

G PROTEIN-COUPLED RECEPTOR KINASE 2 (GRK2) DEGRADATION COMPOUNDS AND USE THEREOF

CROSS-REFERENCE

This application claims priority to the PCT application No. PCT/CN2023/075491 filed on February 10, 2023, the content of which is herein incorporated by reference in its entirety.

TECHNICAL FIELD

The present disclosure relates to novel compounds that degrade G protein-coupled receptor kinase 2 (GRK2) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof, pharmaceutical compositions comprising the same, kits comprising the same, and uses of the same in preventing or treating various diseases or conditions, e.g., diseases or conditions that are at least partially mediated by GRK2 or diseases or conditions that can be benefited from the degradation of GRK2.

BACKGROUND

GRK2, as the most ubiquitous and well-characterized member of G protein-coupled receptor kinases, is known to be widely expressed in a variety of organs and tissues, where it involves in the regulation of various intracellular mechanisms. Like other GRKs, GRK2 recognizes and phosphorylate agonist-activated G protein-coupled receptors (GPCRs) on certain amino acid residues, such as threonine and serine residues. After phosphorylation, the GPCRs undergo desensitization, which is believed to be an important mechanism for the individual to maintain homeostasis and prevent disorders. GRK2 can also bind and phosphorylate non-GPCR substrates, such as platelet-derived growth factor receptor- β (PDGFR β), EGFR, cytoskeletal proteins, transcription factors and certain mitochondrial proteins.

GRK2 has been suggested to be implicated in a great many diseases or conditions. In particular, GRK2 is known to play an essential role in the maintenance of heart structure and function. Consequently, dysregulation of GRK2 may contribute to the development of cardiovascular diseases or conditions. Besides, it is also known that the expression and/or function of GRK2 is changed in certain inflammations and cancers. Thus, inhibition of GRK2 has been proposed as a promising approach for the development of novel therapies for various diseases or conditions.

However, despite its therapeutic importance, relatively few examples of GRK2 degraders are known to date. Consequently, there is an enormous unmet need for novel compounds which can effectively degrade GRK2 and/or inhibit the activity of GRK2.

SUMMARY

Provided herein are novel compounds that degrade GRK2 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof, pharmaceutical compositions comprising the same, and kits comprising the same. Also provided herein are uses of the novel compounds or the pharmaceutical compositions in preventing or treating various diseases or conditions, e.g., diseases or conditions that are at least partially mediated by GRK2 or diseases or conditions that can be benefited from the degradation of GRK2.

In some aspects, the present disclosure provides a compound represented by Formula (1):

GBM-DT

(1)

or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof;

wherein:

GBM is a GRK2 binding moiety; and

DT is a degradation tag having E3 ligase binding capacity.

In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof and one or more pharmaceutically acceptable excipients.

In some aspects, the present disclosure provides a kit comprising a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein and optionally an instruction for use.

In some aspects, the present disclosure provides a method for preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject, comprising administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

In some aspects, the present disclosure provides a method for inhibiting the growth or preventing the relapse of a tumor in a subject, comprising administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

In some aspects, the present disclosure provides a method for degrading GRK2 or inhibiting the activity of GRK2 in a subject, comprising administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in therapy.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein and one or more pharmaceutically acceptable excipients, for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.

INCORPORATION BY REFERENCE

All publications, patent applications or patents cited in this specification are herein incorporated by reference to the same extent as if each individual publication, patent application or patent was individually and specifically indicated to be incorporated by reference. To the extent publications, patent applications or patents incorporated by reference contradict or are not consistent with the present disclosure contained in the specification, the specification is intended to take precedence over any such contradictory materials.

BRIEF DESCRIPTION OF THE DRAWINGS

The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of present disclosure are utilized, and the accompanying drawings of which:

Figure 1 shows the image of a PVDF membrane for cellular proteins extracted from PASMCs originated from human (h-PASMC) treated under hypoxic condition in the presence of various test substances.

Figure 2 shows the image of another PVDF membrane for cellular proteins extracted from h-PASMC treated under hypoxic condition in the presence of various test substances.

Figure 3 shows the ratio of the expression level of GRK2 to that of β -actin (represented by the ratio of "GRK2/ β -actin") in h-PASMC treated under hypoxic condition in the presence of various test substances.

Figure 4 shows the image of a PVDF membrane for cellular proteins extracted from PASMCs originated from mouse (m-PASMC) treated under hypoxic condition in the presence of various test substances.

Figure 5 shows the image of another PVDF membrane for cellular proteins extracted from m-PASMC treated under hypoxic condition in the presence of various test substances.

Figure 6 shows the ratio of the expression level of GRK2 to that of β -actin (represented by the ratio of "GRK2/ β -actin") in m-PASMC treated under hypoxic condition in the presence of various test substances.

Figure 7 shows the image of a PVDF membrane for cellular proteins extracted from PASMCs originated from rat (r-PASMC) treated under hypoxic condition in the presence of various test substances.

Figure 8 shows the image of another PVDF membrane for cellular proteins extracted from r-PASMC treated under hypoxic condition in the presence of various test substances.

Figure 9 shows the timeline for establishment of a pulmonary artery hypertension (PAH) model in mice.

Figure 10A shows the echocardiogram of the right heart of the mice from the normoxia group two weeks post modeling. Figure 10B shows the echocardiogram of the right heart of the mice from the hypoxia group two weeks post modeling. Figure 10C shows the echocardiogram of the right heart of the mice from the hypoxia + compound 1 group two weeks post modeling.

Figure 11A shows the data of body weight (g) of the mice from the hypoxia group and the hypoxia + compound 1 group two weeks post modeling. No statistical difference was found between the data of body weight of the two experimental groups. Figure 11B shows the data of the right ventricular internal dimension (RVID) (mm) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group two weeks post modeling. Figure 11C shows the data of the right ventricular anterior wall (RVAW) thickness (mm) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group two weeks post modeling.

Figure 12A schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the normoxia group two weeks post modeling. Figure 12B schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the hypoxia group two weeks post modeling. Figure 12C schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the hypoxia + compound 1 group two weeks post modeling.

Figure 13 shows the ratio of PAT/PET of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group two weeks post modeling.

Figure 14A schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the normoxia group two weeks post modeling. Figure 14B schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the hypoxia group two weeks post modeling. Figure 14C schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the hypoxia + compound 1 group two weeks post modeling.

Figure 15 shows the ratio of TVE/TVA (i.e., TV E/A) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group two weeks post modeling.

Figure 16A schematically shows the right ventricular systolic pressure (RVSP) of the mice from the normoxia group four weeks post modeling. Figure 16B schematically shows the

right ventricular systolic pressure (RVSP) of the mice from the hypoxia group four weeks post modeling. Figure 16C schematically shows the right ventricular systolic pressure (RVSP) of the mice from the hypoxia + compound 1 group four weeks post modeling.

Figure 17A shows the data of the right ventricular systolic pressure (RVSP) (mmHg) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling. Figure 17B shows the data of the right ventricular hypertrophy index (RVHI, calculated according to the formula of $RV/(LV + S)$) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling.

Figure 18A shows the echocardiogram of the right heart of the mice from the normoxia group four weeks post modeling. Figure 18B shows the echocardiogram of the right heart of the mice from the hypoxia group four weeks post modeling. Figure 18C shows the echocardiogram of the right heart of the mice from the hypoxia + compound 1 group four weeks post modeling.

Figure 19A shows the data of the right ventricular internal dimension (RVID) (mm) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling. Figure 19B shows the data of the right ventricular anterior wall (RVAW) thickness (mm) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling.

Figure 20A schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the normoxia group four weeks post modeling. Figure 20B schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the hypoxia group four weeks post modeling. Figure 20C schematically shows the pulmonary artery acceleration time (PAT) and pulmonary artery ejection time (PET) of the mice from the hypoxia + compound 1 group four weeks post modeling.

Figure 21 shows the ratio of PAT/PET of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling.

Figure 22A schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the normoxia group four weeks post modeling. Figure 22B schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the hypoxia group four weeks post modeling. Figure 22C schematically shows the blood flow velocity of tricuspid valve orifice E peak (TVE) and the blood flow velocity of tricuspid valve orifice A peak (TVA) of the mice from the hypoxia + compound 1 group four weeks post modeling.

Figure 23 shows the ratio of TVE/TVA (i.e., TV E/A) of the mice from the normoxia group, the hypoxia group and the hypoxia + compound 1 group four weeks post modeling.

Figure 24 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 2 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 2 plus 1 μ M MG132).

Figure 25 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 3 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 3 plus 1 μ M MG132).

Figure 26 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 20 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 20 plus 1 μ M MG132).

Figure 27 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 21 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 21 plus 1 μ M MG132).

Figure 28 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 22 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 22 plus 1 μ M MG132).

Figure 29 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 23 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 23 plus 1 μ M MG132).

Figure 30 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 25 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 25 plus 1 μ M MG132).

Figure 31 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 26 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 26 plus 1 μ M MG132).

Figure 32 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 27 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 27 plus 1 μ M MG132).

Figure 33 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 28 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 28 plus 1 μ M MG132).

Figure 34 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 29 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 29 plus 1 μ M MG132).

Figure 35 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 30 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 30 plus 1 μ M MG132).

Figure 36 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 33 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 33 plus 1 μ M MG132).

Figure 37 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 34 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 34 plus 1 μ M MG132).

Figure 38 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 35 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 35 plus 1 μ M MG132).

Figure 39 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 37 (20 μ M), MG132 (1 μ M) and the combination thereof (20 μ M compound 37 plus 1 μ M MG132).

Figure 40 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 1-P1 (0.1 nM, 1 nM, 10 nM, 100 nM, 1 μ M and 10 μ M).

Figure 41 shows the image of a PVDF membrane for cellular proteins extracted from h-PASMCs treated under hypoxic condition in the presence of compound 1-P2 (0.1 nM, 1 nM, 10 nM, 100 nM, 1 μ M and 10 μ M).

DETAILED DESCRIPTION

I. Definitions

Unless defined otherwise, all scientific and technical terms used in the present disclosure have the same meaning as is commonly understood by the person skilled in the art.

As used in the specification and claims, when referring to a noun as used in the present disclosure, unless the context clearly dictates otherwise, the singular form “a” or “an” encompasses both singular and plural units of the noun (i.e., encompasses the expression “at least one” or “one or more”), and vice versa.

As used in the specification and claims, ranges are intended to explicitly disclose each of the endpoints of the range and each integer included in the range, unless otherwise indicated. Additionally, any sub-ranges consisting of these integers are intended to be included within the scope of this disclosure.

The terms “GRK2” and “GRK2 protein” are used interchangeably and refer to G-protein-coupled receptor kinase 2, which belongs to the G-protein-coupled receptor kinase subfamily of the Ser/Thr protein kinases. GRK2 is known to be encoded by the ADRBK1 gene. It is intended that both wild-type GRK2 and natural variants of the same, such as those having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type GRK2, are encompassed by the terms.

The term “degrade(s)”, “degrading” or “degradation”, when used in the context of a protein (e.g., GRK2), refers to decomposing or metabolizing said protein *in vivo* or *in vitro*. Generally, degrading GRK2 leads to a reduction of the GRK2 activity or a downstream effect relative to a baseline or control level of GRK2 activity.

The term “degrader” refers to a small molecule compound, when interacts with a protein (e.g., GRK2) *in vivo* or *in vitro*, results in partial or complete degradation of the protein.

The term “degradation tag” refers to a moiety whose binding with E3 ligase results in partial or complete degradation of a protein (e.g., GRK2).

The term “moiety” is used interchangeably with “chemical moiety” or “structural fragment” and refers to a part or functional group of a molecule. A moiety may contain smaller moieties and functional groups.

The term “about”, when used in conjunction with a number, includes the specific point value as well as a range of the number (e.g., a range of $\pm 10\%$, $\pm 5\%$, $\pm 4\%$, $\pm 3\%$, $\pm 2\%$ or $\pm 1\%$ with respect to a specific point value) that is recognized as having substantially the same effect by the person skilled in the art.

The terms “comprise”, “include”, “contain” and variations thereof are intended to mean open-ended transitional phrases that do not exclude the possibilities of additional substances or methods. When such terms are used to describe a certain pharmaceutical composition, kit, use or method of the present disclosure, it also encompasses the situation that the pharmaceutical composition, kit, use or method consists of the recited substances or methods. In the context of this disclosure, the term “consisting of” is intended to mean a close-ended transitional phrase, which excludes the possibilities of additional substances or methods.

The term “C_{x-y}”, when used in conjunction with a chemical moiety such as alkyl, alkenyl, or alkynyl, is meant to include chemical moieties that contain from x to y carbons in the chain thereof. For example, the term “C₁₋₆ alkyl” refers to an alkyl, including straight-chain alkyl and branched-chain alkyl groups that contain from 1 to 6 carbons.

The term “alkyl” refers to a saturated monovalent linear or branched hydrocarbon group. An alkyl used in the context of the present disclosure may contain 1-20 carbon atoms (*i.e.*, C₁₋₂₀

alkyl), e.g., 1-18, 1-16, 1-14, 1-12, 1-10, 1-8, 1-6, 1-4, 1-3, or 1-2 carbon atoms. Examples of an alkyl group include, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, and decyl. An alkyl group is attached to the rest of the molecule by a single bond.

The term “alkenyl” refers to an unsaturated monovalent linear or branched hydrocarbon group comprising at least one C=C double bond. An alkenyl used in the context of the present disclosure may contain 2-20 carbon atoms (*i.e.*, C₂₋₂₀ alkenyl), e.g., 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, 2-4, 2-3, or 2 carbon atoms. Examples of the alkenyl group include, but not limited to ethenyl (*i.e.*, vinyl), prop-1-enyl, prop-2-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, pent-1-enyl, penta-1,4-dienyl, hex-1-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-1,3-dienyl, and the like.

The term “alkynyl” refers to an unsaturated monovalent linear or branched hydrocarbon group comprising at least one C≡C triple bond. An alkynyl used in the context of the present disclosure may contain 2-20 carbon atoms (*i.e.*, C₂₋₂₀ alkynyl), e.g., 2-18, 2-16, 2-14, 2-12, 2-10, 2-8, 2-6, 2-4, 2-3, or 2 carbon atoms. Examples of the alkynyl group include, but not limited to ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

The term “halogen” or “halo” refers to fluoro, chloro, bromo, or iodo.

The term “CN” or “cyano” refers to -C≡N.

The term “haloalkyl” refers to an alkyl group that is substituted by one or more halogens. Examples of the haloalkyl include, but not limited to fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1,2-difluoroethyl, 3-bromo-2-fluoropropyl, and 1,2-dibromoethyl.

The term “heteroalkyl” refers to an alkyl group, as defined above, wherein at least one of the constituent carbon atoms have been replaced by one or more heteroatoms. Examples of heteroatoms include, but not limited to O, N, P, Si, or S, preferably O, N, or S, wherein the N, S, or P atom may optionally be oxidized, and the N heteroatom may optionally be quaternized. Connection to the rest of the molecule may be through either a heteroatom or a carbon in the heteroalkyl group.

The term “carbocyclyl” refers to a non-aromatic ring or ring system in which each member atom of the ring or ring system is carbon. A “non-aromatic ring or ring system” refers to a carbocyclic or heterocyclic ring or ring system that does not meet the requirements set forth below for an aromatic ring or ring system, and can be either saturated or partially unsaturated. A carbocyclyl used in the context of the present disclosure typically contains 3-12 carbon atoms (*i.e.*, 3- to 12-membered carbocyclyl), e.g., 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-6, 4-5 or 5-6 carbon atoms. The carbocyclyl may be a monocyclic ring (e.g., 3- to 12-, 3- to 10-, 3- to 8-, 3- to 6-, 3- to

4-, or 5- to 6-membered) or a polycyclic ring, such as a bicyclic ring (e.g., 6- to 12-membered) or a tricyclic ring (e.g., 11- to 14-membered). Each ring of a polycyclic carbocyclyl may be selected from saturated, partially unsaturated and aromatic rings, provided that at least one ring of the polycyclic carbocyclyl is not an aromatic ring. Polycyclic carbocyclyl may be fused, bridged or spiro-ring systems. In some embodiments, the carbocyclyl is a cycloalkyl. In some embodiments, the carbocyclyl is a cycloalkenyl. In some embodiments, the carbocyclyl is a cycloalkynyl. In some embodiments, an aromatic ring, e.g., phenyl, may be fused to a saturated or partially unsaturated ring, e.g., cyclohexyl, cyclopentyl, or cyclohexenyl. Examples of the carbocyclyl include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclopentenyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexenyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclohexadienyl, adamantyl, 1,2-dihydronaphthalenyl, 1,4-dihydronaphthalenyl, tetraenyl, decalyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl.

The term “cycloalkyl” refers to a fully saturated carbocyclyl. A cycloalkyl used in the context of the present disclosure typically contains 3-12 carbon atoms (i.e., 3- to 12-membered cycloalkyl), e.g., 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-6, 4-5 or 5-6 carbon atoms. The cycloalkyl may be a monocyclic ring (e.g., 3- to 12-, 3- to 10-, 3- to 8-, 3- to 6-, 3- to 4-, or 5- to 6-membered) or a polycyclic ring, such as a bicyclic ring (e.g., 6- to 12-membered) or a tricyclic ring (e.g., 11- to 14-membered). Polycyclic cycloalkyls may be fused, bridged or spiro-ring systems. Examples of the monocyclic cycloalkyl include, but not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Examples of the bicyclic cycloalkyl include, but not limited to bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octanyl, and bicyclo[3.2.2]nonyl.

The term “aryl” refers to an aromatic ring or ring system wherein each of the atoms forming the ring or ring system is a carbon atom. An “aromatic ring or ring system” refers to a carbocyclic or heterocyclic ring or ring system that contains conjugated, planar ring systems with delocalized π electron orbitals comprised of $[4n+2]p$ orbital electrons, wherein n is an integer of 0 to 6. An aryl used in the context of the present disclosure typically contains 6-12 carbon atoms. The aryl may be a monocyclic aryl, for example, phenyl; a bicyclic aryl, for example, naphthyl and indenyl; and tricyclic aryl, for example, fluorenyl. Examples of the aryl include, but are not limited to phenyl and naphthyl.

The term “heterocyclyl” refers to a non-aromatic ring or ring system comprising one or more carbon atoms and one or more heteroatoms (e.g., 1, 2, 3, or 4, preferably 1 or 2 heteroatoms). A heterocyclyl used in the context of the present disclosure typically contains 3-12 member atoms (i.e., 3- to 12-membered heterocyclyl), e.g., 3-10, 3-9, 3-8, 3-7, 3-6, 3-5, 3-4, 4-6, 4-5 or 5-6

member atoms (i.e., carbon atoms or heteroatoms). Examples of heteroatoms include, but not limited to O, N, P, Si, or S, preferably O, N, or S, wherein the N, S, or P atom may optionally be oxidized, and the N heteroatom may optionally be quaternized. When the total number of S and O atoms in the heterocyclyl exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heterocyclyl is not more than 2, preferably not more than 1. The heterocyclyl may be a monocyclic ring (e.g., 3- to 12-, 3- to 10-, 3- to 8-, 3- to 6-, 3- to 4-, or 5- to 6-membered) or a polycyclic ring, such as a bicyclic ring (e.g., 6- to 12-membered) or a tricyclic ring (e.g., 11- to 14-membered). Each ring of a polycyclic heterocyclyl may be selected from saturated, partially unsaturated and aromatic rings, provided that at least one ring of the polycyclic heterocyclyl is not an aromatic ring. The heterocyclyl may be attached to the rest of the molecule through any atom of the heterocyclyl, valence permitting, such as a carbon or nitrogen atom of the heterocyclyl. Polycyclic heterocyclyls may be fused, bridged or spiro-ring systems. In some embodiments, the heterocyclyl is a heterocycloalkyl. In some embodiments, the heterocyclyl is a heterocycloalkenyl. In some embodiments, the heterocyclyl is a heterocycloalkynyl. Examples of the heterocyclyl include, but not limited to oxiranyl, aziridinyl, thiiranyl, azetidiny, oxetanyl, thietanyl, dithietanyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, oxathianyl, dioxepanyl, oxathiepanyl, oxaazepanyl, dithiepanyl, thiazepanyl, diazepanyl, dithianyl, azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranly, tetrahydrofuranly, tetrahydrothienyl, tetrahydropyranly, tetrahydrothiopyranly, pyrrolinyl, indolinyl, dioxanyl, dioxolanyl, pyrazolinyl, dithiolanyl, pyrazolidinyl, imidazolinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. It is understood that when referring to the number of carbon atoms in a heterocyclyl, the number of carbon atoms in the heterocyclyl is not the same as the total number of atoms (including the heteroatoms) that make up the heterocyclyl (i.e. member atoms of the heterocyclyl ring).

The term “heteroaryl” refers to an aromatic ring or ring system comprising one or more carbon atoms and one or more heteroatoms (e.g., 1, 2, 3, or 4, preferably 1 or 2 heteroatoms). A heteroaryl used in the context of the present disclosure typically contains 5-12 member atoms (i.e., 5- to 12-membered heteroaryl), e.g., 5-6 or 8-12 member atoms (i.e., carbon atoms or heteroatoms). Examples of heteroatoms include, but not limited to N, O, and S atoms. When the total number of S and O atoms in the heteroaryl exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl is not more than 2, preferably not more than 1. The heteroaryl may be a monocyclic ring (e.g., 5- to 6-

membered) or a polycyclic ring, such as a bicyclic ring (e.g., 8- to 12-membered) or a tricyclic ring (e.g., 11- to 14-membered). Examples of the heteroaryl group include, but are not limited to pyrazolyl, imidazolyl (such as 2,4-imidazolyl), imidazopyridinyl, pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl (such as 1-oxa-2,3-diazolyl, 1-oxa-2,4-diazolyl, 1-oxa-2,5-diazolyl, or 1-oxa-3,4-diazolyl), thiazolyl, isothiazolyl, thiadiazolyl (such as 1-thia-2,3-diazolyl, 1-thia-2,4-diazolyl, 1-thia-2,5-diazolyl, or 1-thia-3,4-diazolyl), triazolyl, pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, pyrimidinyl (such as 2,4-pyrimidinyl, or 3,5-pyrimidinyl), pyridazinyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, phthalazinyl, pyrazinyl, quinolinyl, isoquinolinyl, pyrrolopyridinyl, pyrazolopyridinyl, benzoxazolyl, pteridinyl, purinyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as 1H-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinolinyl.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbon atoms or heteroatoms that are substitutable, e.g., a nitrogen atom of a compound. Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left. For example, $-\text{CH}_2\text{O}-$ is equivalent to $-\text{OCH}_2-$. As used in the present disclosure, the term “substituted” is contemplated to include all permissible substituents of organic compounds, including acyclic and cyclic, linear and branched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this disclosure, heteroatoms such as nitrogen atom may have hydrogen substituents and/or any permissible substituents of organic compounds described in the present disclosure which satisfy the valences of the heteroatoms. Substituents can include any substituents described in the present disclosure, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, an acetyl or a formyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate group), an alkoxyl, a phosphoryl, a phosphate group, a phosphonate group, a phosphinate group, an amino, an amido, an amidine group, an imino, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate group, a sulfonate group, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, a carbocyclyl, a heterocyclyl, a cycloalkyl, a heterocycloalkyl, an aryl and an heteroaryl moiety. It is to be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, *i.e.*, a compound which does not spontaneously undergo transformation such as by rearrangement,

cyclization, elimination, etc. In some embodiments, “substituted” refers to moieties having substituents replacing two hydrogen atoms on the same carbon atom, such as substituting the two hydrogen atoms on a single carbon with an oxo, imino or thioxo group. It is to be understood by the person skilled in the art that substituents can themselves be substituted, if appropriate.

The term “optional(ly)” means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted aryl” means that the aryl group may or may not be substituted and that the aforesaid description includes both substituted aryl groups and unsubstituted aryl groups.

The term “isomers” refers to different compounds that have the same molecular formula. Certain compounds as described in the present disclosure contain one or more asymmetric centers and can thus give rise to stereoisomeric forms, including enantiomers, diastereomers, and other stereoisomers, the asymmetric centers of which can be defined, in terms of absolute stereochemistry, as (R)- or (S)-. The compounds as described in the present disclosure may in some embodiments exist as diastereomers, enantiomers, other stereoisomeric forms as well as the appropriate mixtures thereof. When a compound is a pure enantiomer, the stereochemistry at each chiral carbon can be specified by either R or S. “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” or “diastereomers” are stereoisomers that have at least two asymmetric atoms but are not mirror images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextrorotatory or levorotatory) in which they rotate plane polarized light at the wavelength of the sodium D line. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible stereoisomers, including racemic mixtures, optically pure forms, mixtures of diastereomers and intermediate mixtures. Optically active (R)- and (S)-isomers can be prepared using chiral synthons or chiral reagents or resolved using conventional techniques. The optical activity of a compound can be analyzed via any suitable method, including but not limited to chiral chromatography and polarimetry, and the degree of predominance of one stereoisomer over the other isomer can be determined. Unless mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is unspecified, all possible isomers are included.

The compounds as described in the present disclosure having carbon-carbon double bonds or carbon-nitrogen double bonds may exist in Z- or E- form (or cis- or trans- form).

Furthermore, some compounds as described in the present disclosure may exist in various tautomeric forms (i.e., tautomers). The term “tautomer” refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. In some embodiments, the compounds as described in the present disclosure may exist as tautomers. Under the circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers will be dependent on several factors, including temperature, solvent, physical state and pH. For example, compounds including $\text{-CH}_2\text{C(O)-}$ groups (keto forms) may undergo tautomerism to form -CH=C(OH)- groups (enol forms). Unless otherwise specified, the compounds as described in the present disclosure are intended to include all Z-, E- and tautomeric forms as well.

Separation of stereoisomers may be performed by chromatography or by forming diastereomers and separating by recrystallization, or chromatography, or any combination thereof. See Jean Jacques, Andre Collet, Samuel H. Wilen, “Enantiomers, Racemates and Resolutions”, John Wiley And Sons, Inc., 1981, herein incorporated by reference for this disclosure. Stereoisomers may also be obtained by stereoselective synthesis.

