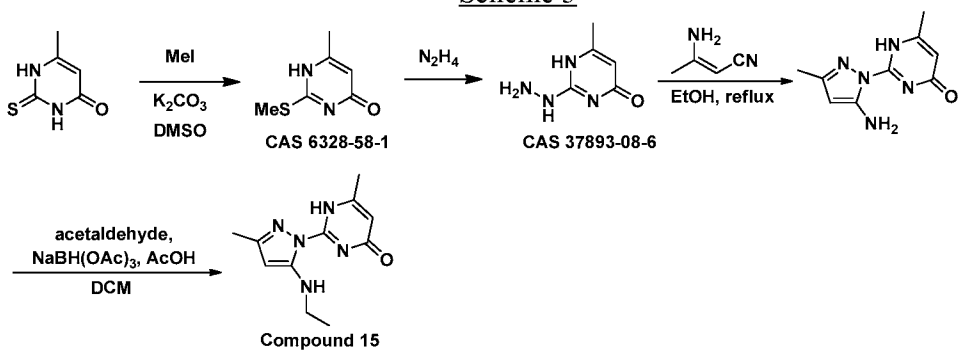
Scheme 2



Compound 6

Scheme 3 illustrates an alternative route to the synthesis of 5-alkylamino pyrrazoles. The pyrrazole core is prepared as presented in Scheme 1 and 2. Then reductive amination with the complete pyrrazole core and an appropriate aldehyde, with suitable reducing agent, can afford compounds such as Compound **15**.

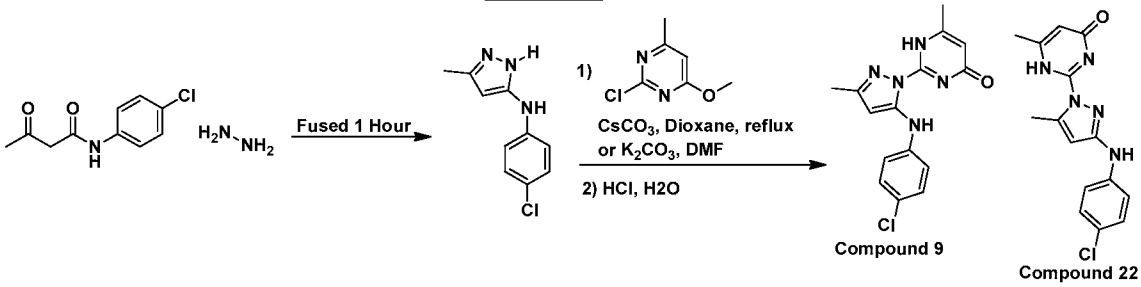
Scheme 3



Compound 15

Scheme 4 is another alternative route to pyrazole heterocycles. The appropriate β-ketoamide is treated with hydrazine.[26] The resulting pyrazole is alkylated with the appropriate aromatic chloride to afford the desired product.[27]

Scheme 4



Compound 9

Compound 22

The invention encompasses pharmaceutically acceptable salts of the compounds described herein. Thus, in certain aspects, the invention is directed to pharmaceutically acceptable salts of compounds of Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI),

(VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb). As used herein, a "pharmaceutically acceptable salt" includes an ionic bond-containing product of the reaction between the disclosed compound with either an acid or a base, suitable for administering to a subject. Pharmaceutically acceptable salts are well known in the art and are described, for example, in Berge et al. (1977), Pharmaceutical Salts, Journal of Pharmaceutical Sciences, 69(1): 1-19, the contents of which are herein incorporated by reference. A non-limiting example of a pharmaceutically acceptable salt is an acid salt of a compound containing an amine or other basic group which can be obtained by reacting the compound with a suitable organic or inorganic acid. Examples of pharmaceutically acceptable salts also can be metallic salts including, but not limited to, sodium, magnesium, calcium, lithium and aluminum salts. Further examples of pharmaceutically acceptable salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures), succinates, benzoates and salts with amino acids such as glutamic acid. Salts can also be formed with suitable organic bases when the compound comprises an acid functional group such as -COOH or -SO_3H. Such bases suitable for the formation of a pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases that are nontoxic and strong enough to react with the acid functional group. Such organic bases are well known in the art and include amino acids such as arginine and lysine, mono-, di-, and triethanolamine, choline, mono-, di-, and trialkylamine, such as methylamine, dimethylamine, and trimethylamine, guanidine, *N*-benzylphenethylamine, *N*-methylglucosamine, *N*-methylpiperazine, morpholine, ethylendiamine, tris(hydroxymethyl)aminomethane and the like.

The invention also includes hydrates of the compounds described herein, including for example solvates of the compounds described herein. In some embodiments, the invention is to solvates of compounds of Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb).

Also included in the present invention are prodrugs of the compounds described herein, for example, prodrugs of compounds of Formulae ((Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb).

The invention additionally includes clathrates of the compounds described herein. In some embodiments, the invention is directed to clathrates of compounds of Formulae

(Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb).

As discussed above, the invention includes pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and a compound described herein. The compound of any one of Formula (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) or (XIIa-XIIb), or a pharmaceutically acceptable salt, solvate, clathrate or prodrug of any of thereof, can be administered in pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient. The excipient can be chosen based on the expected route of administration of the composition in therapeutic applications. The route of administration of the composition depends on the condition to be treated. For example, intravenous injection may be preferred for treatment of a systemic disorder and oral administration may be preferred to treat a gastrointestinal disorder. The route of administration and the dosage of the composition to be administered can be determined by the skilled artisan without undue experimentation in conjunction with standard dose-response studies. Relevant circumstances to be considered in making those determinations include the condition or conditions to be treated, the choice of composition to be administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

Pharmaceutical compositions comprising compounds of Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb), and pharmaceutically acceptable salts, solvates, clathrates or prodrugs of any of thereof, can be administered by a variety of routes including, but not limited to, parenteral, oral, pulmonary, ophthalmic, nasal, rectal, vaginal, aural, topical, buccal, transdermal, intravenous, intramuscular, subcutaneous, intradermal, intraocular, intracerebral, intralymphatic, intraarticular, intrathecal and intraperitoneal.

The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the pharmacologic agent or composition. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like. Pharmaceutical compositions can also include large, slowly metabolized

macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized SEPHAROSE™, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes).

The compositions can be administered parenterally such as, for example, by intravenous, intramuscular, intrathecal or subcutaneous injection. Parenteral administration can be accomplished by incorporating a composition into a solution or suspension. Such solutions or suspensions may also include sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents. Parenteral formulations may also include antibacterial agents such as, for example, benzyl alcohol or methyl parabens, antioxidants such as, for example, ascorbic acid or sodium bisulfite and chelating agents such as EDTA. Buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose may also be added. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Additionally, auxiliary substances, such as wetting or emulsifying agents, surfactants, pH buffering substances and the like can be present in compositions. Other components of pharmaceutical compositions are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions.

Injectable formulations can be prepared either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can also be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above. Langer, *Science* 249: 1527, 1990 and Hanes, *Advanced Drug Delivery Reviews* 28: 97-119, 1997. The compositions and pharmacologic agents described herein can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

Additional formulations suitable for other modes of administration include oral, intranasal, and pulmonary formulations, suppositories, and transdermal applications. For suppositories, binders and carriers include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from mixtures containing the active

ingredient in the range of about 0.5% to about 10%, preferably about 1%- to about 2%. Oral formulations include excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate. Topical application can result in transdermal or intradermal delivery. Transdermal delivery can be achieved using a skin patch or using transferosomes. [Paul et al., Eur. J. Immunol. 25: 3521-24, 1995; Cevc et al., *Biochem. Biophys. Acta* 1368: 201-15, 1998].

For the purpose of oral therapeutic administration, the pharmaceutical compositions can be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. Tablets, pills, capsules, troches and the like may also contain binders, excipients, disintegrating agent, lubricants, glidants, sweetening agents, and flavoring agents. Some examples of binders include microcrystalline cellulose, gum tragacanth or gelatin. Examples of excipients include starch or lactose. Some examples of disintegrating agents include alginic acid, corn starch and the like. Examples of lubricants include magnesium stearate or potassium stearate. An example of a glidant is colloidal silicon dioxide. Some examples of sweetening agents include sucrose, saccharin and the like. Examples of flavoring agents include peppermint, methyl salicylate, orange flavoring and the like. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used. In another embodiment, the composition is administered as a tablet or a capsule.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor, and the like. For vaginal administration, a pharmaceutical composition may be presented as pessaries, tampons, creams, gels, pastes, foams or spray.

The pharmaceutical composition can also be administered by nasal administration. As used herein, nasally administering or nasal administration includes administering the composition to the mucus membranes of the nasal passage or nasal cavity of the patient. As used herein, pharmaceutical compositions for nasal administration of a composition include therapeutically effective amounts of the compounds prepared by well-known methods to be administered, for example, as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. Administration of the composition may also take place using a nasal tampon or nasal sponge.

For topical administration, suitable formulations may include biocompatible oil, wax, gel, powder, polymer, or other liquid or solid carriers. Such formulations may be administered by applying directly to affected tissues, for example, a liquid formulation to treat infection of conjunctival tissue can be administered dropwise to the subject's eye, or a cream formulation can be administered to the skin.

Rectal administration includes administering the pharmaceutical compositions into the rectum or large intestine. This can be accomplished using suppositories or enemas. Suppository formulations can easily be made by methods known in the art. For example, suppository formulations can be prepared by heating glycerin to about 120°C, dissolving the pharmaceutical composition in the glycerin, mixing the heated glycerin after which purified water may be added, and pouring the hot mixture into a suppository mold.

Transdermal administration includes percutaneous absorption of the composition through the skin. Transdermal formulations include patches, ointments, creams, gels, salves and the like.

In addition to the usual meaning of administering the formulations described herein to any part, tissue or organ whose primary function is gas exchange with the external environment, for purposes of the present invention, "pulmonary" will also mean to include a tissue or cavity that is contingent to the respiratory tract, in particular, the sinuses. For pulmonary administration, an aerosol formulation containing the active agent, a manual pump spray, nebulizer or pressurized metered-dose inhaler as well as dry powder formulations are contemplated. Suitable formulations of this type can also include other agents, such as antistatic agents, to maintain the disclosed compounds as effective aerosols.

A drug delivery device for delivering aerosols comprises a suitable aerosol canister with a metering valve containing a pharmaceutical aerosol formulation as described and an actuator housing adapted to hold the canister and allow for drug delivery. The canister in the drug delivery device has a head space representing greater than about 15% of the total volume of the canister. Often, the compound intended for pulmonary administration is dissolved, suspended or emulsified in a mixture of a solvent, surfactant and propellant. The mixture is maintained under pressure in a canister that has been sealed with a metering valve.

"Treating" or "treatment" includes preventing or delaying the onset of the symptoms, complications, or biochemical indicia of a disease, alleviating or ameliorating

the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. A "patient" is a human subject in need of treatment.

An "effective amount" refers to that amount of the therapeutic agent that is sufficient to ameliorate of one or more symptoms of a disorder and/or prevent advancement of a disorder, cause regression of the disorder and/or to achieve a desired effect.

As used herein, the term "inhibiting" or "decreasing" encompasses causing a net decrease by either direct or indirect means. The term "increasing" means to cause a net gain by either direct or indirect means.

The invention encompasses the treatment of a condition associated with a dysfunction in proteostasis. Proteostasis refers to protein homeostasis. Dysfunction in protein homeostasis is a result of protein misfolding, protein aggregation, defective protein trafficking or protein degradation. Exemplary proteins of which there can be a dysfunction in proteostasis, for example that can exist in a misfolded state, include, but are not limited to, glucocerebrosidase, hexosamine A, cystic fibrosis transmembrane conductance regulator, aspartylglucsaminidase, α-galactosidase A, cysteine transporter, acid ceremidase, acid α-L-fucosidase, protective protein, cathepsin A, acid β-glucosidase, acid β-galactosidase, iduronate 2-sulfatase, α-L-iduronidase, galactocerebrosidase, acid α -mannosidase, acid β -mannosidase, arylsulfatase B, arylsulfatase A, *N*-acetylgalactosamine-6-sulfate sulfatase, acid β -galactosidase, *N*-acetylglucosamine-1-phosphotransferase, acid sphingmyelinase, NPC-1, acid α-glucosidase, β-hexosamine B, heparin *N*-sulfatase, α -*N*-acetylglucosaminidase, α -glucosaminide *N*-acetyltransferase, *N*-acetylglucosamine-6-sulfate sulfatase, α -*N*-acetylgalactosaminidase, α -neuramidase, β -glucuronidase, β-hexosamine A and acid lipase, polyglutamine, α -synuclein, Aβ peptide, tau protein transthyretin and insulin.

In certain embodiments, the protein is selected from the group consisting of huntingtin, tau, alpha-synuclein, α1 anti-trypsin, cystic fibrosis transmembrane conductance regulator and superoxide dismutase.

Protein conformational diseases encompass gain of function disorders and loss of function disorders. In one embodiment, the protein conformational disease is a gain of function disorder. The terms "gain of function disorder," "gain of function disease," "gain of toxic function disorder" and "gain of toxic function disease" are used interchangeably herein. A gain of function disorder is a disease characterized by increased aggregation-

associated proteotoxicity. In these diseases, aggregation exceeds clearance inside and/or outside of the cell. Gain of function diseases include, but are not limited to neurodegenerative diseases associated with aggregation of polyglutamine, Lewy body diseases, amyotrophic lateral sclerosis, transthyretin-associated aggregation diseases, Alzheimer's disease and prion diseases. Neurodegenerative diseases associated with aggregation of polyglutamine include, but are not limited to, Huntington's disease, dentatorubral and pallidoluysian atrophy, several forms of spino-cerebellar ataxia, and spinal and bulbar muscular atrophy. Alzheimer's disease is characterized by the formation of two types of aggregates: extracellular aggregates of Aβ peptide and intracellular aggregates of the microtubule associated protein tau. Transthyretin-associated aggregation diseases include, for example, senile systemic amyloidoses and familial amyloidotic neuropathy. Lewy body diseases are characterized by an aggregation of α-synuclein protein and include, for example, Parkinson's disease. Prion diseases (also known as transmissible spongiform encephalopathies or TSEs) are characterized by aggregation of prion proteins. Exemplary human prion diseases are Creutzfeldt-Jakob Disease (CJD), Variant Creutzfeldt-Jakob Disease, Gerstmann-Straussler-Scheinker Syndrome, Fatal Familial Insomnia and Kuru.

In a further embodiment, the protein conformation disease is a loss of function disorder. The terms "loss of function disease" and "loss of function disorder" are used interchangeably herein. Loss of function diseases are a group of diseases characterized by inefficient folding of a protein resulting in excessive degradation of the protein. Loss of function diseases include, for example, cystic fibrosis and lysosomal storage diseases. In cystic fibrosis, the mutated or defective enzyme is the cystic fibrosis transmembrane conductance regulator (CFTR). One of the most common mutations of this protein is ΔF508 which is a deletion (Δ) of three nucleotides resulting in a loss of the amino acid phenylalanine (F) at the 508th (508) position on the protein. Lysosomal storage diseases are a group of diseases characterized by a specific lysosomal enzyme deficiency which may occur in a variety of tissues, resulting in the build-up of molecules normally degraded by the deficient enzyme. The lysosomal enzyme deficiency can be in a lysosomal hydrolase or a protein involved in the lysosomal trafficking. Lysosomal storage diseases include, but are not limited to, aspartylglucosaminuria, Fabry's disease, Batten disease, Cystinosis, Farber, Fucosidosis, Galactasidosialidosis, Gaucher's disease (including Types 1, 2 and 3), Gm1 gangliosidosis, Hunter's disease, Hurler-Scheie's disease, Krabbe's

disease, a-Mannosidosis, B-Mannosidosis, Maroteaux-Lamy's disease, Metachromatic Leukodystrophy, Morquio A syndrome, Morquio B syndrome, Mucolipidosis II, Mucolipidosis III, Neimann-Pick Disease (including Types A, B and C), Pompe's disease, Sandhoff disease, Sanfilippo syndrome (including Types A, B, C and D), Schindler disease, Schindler-Kanzaki disease, Sialidosis, Sly syndrome, Tay-Sach's disease and Wolman disease.