The term “isotope” refers to the compounds as described in the present disclosure wherein one or more of the atoms constituting the compounds are artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The compounds as described in the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^2H), tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^2H , ^{11}C , ^{13}C , ^{14}C , ^{15}C , ^{12}N , ^{13}N , ^{15}N , ^{16}N , ^{16}O , ^{17}O , ^{14}F , ^{15}F , ^{16}F , ^{17}F , ^{18}F , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{35}Cl , ^{37}Cl , ^{79}Br , ^{81}Br , and ^{125}I are all contemplated. All isotopes of the compounds as described in the present disclosure, whether radioactive or not, are encompassed within the scope of the present disclosure. For example, hydrogen has three naturally occurring isotopes, denoted ^1H (protium), ^2H (deuterium), and ^3H (tritium). Protium is the most abundant isotope of hydrogen in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increased in vivo half-life and/or exposure, or may provide a compound useful for investigating in vivo routes of drug elimination and metabolism. In some embodiments, the compounds as described in the present disclosure are deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. Radioactive isotopes, such as tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C) may be used in accordance with the present disclosure. Isotopically-enriched compounds may be prepared by conventional techniques well known to the person skilled in the art.

The term “prodrug” refers to any compounds which, under physiologic conditions, are converted into compounds as described in the present disclosure. In some embodiments, the compounds or salts thereof may exist as prodrugs, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or carboxylic acid present in the parent compound is presented as an ester. Prodrugs are useful because they may be easier to administer than the parent drug under some circumstances. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. Prodrugs may help enhance the cell permeability of a compound relative to the parent drug. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. Prodrugs may be designed as reversible drug derivatives, for use as modifiers to enhance drug transport to site-specific tissues or to increase drug residence inside of a cell. One method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to expose the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal such as specific target cells in the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids and esters of phosphonic acids) are preferred prodrugs of the present disclosure.

The term “solvate” refers to an aggregate that consists of a solute ion or molecule with one or more solvent molecules. The compounds as described in the present disclosure can exist in unsolvated forms as well as solvated forms (i.e., solvates) with one or more pharmaceutically acceptable solvents such as water (i.e., hydrate), ethanol (i.e., ethanolate), and the like. When the solvent is water, “solvate” is specifically termed as “hydrate”.

The term “polymorph” refers to various forms of a solid material that exists in more than one form. In the context of the present disclosure, the term “polymorph” encompasses both “amorphous form” and “crystalline forms”. Accordingly, the compounds as described in the present disclosure may be present as amorphous forms as well as crystalline forms.

The phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and other animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase “pharmaceutically acceptable excipient” refers to a pharmaceutically acceptable material, carrier, or vehicle which are used for the preparation of the pharmaceutical compositions or dosage forms in accordance with the present disclosure. Each excipient must be “acceptable” in the sense of being compatible with the other ingredients of the pharmaceutical compositions or dosage forms and not injurious to the patient.

The term “pharmaceutically acceptable salt” refers to salts derived from a variety of pharmaceutically acceptable organic or inorganic counter ions well known in the art. The compounds as described in the present disclosure which possess an acidic, a basic, or both functional groups, may react with any of a number of inorganic and organic acids and inorganic and organic bases to form a salt. Alternatively, compounds that are inherently charged, such as those with a quaternary nitrogen, can form a salt with an appropriate counterion, e.g., a halide ion such as bromide, chloride, or fluoride. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids or organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, glycolic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is selected from ammonium, potassium, sodium, calcium, and magnesium salts. Examples of suitable pharmaceutically acceptable salts can be found, for example, in S. M. Berge, *et al. J. Pharmaceutical Sciences*, 1977, 66, pp. 1 to 19.

The terms “subject”, “individual” and “patient” are used interchangeably and refer to humans as well as non-human mammals (e.g., non-human primates, canines, equines, felines, porcines, bovines, ungulates, lagomorphs, and the like). In some embodiments, the subject can be a human (e.g., male child, female child, adolescent male, adolescent female, adult male, adult female) under the care of a physician or other health worker in a hospital, as an outpatient, or other clinical context. In some embodiments, the subject may not be under the care or prescription of a physician or other health worker.

The phrase “a subject in need thereof” refers to a subject that suffers from, or is at risk for, a pathology to be preventively or therapeutically treated with a compound, a composition, or a dosage form as described in the present disclosure.

The terms “administer”, “administered”, “administers” and “administering” are defined as providing a compound, a composition, a formulation and/or a dosage form in accordance with

the present disclosure to a subject in need thereof via a route known in the art, including but not limited to oral, buccal, topical, transmucosal, transdermal, rectal, and parenteral routes of administration. In some embodiments, an oral route of administration is used. In some embodiments, a parenteral route of administration, including intravenous, intraarterial, intramuscular, subcutaneous, intraosseous, and intraperitoneal is used.

The term “effective amount” or “therapeutically effective amount” refers to that amount of a compound as described in the present disclosure that is sufficient to produce the intended application including but not limited to disease treatment, as defined below. The therapeutically effective amount may vary depending on the intended application (*in vitro* or *in vivo*), or the subject and disease or condition being treated, e.g., the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by the person skilled in the art. The term can also apply to a dose that can induce a particular response in target cells, e.g., up or down regulation of activity of a target protein. The specific dose can vary depending on the particular compounds chosen, the dosing regimen to be followed, whether it is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which it is carried.

The term “prevent”, “prevention” or “preventing” as related to a disease or condition may refer to a a compound, a composition, or a dosage form as described in the present disclosure that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated control sample. In some embodiments, for preventive benefit, the compound, composition, or dosage form as described in the present disclosure is administered to a subject at risk of developing a particular disease or condition, porting one or more of the physiological symptoms of a disease or condition, even though a diagnosis of this disease or condition may not have been made.

The term “treat”, “treatment” or “treating” refers to an approach for obtaining beneficial or desired results (i.e., therapeutic benefits) with respect to a disease or condition. In some embodiments, treat, treatment or treating involves administering a compound, a composition, a dosage form as described in the present disclosure to a subject. Treating can include, for example, reducing, delaying or alleviating the severity of one or more symptoms of the disease, disorder, or condition, or it can include reducing the frequency with which symptoms of a disease, defect, disorder, or adverse condition, and the like, are experienced by a patient. In some embodiments, a therapeutic benefit may include the eradication or amelioration of the underlying disorder being treated. In some embodiments, a therapeutic benefit may be achieved with the

eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder, such as observing an improvement in the subject, notwithstanding that the subject may still be afflicted with the underlying disorder.

II. Compounds

Provided herein are novel compounds that degrade GRK2 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof. The compounds are bivalent compounds including a GRK2 binding moiety conjugated to a degradation tag having E3 ligase binding capacity.

Without wishing to be bound by any particular theory, it is believed that, at least in some embodiments, attaching the degradation tag as described herein to the GRK2 binding moiety as described herein can recruit the corresponding ubiquitination machinery to GRK2, leading to the subsequent degradation of GRK2 in or near the proteasome and/or loss of function of GRK2.

Without wishing to be bound by any particular theory, it is believed that novel compounds as described herein which degrade GRK2 potentially are useful in preventing or treating various diseases or conditions, e.g., diseases or conditions that are at least partially mediated by GRK2 or diseases or conditions that can be benefited from the degradation of GRK2, including but not limited to a hyperproliferative disease (e.g., a tumor), a cardiovascular disease (e.g., hypertension, more specifically, pulmonary (arterial) hypertension), a hematological disease, an infective disease, an endocrinological disease, a metabolic disease, a gastroenterological disease, a respiratory disease, an inflammation, opioid addiction and a urological disease.

Thus, in some aspects, the present disclosure provides a compound represented by Formula (1):



(1)

or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof;

wherein:

GBM is a GRK2 binding moiety; and

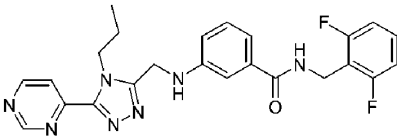
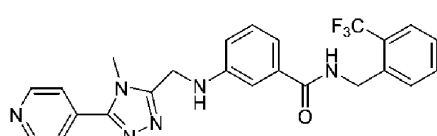
DT is a degradation tag having E3 ligase binding capacity.

In some embodiments, the GBM is a moiety derived from polyanionic and polycationic compounds.

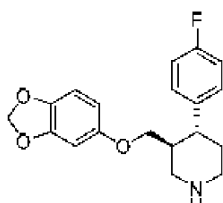
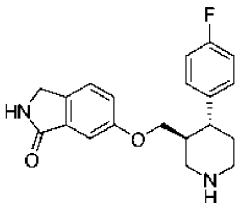
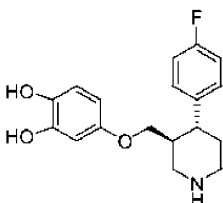
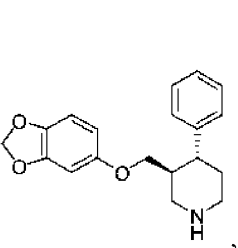
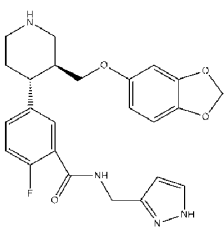
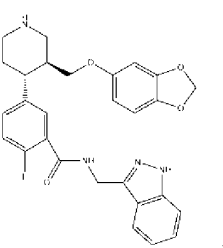
In some embodiments, the polyanionic and polycationic compounds is selected from heparin and dextran sulfate.

In some embodiments, the GBM is a moiety derived from balanol, or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

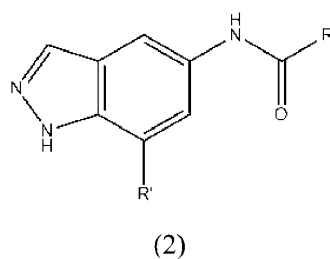
In some embodiments, the GBM is a moiety derived from Takeda inhibitors selected

from  and , or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

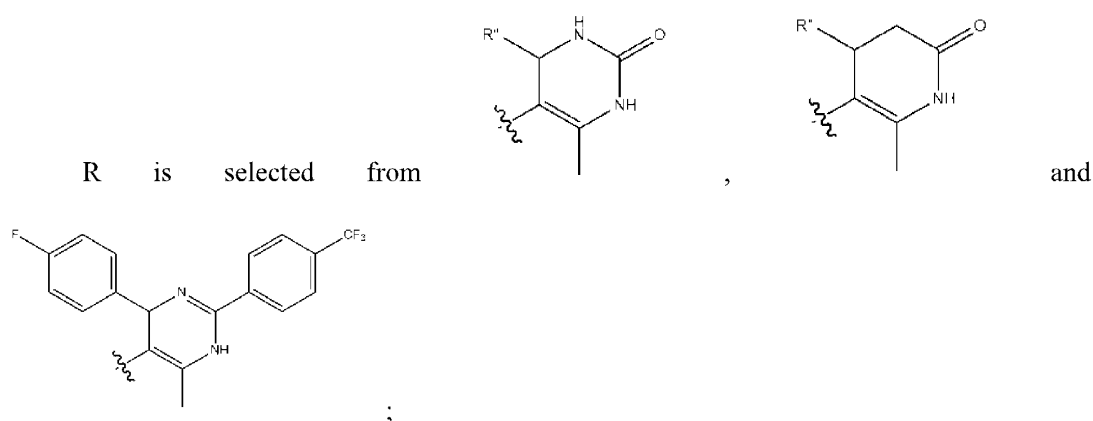
In some embodiments, the GBM is a moiety derived from paroxetine series selected

from , , , ,  and , or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

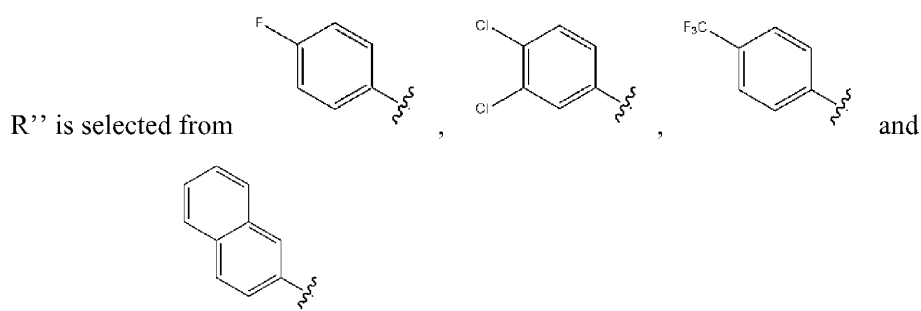
In some embodiments, the GBM is a moiety derived from indazole or dihydropyrimidine series represented by Formula (2), or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof



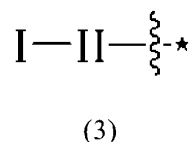
wherein



R' is selected from H and halogen; and



In some embodiments, the GBM is represented by Formula (3):

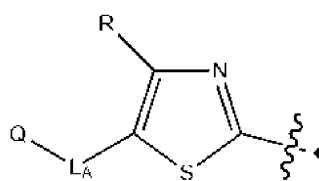


wherein $\star$ denotes the point of attachment with the DT;

the Formula I is a moiety covalently linked to the Formula II, wherein the Formula I comprises a thiazole ring or triazole ring in its backbone and is capable of binding to GRK2 by itself or along with the Formula II; and

the Formula II is a moiety covalently linked to both the Formula I and the DT, wherein the Formula II comprises an acyclic or cyclic saturated or unsaturated carbon, ethylene glycol group, amide group, ester group, amino group, oxy group, thio group, ether group, urea group, carbamate group, aromatic group, heteroaromatic group, heterocyclic group, carbonyl group or the combination thereof.

In some embodiments, the Formula I is represented by Formula (4):



(4)

wherein:

◆ denotes the point of attachment with the Formula II;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -

$\text{NR}_d\text{C}(=\text{O})\text{OR}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{SN}(=\text{O})$, $-\text{NR}_d\text{N}(=\text{O})$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

each of R_b and R_c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-\text{OR}_a$, $-\text{NR}_b\text{R}_c$, $-\text{C}(=\text{O})\text{R}_a$, $-\text{C}(=\text{O})\text{OR}_a$, $-\text{OC}(=\text{O})\text{R}_a$, $-\text{NO}_2$, $=\text{O}$, $-\text{CN}$ and C_{3-6} cycloalkyl.

In some embodiments, Q is selected from optionally substituted C_{1-6} alkyl, $-\text{OR}_a$, $-\text{SR}_a$, $-\text{NR}_b\text{R}_c$ and Cy.

In some embodiments, Q is selected from C_{1-6} alkyl, $-\text{SR}_a$, and Cy.

In some embodiments, Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

In some embodiments, Q is selected from isopropyl, isopropylthio and Cy.

In some embodiments, Q is Cy.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C_{3-8} carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R' .

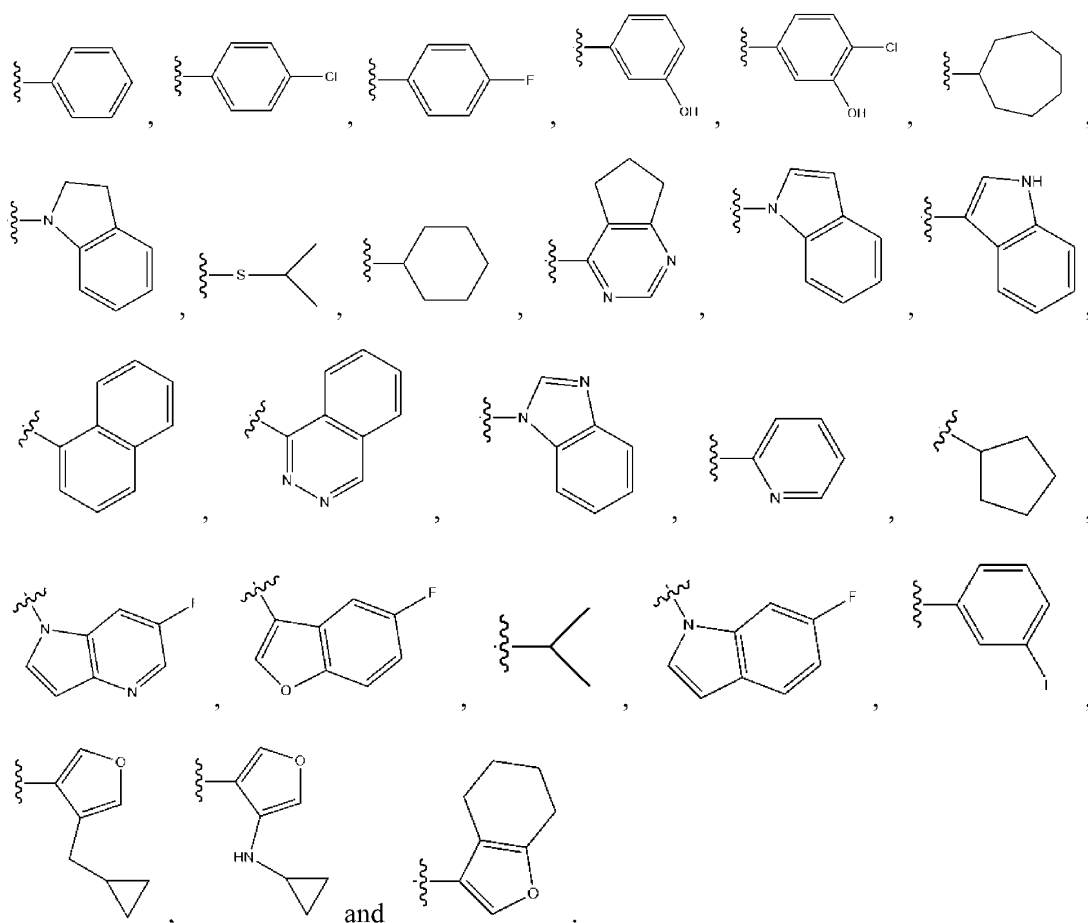
In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl,

carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridiny, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

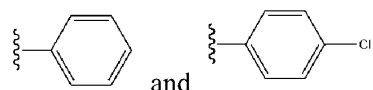
In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Q is selected from:



In some embodiments, Q is selected from:



In some embodiments, L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is $-CH_2-$.

In some embodiments, R is selected from H , halogen, $-CN$, $-NO_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

In some embodiments, R is selected from H , halogen, $-CN$, $-NO_2$, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

In some embodiments, R is selected from H , halogen, $-CN$, $-NO_2$, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

In some embodiments, R is selected from H , F , Cl , Br , methyl, ethyl, propyl, $-OH$, $-O(CH_3)$ and $-NH_2$.

In some embodiments, R is selected from H and $-OH$.

In some embodiments, R is H .

In some embodiments, each of R_1 and R_2 is independently selected from H , halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

In some embodiments, each of R_1 and R_2 is independently selected from H , halogen, C_1-C_6 alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

In some embodiments, each of R_1 and R_2 is independently selected from H , halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

In some embodiments, each of R_1 and R_2 is independently selected from H , F , Cl , Br , methyl, ethyl and propyl.

In some embodiments, each of R₁ and R₂ is independently selected from H and F.

In some embodiments, both of R₁ and R₂ are H.

In some embodiments, both of R₁ and R₂ are F.

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_a is independently H or isopropyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_d is independently H or methyl.

In some embodiments, a is selected from 0 and 1 and b is selected from 0 and 1.

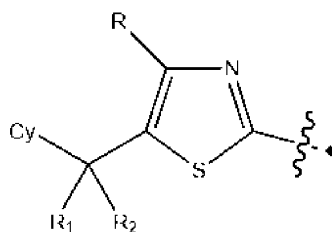
In some embodiments, a is 0 and b is 0.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

In some embodiments, the Formula I is represented by Formula (4A):



(4A)

wherein:

◆ denotes the point of attachment with the Formula II;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted

C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; and

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, C₁₋₆alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3

halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R₁ and R₂ is independently selected from H and F.

In some embodiments, both of R₁ and R₂ are H.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H and -OH.

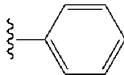
In some embodiments, R is H.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from:  and .

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

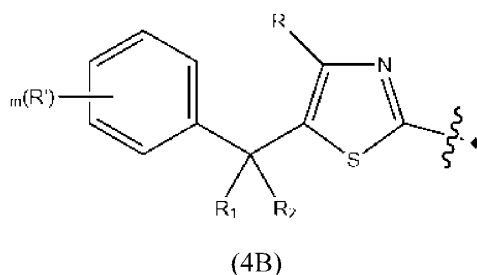
In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

In some embodiments, the Formula I is represented by Formula (4B):



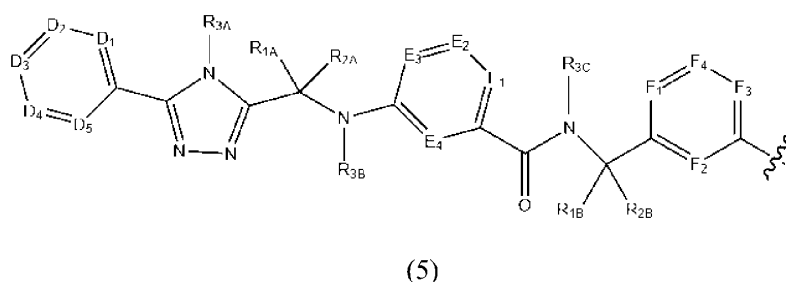
wherein

m is selected from 0, 1, 2, 3, 4 and 5.

In some embodiments, m is selected from 0, 1 and 2.

In some embodiments, m is 0 or 1.

In some embodiments, the Formula I is represented by Formula (5):



wherein:

◆ denotes the point of attachment with the Formula II;

each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆

alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R_{1A} and R_{2A} or R_{1B} and R_{2B} may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

each of R_{3A}, R_{3B} and R_{3C} is independently selected from H, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -S(=O)R_a, -S(=O)₂R_a, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of D₁, D₂, D₃, D₄ and D₅ is independently N or CR_{4A};

each of E₁, E₂, E₃ and E₄ is independently N or CR_{4B};

each of F₁, F₂, F₃ and F₄ is independently N or CR_{4C};

each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H and F.

In some embodiments, each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently H.

In some embodiments, each of R_{3A} , R_{3B} and R_{3C} is independently selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl and optionally substituted C_{2-6} alkynyl.

In some embodiments, each of R_{3A} , R_{3B} and R_{3C} is independently selected from H, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen and C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen.

In some embodiments, each of R_{3A} , R_{3B} and R_{3C} is independently selected from H, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen and propyl optionally substituted by 1, 2 or 3 halogen.

In some embodiments, each of R_{3A} , R_{3B} and R_{3C} is independently selected from H, methyl, ethyl and propyl.

In some embodiments, each of R_{3A} , R_{3B} and R_{3C} is independently selected from H.

In some embodiments, at least one of D_1 , D_2 , D_3 , D_4 and D_5 is N, and the others are CR_A.

In some embodiments, one of D_1 , D_2 , D_3 , D_4 and D_5 is N, and the others are CR_A.

In some embodiments, D_3 is N, and the others are CR_{4A}.

In some embodiments, each of E_1 , E_2 , E_3 and E_4 is independently CR_{4B}.

In some embodiments, each of F₁, F₂, F₃ and F₄ is independently CR_{4C}.

In some embodiments, each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, each of R_{4A}, R_{4B} and R_{4C} is independently H.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

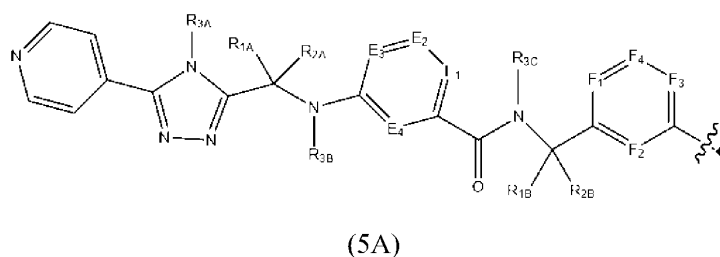
In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

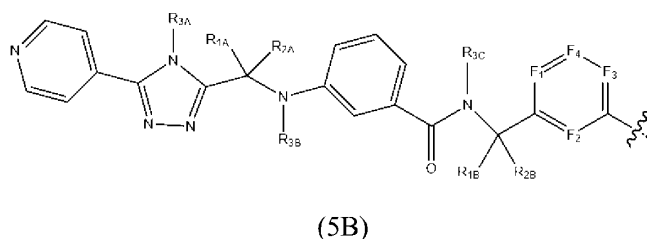
In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

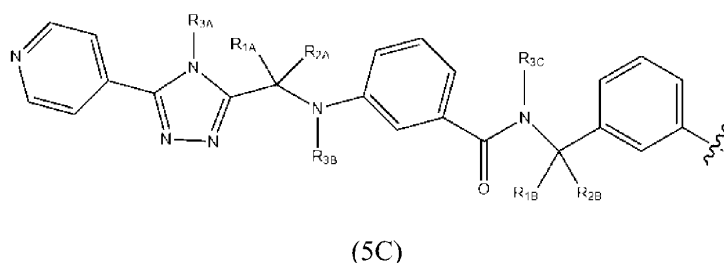
In some embodiments, the Formula I is represented by Formula (5A):



In some embodiments, the Formula I is represented by Formula (5B):

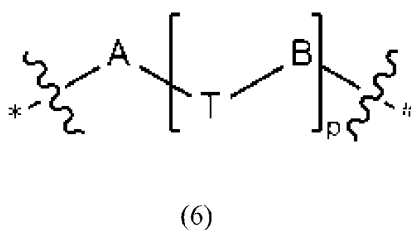


In some embodiments, the Formula I is represented by Formula (5C):



In some embodiments, the Formula II comprises an amide group or an ester group.

In some embodiments, the Formula II is represented by Formula (6):



wherein

* denotes the point of attachment with the Formula I;

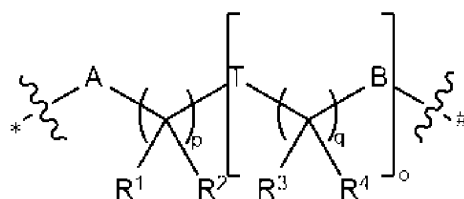
denotes the point of attachment with the DT;

A, T, and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR¹-, -C(=S)NR¹-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR¹-, -NR¹-, -NR¹C(=O)-, -NR¹C(=O)NR²-, -NR¹C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

R¹ and R² are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl; and

p is 0 to 15.

In some embodiments, the Formula II is represented by Formula (6A):



(6A)

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

R¹, R², R³, and R⁴, at each occurrence, are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered

heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

A, T, and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR⁵-, -C(=S)NR⁵-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR⁵-, -NR⁵-, -NR⁵C(=O)-, -NR⁵C(=O)NR⁶-, -NR⁵C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

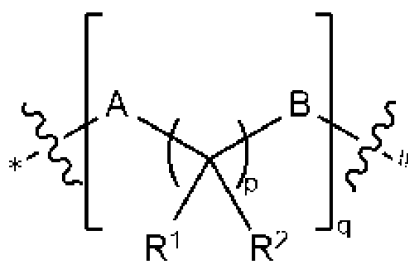
R⁵ and R⁶ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

p is 0 to 15;

each q is 0 to 15; and

o is 0 to 15.

In some embodiments, the Formula II is represented by Formula (6B):



(6B)

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

each R^1 , and each R^2 are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, and optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, or C₁-C₆alkylaminoC₁-C₆alkyl;

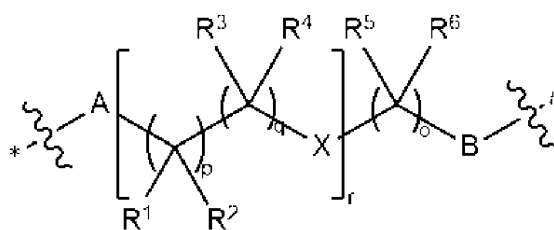
each A and each B are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR³-, -C(=S)NR³-, -O-, -S-, -S(=O)-, -S(=O)₂NR³-, -NR³-, -NR³C(=O)-, -NR³C(=O)NR⁴-, -NR³C(=S)-, and optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, or C₃-C₁₃ spiro heterocyclyl, wherein

R^3 and R^4 are independently selected from hydrogen, and optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, or C₁-C₆alkylaminoC₁-C₆alkyl;

each p is 0 to 15; and

q is 0 to 15.

In some embodiments, the Formula II is represented by Formula (6C):



(6C),

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

X is selected from -O-, -NH-, and -NR⁷-;

R¹, R², R³, R⁴, R⁵, and R⁶, at each occurrence, are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

A and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, -C(=S)NR⁷-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR⁷-, -NR⁷-, -NR⁷C(=O)-, -NR⁷C(=O)NR⁸-, -NR⁷C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

R⁷ and R⁸ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

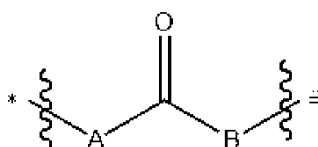
each p is 0 to 15;

each q is 0 to 15;

o is 0 to 15; and

r is 0 to 15.

In some embodiments, the Formula II is represented by Formula (7A):



(7A)

wherein * denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

A is selected from C₁₋₂₀alkylene, -O-, -S-, -N(R_e)- and -N(R_e)-C₁₋₂₀alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₂₀alkylene group is independently replaced with a group selected from -O-, -S-, -N(R_e)-, -C(=O)- and -C(=S)-;

B is a bond or is selected from arylene, C₃₋₁₂ carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

R_e is selected from H and optionally substituted C₁₋₆alkyl; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments, A is selected from C₁₋₈alkylene, -O-, -NH-, -N(CH₃)-, -N(C₂H₅)-, -NH-C₁₋₈alkylene, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₈alkylene group is independently replaced with a group selected from -O- and -C(=O)-.

In some embodiments, A is selected from -CH₂-, -O-, -NH-, -NH-(CH₂)₃-, -NH-(CH₂)₅- and -NH-C(=O)-(CH₂)₃-O-(CH₂)₃-.

In some embodiments, A is selected from -CH₂-, -O- and -NH-.

In some embodiments, A is -NH-.

In some embodiments, B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolylene, imidazolylene, oxazolylene, isoxazolylene, oxadiazolylene, thiazolylene, isothiazolylene, thiadiazolylene, pyridinylenes, pyranylene, pyrazinylenes, pyrimidinylene, pyrazinylenes, triazolylene, tetrazolylene and triazinylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

In some embodiments, B is a bond or phenylene.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

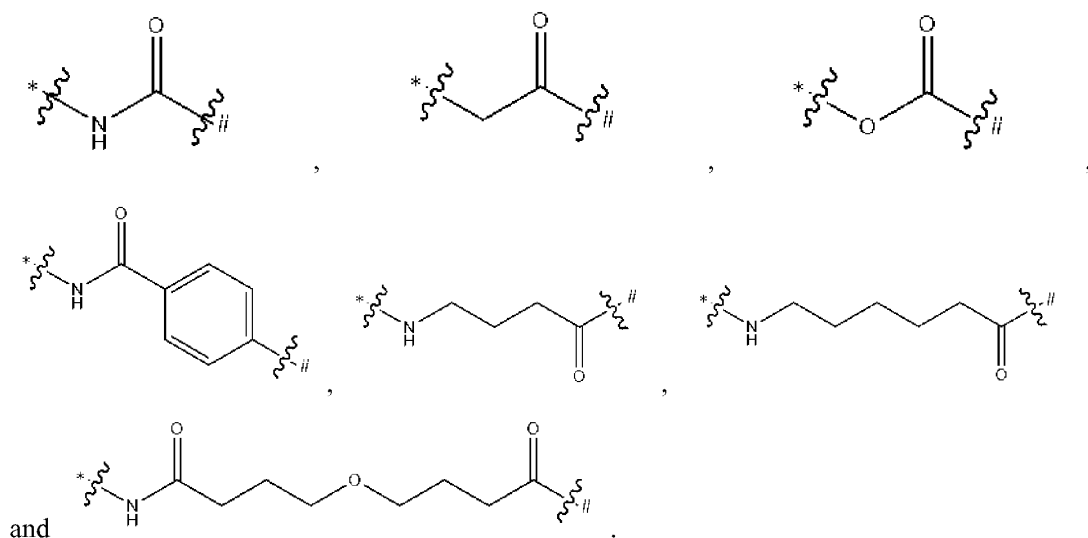
In some embodiments, R_e is H.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

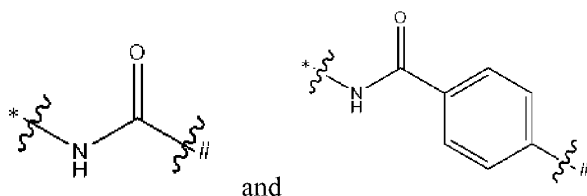
In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

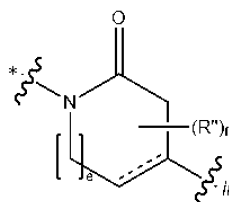
In some embodiments, Formula (7A) is a moiety selected from:



In some embodiments, Formula (7A) is a moiety selected from:



In some embodiments, the Formula II is represented by Formula (7B):



(7B)

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

--- is a single bond or a double bond;

R' is selected from halogen, $-\text{CN}$, $-\text{N}(=\text{O})$, $-\text{NO}_2$, $-\text{ON}(=\text{O})$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-\text{OR}_a$, $-\text{C}(=\text{O})\text{R}_a$, $-\text{C}(=\text{S})\text{R}_a$, $-\text{C}(=\text{O})\text{OR}_a$, $-\text{OC}(=\text{O})\text{R}_a$, $-\text{SR}_a$, $-\text{S}(=\text{O})\text{R}_a$, $-\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_b\text{R}_c$, $-\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{C}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{OR}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{SN}(=\text{O})$, $-\text{NR}_d\text{N}(=\text{O})$, optionally substituted aryl, optionally substituted

C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

e is 0 or 1;

f is selected from 0, 1, 2 and 3; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments,  is a single bond.

In some embodiments,  is a double bond.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

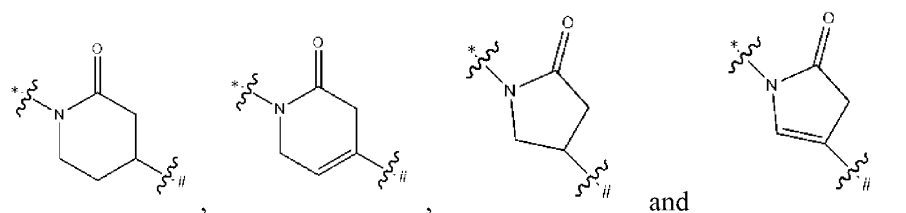
In some embodiments, R'' is selected from F, Cl, Br, methyl, ethyl, propyl, -OH and -NH₂.

In some embodiments, e is 0.

In some embodiments, e is 1.

In some embodiments, f is 0.

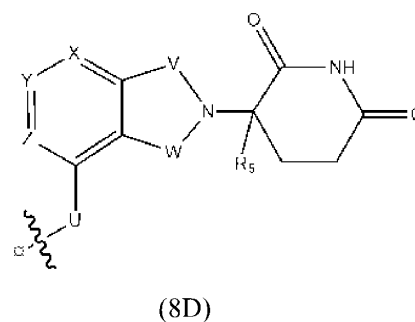
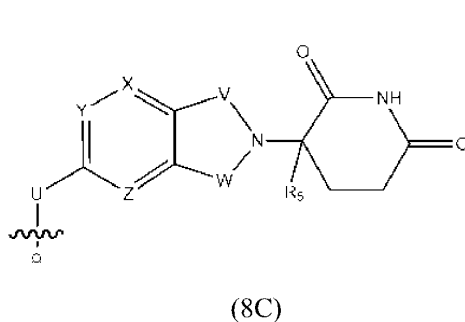
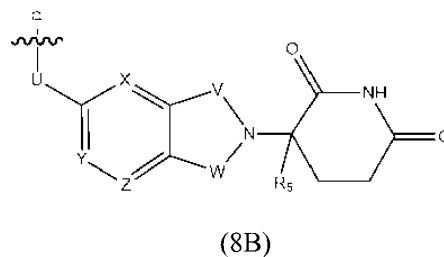
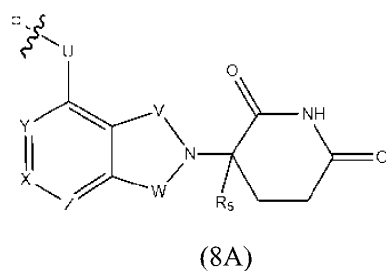
In some embodiments, Formula (7B) is a moiety selected from:



In some embodiments, the DT is capable of binding to an E3 ligase for recruitment of the corresponding ubiquitination machinery to GRK2, leading to the subsequent degradation of GRK2 in or near the proteasome and/or loss of function of GRK2.

In some embodiments, the DT is selected from the group consisting of cereblon ligands, VHL ligands, MDM2 ligands, TRIM24 ligands, TRIM21 ligands, KEAP1 ligands, RNF114 ligands, IAP ligands, DCAF16 ligands, DCAF15 ligands, FEM1B ligands, and ligands of arylhydrocarbon receptors.

In some embodiments, the DT is a moiety represented by Formula (8A), (8B), (8C) or (8D):



wherein,

□ denotes the point of attachment with the Formula II;

U is independently selected from -CH₂-, -NH- and -O-;

each of V and W is independently selected from -C(=O)- and -CH₂-;

each of X, Y, and Z is independently selected from CR₆ and N;

R₅ is selected from H, halogen and optionally substituted C₁-C₆ alkyl; and

R₆ is selected from H, halogen and optionally substituted C₁-C₆ alkyl.

In some embodiments, U is -CH₂-.

In some embodiments, U is -O-.

In some embodiments, U is -NH-.

In some embodiments, V is -C(=O)- and W is -CH₂-.

In some embodiments, V is -CH₂- and W is -C(=O)-.

In some embodiments, both of V and W are -C(=O)-.

In some embodiments, each of X, Y, and Z is independently selected from CR₆.

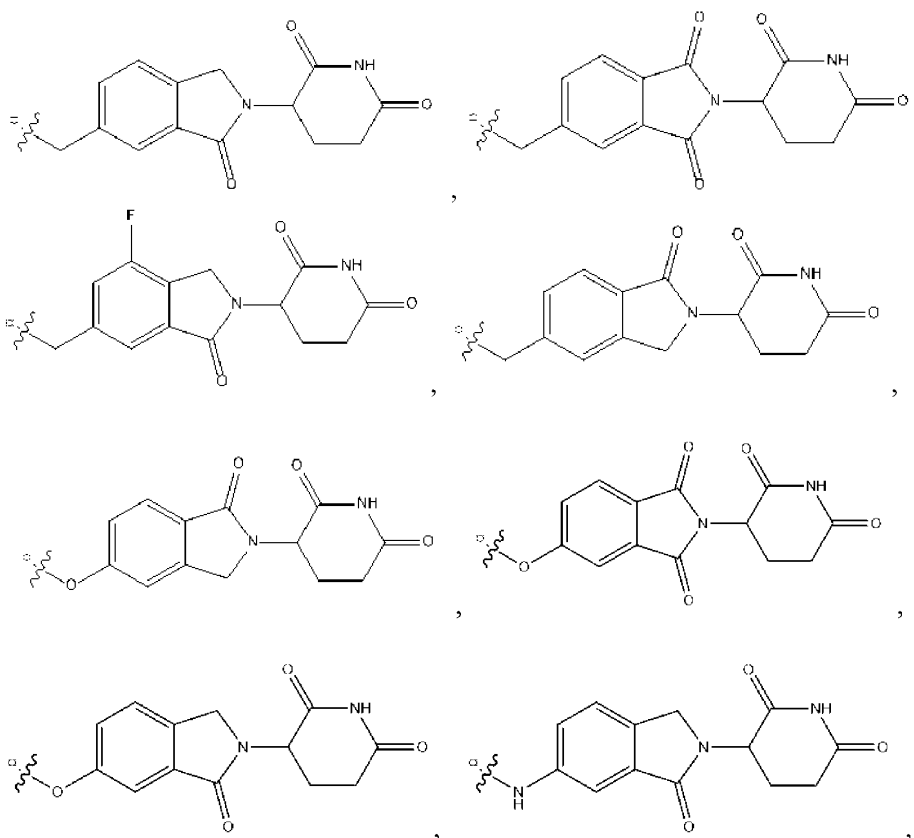
In some embodiments, R₅ is selected from H, F, Cl and Br.

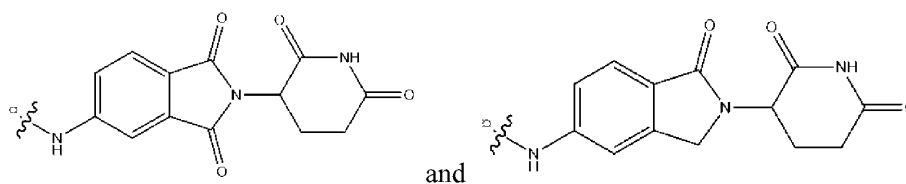
In some embodiments, R₅ is H.

In some embodiments, R₆ is selected from H, F, Cl and Br.

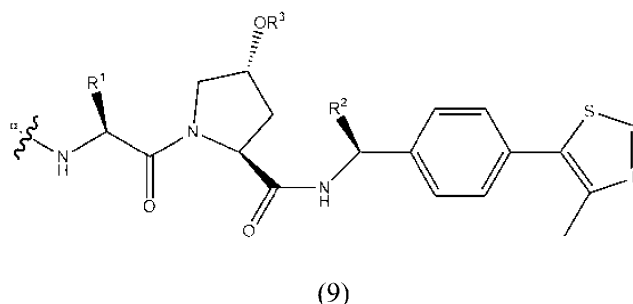
In some embodiments, R₆ is H or F.

In some embodiments, the DT is a moiety selected from:





In some embodiments, the DT is a moiety represented by Formula (9):



wherein

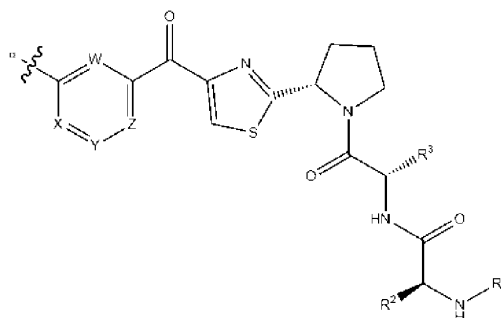
$\square$ denotes the point of attachment with the Formula II;

R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_1 - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted C_1 - C_8 haloalkyl, optionally substituted C_1 - C_8 hydroxyalkyl, optionally substituted C_1 - C_8 aminoalkyl, optionally substituted C_1 - C_8 alkylamino C_1 - C_8 alkyl, optionally substituted C_3 - C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2 - C_8 alkenyl, and optionally substituted C_2 - C_8 alkynyl;

R^3 is hydrogen, optionally substituted $-C(=O)C_1$ - C_8 alkyl, optionally substituted $-C(=O)C_1$ - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted $-C(=O)C_1$ - C_8 haloalkyl, optionally substituted $-C(=O)C_1$ - C_8 hydroxyalkyl, optionally substituted $-C(=O)C_1$ - C_8 aminoalkyl, optionally substituted $-C(=O)C_1$ - C_8 alkylamino C_1 - C_8 alkyl, optionally substituted $-C(=O)C_3$ - C_7 cycloalkyl, optionally substituted $-C(=O)(3-7$ membered heterocyclyl), optionally substituted $-C(=O)C_2$ - C_8 alkenyl, optionally substituted $-C(=O)C_2$ - C_8 alkynyl, optionally substituted $-C(=O)OC_1$ - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted $-C(=O)OC_1$ - C_8 haloalkyl, optionally substituted $-C(=O)OC_1$ - C_8 hydroxyalkyl, optionally substituted $-C(=O)OC_1$ - C_8 aminoalkyl, optionally substituted $-C(=O)OC_1$ - C_8 alkylamino C_1 - C_8 alkyl, optionally substituted $-C(=O)OC_3$ - C_7 cycloalkyl, optionally substituted $-C(=O)O(3-7$ membered heterocyclyl), optionally substituted $-C(=O)OC_2$ - C_8 alkenyl, optionally substituted $-C(=O)OC_2$ - C_8 alkynyl, optionally substituted $-C(=O)NC_1$ - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted $-C(=O)NC_1$ - C_8 haloalkyl, optionally substituted $-C(=O)NC_1$ - C_8 hydroxyalkyl, optionally substituted $-C(=O)NC_1$ - C_8 aminoalkyl, optionally substituted $-C(=O)NC_1$ - C_8 alkylamino C_1 - C_8 alkyl, optionally substituted $-C(=O)NC_3$ - C_7 cycloalkyl, optionally substituted $-C(=O)N(3-7$ membered heterocyclyl), optionally substituted

-C(=O)NC₂-C₈ alkenyl, optionally substituted -C(=O)NC₂-C₈ alkynyl, optionally substituted -P(=O)(OH)₂, optionally substituted -P(=O)(OC₁-C₈ alkyl)₂, and optionally substituted -P(=O)(OC₁-C₈ aryl)₂.

In some embodiments, the DT is a moiety represented by Formula (10):



(10)

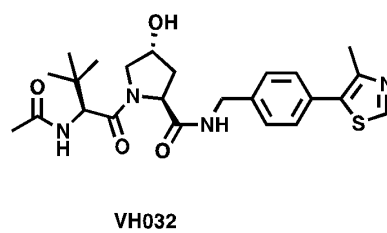
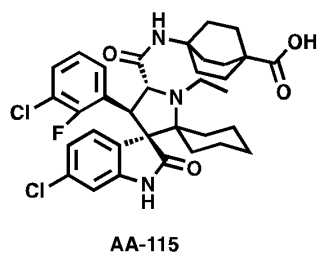
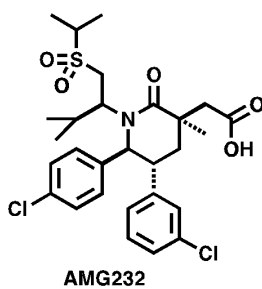
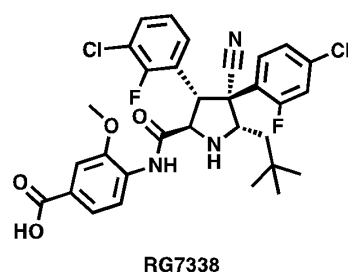
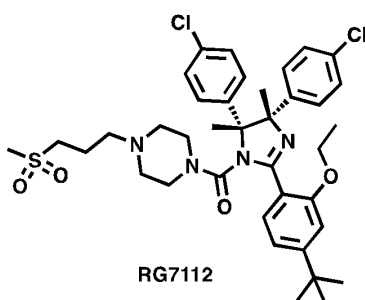
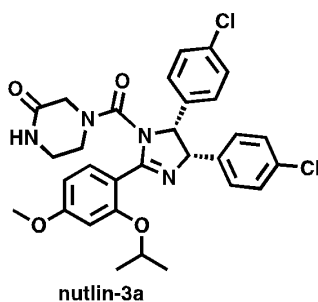
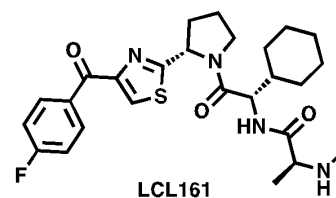
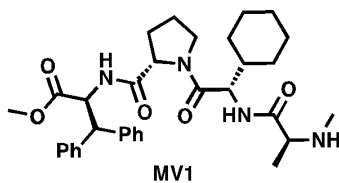
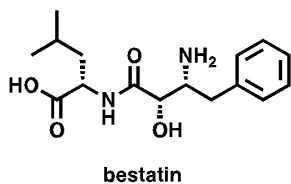
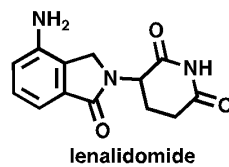
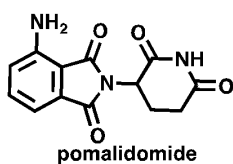
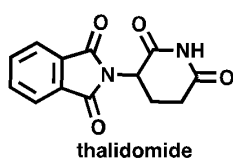
wherein

□ denotes the point of attachment with the Formula II;

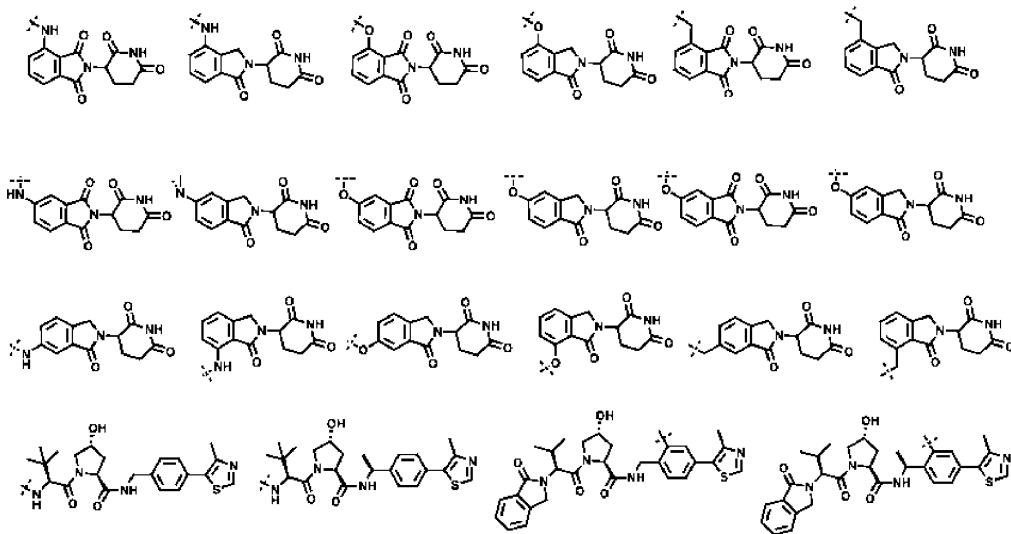
V, W, X, and Z are independently selected from CR⁴ and N;

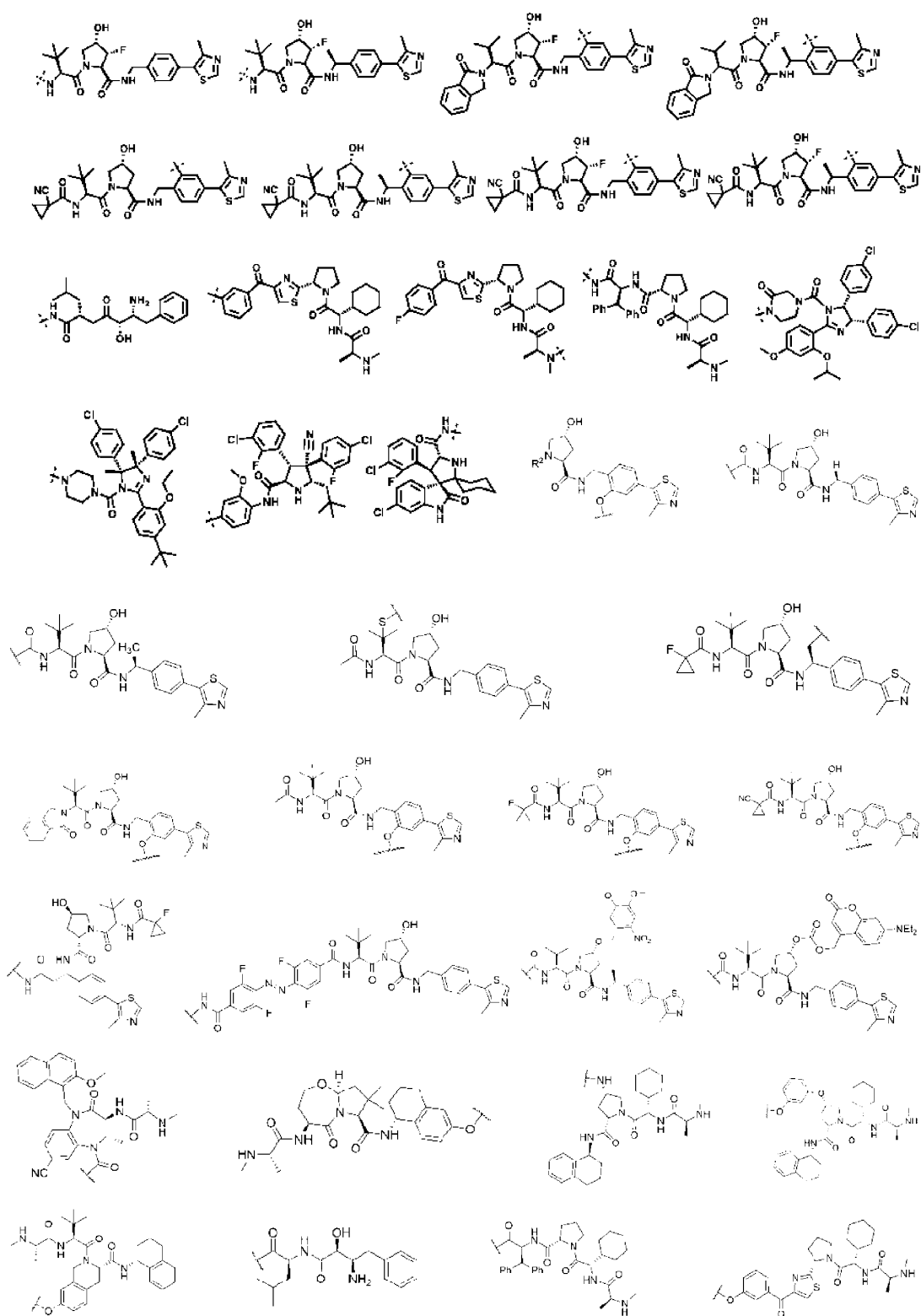
R¹, R², R³, and R⁴ are independently selected from hydrogen, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₃-C₇ cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C₂-C₈ alkenyl, and optionally substituted C₂-C₈ alkynyl.