In another embodiment, the disease associated with a dysfunction in proteostasis and/or in the heat shock response is a cardiovascular disease. Cardiovascular diseases include, but are not limited to coronary artery disease, myocardial infarction, stroke, restenosis and arteriosclerosis. Conditions associated with a dysfunction of proteostasis also include ischemic conditions, such as, ischemia/reperfusion injury, myocardial ischemia, stable angina, unstable angina, stroke, ischemic heart disease and cerebral ischemia.

In yet another embodiment, the disease associated with a dysfunction in proteostasis is diabetes or diabetic retinopathy.

In some embodiments, the condition is selected from the group consisting of cystic fibrosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, diabetic retinopathy, diabetes, and other retinal disorders. In one embodiment, the condition is cystic fibrosis.

In an additional embodiment, the invention is directed to a pharmaceutical composition comprising a compound of any one of Formulae (Ia-Ib), (IIa-IId), (IIIa-IIIb), (IV), (V), (VI), (VIIa-VIIc), (VIII), (IXa-IXb), (Xa-Xb), (XIa-XIb) and (XIIa-XIIb), and a second agent, wherein the second agent is selected from the group consisting of a pharmacologic chaperone and a proteostasis regulator. The invention also encompasses a method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering a therapeutically effective amount of a compound of the invention and a second agent, wherein the second agent is a pharmacologic chaperone. Pharmacologic chaperones or kinetic stabilizers refer to compounds that bind an existing steady state level of the folded mutant protein and chemically enhance the folding equilibrium by stabilizing the fold [Bouvier, *Chem Biol* **14:** 241-242, 2007; Fan et al., *Nat Med* **5:** 112-115, 1999; Sawkar et al., *Proc Natl Acad Sci U S A* **99:**15428-15433, 2002; Johnson and Kelly, *Accounts of Chemical Research* **38:** 911-921, 2005]. The pharmacologic chaperone is administered in amount that in combination with a compound described herein in an amount that is sufficient to treat a patient suffering from a condition

associated with a dysfunction in proteostasis. Exemplary pharmacologic chaperones are described in U.S. Patent Publication No's. 20080056994, 20080009516, 20070281975, 20050130972, 20050137223, 20050203019, 20060264467 and 20060287358, the contents of which are incorporated by reference herein.

In another embodiment, the invention is a method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering therapeutically effective amount of a compound of the invention and a second agent, wherein the second agent is a proteostasis regulator. The term "proteostasis regulator" refers to small molecules, siRNA and biologicals (including, for example, proteins) that enhance cellular protein homeostasis. For example, proteostasis regulators can be agents that influence protein synthesis, folding, trafficking and degradation pathways. Proteostasis regulators encompass pharmacologic agents that stimulate the HSR signaling activity. Proteostasis regulators function by manipulating signaling pathways, including, but not limited to, the heat shock response or the unfolded protein response, or both, resulting in transcription and translation of proteostasis network components. Proteostasis regulators can enhance the folding, trafficking and function of proteins (for example, mutated proteins). Proteostasis regulators can also regulate protein chaperones by upregulating transcription or translation of the protein chaperone, or inhibiting degradation of the protein chaperone. Proteostasis regulators can influence the biology of folding, often by the coordinated increase in chaperone and folding enzyme levels and macromolecules that bind to partially folded conformational ensembles, thus enabling their progression to intermediates with more native structure and ultimately increasing the concentration of folded mutant protein for export. In one aspect, the proteostasis regulator is distinct from a chaperone in that the proteostasis regulator can enhance the homeostasis of a mutated protein but does not bind the mutated protein. In addition, proteostasis regulators can upregulate an aggregation pathway or a disaggregase activity. Exemplary proteostasis regulators are the celastrols, MG-132 and L-type Ca^{2+} channel blockers (e.g., dilitiazem and verapamil). The term "celastrols" refers to celastrol and derivatives or analogs thereof, including, but not limited to, those celastrol derivatives described in Westerheide et al., *J Biol Chem*, 2004. **279**(53): p. 56053-60, the contents of which are expressly incorporated by reference herein. Celastrol derivatives include, for example, celastrol methyl ester, dihydrocelastrol diacetate, celastrol butyl ether, dihydrocelastrol, celastrol benzyl ester, primesterol, primesterol diacetate and triacetate of celastrol. In certain aspects, the proteostasis regulator is a heat shock response activator. A heat shock

response activator is an agent that indirectly or directly activates the heat shock response, for example, by directly or indirectly activating heat shock transcription factor 1 (HSF1), inhibiting Hsp90, and/or activating chaperone expression (Westerheide et al., J Biol Chem, 2004. **279**(53): p. 56053-60, the contents of which are expressly incorporated by reference herein). The terms "heat shock response activator," "heat shock activator," "heat shock response inducer," and "heat shock inducer" are used interchangeably herein. Non-limiting examples of heat shock response activators are celastrols, non-steroidal anti-inflammatory drugs, ansamycin, geldenamycin, radiciol, glucuronic acid, and tributylin. Heat shock response activators have also been described, for example, in U.S. Patent Application Publication No's. 20070259820, 20070207992, 20070179087, 20060148767, the contents of each of which are expressly incorporated by reference herein. In some embodiments, the heat shock response activator is a small molecule heat shock response activator.

The invention also encompasses a method of treating cancer or a tumor in a patient in need thereof comprising administering to said patient an effective amount of a compound described herein. Cancers that can be treated according to methods of the present invention include, but are not limited to, breast cancer, colon cancer, pancreatic cancer, prostate cancer, lung cancer, ovarian cancer, cervical cancer, multiple myeloma, basal cell carcinoma, neuroblastoma, hematologic cancer, rhabdomyosarcoma, liver cancer, skin cancer, leukemia, basal cell carcinoma, bladder cancer, endometrial cancer, glioma, lymphoma, and gastrointestinal cancer. In another embodiment, the invention is a method of treating cancer or a tumor comprising administering an effective amount of a compound described herein in combination with the administration of a chemotherapeutic agent. Chemotherapeutic agents that can be utilized include, but are not limited to, alkylating agents such as cyclosphosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin,

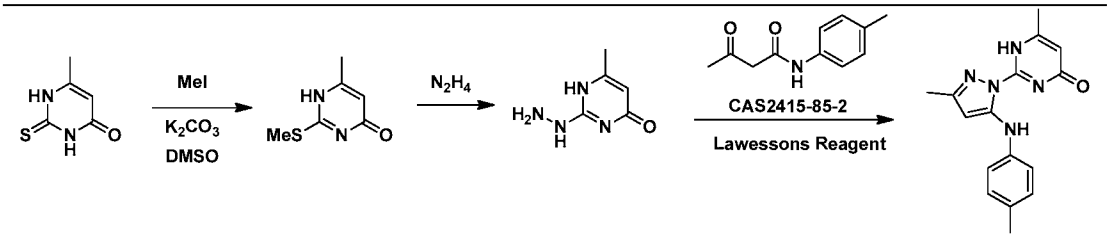
chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2"-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel (TAXOL®, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERE®; Aventis Antony, France); chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above.

In a further embodiment, the invention is a method of treating cancer or a tumor comprising administering to a patient in need thereof an effective amount of a compound described herein in combination with radiation therapy.

The invention is illustrated by the following examples which are not meant to be limiting in any way.

EXEMPLIFICATION

Example 1: 6-Methyl-2-(3-methyl-5-(*p*-tolylamino)-1*H*-pyrazol-1-yl)pyrimidin-4(1*H*)-one



Example 1

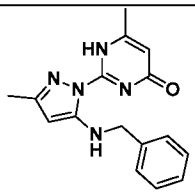
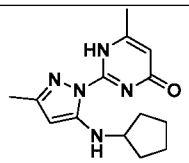
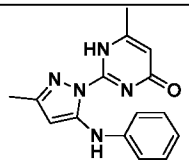
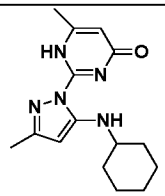
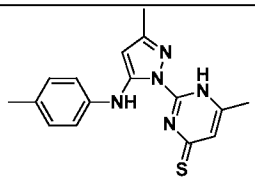
To a solution of 6-methyl-2-thiouracil (30 g, 0.210 mole) in dimethylsulfoxide (300 mL) was added anhydrous potassium carbonate (32 g, 0.230 mol) and methyl iodide (14.2 mL, 0.230 mol). The reaction mixture was allowd to stir overnight followed by the addition of of water (740 mL). The precipitate was filtered, washed with water and dried on the air to give 21g of 6-methyl-2-(methylthio)prymidin-4(1*H*)-one as a white solid. *m/z* (ESI^+)(163 (MNa^+). A mixture of 6-methyl-2-(methylthio)prymidin-4(1*H*)-one (21 g, 0.130 mol), hydrazine hydrate (63 mL, 1.30 mol), anhydrous potassium carbonate (1.4 g, 0.01 mol) and 2-propanol (150 mL) was heated at reflux for 4 hours and then stirred at 60 °C overnight. The precipitate was filtered, washed with methanol, washed with diethyl ether, and dried in air to give 6 g of 2-hydrazinyl-6-methylpryimidin-4(1*H*)-one as a white solid. *m/*z (ESI^+)163 (MNa^+).

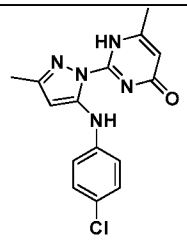
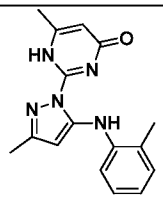
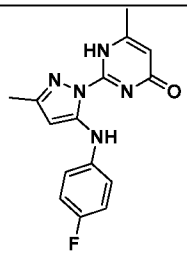
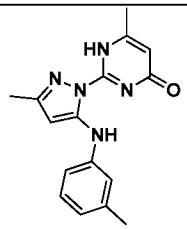
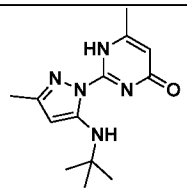
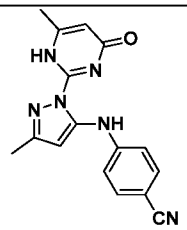
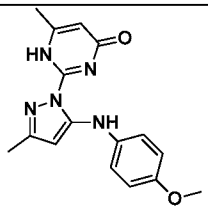
To a mixture of 2-hydrazinyl-6-methylpryimidin-4(1*H*)-one (2 g, 0.0143 mol), *N*-acetoacetyl-*p*-toluidine (2.5g, 0.0130 mol) and Lawesson's reagent (5.8 g, 0.0143 mol) was added dry 1,4-dioxane/pyridine (95/5) solution (137 mL). The reaction mixture was stirred at room temperature for 15 min., then heated at 55 °C (bath temperature) for 3 hours, and then stirred at room temperature overnight. The yellow solid, which precipitated, was filtered off and the filtrate was concentrated under vacuum (max. 55 °C bath temperature). The oily residue was triturated with diethyl ether/methanol (50/1) solution (50 mL). The yellow solid was precipitated and filtered to give 4 g of the crude product. The crude product was purified by flash chromatography on silica using a mixture of dichloromethane/methanol (100:0 to 100:1) as the eluant to give a pale yellow solid. Crystallization from methanol (20 ml) gave 1.1 g of 6-methyl-2-(3-methyl-5-(p-

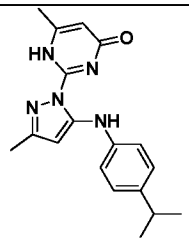
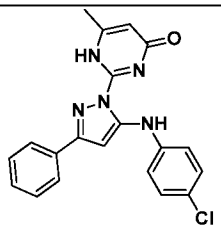
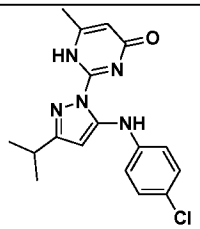
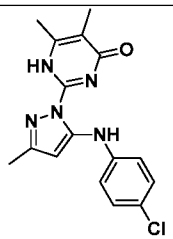
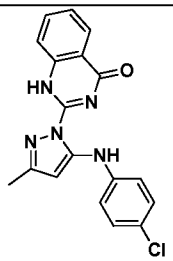
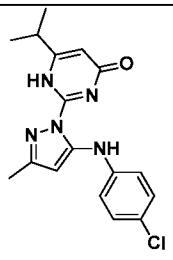
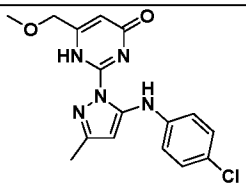
tolylamino)-1*H*-pyrazol-1-yl)pyrimidin-4(1*H*)-one as white needles. *m/z* (ESI^+) 295(MH^+); ^1H NMR (500MHz,d_6-DMSO), δ 10.38 (bs, 1H), 7.16 (d, *J*= 8.5 Hz, 2H), 7.11 (d, *J*= 8.5 Hz, 2H), 6.16 (bs, 1H), 5.98 (s, 1H), 2.33 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H).

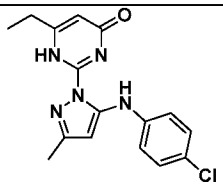
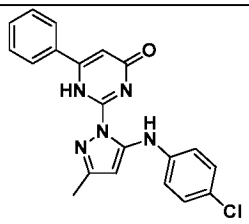
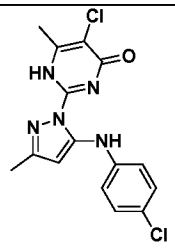
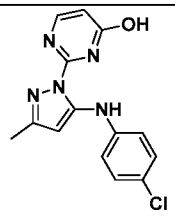
The HCl salt can also be prepared. A round bottom flask, equipped with a stir bar, was charged with 6-methyl-2-(3-methyl-5-(*p*-tolylamino)-1*H*-pyrazol-1-yl)pyrimidin-4(1*H*)-one (340 mg, 1.15 mmol) and dry 1,4-dioxane (10 mL). The flask was placed under a nitrogen atmosphere and the mixture was allowed to stir at room tempearture until all of the solids had dissolved to afford a homogeneous solution. A solution of hydrochloric acid (1 M in diethyl ether) (1.50 ml, 1.50 mmol) was added dropwise via syringe over 2 min to the flask. The mixture was allowed to stir for 15 min and was then condensed in vacuo to afford the salt as a white powder.

Table 2. Further Examples that were prepared according to the general method of Example 1.

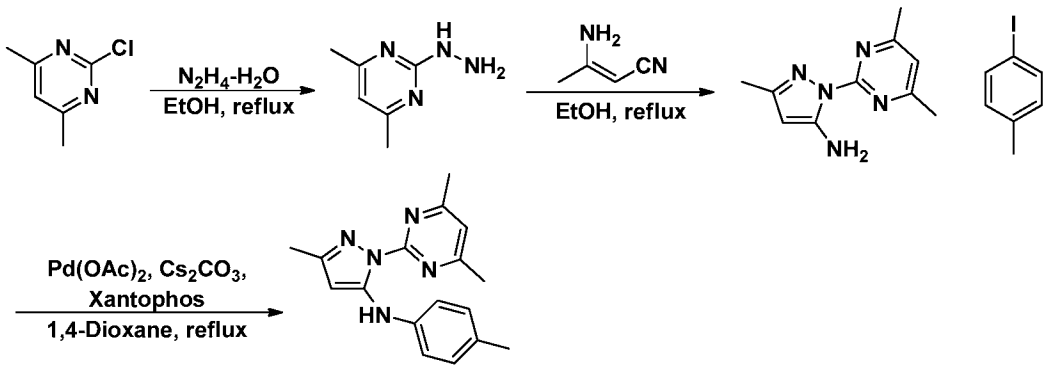
Example	Compound	*m/z* ESI^+/ESI^-
2		296 (MH^+)
3		296 (MNa^+), 274 (MH^+)
4		282 (MH^+)
5		288 (MH^+)
7		312 (MH^+)

9		318/316 (MH^+ $^{37}Cl/^{35}Cl$)
10		318 (MNa^+), 296 (MH^+)
11		322 (MNa^+), 300 (MH^+)
12		318 (MNa^+), 296 (MH^+)
13		262 (MH^+)
16		307 (MNa^+), 329 (MH^+)
18		312 (MH^+)

20		324 (MH^+)
23		380/378 (MH^+ $^{37}Cl/^{35}Cl$)
24		346/344 (MH^+ $^{37}Cl/^{35}Cl$)
25		333/331 (MH^+ $^{37}Cl/^{35}Cl$)
26		354/352 (MH^+ $^{37}Cl/^{35}Cl$)
27		346/344 (MH^+ $^{37}Cl/^{35}Cl$)
28		348/346 (MH^+ $^{37}Cl/^{35}Cl$)

29		332/330 (MH^+ $^{37}Cl/^{35}Cl$)
30		380/378 (MH^+ $^{37}Cl/^{35}Cl$)
31		354/352/350 (MH^+ $^{37}Cl^{37}Cl$ /^{37}Cl $^{35}Cl/^{35}Cl^{35}Cl$)
32		304/302 (MH^+ $^{37}Cl/^{35}Cl$)

Example 6: 1-(4,6-Dimethylpyrimidin-2-yl)-3-methyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine



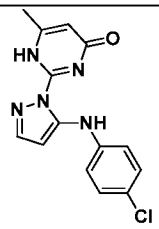
Example 6

Hydrazine monohydrate (1.02 mL, 21.0 mmol) was added to a solution of 2-chloro 4,6-dimethylpyrimidine (2 g, 14.0 mmol) in ethanol (5 mL). The mixture was allowed to stir at room temperature for 2 h. The precipitate that formed was collected by filtration and washed with methanol. The solid was allowed to dry in a stream of air to afford 1 g of 2-hydrazinyl-4,6-dimethylpyrimidine as a white solid (1 g). Yield: 52%; *m/z* (ESI^+) 139 (MH^+).