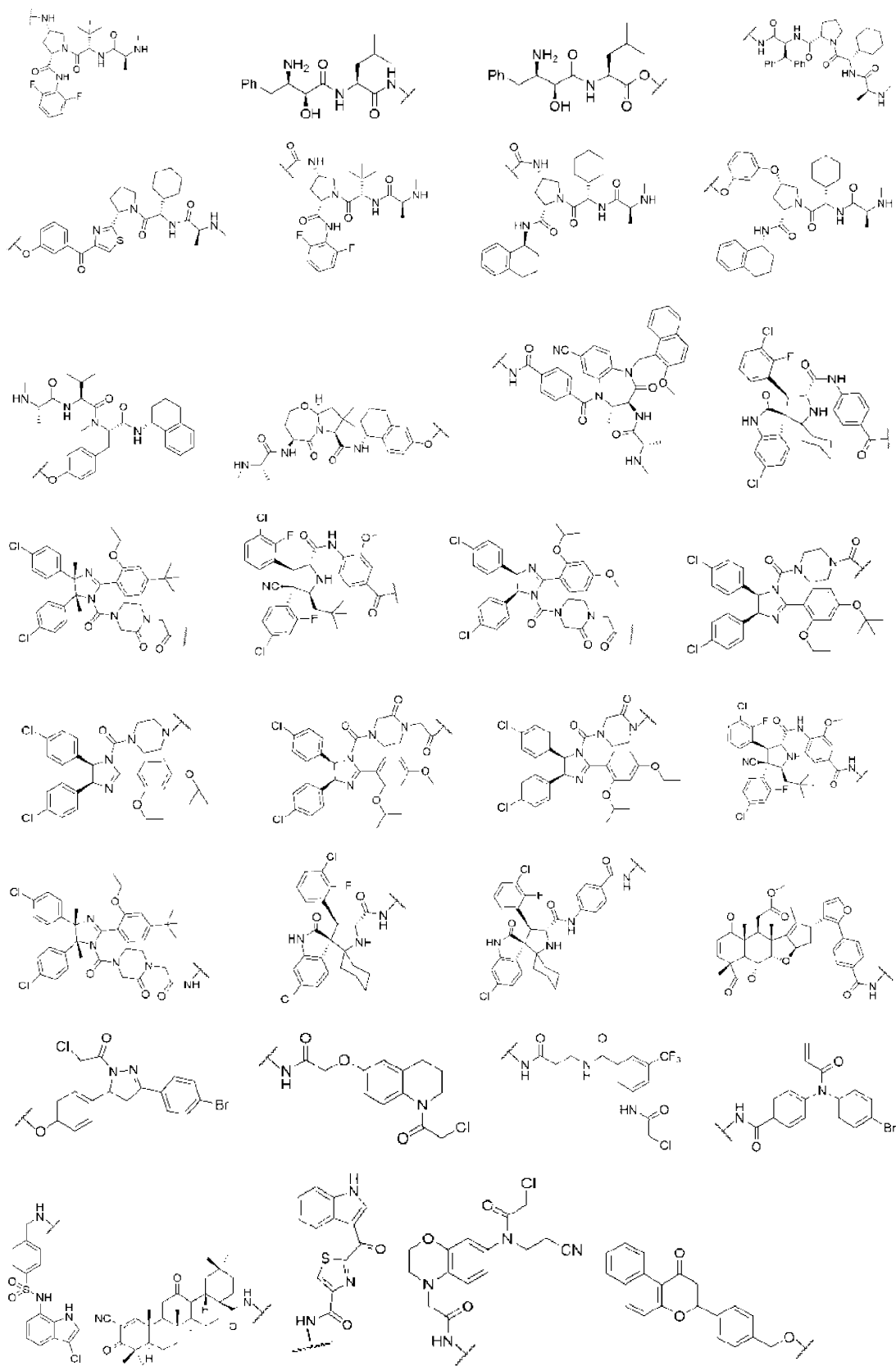
In some embodiments, the DT is a moiety derived from any of the following:



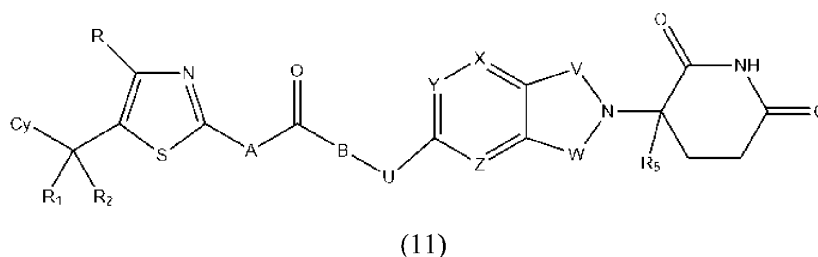
In some embodiments, the DT is selected from the group consisting of:







In some embodiments, the compound is represented by Formula (11)



wherein:

A is selected from C_{1-20} alkylene, -O-, -S-, -N(R_e)- and -N(R_e)- C_{1-20} alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C_{1-20} alkylene group is independently replaced with a group selected from -O-, -S-, -N(R_e)-, -C(=O)- and -C(=S)-;

B is a bond or is selected from arylene, C_{3-12} carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c;

U is independently selected from -CH₂-, -NH- and -O-;

each of V and W is independently selected from -C(=O)- and -CH₂-;

each of X, Y, and Z is independently selected from CR₆ and N;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C_{3-6} carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C_{3-12} carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted

C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R₅ is selected from H, halogen and optionally substituted C₁-C₆ alkyl;

R₆ is selected from H, halogen and optionally substituted C₁-C₆ alkyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

R_e is selected from H and optionally substituted C₁₋₆ alkyl; and

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments, A is selected from C₁₋₈alkylene, -O-, -NH-, -N(CH₃)-, -N(C₂H₅)-, -NH-C₁₋₈alkylene, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₈alkylene group is independently replaced with a group selected from -O- and -C(=O)-.

In some embodiments, A is selected from -CH₂-, -O-, -NH-, -NH-(CH₂)₃-, -NH-(CH₂)₅- and -NH-C(=O)-(CH₂)₃-O-(CH₂)₃-.

In some embodiments, A is selected from -CH₂-, -O- and -NH-.

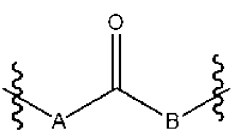
In some embodiments, A is -NH-.

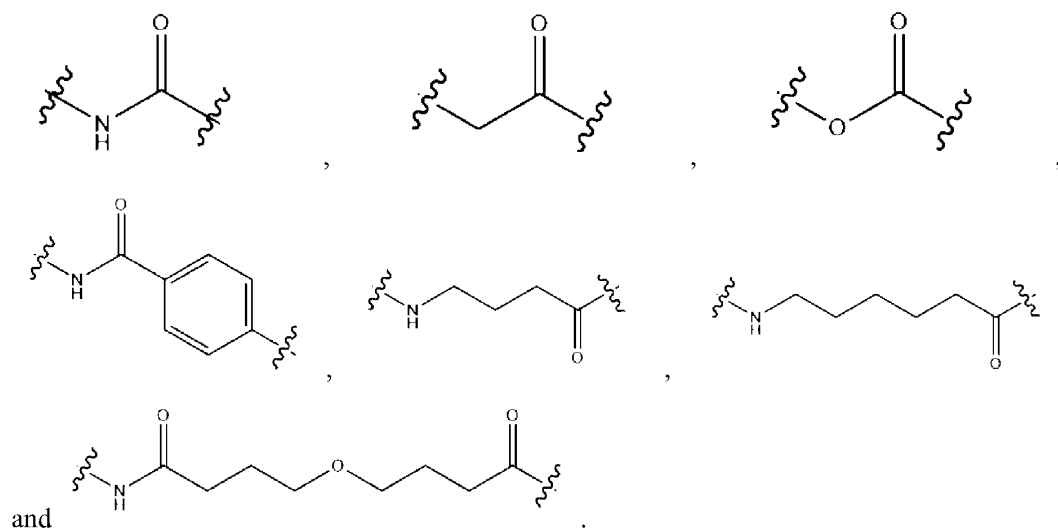
In some embodiments, B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

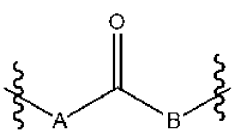
In some embodiments, B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolylene, imidazolylene, oxazolylene, isoxazolylene, oxadiazolylene, thiazolylene, isothiazolylene, thiadiazolylene, pyridinylene, pyranylene, pyrazinylene, pyrimidinylene, pyrazinylene, triazolylene, tetrazolylene and triazinylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

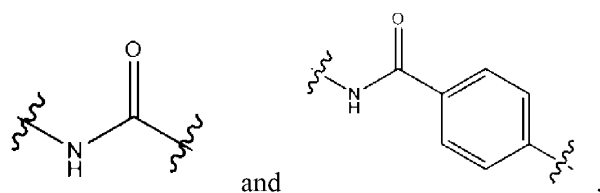
In some embodiments, B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

In some embodiments, B is a bond or phenylene.

In some embodiments,  is a moiety selected from:



In some embodiments,  is a moiety selected from:



In some embodiments, U is $-\text{CH}_2-$.

In some embodiments, U is $-\text{O}-$.

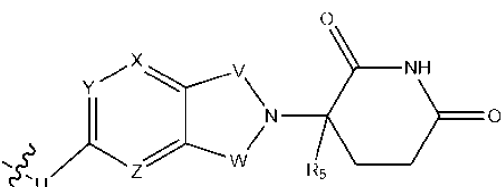
In some embodiments, U is $-\text{NH}-$.

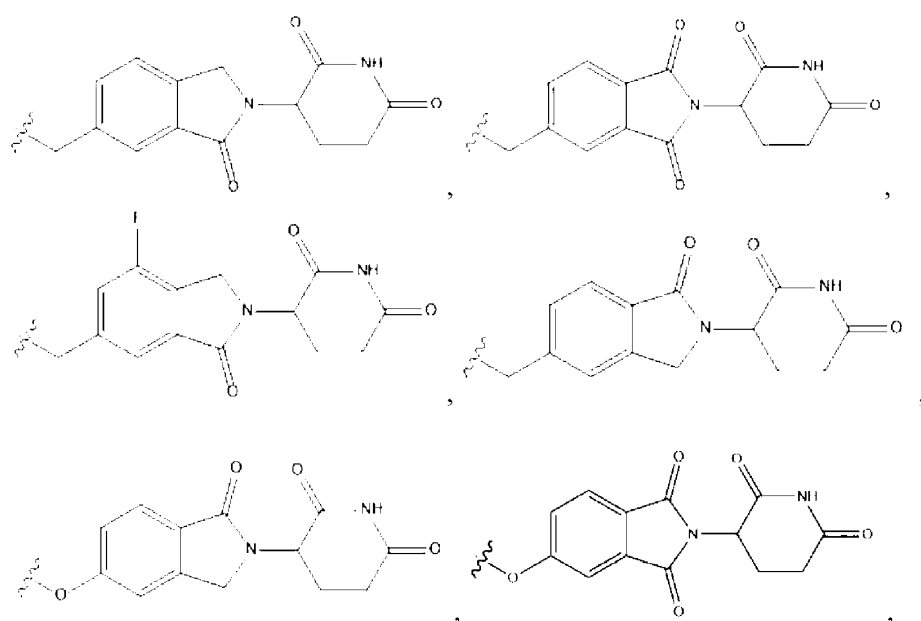
In some embodiments, V is $-\text{C}(=\text{O})-$ and W is $-\text{CH}_2-$.

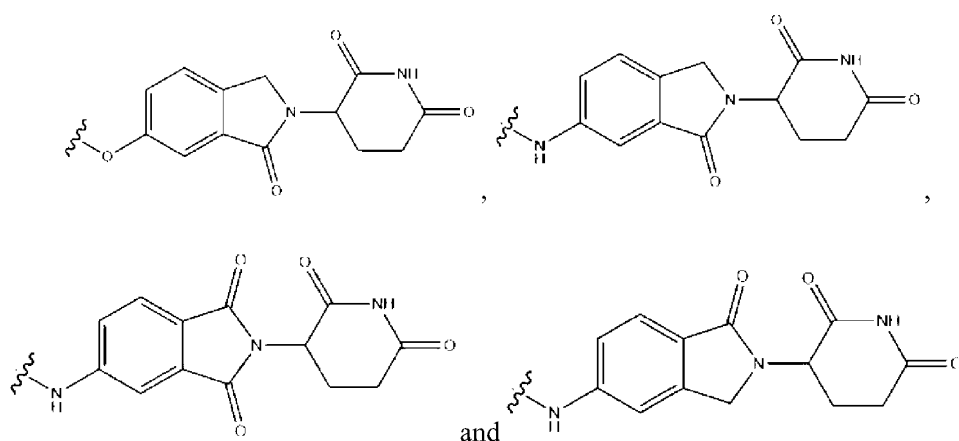
In some embodiments, V is $-\text{CH}_2-$ and W is $-\text{C}(=\text{O})-$.

In some embodiments, both of V and W are $-\text{C}(=\text{O})-$.

In some embodiments, each of X, Y, and Z is independently selected from CR_6 .

In some embodiments,  is a moiety selected from:





In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R_1 and R_2 is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R_1 and R_2 is independently selected from H and F.

In some embodiments, both of R_1 and R_2 are H.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H and -OH.

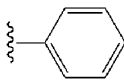
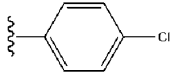
In some embodiments, R is H.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from:  and .

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋

cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl.

In some embodiments, R₅ is selected from H, F, Cl and Br.

In some embodiments, R₅ is H.

In some embodiments, R₆ is selected from H, F, Cl and Br.

In some embodiments, R₆ is H or F.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, R_c is H.

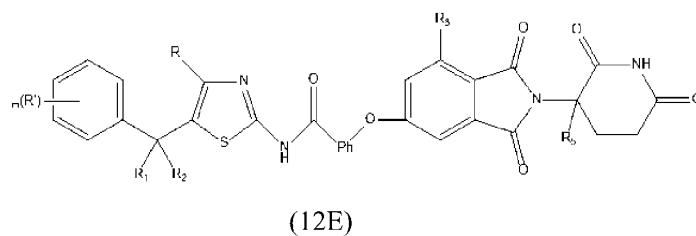
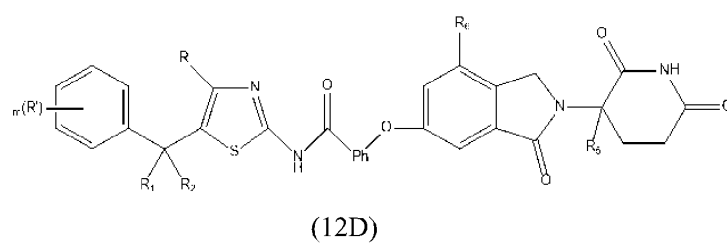
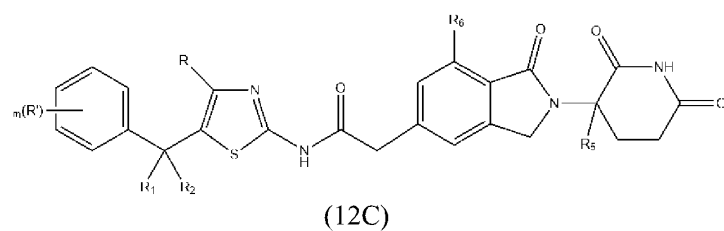
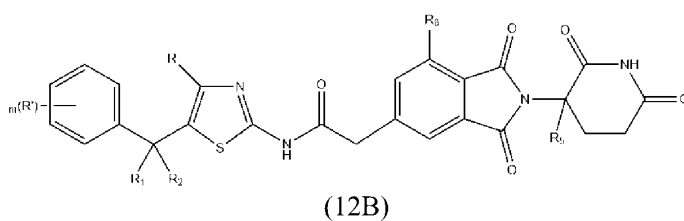
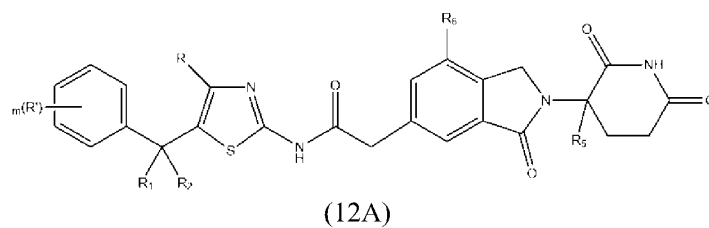
In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

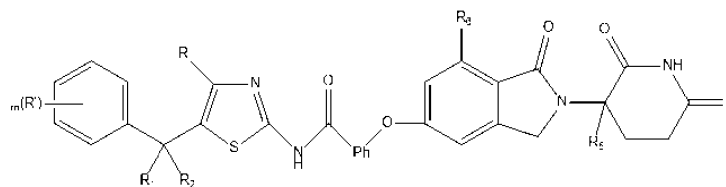
In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally

substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

In some embodiments, wherein the compound is represented by Formula (12A), (12B), (12C), (12D), (12E) or (12F)





(12F)

each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C_{3-6} carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R_1 and R_2 may be taken together along with the atom to which they are attached to form an optionally substituted C_{3-12} carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R_5 is selected from H, halogen and optionally substituted C_{1-6} alkyl;

R_6 is selected from H, halogen and optionally substituted C_{1-6} alkyl;

each R_a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

each of R_b and R_c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen

atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl;

Ph represents phenylene; and

m is selected from 0, 1, 2, 3, 4 and 5.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

In some embodiments, each of R_1 and R_2 is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R_1 and R_2 is independently selected from H and F.

In some embodiments, both of R_1 and R_2 are H.

In some embodiments, R is selected from H, halogen, $-CN$, $-NO_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

In some embodiments, R is selected from H, halogen, $-CN$, $-NO_2$, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H and -OH.

In some embodiments, R is H.

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl.

In some embodiments, R₅ is selected from H, F, Cl and Br.

In some embodiments, R₅ is H.

In some embodiments, R₆ is selected from H, F, Cl and Br.

In some embodiments, R₆ is H or F.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

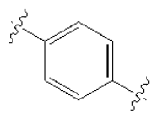
In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl, -OH, -NH₂, -NO₂, -CN and C_{3-6} cycloalkyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

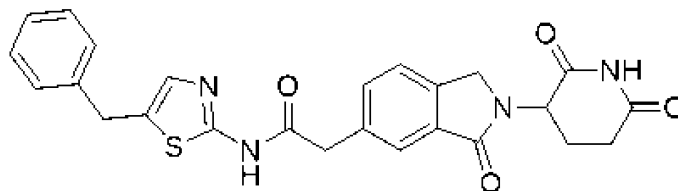


In some embodiments, Ph represents

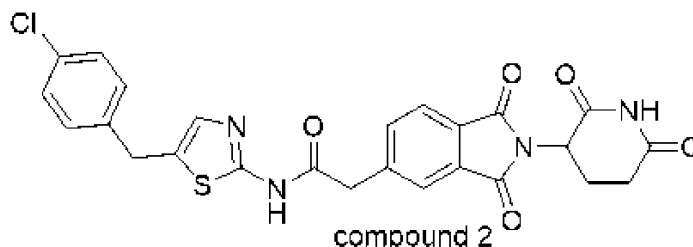
In some embodiments, m is selected from 0, 1 and 2.

In some embodiments, m is 0 or 1.

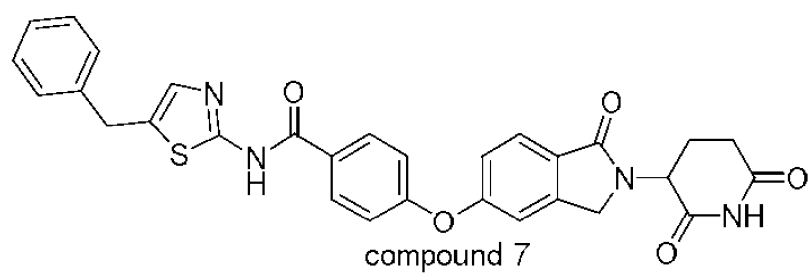
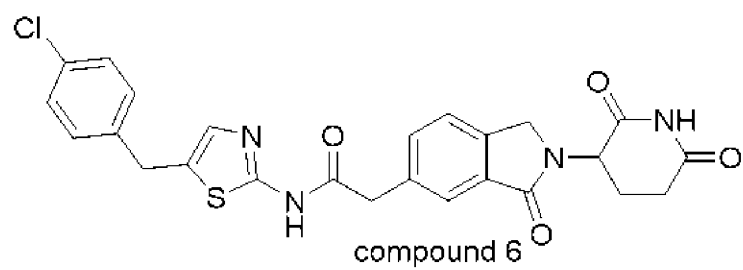
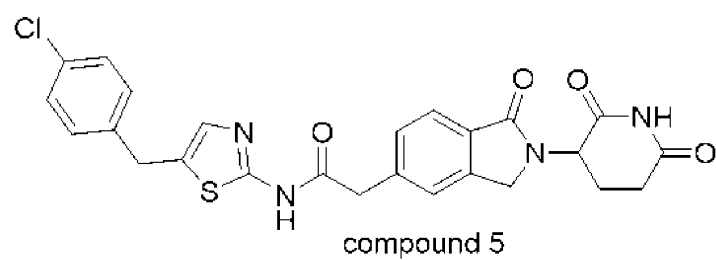
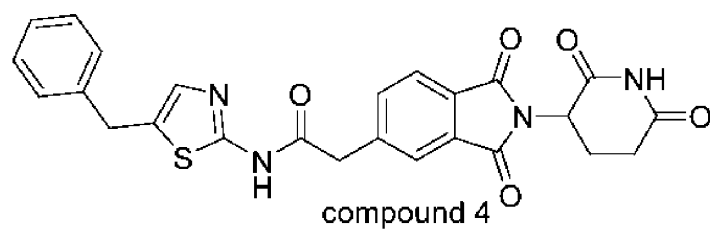
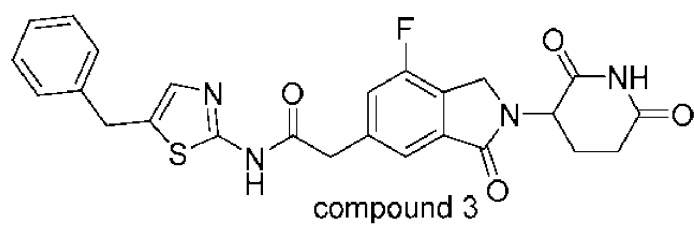
In some embodiments, the compound is selected from the group consisting of

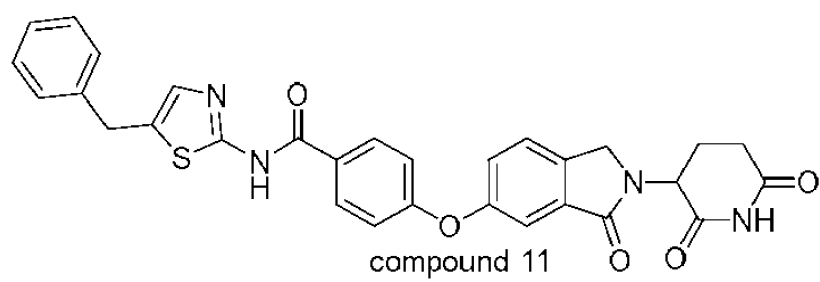
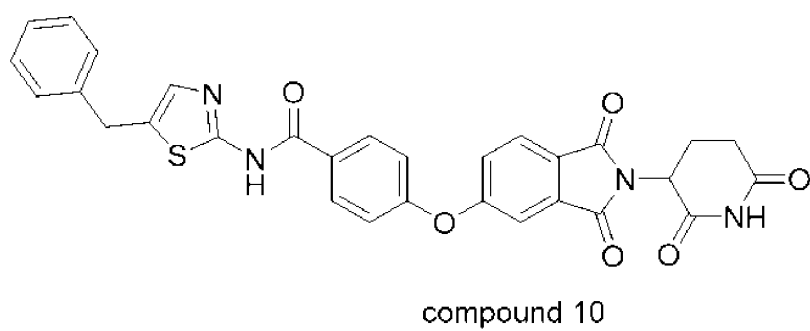
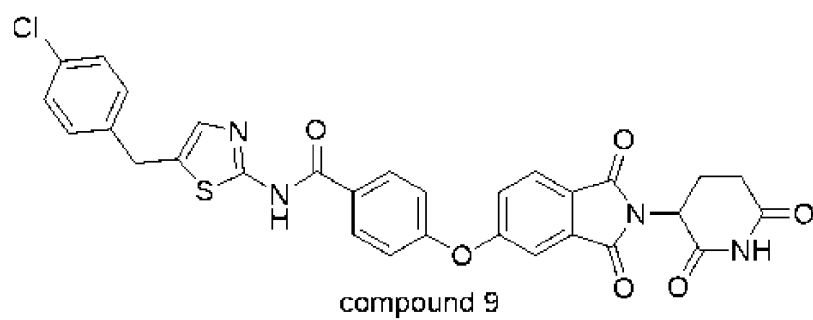
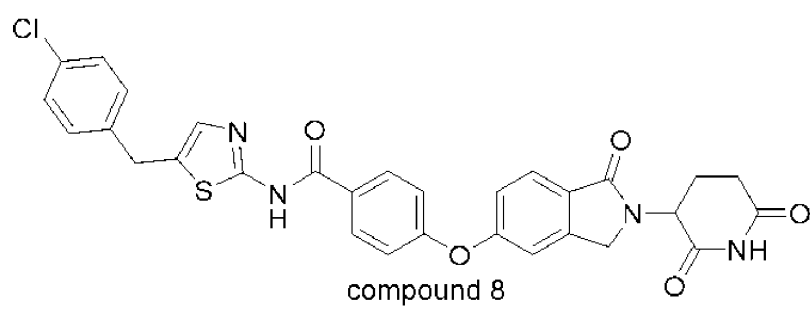