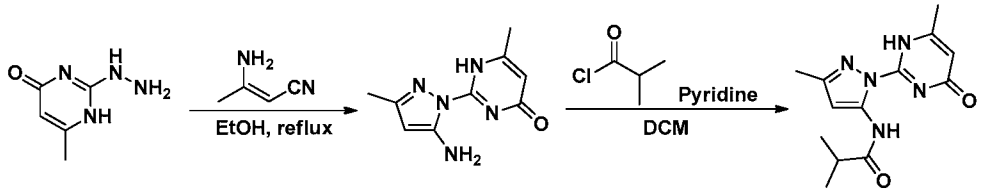
A mixture of 2-hydrazinyl-4,6-dimethylpyrimidine (500 mg, 3.62 mmol) and 3-aminocrotononitrile (312 mg, 3.80 mmol) in ethanol (10 mL) was heated at reflux for 3 h and was then concentrated *in vacuo*. The crude product was recrystallized from methanol to afford 800 mg of 1-(4,6-dimethylpyrimidin-2-yl)-3-methyl-1*H*-pyrazol-5-amine as a pale brown solid. Yield: 90%; *m/z* (ESI^+) 226 (MNa^+), 204 (MH^+).

A mixture of cesium carbonate (1.45 g, 4.44 mmol), 1-(4,6-dimethylpyrimidin-2-yl)-3-methyl-1*H*-pyrazol-5-amine (350 mg, 1.48 mmol), and 4-iodotoluene (452 mg, 2.07 mmol) in 1,4-dioxane (10 mL) was heated at reflux, under argon athmosphere, for 15 min. Xantophos (342 mg, 0.592 mmol), followed by palladium(II) diacetate (83 mg, 0.370 mmol), was added to the reaction mixture at 100 °C. The reaction mixture was maintained at reflux, under argon atmosphere, for 12 h. The reaction mixture was concentrated *in vacuo* and the remaining residue was purified by column chromatography on silica using a mixture of dichloromethane/methanol as the eluant. The product obtained this way was further purified by preparative HPLC and then crystallization from a mixture of methanol and hexanes to afford 61 mg of 1-(4,6-dimethylpyrimidin-2-yl)-3-methyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine as a pale yellow solid. Yield: 14%; *m/z* (ESI^+) 294 (MH^+); ^1H NMR (500 MHz, $CDCl_3$) δ 10.39 (bs, 1H), 7.19 (d, *J*= 8 Hz, 2H), 7.13 (d, *J*= 8 Hz, 2H), 6.93 (s, 1H), 5.84 (s, 1H), 2.56 (s, 6H), 2.39 (s, 3H), 2.37 (s, 3H).

Table 3. Additional Example prepared according to the general method of Example 6.

Example	Compound	*m/z* ESI^+/ESI^-
21		304/302 (MH^+ $^{37}Cl/^{35}Cl$)

Example 8: *N*-(3-Methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)-1*H*-pyrazol-5-yl)isobutyramide

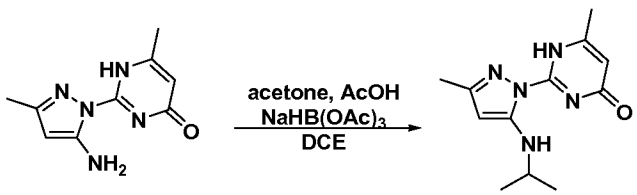


Example 8

Neat 3-aminobut-2-enenitrile (0.81 g, 7.4 mmol) was added in a portionwise manner to a suspension of 2-hydrazinyl-6-methylpyrimidin-4(1*H*)-one (from example 1, 1 g, 7.1 mmol) in ethanol (10 mL) at room temperature. The reaction mixture was heated at reflux for 4 h and was then concentrated *in vacuo*. The crude product was purified by column chromatography using a mixture of dichloromethane/methanol as the eluant to afford 0.6 g of 2-(5-amino-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidin-4(1*H*)-one as a white solid. Yield: 35%; *m/z* (ESI^+) 206 (MH^+).

A mixture of 2-(5-amino-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidin-4(1*H*)-one (0.15 g, 0.730 mmol) and pyridine (0.07 mL, 0.876 mmol) in dichloromethane (8 mL) was treated with a solution of isobutyryl chloride (0.091 mL, 0.876 mmol) in dichloromethane (2 mL). The reaction mixture was allowed to stir a room temperature for 24 h before it was diluted with dichloromethane (20 mL). The mixture was washed with 2M hydrochloric acid, a 5% aqueous solution of sodium bicarbonate, and brine. The organic phase was dried over magnesium sulfate, filtered, and condensed *in vacuo* to afford a solid. The solid was purified by column chromatography on silica using a dichloromethane/methanol gradient (0-10%) and then by preparative HPLC to afford 50 mg of *N*-(3-Methyl-1-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl)-1*H*-pyrazol-5-yl)isobutyramide as a pale yellow solid. Yield: 25%, *m/z* (ESI^+) 298 (MNa^+), 276 (MH^+), ^1H NMR (500 MHz, d_6-DMSO) δ 11.80 (s, 1H), 6.62 (s, 1H), 6.24 (s, 1H), 2.64 (sept, *J*= 6.5 Hz, 1H), 2.34 (s, 3H), 2.21 (s, 3H), 1.19 (d, *J*= 6.5 Hz, 6H).

Example 14: 2-(5-(Isopropylamino)-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidin-4(1*H*)-one

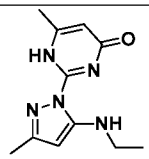


Example 14

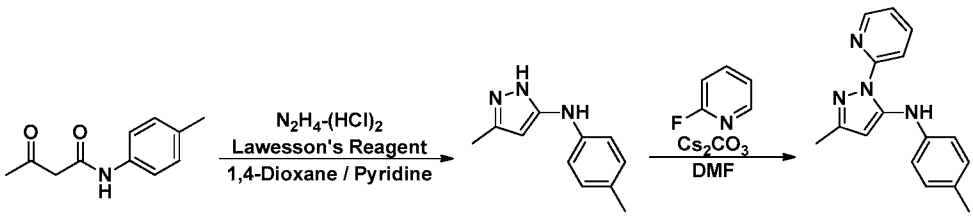
A mixture of 2-(5-amino-3-methyl-1*H*-pyrazol-1-yl)-6-methylpyrimidin-4(1*H*)-one (from example 8, 400 mg, 1.95 mmol), acetone (272 µL, 3.70 mmol), acetic acid (670 µL, 11.7 mmol) and sodium triacetoxyborohydride (1.16 g, 5.46 mmol) in dichloroethane was allowed to stir at room temperature for 2 d. The reaction was quenched through the addition of an aqueous, saturated solution of sodium bicarbonate. The mixture was extracted with dichloromethane and the combined organic extracts were dried over magnesium sulfate, filtered, and condensed *in vacuo*. The crude product was purified by

column chromatography on silica using a mixture of dichloromethane/methanol as the eluant. The product obtained from this purification was further purified in another round of column chromatography on silica using a mixture of ethyl acetate/hexanes as the eluant to afford 130 mg of 2-(5-(isopropylamino)-3-methyl-1H-pyrazol-1-yl)-6-methylpyrimidin-4(1H)-one as a white solid. Yield: 27%; *m/z* (ESI^+) 270 (MNa^+), 248 (MH^+); ^1H NMR (200 MHz, d_6-DMSO) δ 11.51 (bs, 1H), 7.62 (bs, 1H), 5.98 (bs, 1H), 5.33 (s, 1H), 3.42 (sept, *J*= 6.6 Hz, 1H), 2.20 (s, 3H), 2.11 (s, 3H), 1.19 (d, *J*= 6.6 Hz, 6H).

Table 4. Additional Example that was prepared according to the general method of Example 14.

Example	Compound	*m/z* ESI^+/ESI^-
15		234 (MH^+)

Example 17: 3-Methyl-1-(pyridin-2-yl)-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine

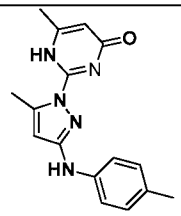
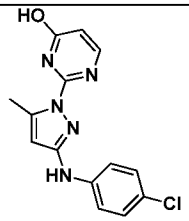


A mixture of 3-oxo-*N*-(*p*-tolyl)butanamide (5 g, 26.1 mmol), hydrazine hydrochloride (3 g, 28.7 mmol), and Lawesson's reagent (11.6 g, 28.7 mmol) in a mixture of 1,4-dioxane/pyridine (190 mL/10 mL) was heated at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature and the solvent was decanted. The remaining solid residue was triturated with ethyl acetate and filtered. The filtrate and solvent from the reaction mixture were combined and condensed *in vacuo*. The crude product was purified by column chromatography on silica using a mixture of dichloromethane/methanol as the eluant to afford 1 g of 3-methyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine as a gray solid. Yield: 22%; *m/z* (ESI^+) 188 (MNa^+).

A mixture of 3-methyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine (300 mg, 1.60 mg), 2-fluoropyridine (128 µL, 1.76 mmol), and cesium carbonate (1.04 g, 3.2 mmol) in *N,N*-dimethylformamide (5 mL) was heated at 120°C for 96 h. The reaction mixture was

allowed to cool to room temperature and the resulting suspension was filtered. The filtrate was evaporated under reduced pressure, dissolved in dichloromethane and washed with water. The organic phase was dried over magnesium sulfate, filtered, and condensed *in vacuo*. The crude product was purified by column chromatography on silica using a mixture of hexanes/ethyl acetate as the eluant to afford 20 mg of 3-methyl-1-(pyridin-2-yl)-*N*-(*p*-tolyl)-1H-pyrazol-5-amine as a yellow solid. Yield: 5%; *m/z* (ESI^+) 265 (MH^+); ^1H NMR (500 MHz, $CDCl_3$) δ 10.42 (bs, 1H), 8.34 (d, *J*= 5 Hz, 1H), 8.00 (d, *J*= 9 Hz, 1H), 7.79 (t, *J*= 9 Hz, 1H), 7.13-7.07 (m, 5H), 5.83 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H).

Table 5. Further Examples that were prepared according to the general method of Example 17.

Example	Compound	*m/z* ESI^+/ESI^-
19		296 (MH^+)
22		304/302 (MH^+ $^{37}Cl/^{35}Cl$)

Example 33: CFTR Folding and Trafficking Assay

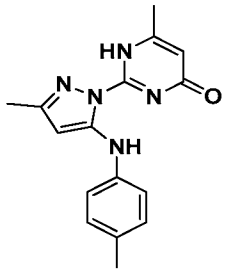
CFTR transport assays. ΔF508 expressing CFBE41^{o-} lung cells were cultured in the presence of compound 1 in 12 well Sarstedt dishes, harvested, lysed and the processing of CFTR from the band B to the band C glycoform detected by SDS-PAGE and immunoblotting using either monoclonal 3G11 or M3A7.

Quantitation of CFTR glycoforms. Immunoblot exposures were selected to allow visualization of CFTR recovery under identical protein loads in same SDS-PAGE for all treatments. Given the dynamic range, quantitation of the band B and C glycoforms was made by analysis of band intensities that were in the linear range. The x-ray films were exposed for increasing time and the different exposures were quantified using a FluroChemSP (Alpha Inotech) densitometer/software package. Where band B and C were

quantified from different exposures, an internal reference was used to normalize the signal intensity. This method has been described in detail in Hutt et al. (2010),[28] Reduced histone deacetylase 7 activity restores function to misfolded CFTR in cystic fibrosis, Nature Chemical Biology, 6(1), 25-33, the contents of which are expressly incorporated by reference herein.

Immunoblot Analysis.

CFBE41^{o-} lung cells were cultured in the presence and absence of compound 1 as described by Hutt et al. (2010).[28] Immunoblot analysis shown in the Figure indicates enhanced levels of band B and C.



Compound 1

Example 34: CFTR Functional Assays

CFTR Iodide Flux Assay:

Ninety six well microplates containing CFBE41^{o-} cells stably expressing ΔF508-CFTR and halide-sensitive YFP were incubated at 27°C for 20 to 24 h. After incubation, cells were washed with PBS (containing 137 mM NaCl, 2.7 mM KCl, 8.1 mM Na_2HPO4, 1.5 mMKH_2PO_4, 1mM$CaCl_2$, 0.5mM$MgCl_2$) and stimulated for 20 min with forskolin and test compounds. Microplates were read using a plate reader equipped with excitation (HQ500/20X: 500 nm) and emission (HQ535/30M: 535 nm) filters for yellow fluorescent protein. Each assay consisted of a continuous 30-s fluorescence reading (5 points per second) with 3 s before and 27 s after injection of 165 ul of an iodide-containing solution (PBS with Cl^- replaced by I^-). Final iodide concentration in the wells was 100 mM. These data were normalized to the initial background subtracted fluorescence.

Biological Activity of Select Compounds:

Iodide Flux Assay

Table 6 shows percent quenching of yellow fluorescent protein (YFP) by select compounds described in the invention. Quenching values for the selected compounds were obtained at 10 μM. Quenching of YFP signal is an indirect measure of CFTR function.

Table 6: Activities for select compounds of the invention for the CFBE-YFP Quenching Assay

Percent Quenching of YFP at 10 μM	Example/Compound Number
<15%	5, 7, 20, 29, 30
15-20%	1, 2, 6, 8, 11, 12, 13, 16, 17, 21, 22, 23, 28
>20%	3, 4, 9, 10, 14, 15, 18, 19

Example 35: HSF-1 Modulation Assay

Multigene Assay: Monitoring of HSF-1 Activity via HSPA5 Transcript Levels in IMR 32 Human Neuroblastoma Cells

This assay uses the QuantiGene Plex 2.0 Reagent System from Affymetrix. This assay combines the use of bDNA (branch DNA) and xMAP magnetic capture beads from Luminex Technologies to quantitatively and simultaneously detect multiple mRNA transcripts per well.

Procedure:

Warm up the Lysis mixture for 30 minutes at 37 °C prior to making the lysis buffer. Proteinase K should be used cold. Use 10ul of Proteinase K per 1ml of Lysis mixture to make the lysis buffer. Add 50% v/v of the lysis mixture per well. Mix well to ensure proper lysing. Seal the plates with adhesive aluminum plate seals and incubate at 50°C for 30 minutes. Mix well again 10 times. Store plates at -80°C until assay is performed.

The overall procedure was performed according to the QuantiGene Plex 2.0 Reagent System instruction manual from Affymetrix.

Day 1 Procedure (for multiplex, 8-plates assay):

Prepare a master mix pool without beads. Distribute the master mix equally in 8 tubes and then add the respective bead mix to each tube. Vortex and add 20ul/well of the master mix to the 96-well plate. After transfer, add 80ul/well of the lysates to respective plates. The amount of cell lysate to be used in the assay should be determined either by performing an assay linearity test or by determining the sample input empirically for each cell line. In order to avoid signal saturation, sample input should be less than 400 cells/ul. Dilute cell lysates with DLM.

Keep three wells in each plate as assay background (no cell lysates in these wells, only diluted lysis mixture as described previously and on the next page).

1. Prepare the **Hybridization Master Mix for** for the 1st day hybridization

- Total reaction per 96 well is 100 ul

Amount per 1 well, Lysis Mixture 6.7 ul; Proteinase K 0.2 u; Blocking Reagent 2.0 ul; Probe mix 5.0 ul; Bead mix 1.0 ul; Water 5.1 ul; TOTAL 20 ul (80 ul of lysate + 20 ul of master mix = 100 ul).

Master Mix for 8 Plex Sets

Amount per 1 well for 8 Plex Set (10 rxn)

-	Lysis Mixture	67 ul
-	Proteinase K	2 ul
-	Blocking Reagent	20 ul
-	Probe mix	50 ul
-	Bead mix	0 ul
-	Water	51 ul
-	TOTAL	190 ul

19 ul +1 ul (Plex 1)

19 ul +1 ul (Plex 2)…

19 ul +1 ul (Plex 8)

20 ul of master mix
+80 ul of sample

Dilute Lysis Mixture (DLM): 2:1 ratio (2 parts water, one part lysis mixture).
For example: to make 3 ml of DLM, dilute 1 mL of lysis mixture into 2 mL of water.

Total RNA Sample Prep: 80 ul of DLM (33% lysis mixture) + 1 ul of RNA (250 ng/ul).

Cell lysate Sample Prep: Maximum cell lysate input is 80 ul per well.
Shake plates for 16-22 hours at 54°C ± 1°C and appropriate rpm. (I use 300rpm for ThermoMax plate shakers).

Standard Operating Procedure FOR DAY 2 OF MGE ASSAY (SIGNAL AMPLIFICATION AND TARGET RNA DETECTION)

General procedure:

1. Warm up the Amplifier Diluent, Label Probe Diluent, and SAPE Diluent at 37°C for 20 minutes to dissolve any precipitates. Mix Amplifier diluent well by inversion before use. Bring all diluents to room temperature before use.

For washing plates using the BioTek ELx-405 Magnetic plate washer, prepare Wash Buffer 2.0:

(Use 200 ml for priming the washer and 200 ml for the series of wash steps = 400ml total)

Wash Buffer (400ml):

380ml water (can use Deionized water)

+ 1.2ml Wash Buffer Component 1

+ 20ml Wash Buffer Component 2

Be sure to mix each wash buffer component in the water before adding the next wash buffer component, otherwise they may precipitate and may take a long time to go back into solution. For other quantities, scale the ingredients accordingly. Do not store the Wash Buffer. Make fresh for every use.

2. Transfer the overnight hybridization mixture to the Magnetic Separation Plate.

a. Remove the overnight hybridization plate from the shaking incubation and centrifuge at 240 x g for one minute.

b. Pipet up and down 5 times using the Biomek FX robot and completely transfer the mixture to the magnetic separation plate (at this step, the plate should be kept on the magnet).

c. For multiplex plates, program the Biomek FX to mix and transfer each plate mixture to the magnetic separation plate on a magnet with 80 second incubation intervals between transfers.

3. Shake plate on room temperature plate shaker for two minutes and then wash the unbound sample away using the magnetic plate washer.

For Multiplex:

Prepare Working Solution for one 96 well PlexPlex format:

Warm up Amplifier diluents, Label Probe diluents and Sape diluents at 37°C for 30 mins.

Preamplifier Solution: Add 7.5 ul of preamplifier to every 1ml of Amplifier Diluent.

Amplifier Solution: Add 7.5 ul of Amplifier to every 1ml of Amplifier Diluent.

Label Probe Solution: Add 7.5 ul of Label Probe to every 1ml of Label Probe Diluent.
SAPE Solution: Add 3.0 ul of SAPE to every 1ml of SAPE Diluent.

Procedure:

1. PreAmplifier Hyb Step: Soak compression plate for 2 min on Magnetic Separation device. Compression plate should make contact with the magnetic device at all time. Wash plate 4 times with 100 ul QGP 2.0 wash buffer, 60 second soak in between each wash required. Remove wash buffer from the final wash. Add 60 ul of Preamp solution per well. Incubate at 50°C for 1 hr with 300 RPM shaking (ThermoMaxQ plate shaker).
2. Amplifier Hyb Step: Soak compression plate for 2 min on Magnetic Separation Device. Compression plate should make contact with the magnetic device at all time. Wash plate 4 times with 100 ul QGP 2.0 wash buffer, 60 second soak in between each wash required. Remove wash buffer from the final wash. Add 60 ul of Amp solution per well. Incubate at 50°C for 1 hr with 300 RPM shaking (ThermoMaxQ plate shaker).
3. Label Probe Hyb Step: Soak compression plate for 2 min on Magnetic Separation Device. Compression plate should make contact with the magnetic device at all time. Wash plate 4 times with 100 ul QGP 2.0 wash buffer, 60 second soak in between each wash required. Remove wash buffer from the final wash. Add 60 ul of Label Probe solution per well. Incubate at 50°C for 1 hr with 300 RPM shaking (ThermoMaxQ plate shaker).
4. SAPE Hyb Step: Soak compression plate for 2 min on Magnetic Separation Device. Compression plate should make contact with the magnetic device at all time. Wash plate 4 times with 100 ul QGP 2.0 wash buffer, 60 second soak in between each wash required. Remove wash buffer from the final wash. Add 60 ul of SAPE solution per well. Incubate at room temperature for 30 min with 600 RPM shaking. The plate needs to be protected from light by wrapping in foil or by dimming the light.
5. Soak plate for 2 min on Magnetic Separation Device. Compression plate should make contact with the magnetic device at all time. Wash plate 4 times with 100 ul QGP 2.0 SAPE wash buffer, 60 second soak in between each wash required. Add 130 ul of SAPE wash buffer per well after the final wash. Shake plate at 400-500rpm for 2-3 minutes at room temperature. Plate is ready to read.
6. Use QGP2.0 96 well Luminex setting (Pick up 100 ul of sample, 100 beads/region and 45 second time out). I usually use “no timeout” as an optimal setting because some bead regions reach the 100 bead count slower than the other bead regions. With a no

timeout setting, one can be assured that every region will reach a minimum of 100 beads. The Luminex machine will move to the next sample if, a) All regions have reached 100+ beads, OR, b) Sample has run out.

Control genes used to monitor general transcriptional effects include Tub1 (alpha-tubulin) and TBP (TATA binding protein).

Exemplary compounds with activity in the multigene assay described are described in the Table 7 below.

Table 7: Activities for select compounds described in the invention for their ability to induce induction of the HSPA5 gene in IMR32 cells

Concentration Required to Induce a 1.5-fold Increase in HSPA5 Transcript (μM)	**Compound Number**
≥10	2, 8, 16, 17, 28
<10 – 1	1, 3, 4, 5, 7, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 23, 24, 27, 29, 31, 32
<1	25, 26, 30

References:

1. Riordan, J.R. CFTR function and prospects for therapy. *Annu. Rev. Biochem.* **2008**, *77*, 701-26.

2. Qu, B.H., Strickland, E.H. and Thomas, P.J. Localization and suppression of a kinetic defect in cystic fibrosis transmembrane conductance regulator folding. *J. Biol. Chem.* **1997**, *272*, 15739-44.

3. Boucher, R.C. Evidence for airway surface dehydration as the initiating event in CF airway disease. *J. Intern. Med.* **2007**, *261*, 5-16.

4. Balch, W.E., Morimoto, R.I., Dillin, A. and Kelly, J.W. Adapting proteostasis for disease intervention. *Science.* **2008**, *319*, 916-9.

5. Powers, E.T., Morimoto, R.I., Dillin, A., Kelly, J.W. and Balch, W.E. Biological and chemical approaches to diseases of proteostasis deficiency. *Annu. Rev. Biochem.* **2009**, *78*, 959-91.

6. Hutt, D.M., Powers, E.T. and Balch, W.E. The proteostasis boundary in misfolding diseases of membrane traffic. *FEBS Lett.* **2009**, *583*, 2639-46.

7. Gregersen, N. Protein misfolding disorders: pathogenesis and intervention. *J. Inherit. Metab. Dis.* **2006**, *29*, 456-70.

8. Wang, X. et al. Hsp90 cochaperone Aha1 down regulation rescues misfolding of CFTR in cystic fibrosis. *Cell* **127**, 803-15 (2006).

9. Bruscia, E. et al. Isolation of CF cell lines corrected at DeltaF508-CFTR locus by SFHR-mediated targeting. *Gene Ther* **9**, 683-5 (2002).

10. Bebok, Z. et al. Failure of cAMP agonists to activate rescued deltaF508 CFTR in CFBE41o- airway epithelial monolayers. *J Physiol* 569, 601-15 (2005); Darren M Hutt, David Herman, Ana PC Rodrigues, Sabrina Noel, Joseph M Pilewski, Jeanne Matteson, Ben Hoch, Wendy Kellner, Jeffery W Kelly, Andre Schmidt, Philip J Thomas, Yoshihiro Matsumura, William RSkach, Martina Gentzsch, John RRiordan, Eric J Sorscher, Tsukasa Okiyoneda, John RYates III, Gergely L Lukacs, Raymond A Frizzell, Gerard Manning, Joel M Gottesfeld & William E Balch, Reduced histone deacetylase 7 activity restores function to misfolded CFTRin cystic fibrosis *Nature Chemical Biology* **6**(1), 25-33, (2010).

11. Lei, D.C. et al. Episomal expression of wild-type CFTR corrects cAMP-dependent chloride transport in respiratory epithelial cells. *Gene Ther* **3**, 427-36 (1996).

12. Devor, D.C., Bridges, R.J. & Pilewski, J.M. Pharmacological modulation of ion transport across wild-type and DeltaF508 CFTR-expressing human bronchial epithelia. *Am J Physiol Cell Physiol* **279**, C461-79 (2000).

13. Butterworth, M.B., Edinger, R.S., Johnson, J.P. & Frizzell, R.A. Acute ENaC stimulation by cAMP in a kidney cell line is mediated by exocytic insertion from a recycling channel pool. *J Gen Physiol* **125**, 81-101 (2005).

14. Myerburg, M.M. et al. Airway surface liquid volume regulates ENaC by altering the serine protease-protease inhibitor balance: a mechanism for sodium hyperabsorption in cystic fibrosis. *J Biol Chem* **281**, 27942-9 (2006).

15. Myerburg, M.M. et al. Prostasin expression is regulated by airway surface liquid volume and is increased in cystic fibrosis. *Am J Physiol Lung Cell Mol Physiol* **294**, L932-41 (2008).

16. Gentzsch, M. et al. Endocytic trafficking routes of wild type and DeltaF508 cystic fibrosis transmembrane conductance regulator. *Mol Biol Cell* **15**, 2684-96 (2004).

17. Fulcher, M.L., Gabriel, S., Burns, K.A., Yankaskas, J.R. & Randell, S.H. Well differentiated human airway epithelial cell cultures. *Methods Mol Med* **107**, 183- 206 (2005).

18. Coyne, C.B., Kelly, M.M., Boucher, R.C. & Johnson, L.G. Enhanced epithelial gene transfer by modulation of tight junctions with sodium caprate. *Am J Respir Cell Mol Biol* **23**, 602-9 (2000).

19. David D. Davey, Marc Adler, Damian Arnaiz, Keith Eagen, Shawn Erickson, William Guilford, Margaret Kenrick, Michael M. Morrissey, Mike Ohlmeyer, Gonghua Pan, Vidyadhar M. Paradkar, John Parkinson, Mark Polokoff, Kurt Saionz, Cecile Santos, Babu Subramanyam, Ron Vergona, Robert G. Wei, Marc Whitlow, Bin Ye, Zuchun (Spring) Zhao, James J. Devlin, and Gary Phillips, Design, Synthesis, and Activity of 2-Imidazol-1-ylpyrimidine Derived Inducible Nitric Oxide Synthase Dimerization Inhibitors *J. Med. Chem.* **50**, 1146-1157, (2007).

20. A. V. et al, Synthesis of 2-(Pyrazol-1-yl)pyrimidine Derivatives by Cyclocondensation of Ethyl Acetoacetate (6-Methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone with Aromatic Aldehydes Erkin, *Russian Journal of General Chemistry (Translation of Zhurnal Obshchei Khimii)*, **74**(3), 423-427; (2004).

21. Zoltan Kaleta, Gabor Tarkanyi, AÄgnes Gomory, Ferenc Kalman, Tama´s Nagy, and Tibor Soos, Synthesis and Application of a Fluorous Lawesson's Reagent: Convenient Chromatography-Free Product Purification, Organic Letters **8**, 6, 1093-1095, (2006); One-pot synthesis of 5-(substituted-amino)pyrazoles Dharmpal S. Dodd, and Rogelio L. Martinez, Tetrahedron Letters **45**, 4265–4267 (2004).

22. Arup Maiti, P. V. Narasimha Reddy, Megan Sturdy, Laura Marler, Scott D. Pegan, Andrew D. Mesecar, John M. Pezzuto, and Mark Cushman, Synthesis of Casimiroin and Optimization of Its Quinone Reductase 2 and Aromatase Inhibitory Activities *J. Med. Chem.* **52**, 1873–1884, (2009).

23. A. M. Hussein, A. A. Harb, and I. A. Mousa Oxoanilides in Heterocyclic Synthesis: An Expeditious Synthesis of New Polyfunctionally Substituted Pyridine and Pyrazole Derivatives *J. Heterocyclic Chem.*, **45**, 1819 (2008).

24. Khimiya Geterotsiklicheskikh Soedinenii, (**7**), 963-7; 1981; WO 2007027842; WO 2009031687; WO 2009099193 (Japanese).

25. James Schulte II, Scott R. Tweedie Palladium-Catalyzed Couplings of Heteroaryl Amines with Aryl Halides Using Sodium Phenolate as the Stoichiometric Base *Synlett* 2331, (2007); WO 2008042639; WO 2010020363.

26. Marion C. Lanier, Manisha Moorjani, Zhiyong Luo, Yongsheng Chen, Emily Lin, John E. Tellew, Xiaohu Zhang, John P. Williams, Raymond S. Gross, Sandra M. Lechner, Stacy Markison, Tanya Joswig, William Kargo, Jaime Piercey, Mark Santos, Siobhan Malany, Marilyn Zhao, Robert Petroski, Mari´a I. Crespo, Jose´-Luis Di´az, John Saunders, Jenny Wen, Zhihong O'Brien, Kayvon Jalali, Ajay Madan, and Deborah H. Slee, *J Med Chem* 52, 709 (2009); Thomas M. Stevenson, Thomas P. Selby, Gerard M.

Koether, Joseph E. Drumm, Xian J. Meng, M. P. Moon, Reed A. Coats, Tho V. Thieu, Albert E. Casalnuovo, and Rafael Shapiro 2-Azolyl-4-Benzylpyrimidine Herbicides: Novel Inhibitors of Carotenoid Biosynthesis Part II *Chem of Agrochem* 85 (2001).

27. David Font,a Anthony Linden, Montserrat Herasa, and Jose´ M. Villalgordoa, A simple approach for the regioselective synthesis of imidazo[1,2-a]pyrimidiones and pyrimido[1,2-a]pyrimidinones *Tetrahedron* **62**(7), 1433-144 (2006); Herman Gershon, Anthony Grefic, and Donald D. Clarke, Pyrimidines. 8. Chlorination of 6-methyluracil with Phosphorus Oxychloride in the Presence of Trialkyamines, *Journal of Heterocyclic Chemistry* **24**(1), 205-9 (1987); Herman Gershon and Anthony Grefig, Primidines. 7. A study of the Chlorination of Pyrimidines with Phosphorus Oxychloride in the Presence of N,N-Dimethylaniline *Journal of Heterocyclic Chemistry* **21**(4), 1161-7 (1984).