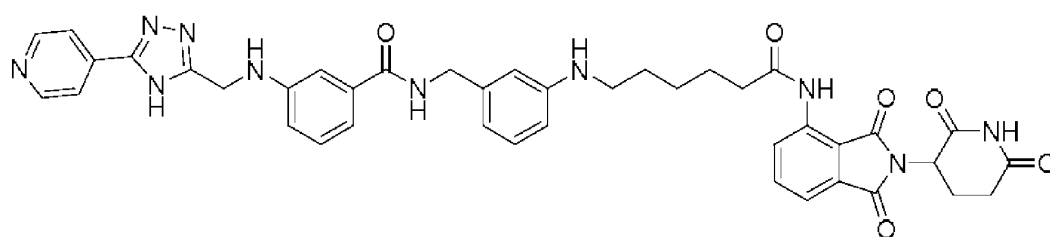
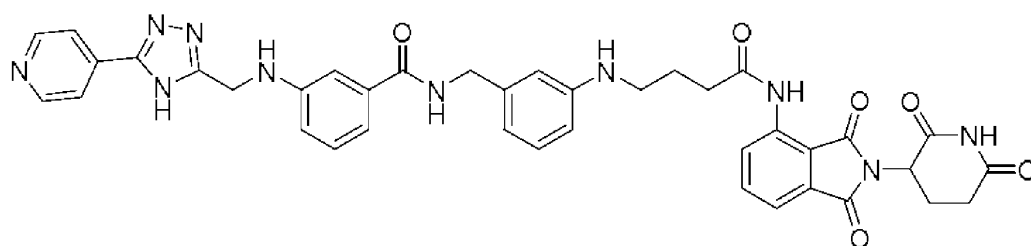
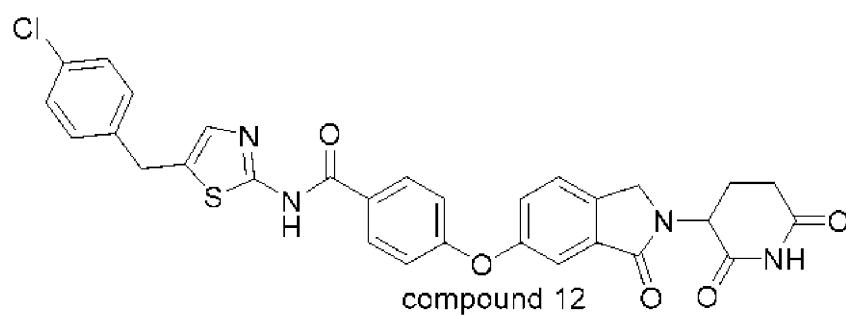
compound 1



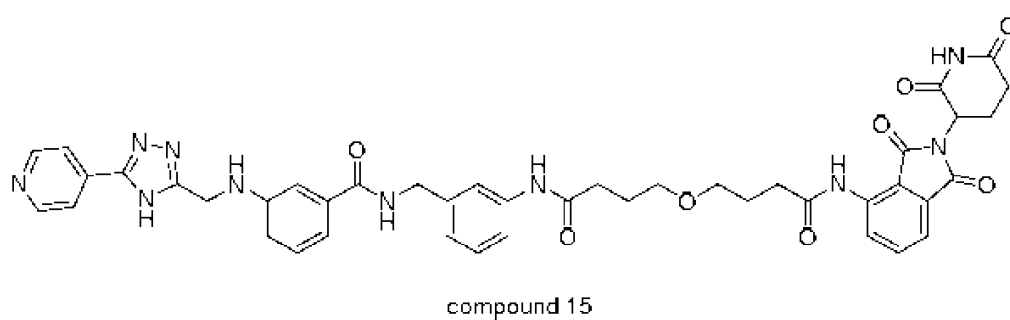
compound 2



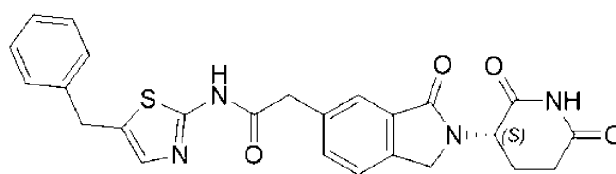




and

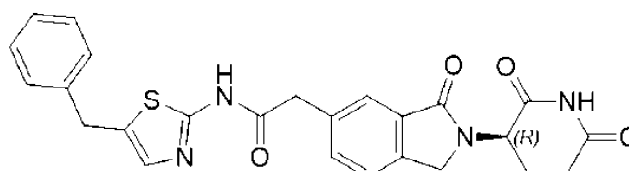


In some embodiments, the compound is selected from the group consisting of



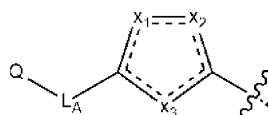
compound 1-P1

and



compound 1-P2

In some embodiments, the Formula I is represented by Formula (13):



(13)

wherein:

◆ denotes the point of attachment with the Formula II;

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

X₁, X₂ and X₃ are each independently selected from CR, S or N;

with the proviso that at least one of X₁, X₂ and X₃ is N and one of X₁, X₂ and X₃ is S;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -

$\text{NR}_d\text{C}(=\text{O})\text{OR}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{SN}(=\text{O})$, $-\text{NR}_d\text{N}(=\text{O})$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_a$, $-\text{SR}_a$, $-\text{NR}_b\text{R}_c$, $-\text{C}(=\text{O})\text{R}_a$, $-\text{C}(=\text{O})\text{OR}_a$, $-\text{OC}(=\text{O})\text{R}_a$, $-\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{S}(=\text{O})\text{R}_a$, $-\text{S}(=\text{O})_2\text{R}_a$, $-\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, optionally substituted C_{3-6} carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R_1 and R_2 may be taken together along with the atom to which they are attached to form an optionally substituted C_{3-12} carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, $-\text{CN}$, $-\text{N}(=\text{O})$, $-\text{NO}_2$, $-\text{ON}(=\text{O})$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-\text{OR}_a$, $-\text{C}(=\text{O})\text{R}_a$, $-\text{C}(=\text{S})\text{R}_a$, $-\text{C}(=\text{O})\text{OR}_a$, $-\text{OC}(=\text{O})\text{R}_a$, $-\text{SR}_a$, $-\text{S}(=\text{O})\text{R}_a$, $-\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_b\text{R}_c$, $-\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{C}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{OR}_a$, $-\text{NR}_d\text{C}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})_2\text{R}_a$, $-\text{NR}_d\text{S}(=\text{O})\text{NR}_b\text{R}_c$, $-\text{NR}_d\text{S}(=\text{O})_2\text{NR}_b\text{R}_c$, $-\text{SN}(=\text{O})$, $-\text{NR}_d\text{N}(=\text{O})$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

each of R_b and R_c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-\text{OR}_a$, $-\text{NR}_b\text{R}_c$, $-\text{C}(=\text{O})\text{R}_a$, $-\text{C}(=\text{O})\text{OR}_a$, $-\text{OC}(=\text{O})\text{R}_a$, $-\text{NO}_2$, $=\text{O}$, $-\text{CN}$ and C_{3-6} cycloalkyl.

In some embodiments, Q is selected from optionally substituted C_{1-6} alkyl, $-\text{OR}_a$, $-\text{SR}_a$, $-\text{NR}_b\text{R}_c$ and Cy .

In some embodiments, Q is selected from C₁₋₆ alkyl, -SR_a, and Cy.

In some embodiments, Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

In some embodiments, Q is selected from isopropyl, isopropylthio and Cy.

In some embodiments, Q is Cy.

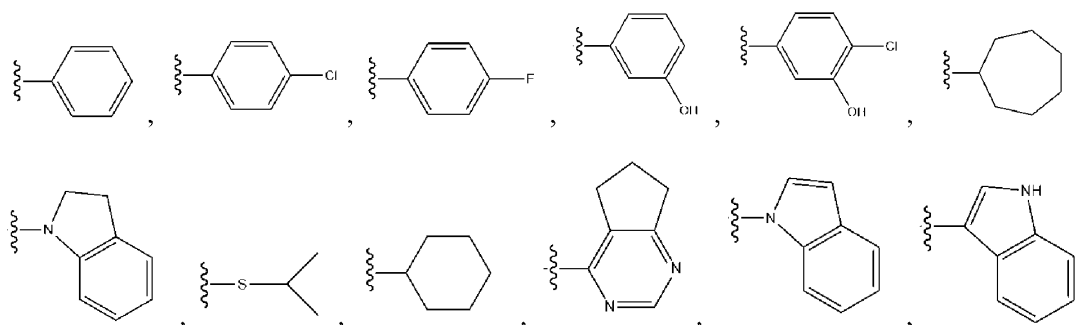
In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

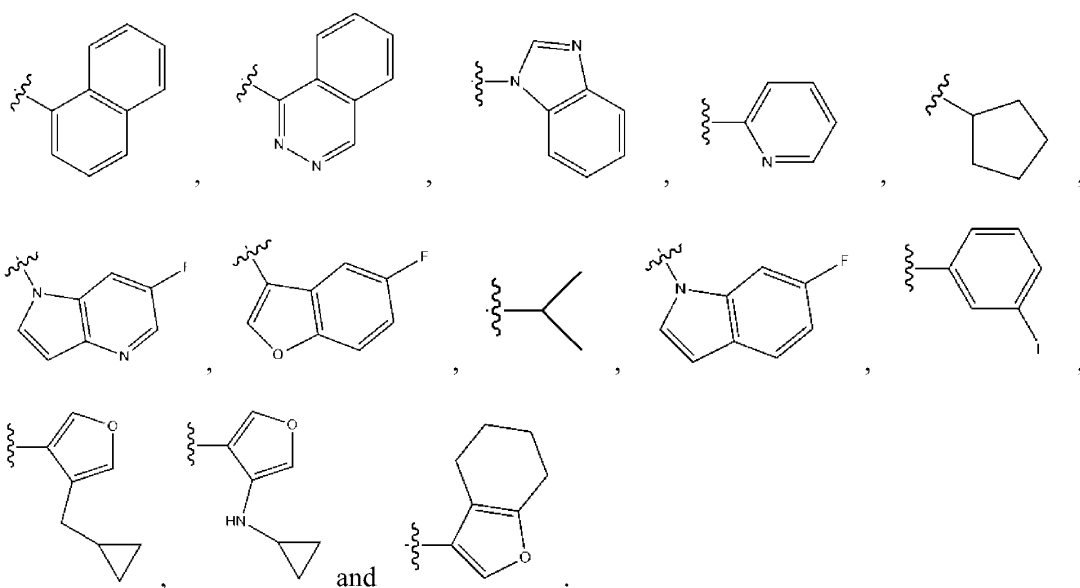
In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranal, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

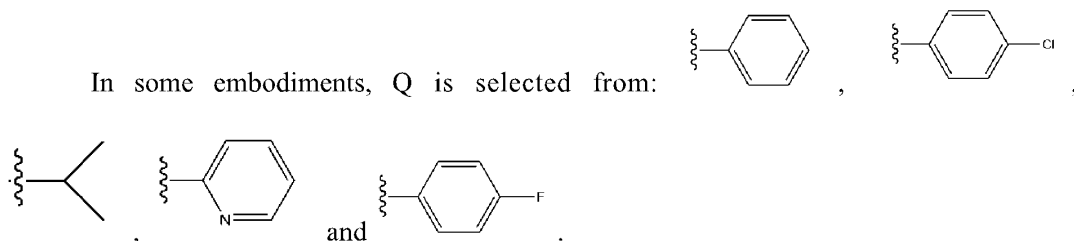
In some embodiments, Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Q is selected from:





In some embodiments, Q is selected from:



In some embodiments, L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

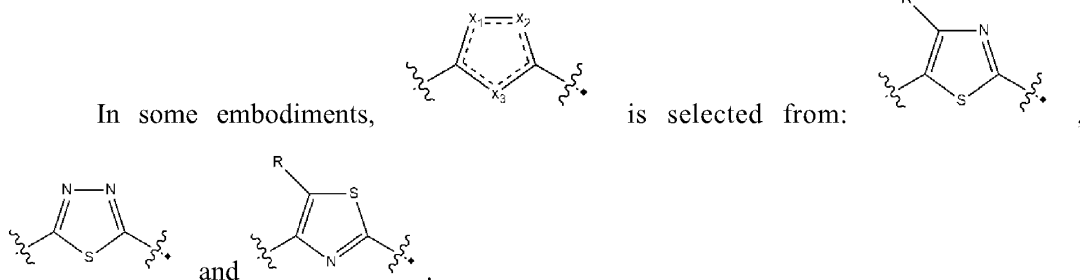
In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is $-CH_2-$.

In some embodiments, X_1 is CR or N.

In some embodiments, X_2 is S or N.

In some embodiments, X_3 is S or N.



In some embodiments, R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H, methyl and -OH.

In some embodiments, R is H.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R₁ and R₂ is independently selected from H and F.

In some embodiments, both of R₁ and R₂ are H.

In some embodiments, both of R₁ and R₂ are F.

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl or F.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_a is independently H or isopropyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_d is independently H or methyl.

In some embodiments, a is selected from 0 and 1 and b is selected from 0 and 1.

In some embodiments, a is 0 and b is 0.

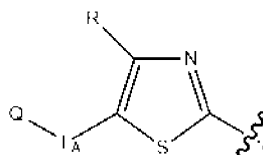
In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally

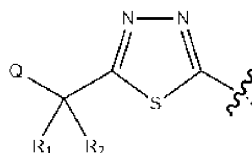
substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

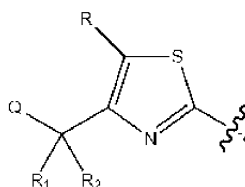
In some embodiments, the Formula I is represented by Formula (14A), (14B) or (14C):



(14A)



(14B)



(14C)

wherein:

◆ denotes the point of attachment with the Formula II;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆ cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆ cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that a + b ≤ 5; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R₁ and R₂ is independently selected from H and F.

In some embodiments, both of R₁ and R₂ are H.

In some embodiments, both of R₁ and R₂ are F.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H, methyl and -OH.

In some embodiments, R is H.

In some embodiments, Q is selected from optionally substituted C₁₋₆ alkyl, -OR_a, -SR_a, -NR_bR_c and Cy.

In some embodiments, Q is selected from C₁₋₆ alkyl, -SR_a, and Cy.

In some embodiments, Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

In some embodiments, Q is selected from isopropyl, isopropylthio and Cy.

In some embodiments, Q is Cy.

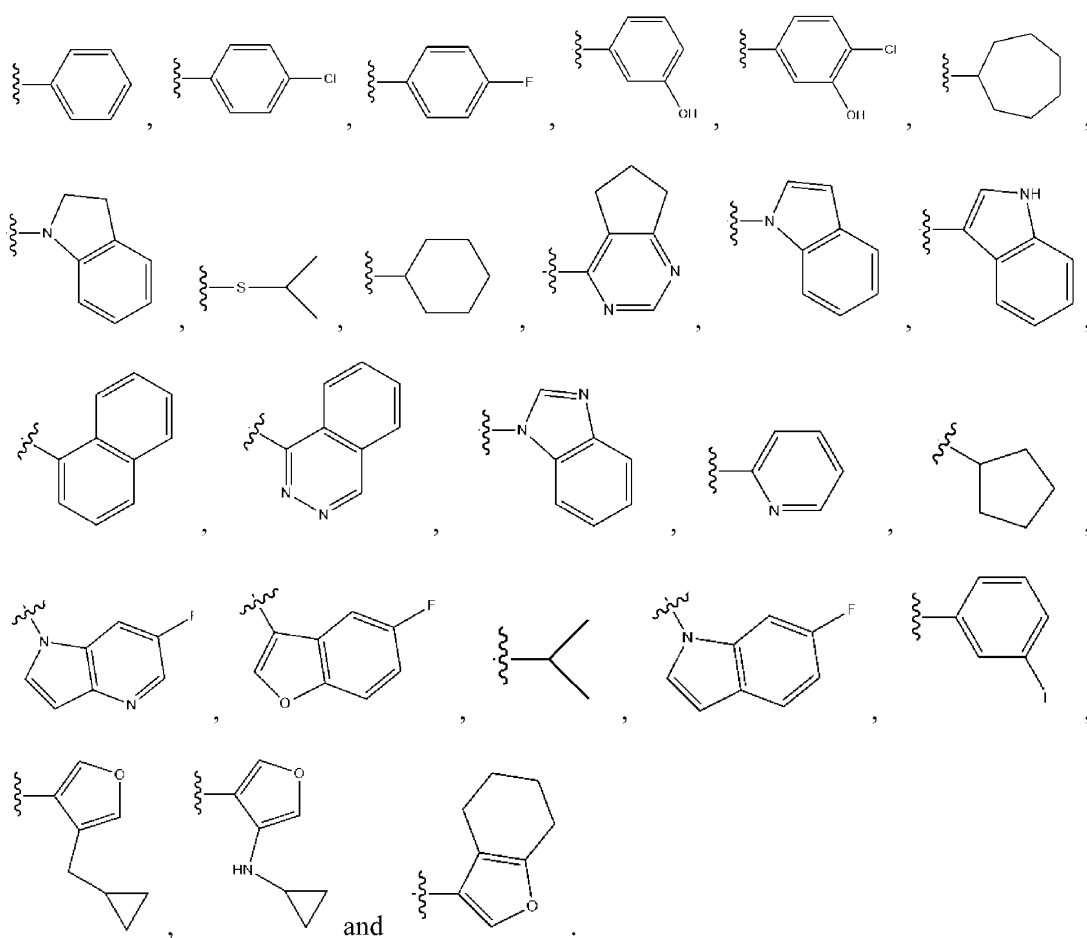
In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranal, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

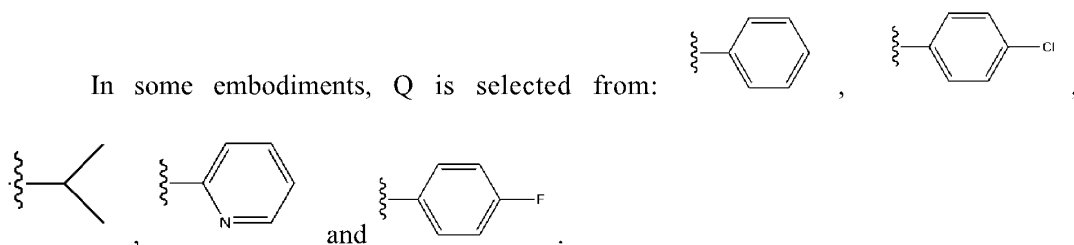
In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Q is selected from:



In some embodiments, Q is selected from:



In some embodiments, L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is $-CH_2-$.

In some embodiments, R' is selected from halogen, $-CN$, $-NO_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl or F.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_a is independently H or isopropyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_d is independently H or methyl.

In some embodiments, a is selected from 0 and 1 and b is selected from 0 and 1.

In some embodiments, a is 0 and b is 0.

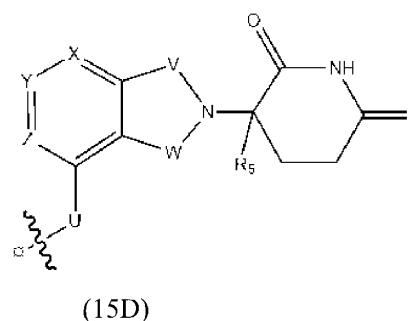
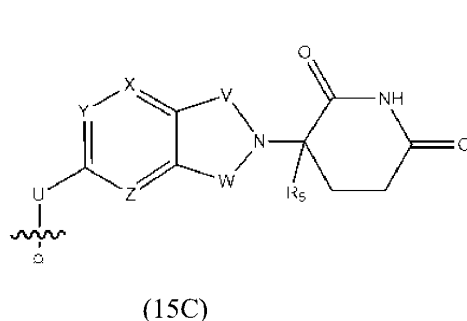
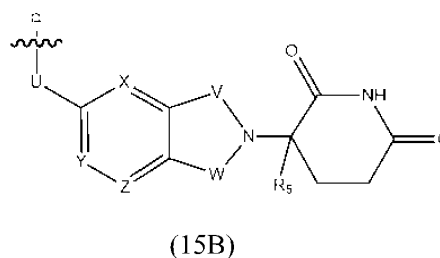
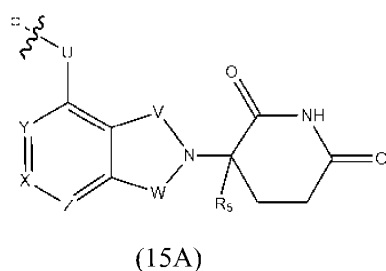
In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

In some embodiments, the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally

substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

In some embodiments, the DT is a moiety represented by Formula (15A), (15B), (15C) or (15D):



wherein,

⊗ denotes the point of attachment with the Formula II;

U is independently selected from a bond, -CH₂-, -NH- and -O-;

each of V and W is independently selected from -C(=O)- and -CH₂-;

each of X, Y, and Z is independently selected from CR₆ and N;

R₅ is selected from H, halogen and optionally substituted C₁-C₆ alkyl; and

R₆ is selected from H, halogen and optionally substituted C₁-C₆ alkyl.

In some embodiments, U is a bond.

In some embodiments, U is -CH₂-.

In some embodiments, V is -C(=O)- and W is -CH₂-.

In some embodiments, V is -CH₂- and W is -C(=O)-.

In some embodiments, both of V and W are -C(=O)-.

In some embodiments, each of X, Y, and Z is independently selected from CR₆.

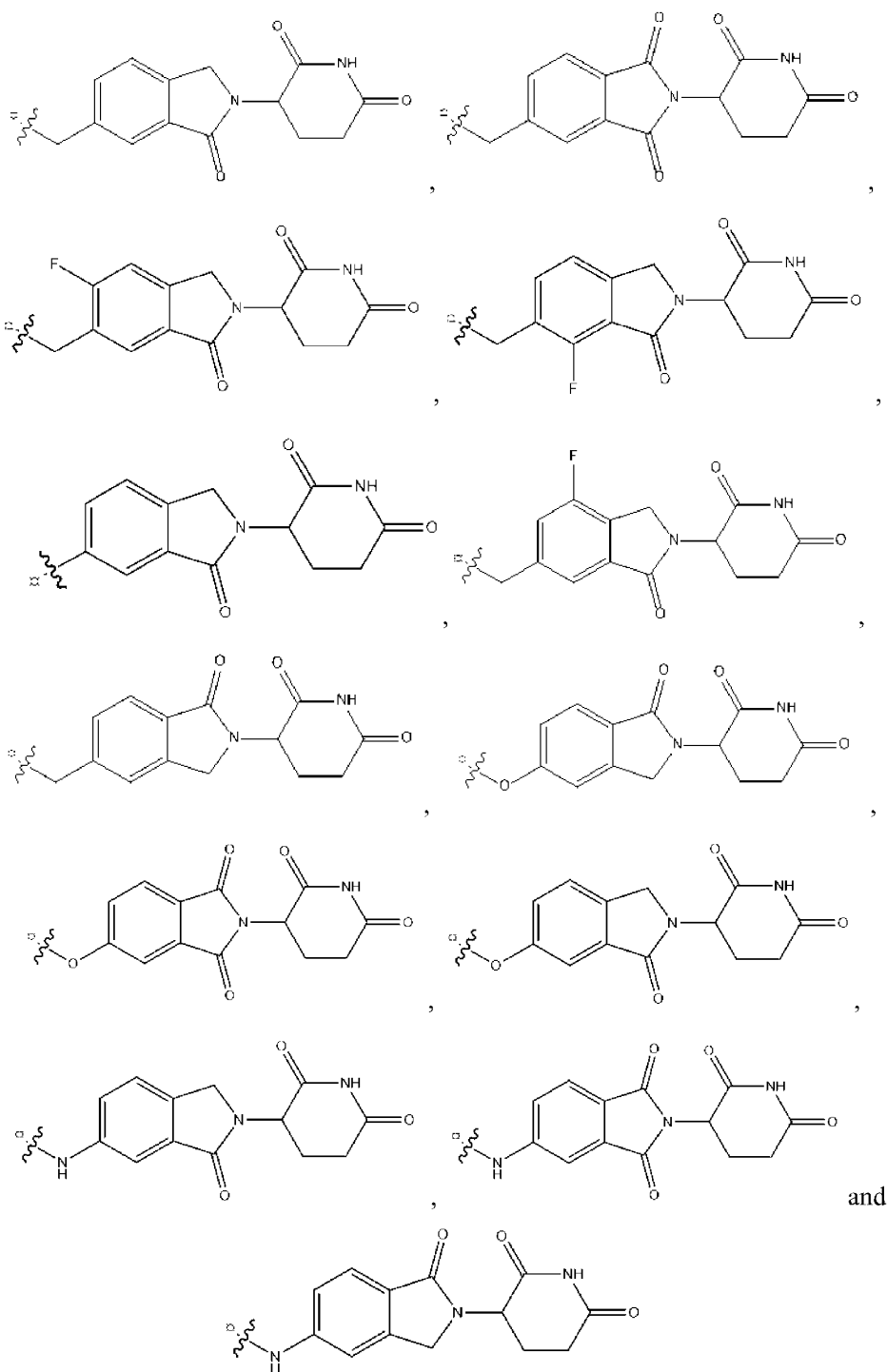
In some embodiments, R₅ is selected from H, F, Cl and Br.

In some embodiments, R₅ is H.