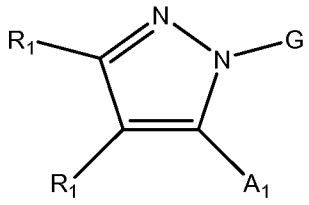
28. Hutt, D.M., Herman. D., Rodrigues, A.P.C., Noel, S., Pilewski, J.M., Matteson, J., Hoch, B., Kellner, W., Kelly, J.W., Schmidt, A., Thomas, P.J., Matsumura, Y., Skach, W.R., Gentzsch, M., Riordan, J.R., Sorscher, E.J., Okiyoneda, T., Yates, J.R. III, Lukacs, G.L., Frizzell, R.A., Manning, G., Gottesfeld, and J.M., Balch, W.E. Reduced histone deacetylase 7 activity restores function to misfolded CFTR in cystic fibrosis. *Nature: Chemical Biology*. **2010**, *6(1),* 25-33.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A compound having the Formula (Ia):



(Ia);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G is a 3- to 7-membered optionally substituted heterocyclic or an optionally substituted heteroaryl, each optionally substituted;

A_1 is $N(R_a)_2$;

each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

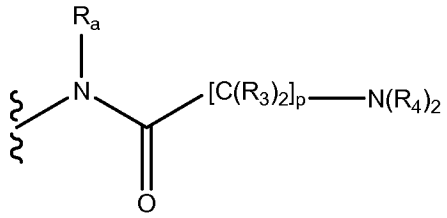
each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are

attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

2. The compound of claim 1, wherein A_1 is:



;

wherein p is 0, 1, 2 or 3;

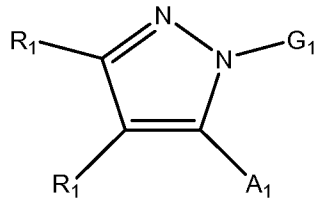
each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the atom to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; or yet alternatively, two vicinal R_3 groups can be taken together with the atoms to which they are attached to form a C_3-C_8 cycloalkyl, C3-C8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

each R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or alternatively, the two R_4 groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl.

3. The compound of any one of claims 1 to 2, wherein G is selected from the group consisting of aziridinyl, azetidinyl, azolidinyl, oxolanyl, thiophenyl, furanyl, pyrrolyl,

pyrazolyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, piperidinyl, pyridyl, pyrimidyl, diazinyl, triazinyl, tetrahydropyranyl each optionally substituted.

4. A compound having the Formula (Ib):



(Ib);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_1 is optionally substituted pyridyl or optionally substituted pyrimidyl;

A_1 is $N(R_a)_2$;

each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

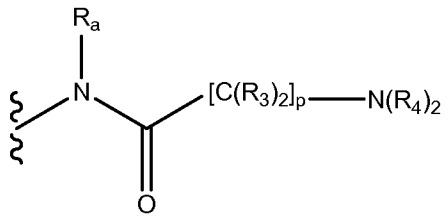
each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl, or two R_b groups are taken together with the atom which they are

attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

5. The compound of claim 4, wherein A_1 is:



;

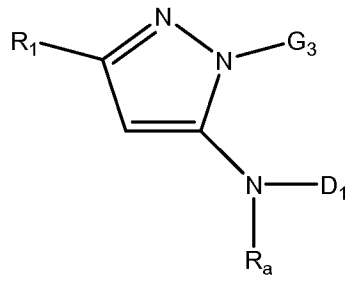
wherein p is 0, 1, 2 or 3;

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; or yet alternatively, two vicinal R_3 groups can be taken together with the atoms to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

each R_4 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or alternatively, the two R_4 groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl.

6. The compound of claim 5, wherein G_1 is an optionally substituted pyrimidyl.

7. A compound having the Formula (IIa):



(IIa);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 8-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

D_1 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-

C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

8. The compound of claim 7, wherein G_3 is a 3- to 8-membered heterocyclic or a heteroaryl, each optionally substituted.

9. The compound of claim 8, wherein G_3 is an optionally substituted, 3- to 8-membered heterocyclic.

10. The compound of claim 8, wherein G_3 is an optionally substituted heteroaryl.

11. The compound of any one of claims 7 to 10, wherein R_1 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

12. The compound of any one of claims 7 to 10, wherein R_1 is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl.

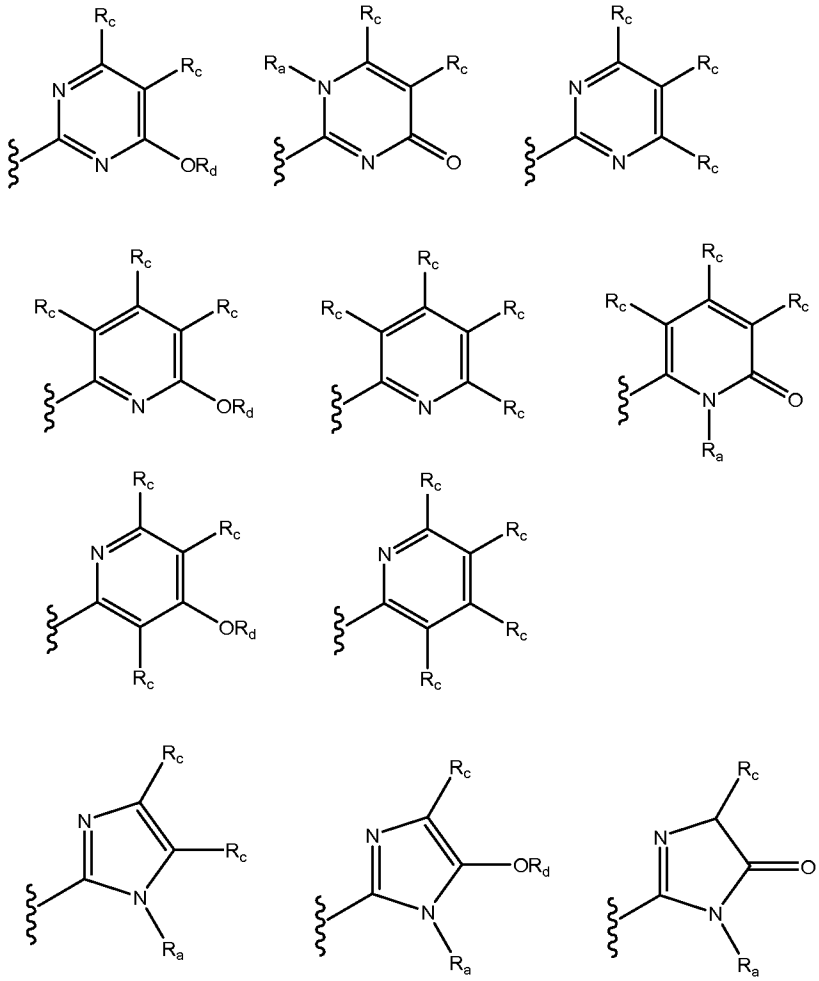
13. The compound of any one of claims 7 to 12, wherein D_1 is phenyl substituted with one or more groups selected from optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, and optionally substituted C_2-C_{10} alkynyl.

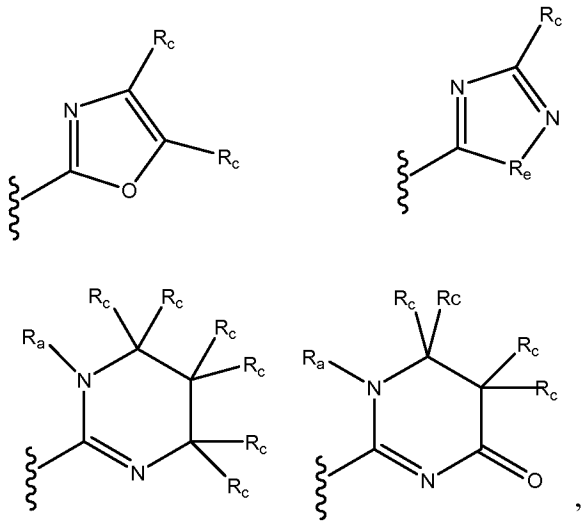
14. The compound of any one of claims 7 to 13, wherein R_a is selected from the group consisting of hydrogen, and optionally substituted C_1-C_{10} alkyl.

15. The compound of any one of claims 7 to 14, wherein G_3 is selected from the group consisting of aziridinyl, azetidinyl, azolidinyl, oxolanyl, thiophenyl, furanyl, pyrrolyl, pyrazolyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, thiadiazolyl, triazolyl, tetrazolyl, piperidinyl, pyridyl, pyrimidyl, diazinyl, triazinyl, tetrahydropyranyl, each optionally substituted.

16. The compound of claim 15, wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

17. The compound of any one of claims 7 and 11 to 14, wherein G_3 is selected from the group consisting of:





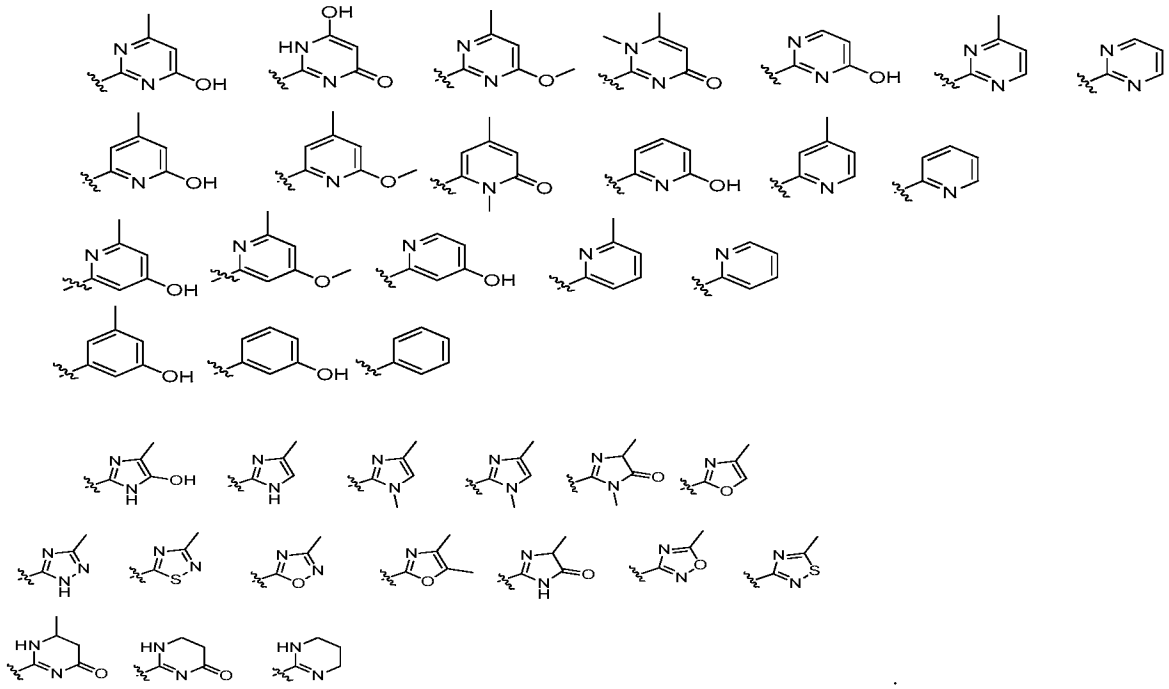
wherein:

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

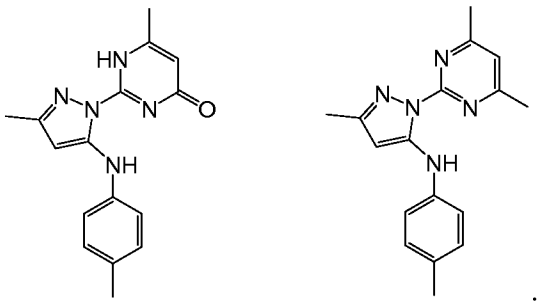
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; and

R_e is $N(R_a)$, O, or S.

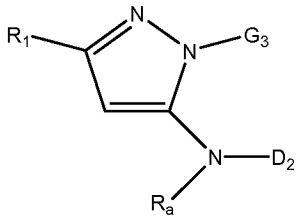
18. The compound of any one of claims 7 and 11 to 14, wherein G_3 is selected from the group consisting of:



19. The compound of claim 7, wherein the compound is selected from the group consisting of:



20. A compound having the Formula (IIb):



(IIb);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

D_2 is selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted benzyl, optionally substituted heteroaryl, and $C(R_5)_3$;

each R_5 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, two R_5 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

n is 0, 1 or 2.

21. The compound of claim 20, wherein G_3 is 3- to 8-membered heterocyclic or heteroaryl, each optionally substituted.

22. The compound of claim 21, wherein G_3 is an optionally substituted, 3- to 8-membered heterocyclic.

23. The compound of claim 21, wherein G_3 is optionally substituted heteroaryl.

24. The compound of any one of claims 20 to 23, wherein R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

25. The compound of claim 24, wherein R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

26. The compound of any one of claims 20 to 25, wherein D_2 is selected from the group consisting of optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted benzyl, and optionally substituted heteroaryl.

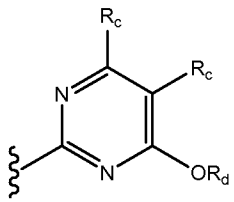
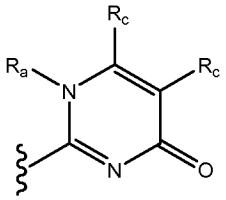
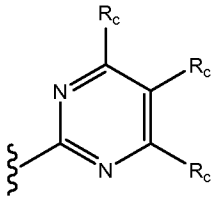
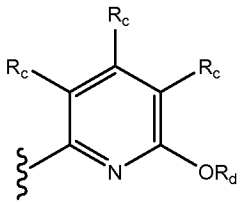
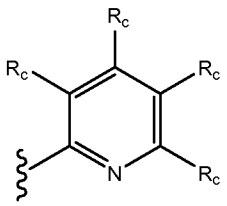
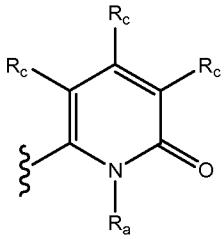
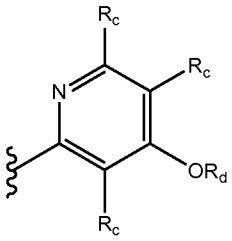
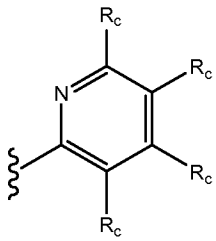
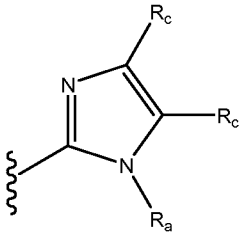
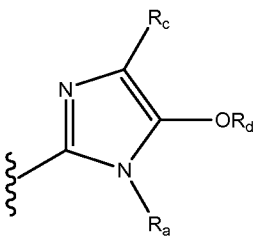
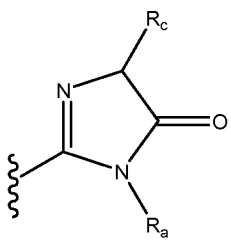
27. The compound of any one of claims 20 to 25, wherein D_2 is $C(R_5)_3$, wherein each R_5 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl,

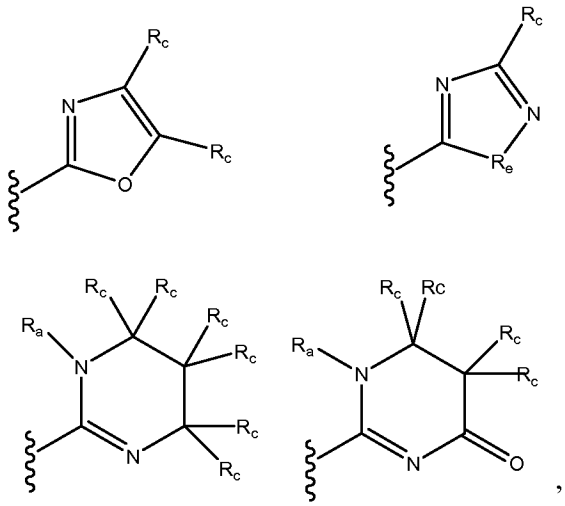
optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl.