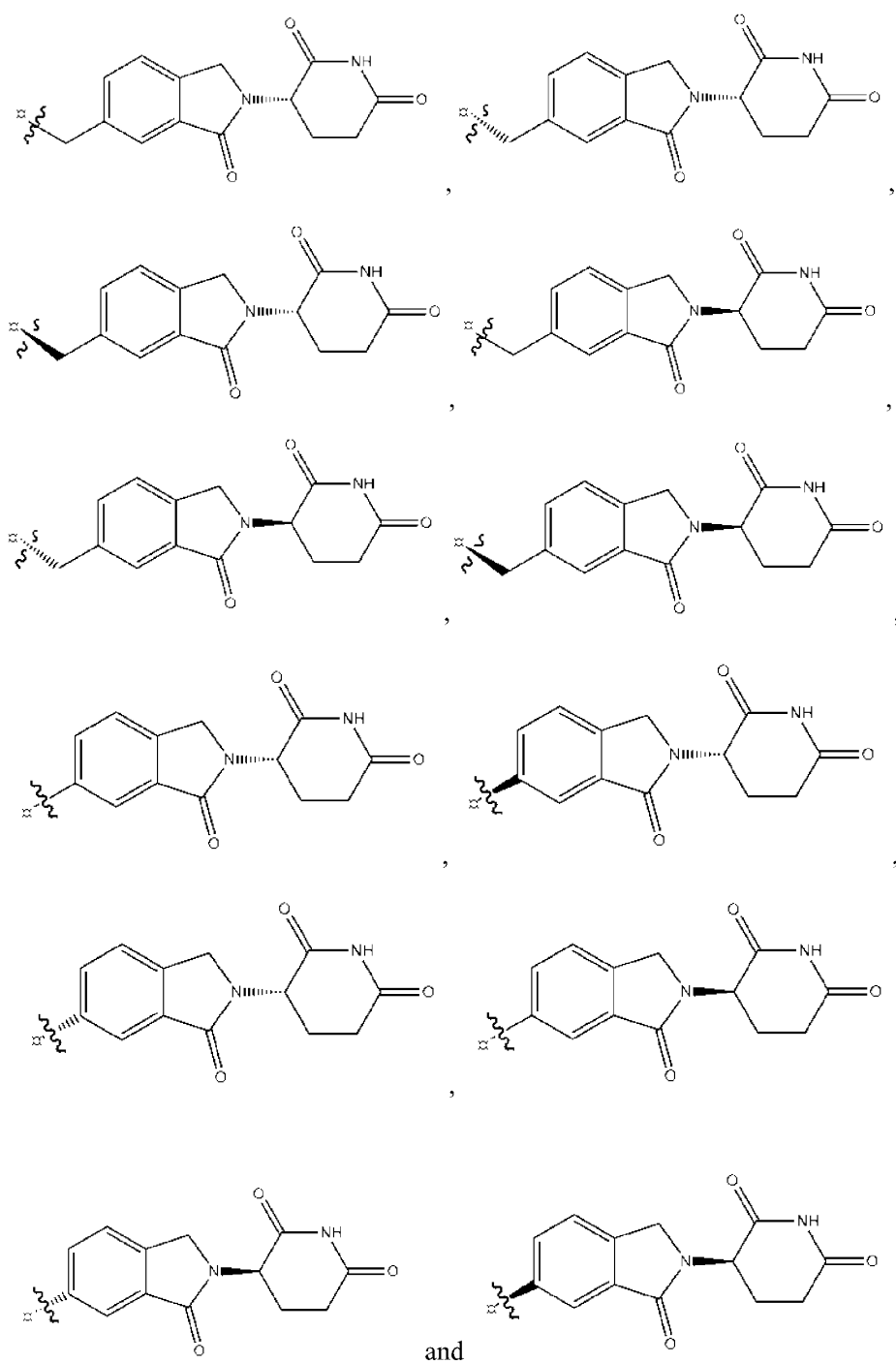
In some embodiments, R₆ is selected from H, F, Cl and Br.

In some embodiments, R₆ is H or F.

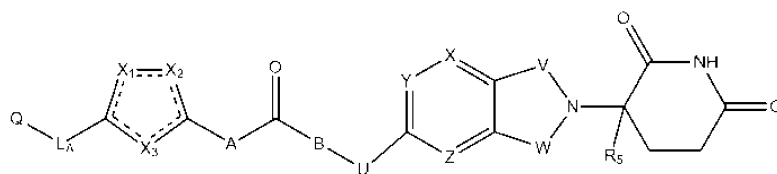
In some embodiments, the DT is a moiety selected from:



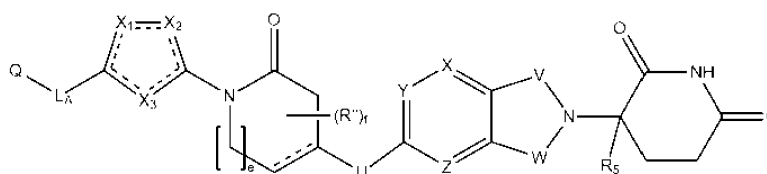
In some embodiments, the DT is a moiety selected from:



In some embodiments, the compound is represented by Formula (16A) or (16B)



(16A)



(16B)

wherein:

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-C(=O)NR_bR_c$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-S(=O)_2NR_bR_c$ and Cy;

Cy is selected from aryl, C_{3-12} carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R' ;

L_A is selected from a bond, $-(CH_2)_aC(R_1)(R_2)(CH_2)_b-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$, $-C(=S)-$, $-S(=O)-$ and $-S(=O)_2-$;

X_1 , X_2 and X_3 are each independently selected from CR, S or N;

with the proviso that at least one of X_1 , X_2 and X_3 is N and one of X_1 , X_2 and X_3 is S;

A is selected from C_{1-20} alkylene, $-O-$, $-S-$, $-N(R_e)-$ and $-N(R_e)-C_{1-20}$ alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C_{1-20} alkylene group is independently replaced with a group selected from $-O-$, $-S-$, $-N(R_e)-$, $-C(=O)-$ and $-C(=S)-$;

B is a bond or is selected from arylene, C_{3-12} carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, $-CN$, $-NO_2$, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-OR_a$, $-SR_a$ and $-NR_bR_c$;

U is independently selected from a bond, $-CH_2-$, $-NH-$ and $-O-$;

each of V and W is independently selected from $-C(=O)-$ and $-CH_2-$;

each of X, Y, and Z is independently selected from CR_6 and N;

each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-C(=O)NR_bR_c$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-S(=O)_2NR_bR_c$, optionally substituted C_{3-6}

carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R'' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R₅ is selected from H, halogen and optionally substituted C₁₋₆ alkyl;

R₆ is selected from H, halogen and optionally substituted C₁₋₆ alkyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

R_e is selected from H and optionally substituted C_{1-6} alkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$;

e is 0 or 1;

f is selected from 0, 1, 2 and 3; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl.

In some embodiments, Q is selected from optionally substituted C_{1-6} alkyl, $-OR_a$, $-SR_a$, $-NR_bR_c$ and Cy.

In some embodiments, Q is selected from C_{1-6} alkyl, $-SR_a$, and Cy.

In some embodiments, Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

In some embodiments, Q is selected from isopropyl, isopropylthio and Cy.

In some embodiments, Q is Cy.

In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C_{3-8} carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R' .

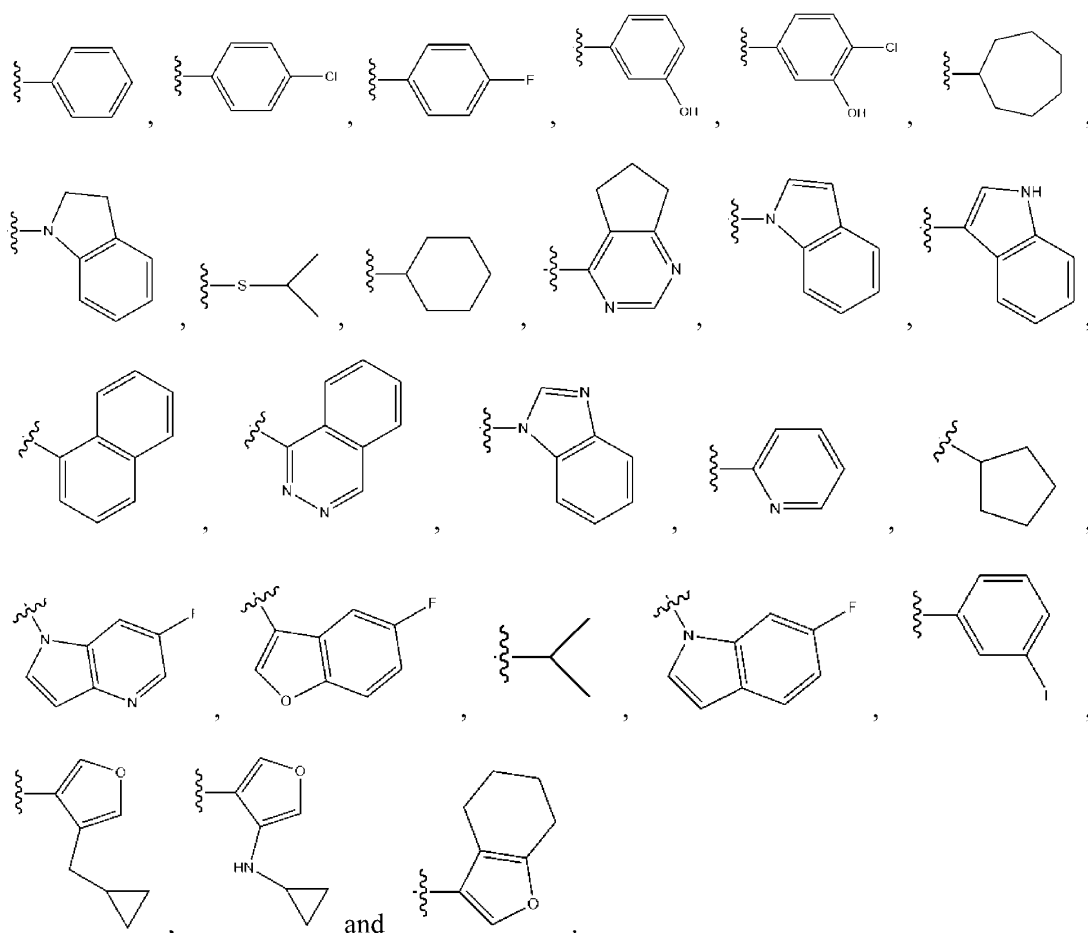
In some embodiments, Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranal, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R' .

In some embodiments, Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-

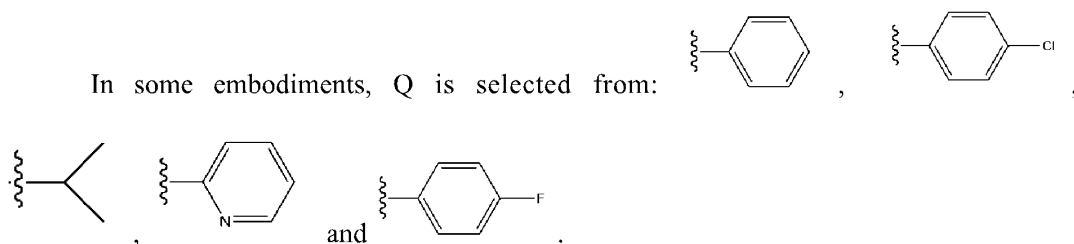
cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

In some embodiments, Q is selected from:



In some embodiments, Q is selected from:



In some embodiments, L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

In some embodiments, L_A is selected from a bond, $-\text{CH}_2-$, $-\text{CF}_2-$, $-\text{NH}-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}(=\text{O})-$ and $-\text{C}(=\text{S})-$.

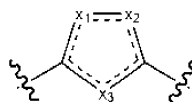
In some embodiments, L_A is $-\text{CH}_2-$.

In some embodiments, X_1 is CR or N.

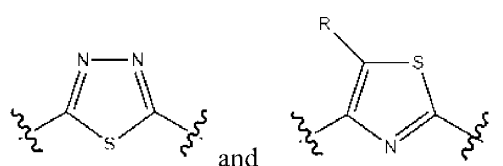
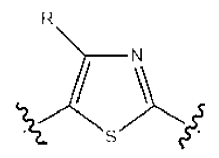
In some embodiments, X_2 is S or N.

In some embodiments, X_3 is S or N.

In some embodiments,



is selected from:



In some embodiments, A is selected from C_{1-8} alkylene, $-\text{O}-$, $-\text{NH}-$, $-\text{N}(\text{CH}_3)-$, $-\text{N}(\text{C}_2\text{H}_5)-$, $-\text{NH}-\text{C}_{1-8}\text{alkylene}$, and optionally wherein 1, 2, 3 or more methylene in the C_{1-8} alkylene group is independently replaced with a group selected from $-\text{O}-$ and $-\text{C}(=\text{O})-$.

In some embodiments, A is selected from $-\text{CH}_2-$, $-\text{O}-$, $-\text{NH}-$, $-\text{NH}-(\text{CH}_2)_3-$, $-\text{NH}-(\text{CH}_2)_5-$ and $-\text{NH}-\text{C}(=\text{O})-(\text{CH}_2)_3-\text{O}-(\text{CH}_2)_3-$.

In some embodiments, A is selected from $-\text{CH}_2-$, $-\text{O}-$ and $-\text{NH}-$.

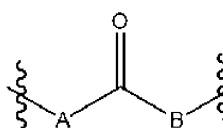
In some embodiments, A is $-\text{NH}-$.

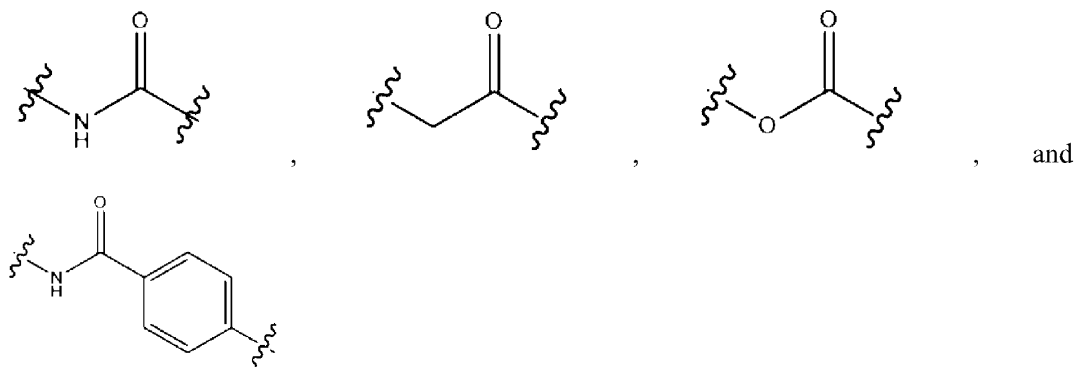
In some embodiments, B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, $-\text{CN}$, $-\text{NO}_2$, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-\text{OH}$, $-\text{O}(\text{CH}_3)$, $-\text{NH}_2$, $-\text{NH}(\text{CH}_3)$ and $-\text{N}(\text{CH}_3)_2$.

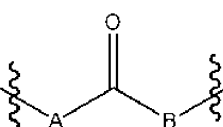
In some embodiments, B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolylen, imidazolylen, oxazolylen, isoxazolylen, oxadiazolylen, thiazolylen, isothiazolylen, thiadiazolylen, pyridinylen, pyranilylen, pyrazinylen, pyrimidinylen, pyrazinylen, triazolylen, tetrazolylen and triazinylen, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

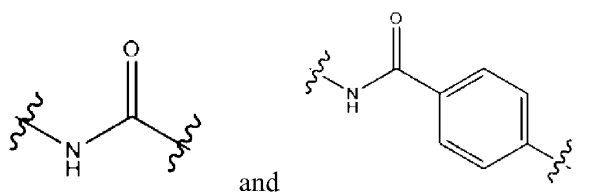
In some embodiments, B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

In some embodiments, B is a bond or phenylene.

In some embodiments,  is a moiety selected from:



In some embodiments,  is a moiety selected from:



In some embodiments, U is a bond.

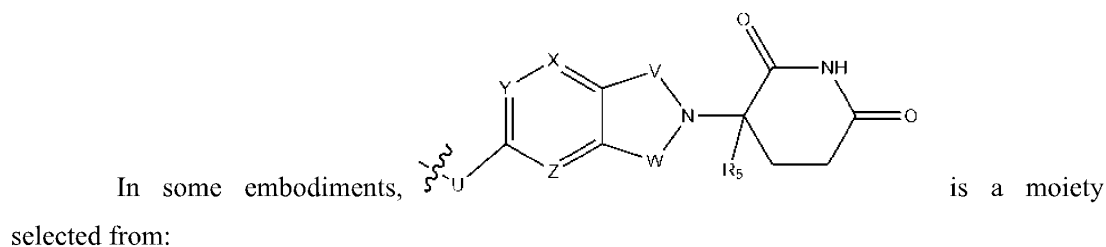
In some embodiments, U is -CH₂-.

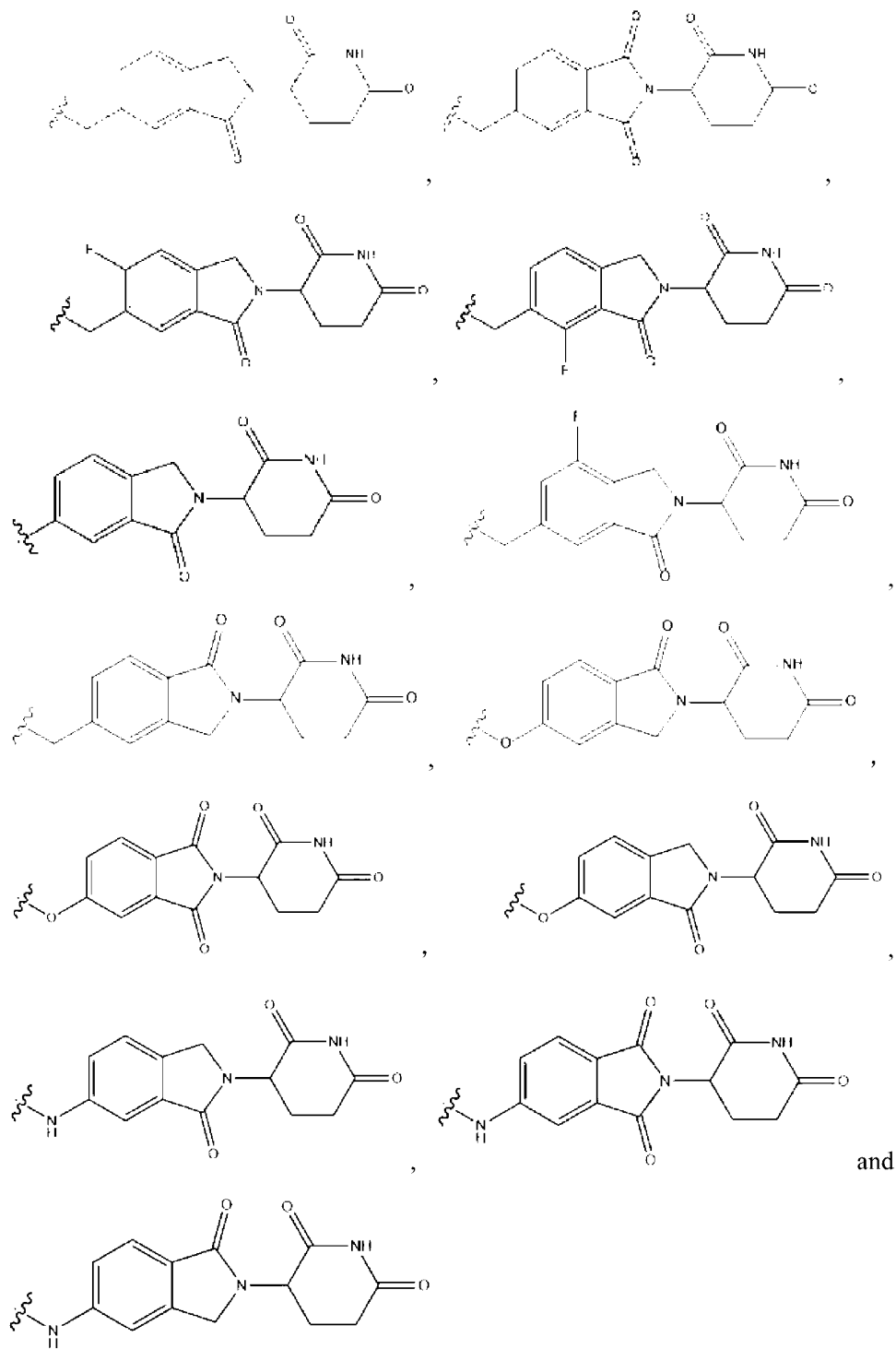
In some embodiments, V is -C(=O)- and W is -CH₂-.

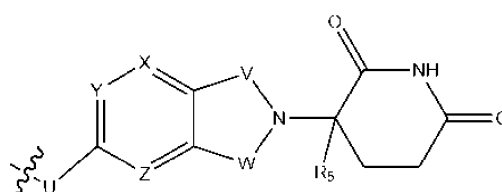
In some embodiments, V is -CH₂- and W is -C(=O)-.

In some embodiments, both of V and W are -C(=O)-.

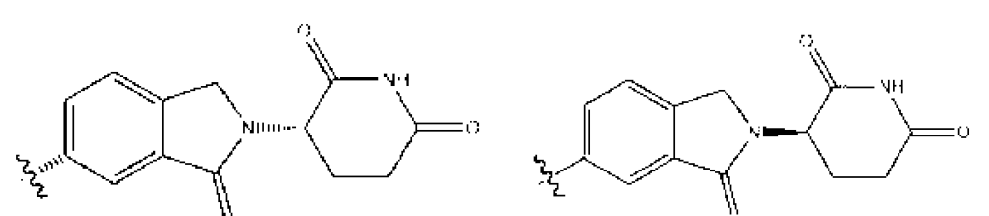
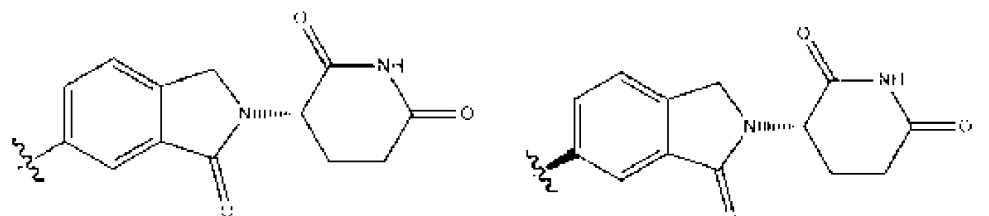
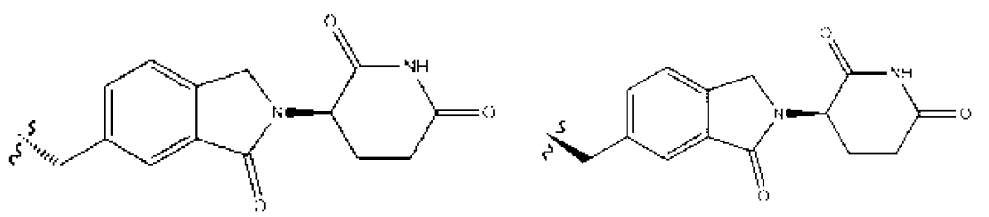
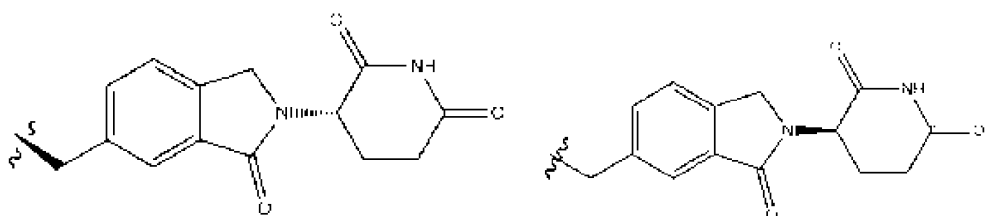
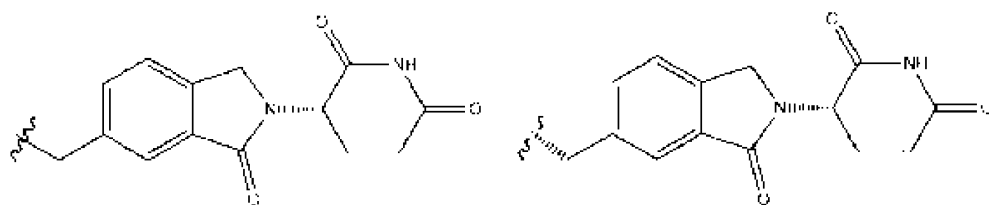
In some embodiments, each of X, Y, and Z is independently selected from CR₆.

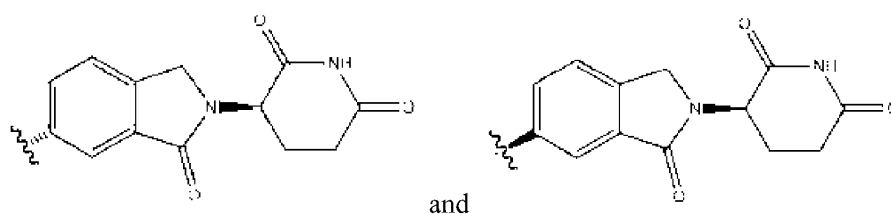






In some embodiments,  is a moiety selected from:





In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, each of R_1 and R_2 is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

In some embodiments, each of R_1 and R_2 is independently selected from H and F.

In some embodiments, both of R_1 and R_2 are H.

In some embodiments, both of R_1 and R_2 are F.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

In some embodiments, R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

In some embodiments, R is selected from H, methyl and -OH.

In some embodiments, R is H.

In some embodiments, R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

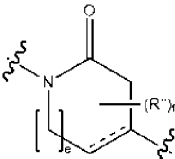
In some embodiments, R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

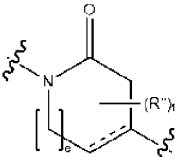
In some embodiments, R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

In some embodiments, R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

In some embodiments, R' is Cl or F.

In some embodiments,  in

is a single bond.

In some embodiments,  in

is a double bond.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c.

In some embodiments, R'' is selected from halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

In some embodiments, R'' is selected from F, Cl, Br, methyl, ethyl, propyl, -OH and -NH₂.

In some embodiments, R₅ is selected from H, F, Cl and Br.

In some embodiments, R₅ is H.

In some embodiments, R₆ is selected from H, F, Cl and Br.

In some embodiments, R₆ is H or F.

In some embodiments, each R_a is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, each R_a is independently H or isopropyl.

In some embodiments, each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

In some embodiments, each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

In some embodiments, each R_d is independently selected from H and C₁₋₆alkyl.

In some embodiments, each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In some embodiments, R_e is H.

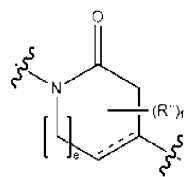
In some embodiments, a is selected from 0 and 1 and b is selected from 0 and 1.

In some embodiments, a is 0 and b is 0.

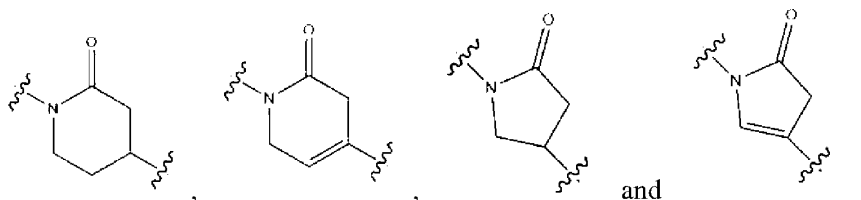
In some embodiments, e is 0.

In some embodiments, e is 1.

In some embodiments, f is 0.



In some embodiments, is a moiety selected from:

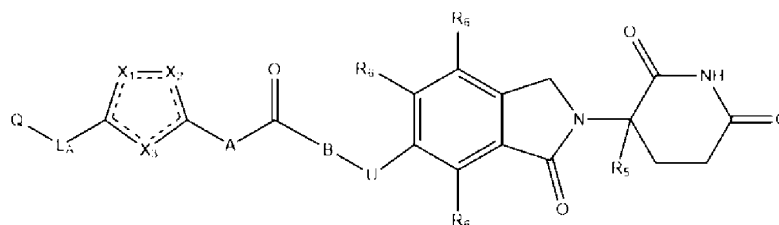


In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

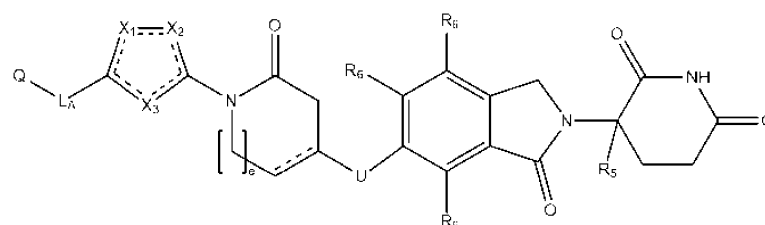
In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In some embodiments, the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

In some embodiments, the compound is represented by Formula (17A) or (17B)



(17A)



(17B)

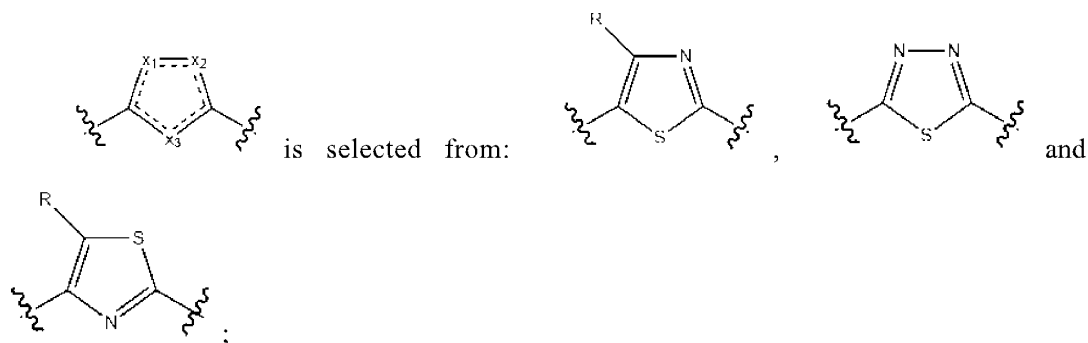
wherein:

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C₁₋₆alkyl, -OR_a, -SR_a, -NR_bR_c and Cy;

Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R';

LA is selected from a bond, -C(R₁)(R₂)-, -N(R₁)-, -O-, -S-, -C(=O)- and -C(=S)-;



A is selected from C_{1-8} alkylene, -O-, -NH-, -N(CH₃)-, -N(C₂H₅)-, -NH- C_{1-8} alkylene, and optionally wherein 1, 2, 3 or more methylene in the C_{1-8} alkylene group is independently replaced with a group selected from -O- and -C(=O)-;

B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂;

U is independently selected from a bond, -CH₂-, -NH- and -O-;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c;

R is selected from H, halogen, -CN, -NO₂, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -SR_a, and -NR_bR_c;

R' is selected from halogen, -CN, -NO₂, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -SR_a and -NR_bR_c;

R₅ is selected from H, F, Cl and Br;

R₆ is selected from H, F, Cl and Br;

each R_a is independently selected from H and C_{1-6} alkyl;

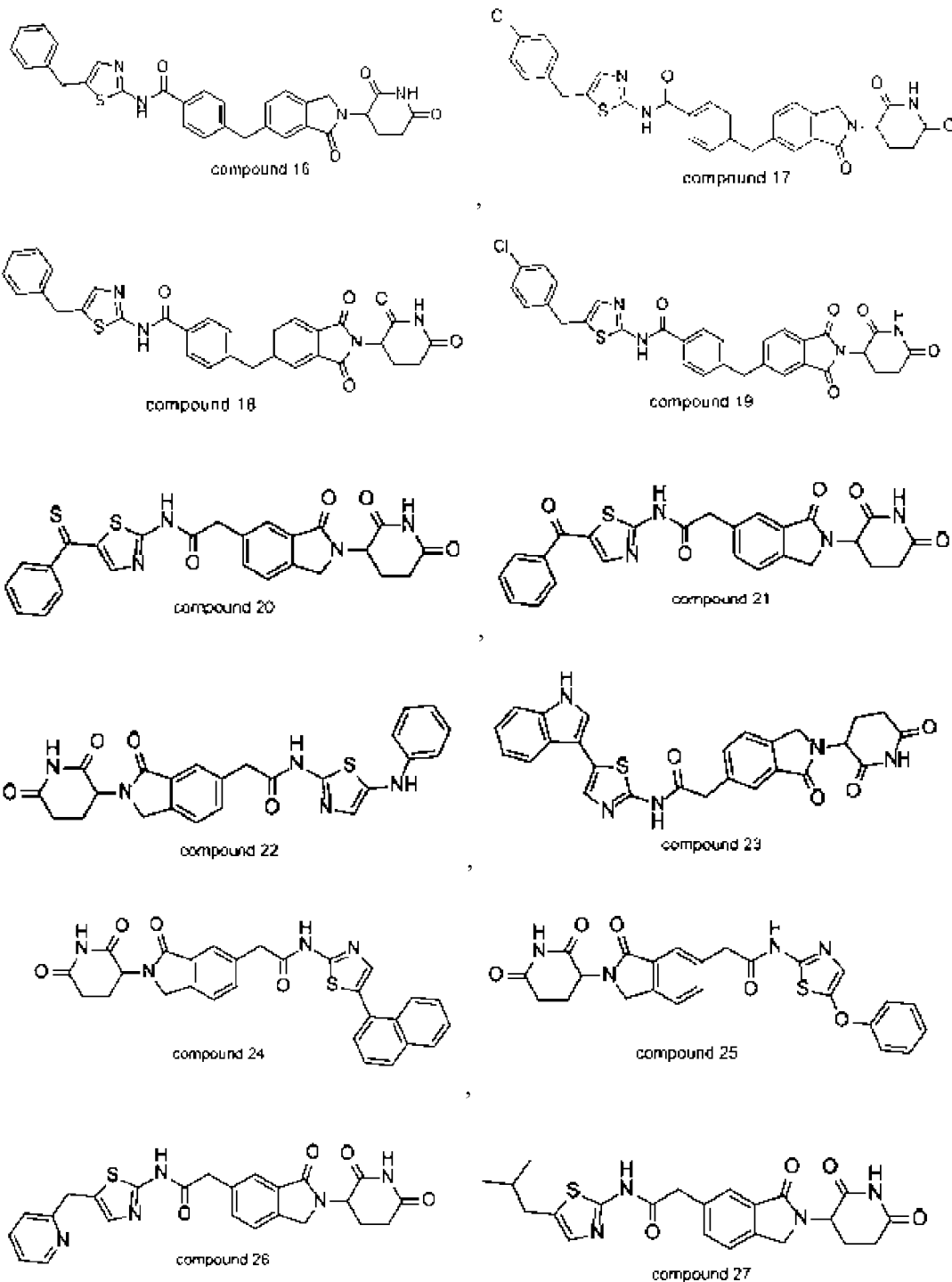
each of R_b and R_c is independently selected from H, C_{1-6} alkyl and C_{3-6} cycloalkyl;

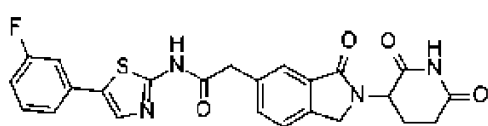
e is 0 or 1; and

wherein the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3

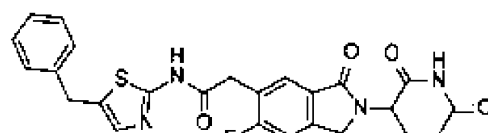
substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

In some embodiments, the compound is selected from the group consisting of

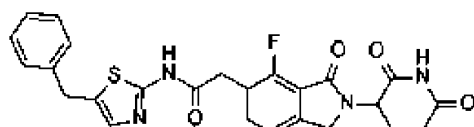




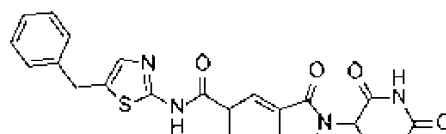
compound 28



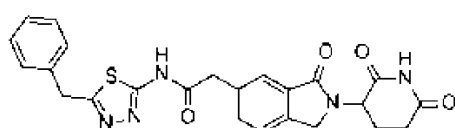
compound 29



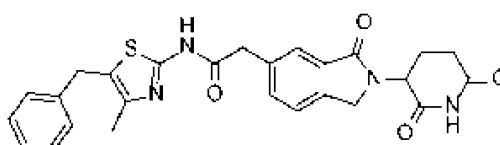
compound 30



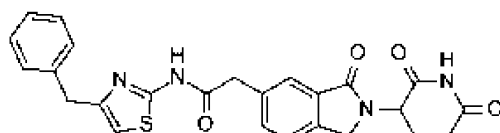
compound 31



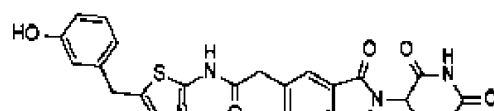
compound 32



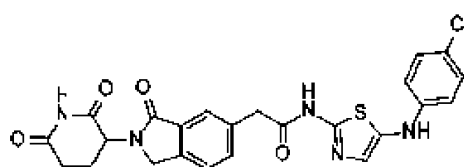
compound 33



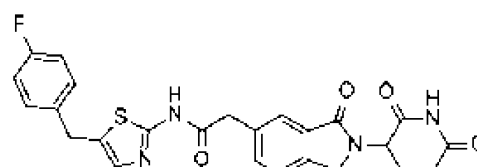
compound 34



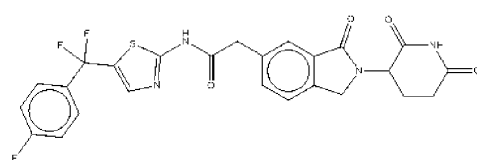
compound 35



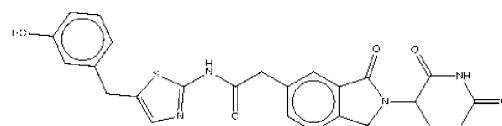
compound 36



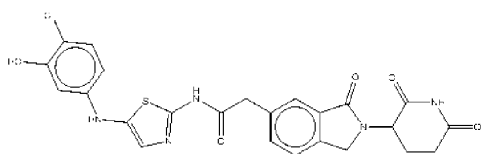
compound 37



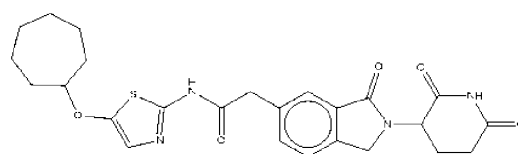
compound 38



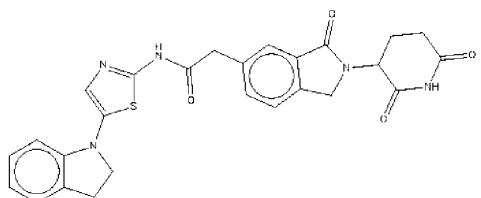
compound 39



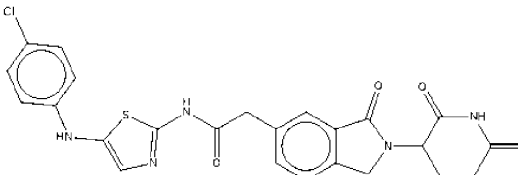
compound 40



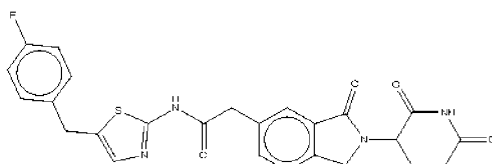
compound 41



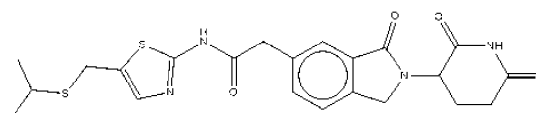
compound 42



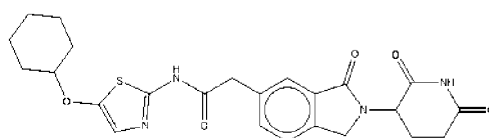
compound 43



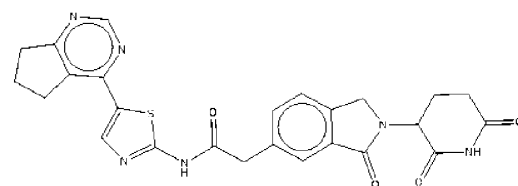
compound 44



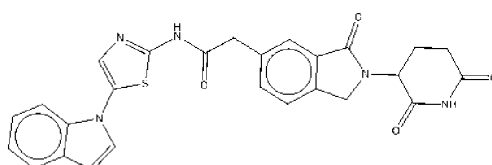
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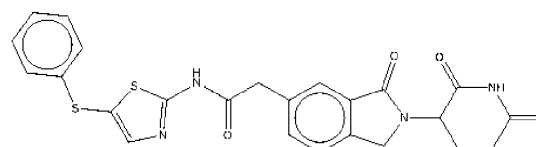
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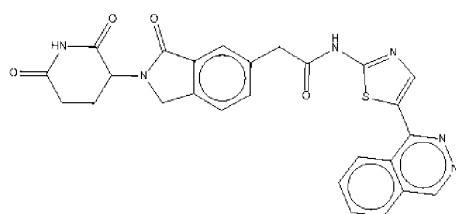
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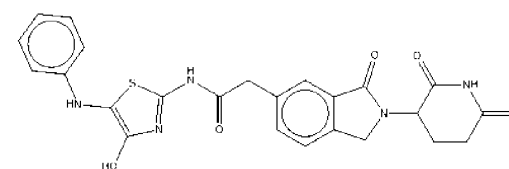
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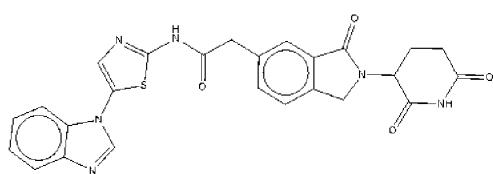
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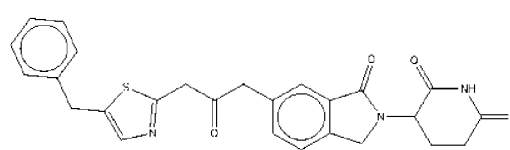
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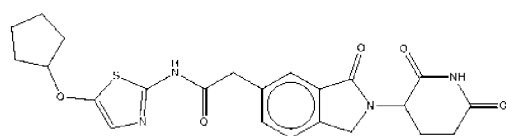
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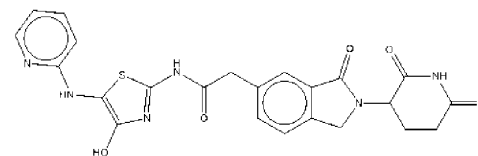
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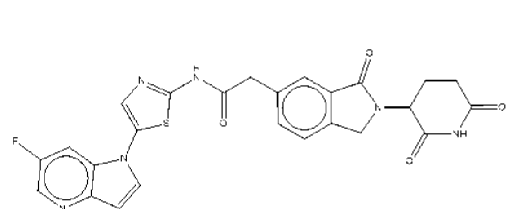
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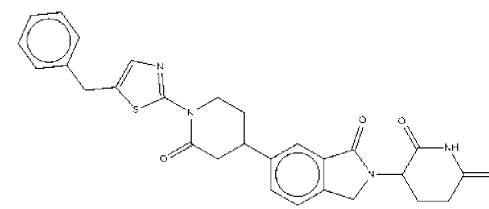
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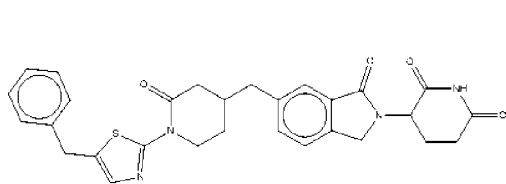
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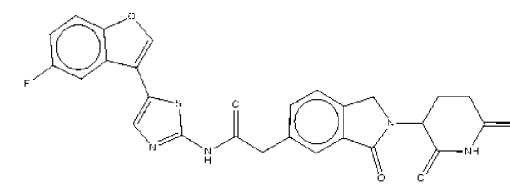
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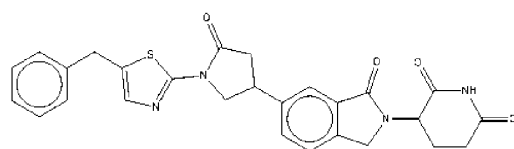
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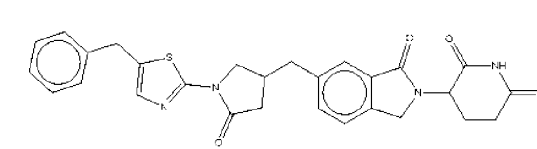
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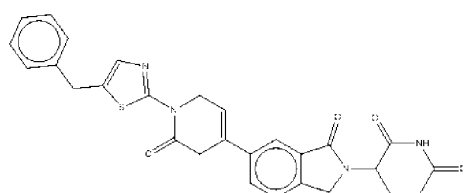
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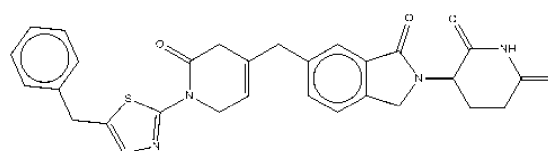
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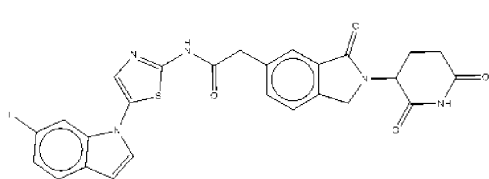
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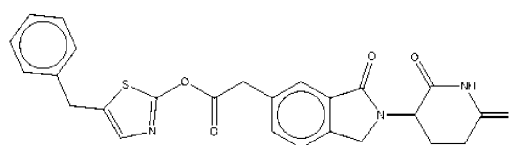
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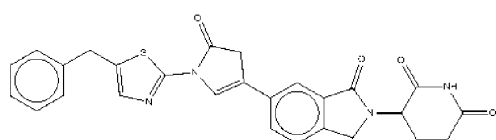
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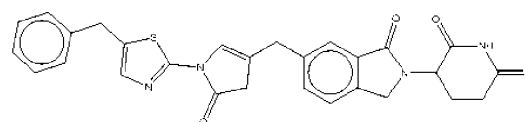
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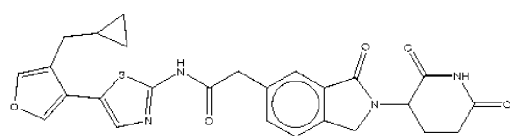
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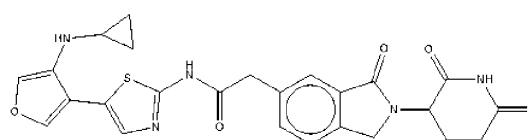
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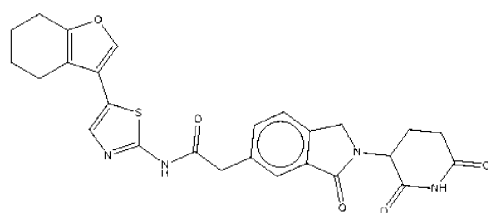
compound 67



compound 68



compound 69



compound 70

and

In some embodiments, the compound is selected from the those listed in Table 1:

Table 1

No.	Structure	Name
1		<i>N</i> -(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
2		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide
3		<i>N</i> -(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-7-fluoro-3-oxoisindolin-5-yl)acetamide
4		<i>N</i> -(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide
5		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)acetamide
6		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
7		<i>N</i> -(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide
8		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide

No.	Structure	Name
9		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide
10		<i>N</i> -(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide
11		<i>N</i> -(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide
12		<i>N</i> -(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide
13		<i>N</i> -(3-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide
14		<i>N</i> -(3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide
15		<i>N</i> -(3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamido)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide
16		<i>N</i> -(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide

No.	Structure	Name
17		N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide
18		N-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide
19		N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide
20		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylcarbonothioyl)thiazol-2-yl)acetamide
21		N-(5-benzoylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
22		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylamino)thiazol-2-yl)acetamide
23		N-(5-(1H-indol-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide

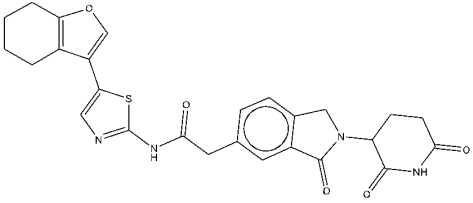
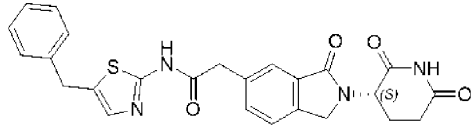
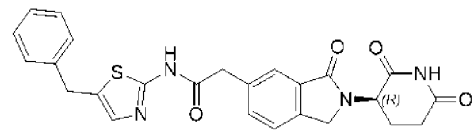
No.	Structure	Name
24		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(naphthalen-1-yl)thiazol-2-yl)acetamide
25		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-phenoxythiazol-2-yl)acetamide
26		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-picolinoylthiazol-2-yl)acetamide
27		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-isobutylthiazol-2-yl)acetamide
28		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-fluorophenyl)thiazol-2-yl)acetamide
29		N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-oxoisindolin-5-yl)acetamide
30		N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-3-oxoisindolin-5-yl)acetamide
31		N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindoline-5-carboxamide

No.	Structure	Name
32		N-(5-benzyl-1,3,4-thiadiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
33		N-(5-benzyl-4-methylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
34		N-(4-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
35		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-hydroxybenzyl)thiazol-2-yl)acetamide
36		N-(5-((4-chlorophenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
37		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4-fluorobenzyl)thiazol-2-yl)acetamide
38		N-(5-(difluoro(4-fluorophenyl)methyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
39		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-hydroxybenzyl)thiazol-2-yl)acetamide

No.	Structure	Name
40		N-(5-((4-chloro-3-hydroxyphenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
41		N-(5-(cycloheptyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
42		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(indolin-1-yl)thiazol-2-yl)acetamide
43		N-(5-((4-chlorophenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
44		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4-fluorobenzyl)thiazol-2-yl)acetamide
45		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-((isopropylthio)methyl)thiazol-2-yl)acetamide
46		N-(5-(cyclohexyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
47		N-(5-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
48		N-(5-(1H-indol-1-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
49		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylthio)thiazol-2-yl)acetamide

No.	Structure	Name
50		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phthalazin-1-yl)thiazol-2-yl)acetamide
51		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(4-hydroxy-5-(phenylamino)thiazol-2-yl)acetamide
52		N-(5-(1H-benzo[d]imidazol-1-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
53		3-(6-(3-(5-benzylthiazol-2-yl)-2-oxopropyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
54		N-(5-(cyclopentyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
55		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(4-hydroxy-5-(pyridin-2-ylamino)thiazol-2-yl)acetamide
56		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(6-fluoro-1H-pyrrolo[3,2-b]pyridin-1-yl)thiazol-2-yl)acetamide
57		3-(6-(1-(5-benzylthiazol-2-yl)-2-oxopiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
58		3-(6-((1-(5-benzylthiazol-2-yl)-2-oxopiperidin-4-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

No.	Structure	Name
59		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(5-fluorobenzofuran-3-yl)thiazol-2-yl)acetamide
60		3-(6-(1-(5-benzylthiazol-2-yl)-5-oxopyrrolidin-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
61		3-(6-((1-(5-benzylthiazol-2-yl)-5-oxopyrrolidin-3-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
62		3-(6-(1-(5-benzylthiazol-2-yl)-2-oxo-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
63		3-(6-((1-(5-benzylthiazol-2-yl)-2-oxo-1,2,3,6-tetrahydropyridin-4-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
64		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(6-fluoro-1H-indol-1-yl)thiazol-2-yl)acetamide
65		5-benzylthiazol-2-yl 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetate
66		3-(6-(1-(5-benzylthiazol-2-yl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
67		3-(6-((1-(5-benzylthiazol-2-yl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
68		N-(5-(4-(cyclopropylmethyl)furan-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
69		N-(5-(4-(cyclopropylamino)furan-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide

No.	Structure	Name
70		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4,5,6,7-tetrahydrobenzofuran-3-yl)thiazol-2-yl)acetamide
1-P1		(S)-N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide
1-P2		(R)-N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide

III. Pharmaceutical Compositions and kits

In some aspects, the present disclosure provides a pharmaceutical composition comprising a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof and one or more pharmaceutically acceptable excipients. For conciseness, “a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof” is also termed as “the compound as described in the present disclosure” hereinafter.