28. The compound of any one of claims 20 to 27, wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

29. The compound of claim 28, wherein G_3 is optionally substituted pyrimidyl.

30. The compound of any one of claims 20 and 24 to 27, wherein G_3 is selected from the group consisting of:



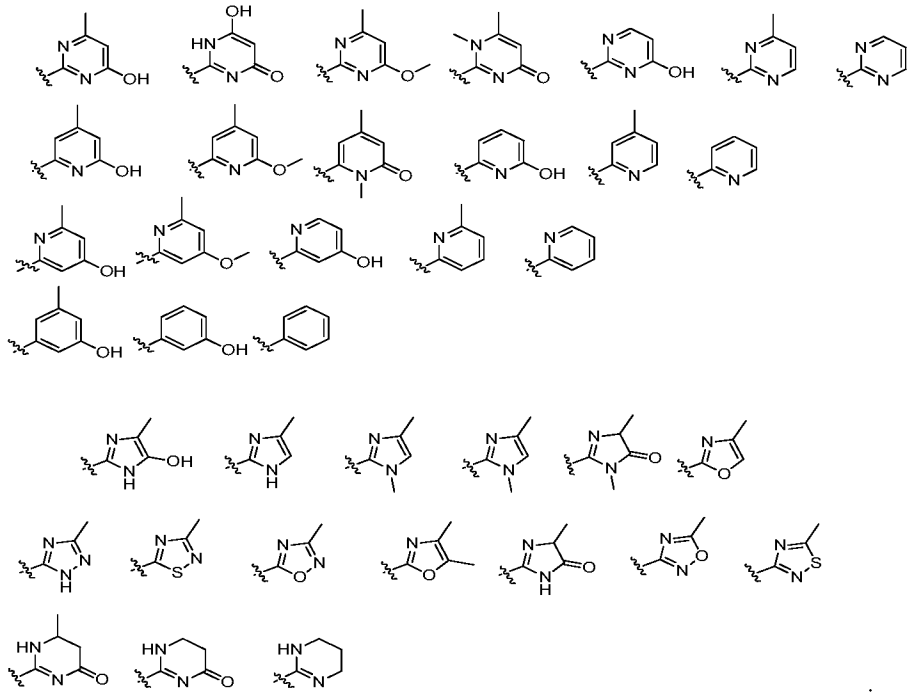
wherein:

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

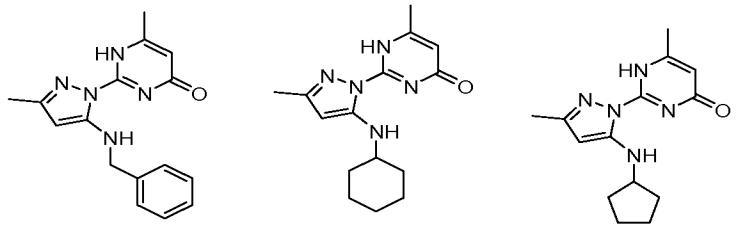
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; and

R_e is $N(R_a)$, O, or S.

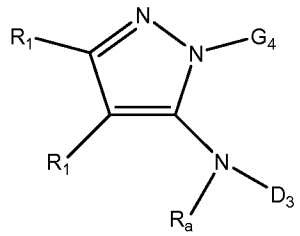
31. The compound of any one of claims 20 and 24 to 27, wherein G_3 is selected from the group consisting of:



32. The compound of claim 20 selected from the group consisting of:



33. A compound having the Formula (IIc):



(IIc);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_4 is a 6-membered heteroaryl containing one or more ring nitrogen atoms;

D_3 is optionally substituted aryl or optionally substituted heteroaryl;

each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

34. The compound of claim 33, wherein R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

35. The compound of claim 34, wherein R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

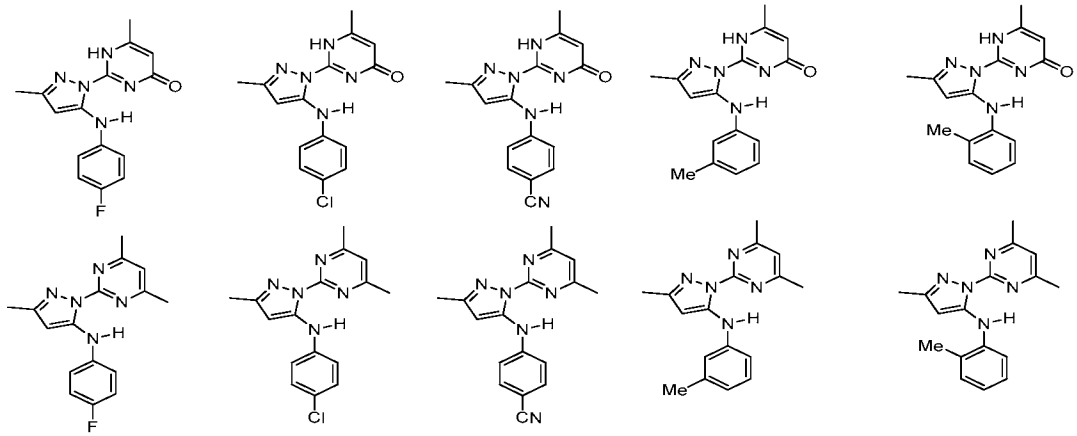
36. The compound of any one of claims 32 to 35, wherein G_4 is selected from the group consisting of optionally substituted pyridyl, optionally substituted pyrimidyl, optionally substituted diazinyl, and optionally substituted traizinyl.

37. The compound of claim 36, wherein G_4 is optionally substituted pyrimidyl.

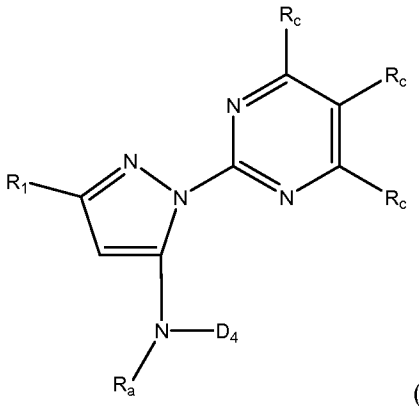
38. The compound of any one of claims 32 to 37, wherein D_3 is optionally substituted phenyl.

39. The compound of any one of claim 38, wherein D_3 is phenyl substituted with one or more optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$.

40. The compound of claim 32, wherein the compound is selected from the group consisting of:



41. A compound having Formula (IId):



(IId);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein;

D_4 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$,

$NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

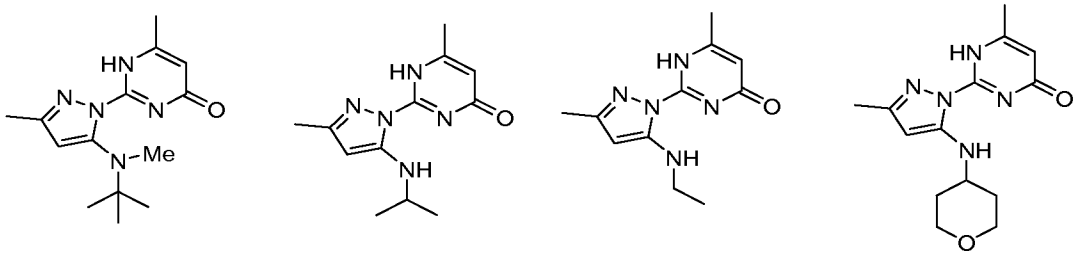
42. The compound of claim 41, wherein R_1 is independently selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

43. The compound of claim 42, wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

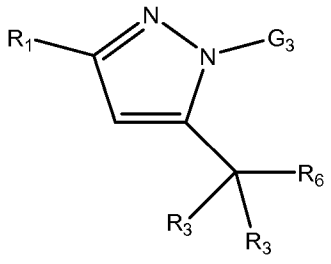
44. The compound of any one of claims 41 to 43, wherein each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl and OR_b.

45. The compound of claim 44, wherein each R_c is selected from the group consisting of hydroxyl and O-C_1-C_4 alkyl.

46. The compound of claim 41, wherein the compound is selected from the group consisting of:



47. A compound having the Formula (IIIa):



(IIIa);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_1 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$,

$OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, the two geminal R_3 groups can be taken together with the carbon atom to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl;

R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

48. The compound of claim 47, wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

49. The compound of claim 48, wherein R_1 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally

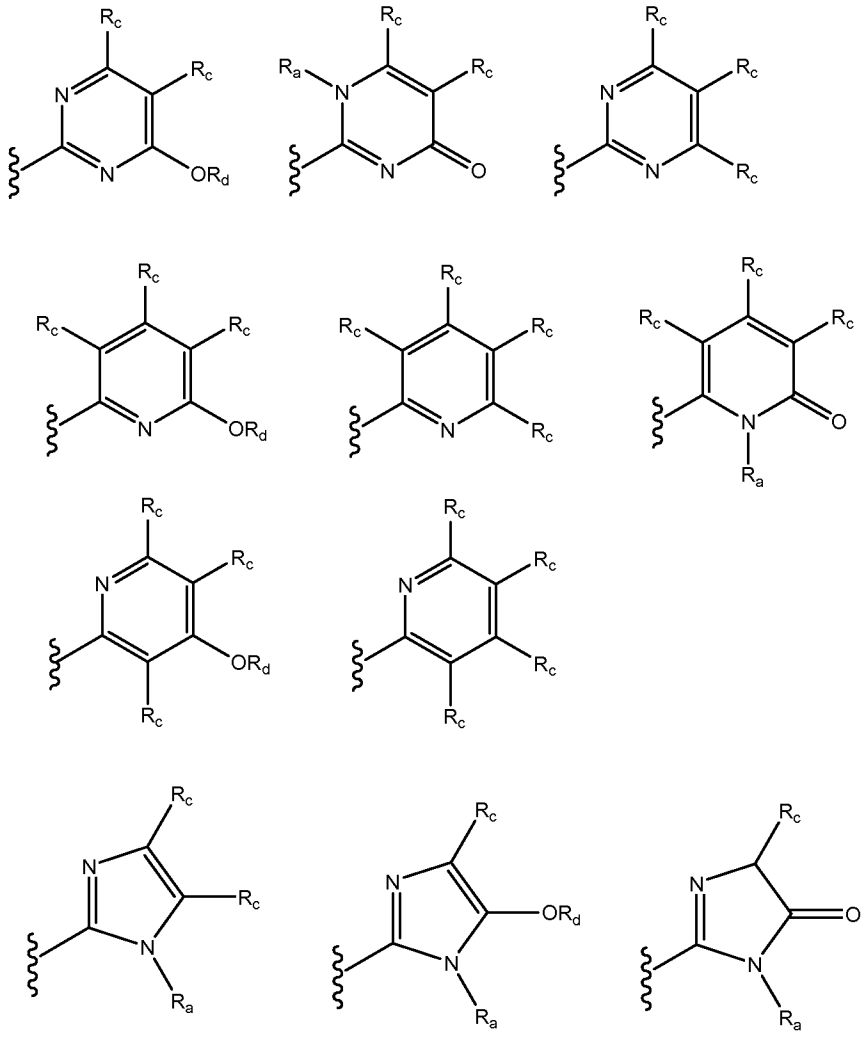
substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

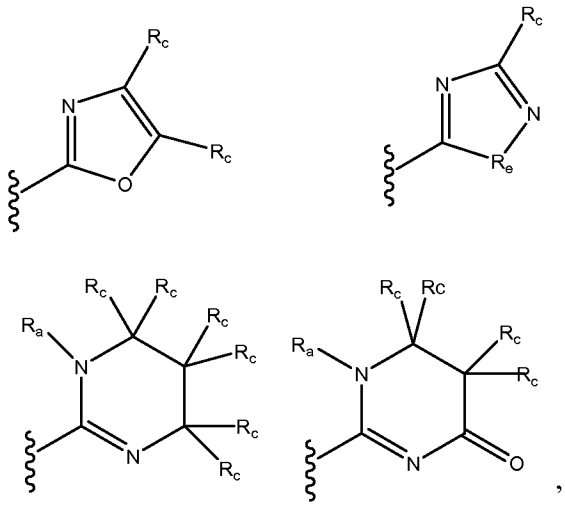
50. The compound of any one of claims 47 to 49, wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl.

51. The compound of claim 50, wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

52. The compound of claim 51, wherein G_3 is optionally substituted pyrimidyl.

53. The compound of claim 47, wherein G_3 is selected from the group consisting of:





wherein:

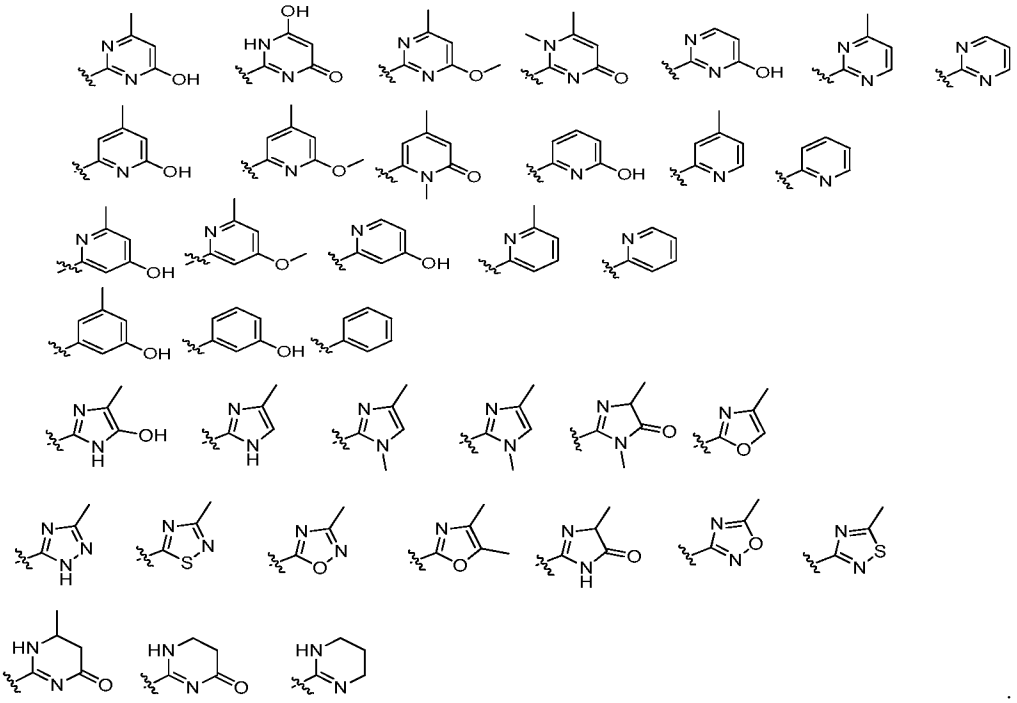
each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

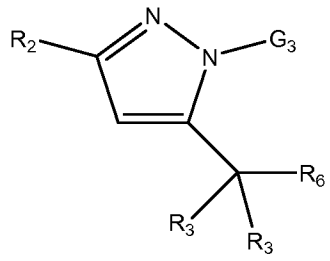
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; and

R_e is $N(R_a)$, O, or S.

54. The compound of claim 47, wherein G_3 is selected from the group consisting of:



55. A compound having the Formula (IIIb):



(IIIb);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, aryl, or heteroaryl, each optionally substituted;

R_2 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, and optionally substituted C_3-C_{12} cycloalkenyl;

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$,

$C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, the two geminal R_3 groups are taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl;

R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

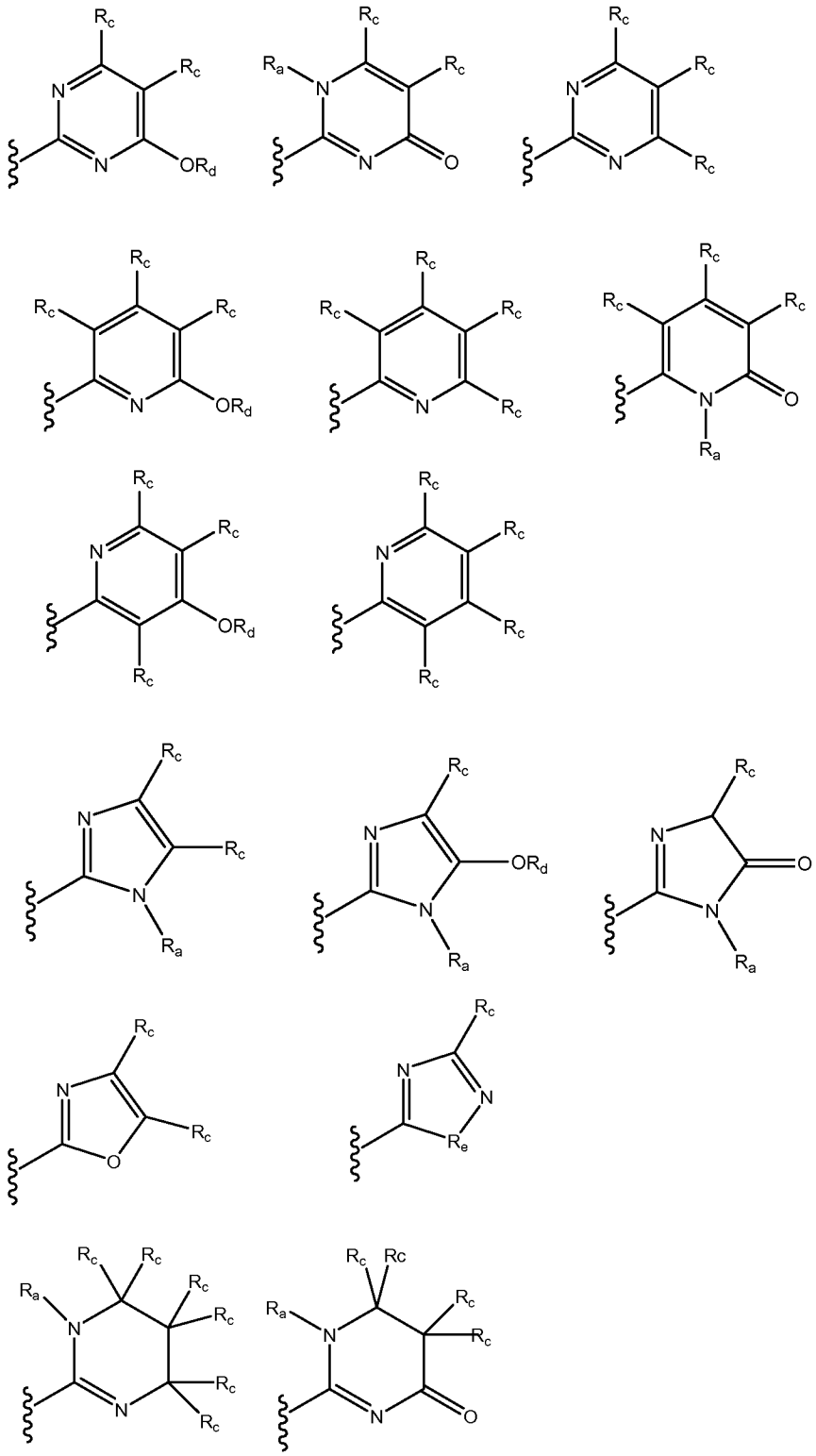
n is 0, 1 or 2.

56. The compound of claim 55, wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl.

57. The compound of claim 56, wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

58. The compound of claim 57, wherein G_3 is optionally substituted pyrimidyl.

59. The compound of claim 54, wherein G_3 is selected from the group consisting of:



wherein:

each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

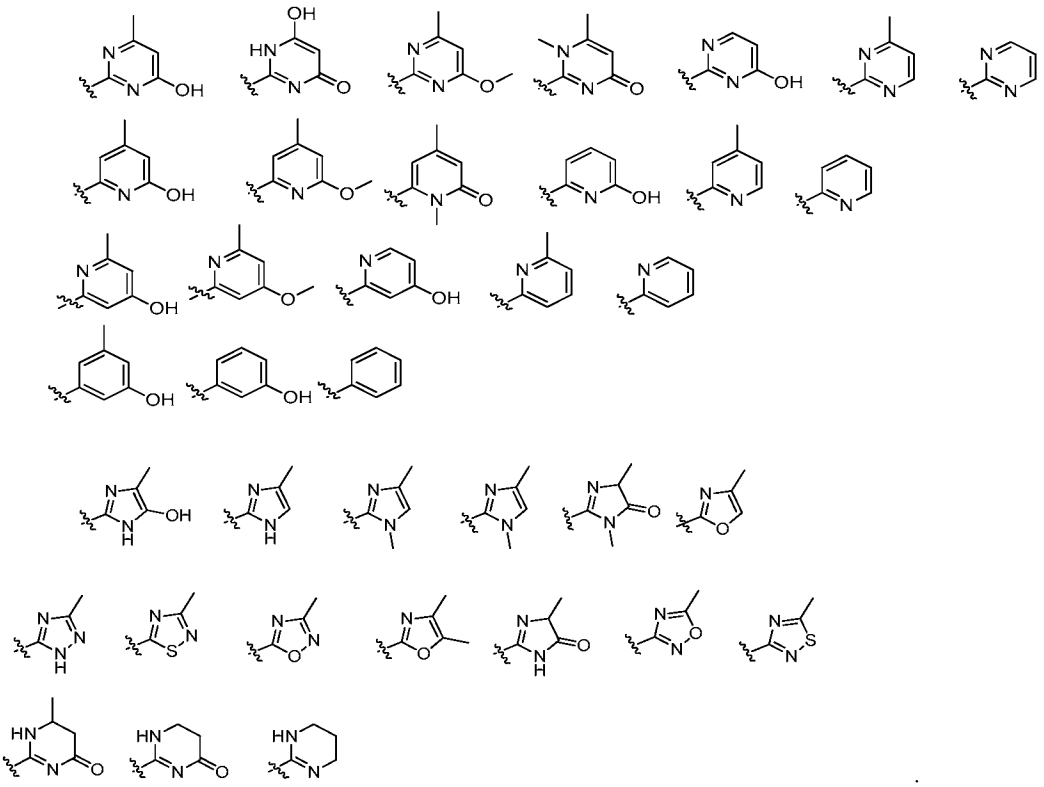
C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

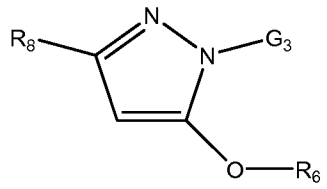
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl; and

R_e is $N(R_a)$, O, or S.

60. The compound of claim 54, wherein G_3 is selected from the group consisting of:



61. A compound having the Formula (IV):



(IV);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_3 is an optionally substituted 3- to 7-membered heterocyclic, an aryl, or a heteroaryl, each optionally substituted;

R_8 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

R_6 is phenyl substituted with one or more substituents selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

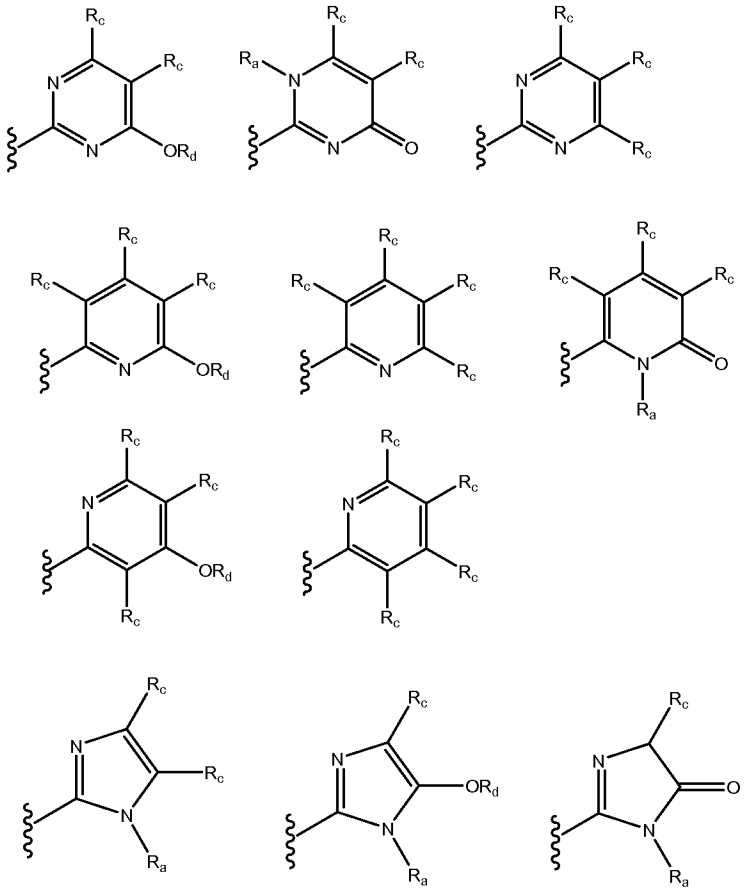
62. The compound of claim 61, wherein R_8 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, and optionally substituted C_3-C_{12} cycloalkenyl.

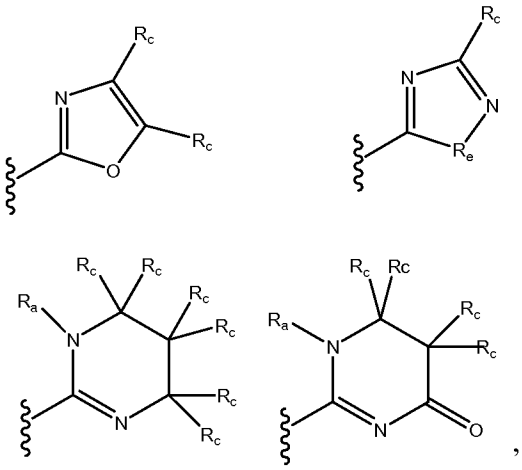
63. The compound of any one of claims 61 to 62, wherein G_3 is selected from the group consisting of optionally substituted heterocyclic and optionally substituted heteroaryl.

64. The compound of any one of claims 61 to 63, wherein G_3 is selected from the group consisting of optionally substituted pyridyl and optionally substituted pyrimidyl.

65. The compound of claim 64, wherein G_3 is optionally substituted pyrimidyl.

66. The compound of any one of claims 61 to 62, wherein G_3 is selected from the group consisting of:





wherein:

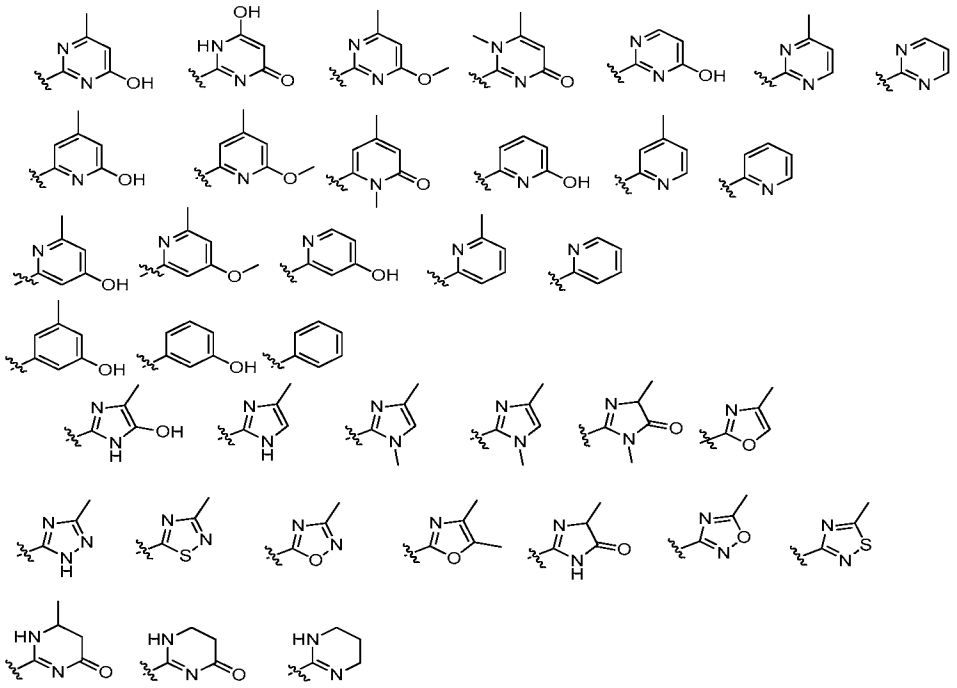
each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

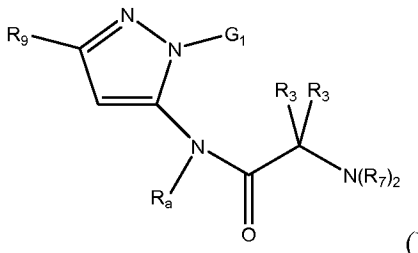
R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

R_e is $N(R_a)$, O, or S.

67. The compound of any one of claims 61 to 62, wherein G_3 is selected from the group consisting of:



68. A compound having the Formula (V):



(V);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_1 is an optionally pyridyl or an optionally substituted pyrimidyl;

R_9 is selected from the group consisting of substituted methyl, optionally substituted C_2-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted

C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl;

R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_7 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; alternatively, the two R_7 are taken together with the nitrogen atom to which they are attached to form a 3- to 7- membered heterocyclic or a heteroaryl;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

and

n is 0, 1 or 2.

69. The compound of claim 68, wherein R_9 is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$,

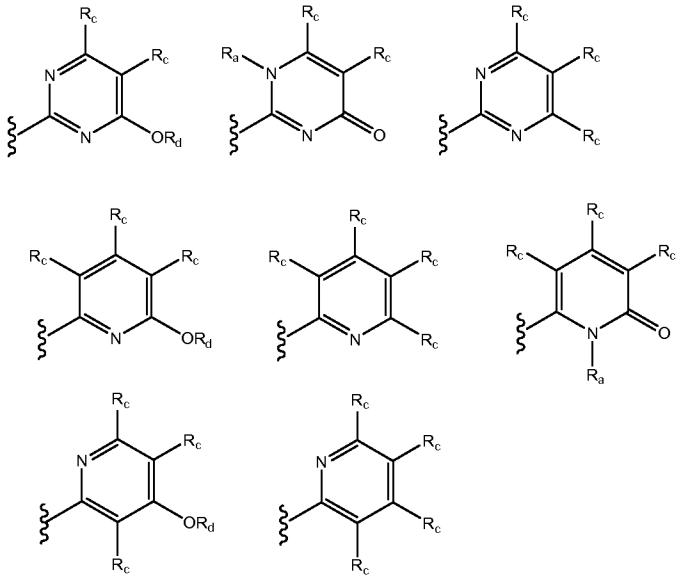
$NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

70. The compound of claim 69, wherein R_9 is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

71. The compound of any one of claims 69 to 70, wherein at least one R_3 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

72. The compound of any one of claims 69 to 71, wherein G_1 is optionally substituted pyrimidyl.

73. The compound of claim 69, wherein G_1 is selected from the group consisting of:



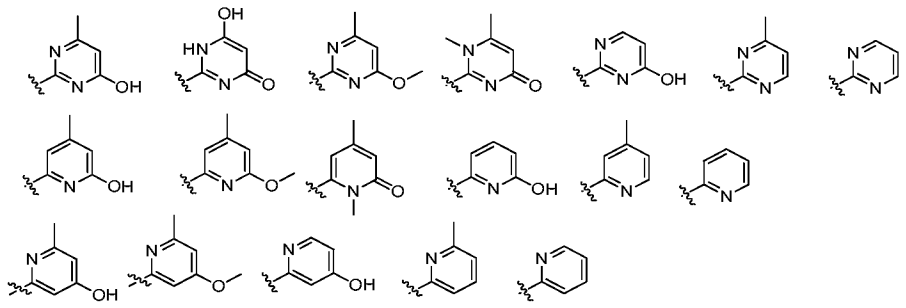
wherein:

each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

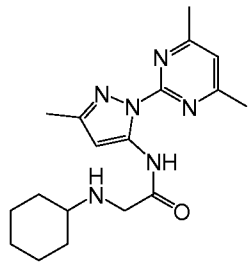
each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$; and

R_d is hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

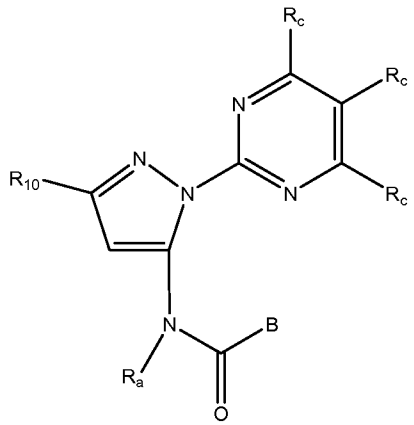
74. The compound of claim 69, wherein G_1 is selected from the group consisting of:



75. The compound of claim 69, wherein the compound is:



76. A compound having the Formula (VI):



(VI);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

B is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl;

R_{10} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl,

optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_a is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; wherein the two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

n is 0, 1 or 2.

77. The compound of claim 76, wherein R_{10} is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_4-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$,

$NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

78. The compound of claim 77, wherein R_{10} is selected from the group consisting of optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_4-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

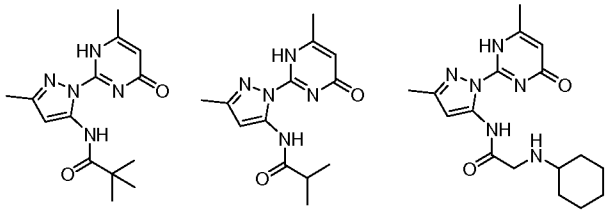
79. The compound of any one of claims 76 to 78, wherein B is $C(R_3)_2N(R_f)_2$: wherein each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, the two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; and

each R_f is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

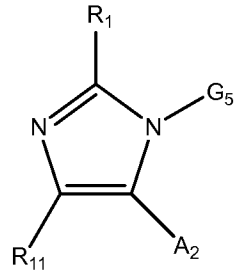
80. The compound of any one of claims 76 to 79, wherein each R_c is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_4 alkyl and OR_b.

81. The compound of claim 80, wherein each R_c is independently selected from the group consisting of hydroxyl and optionally substituted O-C_1-C_4 alkyl.

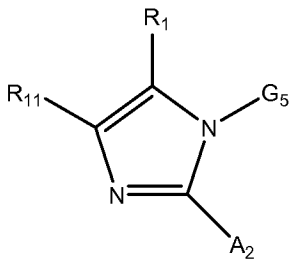
82. The compound of claim 76, wherein the compound is selected from the group consisting of:



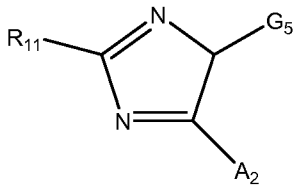
83. A compound having the Formula (VIIa), (VIIb) or (VIIc):



(VIIa)



(VIIb)



(VIIc);

or a pharmaceutically acceptable salt, prodrug or solvate thereof wherein:

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

R_{11} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$,

$NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl, or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

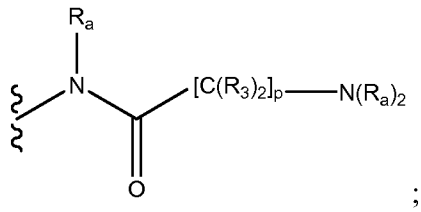
n is 0, 1 or 2.

84. The compound of claim 83, wherein the compound has the Formula (VIIa).

85. The compound of claim 83, wherein the compound has the Formula (VIIb).

86. The compound of claim 83, wherein the compound has the Formula (VIIc).

87. The compound of any one of claims 83 to 86, wherein A_2 is



;

wherein p is 0, 1, 2 or 3; and

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$,

$C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; or yet alternatively, two vicinal R_3 groups can be taken together with the atoms to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl.

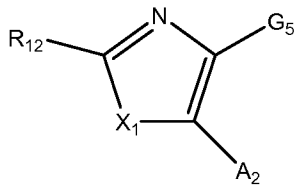
88. The compound of any one of claims 83 to 87, wherein R_{11} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

89. The compound of claim 88, wherein R_{11} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

90. The compound of any one of claims 83 to 89, wherein A_2 is NR_aR_g, wherein R_g is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, and $C(O)C(O)R_b$.

91. The compound of claim 90, wherein each R_g is optionally substituted aryl or optionally substituted heteroaryl.

92. A compound having the Formula (VIII):



(VIII);

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

X_1 is selected from the group consisting of O and S;

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

R_{12} is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups are taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

93. The compound of claim 92, wherein R_{12} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

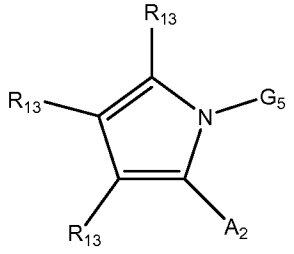
94. The compound of claim 93, wherein R_{12} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

95. The compound of any one of claims 91 to 93, wherein X_1 is O.

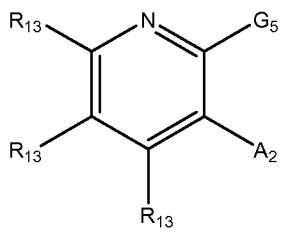
96. The compound of any one of claims 91 to 93, wherein X_1 is S.

97. The compound of any one of claims 91 to 96, wherein A_2 is NR_aR_g, wherein R_g is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, and $C(O)C(O)R_b$.

98. A compound having the Formula (IXa) or (IXb):



(IXa)



(IXb)

G_5 is optionally substituted pyrimidyl;

A_2 is $N(R_a)_2$;

each R_{13} is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

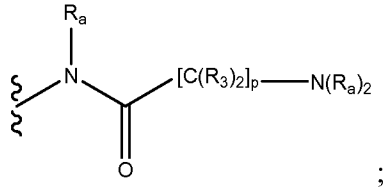
each R_a is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)C(O)R_b$ and $S(O)_nR_b$; or the two R_a groups can be taken together with the nitrogen atom which they are attached to form an optionally substituted 3- to 8-membered heterocyclic or optionally substituted heteroaryl;

each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl; or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted;

n is 0, 1 or 2; and

p is 0, 1, 2 or 3.

99. The compound of claim 98, wherein A_2 is:



;

wherein p is 0, 1, 2 or 3; and

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally

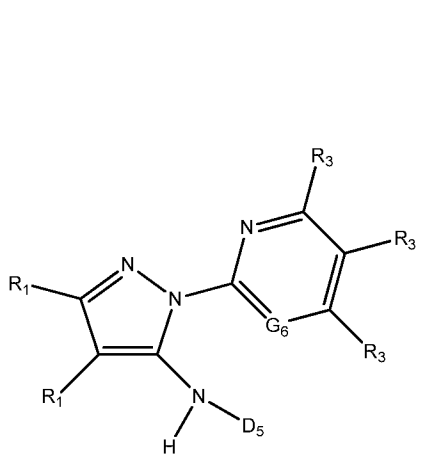
substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$; alternatively, two geminal R_3 groups can be taken together with the carbon to which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl; or yet alternatively, two vicinal R_3 groups can be taken together with the atoms to which they are attached to form a C_3-C_8 cycloalkyl, C3-C8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl.

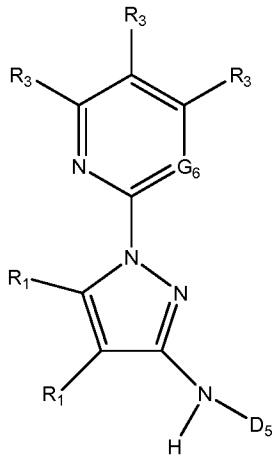
100. The compound of any one of claims 98 to 99, wherein at least one R_{13} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$.

101. The compound of claim 100, wherein at least one R_{13} is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl.

102. The compound of any one of claims 98 to 101, wherein A_2 is NR_aR_g, wherein R_g is optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, and $C(O)C(O)R_b$.

103. A compound represented by the Formula (Xa) or (Xb):


(Xa)


(Xb)

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

G_6 is nitrogen or C-H;

D_5 is selected from the group consisting of optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, $C(O)OR_b$, $C(O)R_b$, $C(O)NR_bR_b$, and $S(O)_nR_b$;

each R_1 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$, $C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C{=}NR_b)R_b$;

both R_1 can join with the carbon atoms to which they are attached to form an optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

each R_3 is independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, optionally substituted heteroaryl, halo, OR_b, SR_b, NR_bR_b, $C(O)OR_b$, NO_2, CN, $C(O)R_b$,

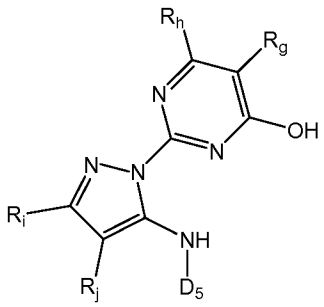
$C(O)C(O)R_b$, $C(O)NR_bR_b$, $NR_bC(O)R_b$, $NR_bC(O)N(R_b)_2$, $NR_bS(O)_nR_b$, $N(R_b)(COOR_b)$, $NR_bC(O)C(O)R_b$, $NR_bC(O)R_b$, $NR_bS(O)_nNR_bR_b$, $NR_bS(O)_nR_b$, $S(O)_nR_b$, $S(O)_nNR_bR_b$, $OC(O)OR_b$, and $(C=NR_b)R_b$;

alternatively, the two R_3 be taken together with the carbon atoms to ahich they are attached to form an optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl, and optionally substituted heteroaryl;

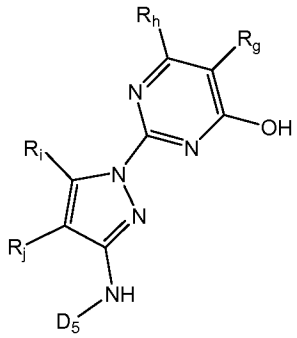
each R_b is independently selected from the group consisting of H, optionally substituted C_1-C_{10} alkyl, optionally substituted C_2-C_{10} alkenyl, optionally substituted C_2-C_{10} alkynyl, optionally substituted C_3-C_{12} cycloalkyl, optionally substituted C_3-C_{12} cycloalkenyl, optionally substituted heterocyclic, optionally substituted aryl and optionally substituted heteroaryl;or two R_b groups are taken together with the atom which they are attached to form a C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, 3- to 8-membered heterocyclic, aryl or heteroaryl, each optionally substituted; and

n is 0, 1 or 2.

104. The compound of claim 103 represented by Formula (XIa) or (XIb):



(XIa)



(XIb)

wherein

R_g and R_h are each independently hydrogen or C_1-C_6-alkyl, or R_g and R_h are taken with the carbon atoms to which they are attached to form an optionally substituted benzo ring;

R_i and R_j are each independently selected from hydrogen and C_1-C_6-alkyl; and

D_5 is C_1-C_6-alkyl, C_5-C_8-cycloalkyl, aryl-C_1-C_6-alkyl or optionally substituted phenyl.

105. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 1 to 104; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

106. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 1 to 3; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

107. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 4 to 6; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

108. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 7 to 19; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

109. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 20 to 32; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

110. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 33 to 40; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

111. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 41 to 46; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

112. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 47 to 54; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

113. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 55 to 60; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

114. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 61 to 67; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

115. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 68 to 75; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

116. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 76 to 82; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

117. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 83 to 91; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

118. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 92 to 97; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

119. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of any one of claims 98 to 102; or a pharmaceutically acceptable salt, solvate, or prodrug of any of thereof.

120. A method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering an effective amount of a compound of any one of claims 1 to 104.

121. A method of treating a patient suffering from a condition associated with a dysfunction in proteostasis comprising administering to said patient a pharmaceutical composition of any one of claims 105 to 119.

122. The method of any one of claims 120 and 121, wherein the condition is associated with a dysfunction in the proteostasis of a protein selected from the group consisting of

hexosamine A, cystic fibrosis transmembrane conductance regulator, aspartylglucsaminidase, α-galactosidase A, cysteine transporter, acid ceremidase, acid α-L-fucosidase, protective protein, cathepsin A, acid β-glucosidase, acid β-galactosidase, iduronate 2-sulfatase, α-L-iduronidase, galactocerebrosidase, acid α -mannosidase, acid β -mannosidase, arylsulfatase B, arylsulfatase A, *N*-acetylgalactosamine-6-sulfate sulfatase, acid β -galactosidase, *N*-acetylglucosamine-1-phosphotransferase, acid sphingmyelinase, NPC-1, acid α-glucosidase, β-hexosamine B, heparin *N*-sulfatase, α -*N*-acetylglucosaminidase, α -glucosaminide *N*-acetyltransferase, *N*-acetylglucosamine-6-sulfate sulfatase, α1 anti-trypsin, α -*N*-acetylgalactosaminidase, α -neuramidase, β -glucuronidase, β-hexosamine A and acid lipase, polyglutamine, α -synuclein, Aβ peptide, tau protein, hERG potassium channel, islet amyloid polypeptide, transthyretin Huntingtin, and superoxide dismutase.

123. The method of claim any one of claims 120 to 122, wherein the condition is selected from the group consisting of Huntington's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, cancer, diabetic retinopathy, diabetes, cancer and cystic fibrosis.

124. The method of claim 123, wherein the condition is cystic fibrosis.

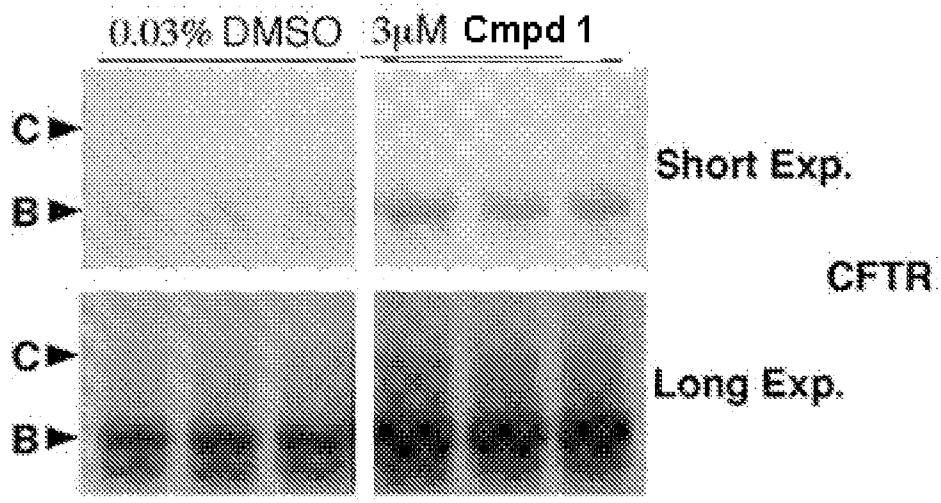
125. The method of any one of claims 120 to 122, wherein an effective amount of a second agent is also administered, wherein the second agent is selected from the group consisting of a proteostasis regulator and a pharmacologic chaperone.

126. A pharmaceutical composition comprising:

a pharmaceutically acceptable carrier or excipient;

an effective amount of a second agent selected from the group consisting of a proteostasis regulator and a pharmacologic chaperone; and

an effective amount of a compound of any one of claims 1 to 104.



THE FIGURE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/37159

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90 (2012.01)
USPC - 514/259.1
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)
USPC - 514/259.1 (see search terms below)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/259.3; 514/256 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO-WEST - PGPB,USPT,USOC,EPAB,JPAB keywords: pyrazole, derivatives, inhibition, CDK2, CDK4, CDK inhibitors, treatment, cancer, cystic fibrosis, pyrimidinyl, Alzheimer's, diabetes, administering, mammal, therapeutically effective amount, pharmaceutical composition, acceptable carrier, crystal structure, CDK4 inhibitors, inhibitor binding pocket.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0160324 A1 (BERDINI et al.) 24 June 2010 (24.06.2010), para [0082] - [0102]; [0105]; [0111]; [0146] - [0149]; [0151]; [0174] - [0175]; [0179]; [0183]; [0189]; [0192]; [0200]; [0202] - [0205]; [0212]; [0250]; [0426].	1-12, 19-25, 32-37, 40-63, 66-71, 73-79, 82-87, 92-94, 98-101, 103-104, 107 and 111-113
Y	IKUTA et al., Crystallographic Approach to Identification of Cyclin-dependent Kinase 4 (CDK4)-specific Inhibitors by Using CDK4 Mimic CDK2 Protein, J Biol Chem 276(29), pp 27548-27554, 2001, Abstract; pg 27551 - pg 27553.	1-12, 19-25, 32-37, 40-63, 66-71, 73-79, 82-87, 92-94, 98-101, 103-104, 107 and 111-113

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"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
13 July 2012 (13.07.2012)	03 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/37159

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.:
because they relate to subject matter not required to be searched by this Authority, namely:

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.: 13-18, 26-31, 38-39, 64-65, 72, 80-81, 88-91, 95-97, 102, 105-106, 108-110 and 114-126
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:

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.