In some embodiments, the compound of formula (1) is selected from anyone of the compounds as described in anyone of the embodiments disclosed under the Section “II. Compounds”. In some embodiments, the compound of formula (1) is selected from anyone of compounds 1-15 as described herein.

In some embodiments, the pharmaceutical composition comprises one or more additional active pharmaceutical agents (e.g., one or more additional active compounds other than “the compound as described in the present disclosure” mentioned above). In some embodiments, the additional active pharmaceutical agents are necessary for the specific indication being prevented or treated by the compound as described in the present disclosure. The additional active pharmaceutical agents may have complementary activities that do not affect the activities of the compound as described in the present disclosure in an adverse manner. Such pharmaceutical agents may be present in combination with the compound as described in the present disclosure in amounts that are effective for the purpose intended.

The pharmaceutical composition as described in the present disclosure may be provided in any suitable form, depending on the route of administration. In some embodiments, the pharmaceutical composition is formulated for oral, buccal, topical, transdermal, rectal, intranasal, intrapulmonary, transmucosal, inhalation, or parenteral such as intravenous, intraarterial, intramuscular, subcutaneous, intraosseous or intraperitoneal administration.

In some embodiments, the pharmaceutical composition is formulated as a dosage form for oral administration. Dosage forms suitable for oral administration can be presented as discrete dosage forms, such as capsules, troches, lozenges, tablets, solutions, suspensions, emulsions or aerosol sprays, each comprising a predetermined amount of active ingredients (i.e., the compound as described in the present disclosure and the optional one or more additional active pharmaceutical agents). In some embodiments, the pharmaceutical composition is formulated as a tablet. The tablet may comprise a coating that protects it from the acidic environment of the stomach. For example, the coating may be an enteric coating that maintains its integrity in the stomach and releases the active ingredients in the intestine. In some embodiments, the pharmaceutical composition is formulated as a capsule. The capsule can contain a liquid excipient such as a fatty oil. In some embodiments, the pharmaceutical composition is formulated as various liquid oral dosage forms, such as aqueous solutions, emulsions, suspensions. In some embodiments, the liquid oral dosage forms are solutions and/or suspensions reconstituted from non-effervescent granules or effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Elixirs are clear, sweetened, hydroalcoholic preparations. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain one or more preservatives. Emulsions are two-phase systems in which one liquid is dispersed in the form of small globules throughout another liquid. Emulsions may be oil-in-water or water-in-oil emulsions. Excipients used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions are heterogeneous mixtures in which the solute particles do not dissolve, but get suspended throughout the bulk of the solvent, left floating around freely in the medium. Suspensions use suspending agents and preservatives. Acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms. In some embodiments, the pharmaceutical composition is formulated as an oral inhalation dosage form. Oral inhalation dosage forms include metered dose inhalers, dry powder inhalers and liquid preparations for administration from a nebulizer or metered dose liquid dispensing system. For both metered dose

inhalers and dry powder inhalers, a crystalline form of the active agents is the preferred physical form to confer longer product stability.

In some embodiments, the pharmaceutical composition is formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used in the present disclosure refer to physically discrete units suitable for a subject in need thereof and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the active ingredients sufficient to produce the desired preventive or therapeutic effect, in association with one or more pharmaceutically acceptable excipients. Examples of unit-dose forms include, but not limited to ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single packaging to be administered in segregated unit-dose form. Examples of multiple-dosage forms include vials, bottles of tablets or capsules, or bottles of pints or gallons. Hence, a multiple dosage form is a multiple of unit-doses which are not segregated in packaging.

The pharmaceutical compositions as described in the present disclosure may be prepared using procedures well known in the art (see, *e.g.*, Ansel, Introduction to Pharmaceutical Dosage Forms, Seventh Edition (1999)). The procedures typically include the step of bringing the active ingredients into association with one or more pharmaceutically acceptable excipients. In general, the pharmaceutical compositions are prepared by uniformly and intimately admixing the active ingredients with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired form. For example, a tablet can be prepared by compression or molding the active ingredients, optionally with one or more pharmaceutically acceptable accessory excipients. In instances in which the active ingredients exhibit insufficient solubility, methods for solubilization may be used such as use of liposomes, prodrugs, complexation/chelation, nanoparticles, or emulsions or tertiary templating.

Any pharmaceutically acceptable excipients which are conventionally used in the pharmaceutical industry may be employed for the preparation of pharmaceutical compositions as described in the present disclosure. The Examples of pharmaceutically acceptable excipients useful for the preparation of the pharmaceutical compositions as described in the present disclosure may include, but not limited to: solvents, such as water, ethanol, glycerin, propylene glycol, DMSO, polyethylene glycol, fatty oils such as sesame oil, corn oil, cottonseed oil, or peanut oil, liquid paraffin, ethyl oleate, or isopropyl myristate; surfactants, such as sulfates, sulfonates, quaternary ammonium compounds, lecithin, Spans, Tweens, Myri, polyoxyl 40 stearate, peregol O, or poloxamers; emulsifying agents, such as gelatin, acacia, tragacanth, bentonite or surfactants such as polyoxyethylene sorbitan monooleate; suspending agents, such as

sodium carboxymethylcellulose, pectin, tragacanth, Veegum or acacia; fillers, such as lactose, sucrose, trehalose, lysine, leucine, kaolin, dicalcium phosphate, mannitol, microcrystalline cellulose, or pregelatinized starch; adhesives such as celluloses, PVP, or dextrin; disintegrants, such as croscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar, or hydroxypropyl starch; lubricants, such as talc, polyethylene glycol, calcium stearate, magnesium stearate, lycopodium or stearic acid; glidants, such as colloidal silicon dioxide; colorants, such as any of the approved certified water soluble FD and C dyes or water insoluble FD and C dyes (e.g., those suspended on alumina hydrate); wetting agents, such as propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate or polyoxyethylene lauryl ether; enteric-coating agents, such as fatty acids, fats, waxes, shellac, ammoniated shellac or cellulose acetate phthalates; film coating agents, such as hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 or cellulose acetate phthalate; modified release agents, such as polymers such as the Eudragit[®] series and cellulose esters; sweeteners, such as fructose, glucose, sucrose, artificial sweetening agents such as sucralose, aspartame or saccharin, agave syrup, maple syrup, or corn syrup; flavoring agents, such as natural flavors extracted from plants such as fruits, peppermint, or methyl salicylate; buffers, such as citrate, phosphate, and other organic acids and/or salts thereof; antioxidants, such as ascorbic acid, methionine, citric acid, D,L- α -tocopherol, BHA, BHT, monothioglycerol, ascorbyl palmitate, ascorbic acid, or propyl gallate; preservatives, such as benzoic acid, sodium benzoate, parabens such as methyl paraben or propyl paraben, sorbic acid or benzalkonium bromide; pH modifying agents, such as citric acid, sodium citrate, hydrochloric acid, NaOH or other mild acids or bases; and chelating agents or other materials capable of binding metal ions, such as ethylene diamine tetra acetic acid (EDTA) or its salts.

In some embodiments, the pharmaceutical composition is formulated as an injection. Examples of injections include, but not limited to a sterile solution, suspension or emulsion in aqueous or oily vehicles. Aqueous solutions in saline are conventionally used for injections. Ethanol, glycerol, propylene glycol, liquid polyethylene glycol, cyclodextrin derivatives, and vegetable oils may also be used. Oily vehicles that may be used in injections include, but are not limited to lipophilic solvents such as fatty oils or synthetic fatty acid esters. Aqueous injection suspensions may also contain substances such as humectants, suspending agents, and/or flocculating agents or deflocculating agents. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. The pharmaceutical composition may also be formulated for bolus injection or continuous infusion. Alternatively, the pharmaceutical

composition may be freeze-dried or in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, immediately before use.

In some embodiments, the pharmaceutical composition is formulated as a topical dosage form, such as for topical application to the skin and mucous membranes, such as in the eyes. A useful topical dosage form for the active ingredients may be a solution, suspension, or emulsion. Alternatively, the active ingredients may be formulated as creams, gels, ointments, elixirs, lotions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other dosage forms suitable for topical administration. The active ingredients may also be formulated as aerosols for topical application, such as by inhalation. These dosage forms for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the dosage form will, in some embodiments, have mass median geometric diameters of less than 5 microns, in other embodiments less than 10 microns.

In some embodiments, the pharmaceutical composition is formulated as microcapsules. The microcapsules may be prepared by coacervation techniques or by interfacial polymerization (e.g., hydroxymethylcellulose or gelatin microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug-delivery systems (e.g., microemulsions, liposomes, microspheres (e.g., albumin microspheres), nano-particles and nanocapsules) or in macroemulsions, for example.

In some embodiments, the pharmaceutical composition is formulated as a sustained release dosage form. Examples of sustained release dosage forms include, but not limited to shaped articles (e.g., films or microcapsules) formed by semipermeable matrices of solid hydrophobic polymers which may contain the compounds as described in the present disclosure and optionally one or more additional active pharmaceutical agents. Examples of sustained-release matrices include, but not limited to hydrogels, polylactides, polyesters, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers, copolymers of L-glutamic acid and γ -ethyl-L-glutamate, and poly-D-(-)-3-hydroxybutyric acid.

In some embodiments, the pharmaceutical composition is formulated as a controlled release dosage form. Such dosage forms can be used to provide controlled release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. All controlled-release dosage forms have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Most controlled-release dosage forms are designed to initially release an amount of an active ingredient that promptly produces the desired

preventive or therapeutic effect, and gradually and continually release of other amounts of the active ingredient to maintain this level of preventive or therapeutic effect over an extended period of time. In order to maintain this constant level of the active ingredient in the body, the active ingredient must be released from the dosage form at a rate that will replace the amount of the active ingredient being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds. Advantages of controlled-release dosage forms include extended activity of the active ingredient, reduced dosage frequency, and increased patient compliance. In addition, controlled-release dosage forms can be used to affect the time of onset of action or other characteristics, such as blood levels of the active ingredient, and can thus affect the occurrence of unwanted side effects. Suitable controlled-release dosage forms can be readily selected for use with the active ingredients provided in the present disclosure.

In some embodiments, the pharmaceutical composition is formulated as a dosage form for rectal administration, such as rectal suppositories, capsules and tablets. Rectal suppositories used in the present disclosure refer to solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more active ingredients. Examples of bases utilized in rectal suppositories include, but not limited to cocoa butter, glycerin-gelatin, carbowax and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. Tablets and capsules for rectal administration are manufactured using the same substance and by the same methods as for dosage forms for oral administration.

In some embodiments, the pharmaceutical composition is subject to sterilization. Sterilization refers to any process which removes, kills, or deactivates all forms of life (particularly microorganisms) and other biological agents such as prions present in or on a specific surface, object, or fluid. Sterilization may be achieved by various means, including heating, chemical action, irradiation, high pressure, and filtration. For example, sterilization can be accomplished by sterile filtration.

The levels of active ingredients in the pharmaceutical composition as described in the present disclosure are effective for delivery of an amount, upon administration that treats, leads to prevention, or amelioration of one or more of the symptoms of diseases or conditions described in the present disclosure. Specifically, the amounts of the compound as described in the present disclosure and the optional additional active pharmaceutical agents will be dependent on the subject being treated, the severity of the diseases or conditions, the rate of administration, the

absorption, inactivation and excretion rates of the active ingredients being administered, the discretion of the prescribing physician as well as other factors known to the person skilled in the art. In some embodiments, the pharmaceutical composition comprises from 0.05% to 80%, from 0.1% to 50%, from 0.2% to 40%, from 0.5% to 25%, from 1% to 20%, from 5% to 15%, or from 7% to 12% (wt/wt) of the compound as described in the present disclosure. In some embodiments, the pharmaceutical compositions comprise from 0% to 50%, 0.05% to 25%, from 0.1% to 20%, from 0.2% to 15%, from 0.5% to 10%, or from 1% to 5% (wt/wt) of the additional active pharmaceutical agents. The balance of the pharmaceutical composition is made up from one or more pharmaceutically acceptable excipients.

In some aspects, the present disclosure provides a kit comprising a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein and optionally an instruction for use. The compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition may be surrounded by a suitable packaging material. Packaging materials for use in packaging kits are well known in the art. Examples of packaging materials include any packaging material suitable for a selected dosage form and intended mode of administration and treatment, including blister packs, tubes, bottles, inhalers, pumps, bags, vials, syringes, bottles, or other containers. The kit may have an instruction for use which is included in a written material. Besides, clinical trial results and discussion of the results, listing of side effects, drug interactions, and/or additional information useful to the health care provider such as scientific literature references may also be included in the written material. In some embodiments, the kit further comprises one or more additional active pharmaceutical agents. In some embodiments, the compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof and one or more additional active pharmaceutical agents are provided as separate compositions, optionally in separate containers within the kit. In some embodiments, the compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof and one or more additional active pharmaceutical agents are provided as a single composition within the same container in the kit. Additional articles for use (e.g., measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) may be included in the kit.

IV. Methods of treatment and therapeutic uses

In some aspects, the present disclosure provides a method for preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject, comprising

administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

In some embodiments, the compound of formula (1) is selected from anyone of the compounds as described in anyone of the embodiments disclosed under the Section “II. Compounds”. In some embodiments, the compound of formula (1) is selected from anyone of compounds 1-15 as described herein.

In some embodiments, the pharmaceutical composition comprises one or more additional active pharmaceutical agents (e.g., one or more additional active compounds other than “the compound as described in the present disclosure” mentioned above). In some embodiments, the additional active pharmaceutical agents are necessary for the specific indication being prevented or treated by the compound as described in the present disclosure. The additional active pharmaceutical agents may have complementary activities that do not affect the activities of the compound as described in the present disclosure in an adverse manner. Such pharmaceutical agents may be present in combination with the compound as described in the present disclosure in amounts that are effective for the purpose intended.

In some embodiments, the method further comprises administration of one or more additional active pharmaceutical agents to the subject in need thereof, wherein the one or more additional active pharmaceutical agents are in the same pharmaceutical composition as the compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof. In some embodiments, the method further comprises administration of one or more additional active pharmaceutical agents to the subject in need thereof, wherein the one or more additional active pharmaceutical agents are in a different composition from that of the compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof, and the one or more additional active pharmaceutical agents are administered administered prior to, at the same time as, or following administration of the compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

In some embodiments, the disease or the condition is selected from a hyperproliferative disease, a cardiovascular disease, a hematological disease, an infective disease, an endocrinological disease, a metabolic disease, a gastroenterological disease, a respiratory disease, an inflammation, opioid addiction and a urological disease.

In some embodiments, the disease or the condition is a hyperproliferative disease.

In some embodiments, the hyperproliferative disease is a tumor.

In some embodiments, the tumor is a cancer or a sarcoma.

In some embodiments, the cancer is a hematopoietic cancer or a solid tumor.

In some embodiments, the hematopoietic cancer is selected from a leukemia, a lymphoma, heavy chain disease, a myeloproliferative disorder, a multiple myeloma, a plasma cell neoplasia, a familial hypereosinophilia, an inflammatory myofibroblastic tumor and an immunocytic amyloidosis.

In some embodiments, the solid tumor is selected from a nervous system cancer, an exocrine cancer, a musculoskeletal cancer, a gastrointestinal cancer, a respiratory cancer, a genitourinary cancer, a gynecological cancer, a skin cancer, a soft tissue cancer, an oral cancer, a head and neck cancer, an esophageal cancer, a liver cancer and a pancreatic cancer.

In some embodiments, the disease or the condition is a cardiovascular disease.

In some embodiments, the cardiovascular disease is selected from atherosclerosis, cardiac hypertrophy, hypertension, a coronary arterial disease, myocarditis, pericarditis, a cardiac valvular disease, stenosis, restenosis, in-stent-stenosis, angina pectoris, myocardial infarction, acute coronary syndromes, coronary artery bypass grafting, a cardio-pulmonary bypass procedure, endotoxemia, ischemia-reperfusion injury, cerebrovascular ischemia, renal reperfusion injury, embolism and myocardial ischemia.

In some embodiments, the disease or the condition is pulmonary hypertension.

In some embodiments, the disease or the condition is pulmonary arterial hypertension.

In some embodiments, the disease or the condition is selected from idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension, drug- or toxin-induced pulmonary arterial hypertension, idiopathic pulmonary veno-occlusive disease, heritable pulmonary veno-occlusive disease, drug, toxin or radiation-induced pulmonary veno-occlusive disease, idiopathic pulmonary capillary hemangiomatosis, heritable pulmonary capillary hemangiomatosis, drug, toxin or radiation-induced pulmonary capillary hemangiomatosis and persistent pulmonary hypertension of the newborn.

In some aspects, the present disclosure provides a method for inhibiting the growth or preventing the relapse of a tumor in a subject, comprising administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

In some aspects, the present disclosure provides a method for degrading GRK2 or inhibiting the activity of GRK2 in a subject, comprising administering an effective amount of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a

prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein to a subject in need thereof.

For use to treat or prevent the diseases or conditions as described in the present disclosure, the active ingredients are administered in a therapeutically effective amount. The attending physician will determine the dosage regimen that is most appropriate according to the age, weight, stage of the disease and other factors specific to the subject to be treated. The therapeutically effective amount of an active ingredient will vary with the nature and severity of the disease or condition, and the route by which the active ingredient is administered. The frequency and dose (or dosage) will also vary according to factors specific for each subject. The active ingredients may be administered at once or may be divided into a number of smaller doses to be administered at intervals of time. Exemplary doses (or dosages) of the compounds as described in the present disclosure, the one or more additional active pharmaceutical agents, or the combination thereof include, but not limited to from about 1 mg/kg to about 100 mg/kg, from about 2 mg/kg to about 75 mg/kg, from about 5 mg/kg to about 50 mg/kg, or from about 10 mg/kg to about 25 mg/kg. It is to be understood that the precise dosage and duration of treatment is a function of the diseases or conditions being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data or subsequent clinical testing. It is to be understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration behavior. In some cases, it may be necessary to use doses (or dosages) of the active ingredients outside the ranges disclosed in the present disclosure as will be apparent to the person skilled in the art. Furthermore, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with subject response.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in therapy.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein and one or more pharmaceutically

acceptable excipients, for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

In some aspects, the present disclosure provides a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein, for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

In some aspects, the present disclosure provides use of a compound of formula (1) or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or a pharmaceutical composition as described herein for the preparation of a medicament for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.

V. General Synthetic Scheme

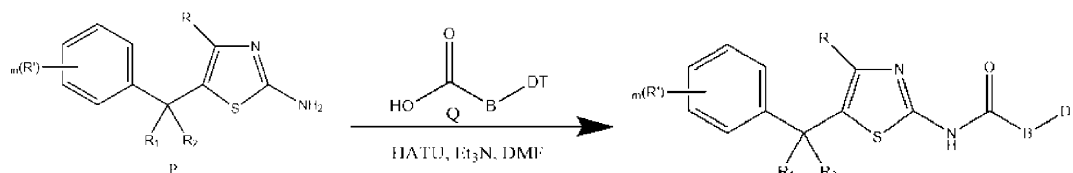
The compound as described in the present disclosure can be synthesized according to organic synthesis techniques known to the person skilled in this art, in view of suitable reference books that describe the synthesis of reactants useful in the synthesis of compound as described in the present disclosure or provide references to articles that describe the synthesis (e.g., "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York), starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" may be obtained from standard commercial sources, including but not limited to Fisher Scientific Co. (Pittsburgh, PA). Moreover, chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses provide custom synthesis services.

The following general synthetic scheme for the compound as described in the present disclosure is provided for purpose of illustration only. It is understood that the person skilled in the art may be able to prepare these compounds by similar methods or by combining other methods known to the person skilled in the art. It is also to be understood that the person skilled in the art

would be able to make, in a similar manner as described below by using the appropriate starting materials and modifying the synthetic route as needed.

Scheme 1

Scheme 1 illustrates a general synthetic method for synthesizing the compounds according to the present application comprising a thiazole ring in its backbone:



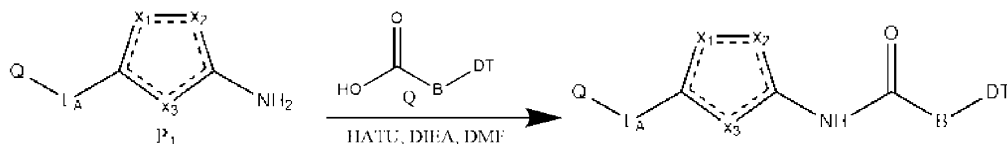
Scheme 1

wherein R, R₁, R₂, R', m, B and DT are as defined above.

Various target compounds according to the present application could be synthesized by reacting the corresponding precursor compound P with compound Q according to the Scheme 1. Briefly, in an embodiment, a compound P (0.9 mmol) is dissolved in 5 ml of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (3.6 mmol), a compound Q (0.9 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 500 mg, 1.32 mmol) are added sequentially at room temperature. After reacting for about 1 hour, the reaction of the starting material compound Q is complete (e.g., by LCMS detection). The reaction is quenched by adding 20 ml of distilled water and ethyl acetate is added to extract and separate the liquids. The extraction is repeated for three times until the extraction is complete. The organic phases are combined and washed with saturated brine, dried and concentrated, and the concentrate is purified by column chromatography (solvent: dichloromethane : methanol = 100:1 to 20:1) or by reverse-phase high performance liquid chromatography (eluent: acetonitrile-water, gradient 35 to 60%) to obtain a white or off-white solid product, i.e. compound AF.

Scheme 2

Scheme 2 illustrates another general synthetic method for synthesizing the compounds according to the present application:



Scheme 2

wherein Q, L_A, X₁, X₂, X₃, B and DT are as defined above. Various target compounds according to the present application could be synthesized by reacting the corresponding precursor compound P₁ with compound Q according to the Scheme 2. Briefly, in an embodiment, to a mixture of a compound Q (0.066 mmol) and a compound P₁ (0.066 mmol) in DMF (3 mL), DIEA (0.099 mmol) and HATU (0.073 mmol) are added. The solution is stirred at RT for 4 hours. Water (20 mL) is added to the residue and the mixture is extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the target compound. It is understood by the person skilled in the art that the reagents and procedures as mentioned above are for illustrative purpose only and shall not be constructed as limiting. For example, in another embodiment, the DIEA may be interchangeable with similar bases, e.g., TEA.

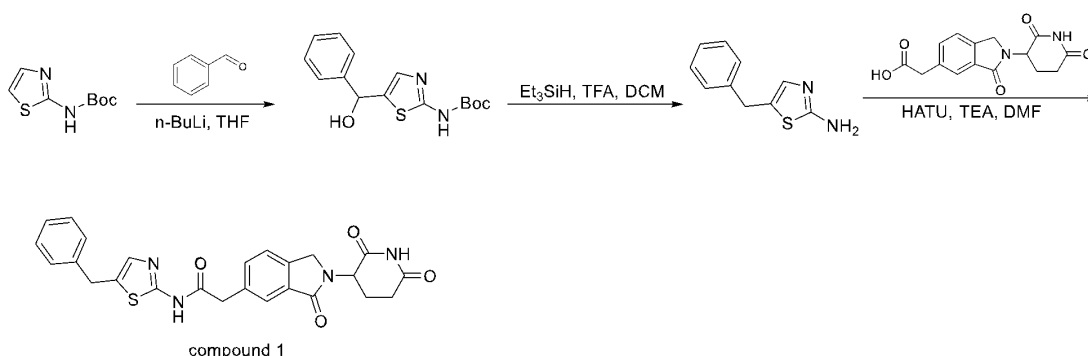
EXAMPLES

The present disclosure will now be described with reference to the following Examples, which are intended to illustrate, but not limit, the invention. Unless otherwise specified, if the specific conditions are not indicated in the Examples, it is carried out in accordance with the conventional conditions, or the conditions suggested by the manufacturer. The reagents or instruments used without the manufacturer's indication are conventional products that commercially available. The person skilled in the art would understand that the Examples described herein are not intended to limit the scope of the invention as claimed.

As used herein, in case of discrepancy between the structure and chemical name provided for a particular compound, the structure shall control.

Synthetic Examples

Example 1: Preparation of *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 1)



Step 1: Synthesis of tert-butyl (5-(hydroxy(phenyl)methyl)thiazol-2-yl)carbamate

N-Boc-2-aminothiazole (2 g, 10 mmol) was dissolved in tetrahydrofuran (20 mL) and the reaction was cooled to -70 °C, and n-butyllithium solution (10 mL, 2.5 N THF solution) was

slowly added dropwise under argon protection. The reaction was allowed to continue at this temperature for 30 minutes. Benzaldehyde (1.27 g, 12 mmol) was dissolved in tetrahydrofuran (10 mL) and added dropwise to the above reaction and the reaction was allowed to continue at -70°C for 30 minutes, and then the reaction was slowly heated to room temperature. After the reaction was complete, the reaction was quenched by adding saturated ammonium chloride solution thereto, and extracted with ethyl acetate. The organic phase was collected and washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to remove the solvent, and the concentrate was separated and purified by column chromatography to obtain the target product compound *tert-butyl* (5-(hydroxy(phenyl)methyl)thiazol-2-yl)carbamate (2.9 g, yield 95%) as off-white solid.

Step 2: Synthesis of 5-benzyl-2-aminothiazole

Compound *tert-butyl* (5-(hydroxy(phenyl)methyl)thiazol-2-yl)carbamate (1.84 g, 6 mmol) was dissolved in dichloromethane (36 mL) solvent, and triethylsilane (2.09 g, 18 mmol) and trifluoroacetic acid (6.83 g, 60 mmol) were sequentially added dropwise while stirring in an ice bath. After completion of dropwise addition, the stirring of the reaction was continued at room temperature for about 2 hours. After the reaction was complete, the solvent was removed by concentration, water was added and the pH was adjusted to about 7 with saturated sodium bicarbonate solution. The liquids were extracted and separated with dichloromethane. The organic phase was collected and washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to remove the solvent, and the concentrate was separated and purified by column chromatography to obtain the target product compound 5-benzyl-2-aminothiazole (0.97 g, yield 85%) as an off-white solid.

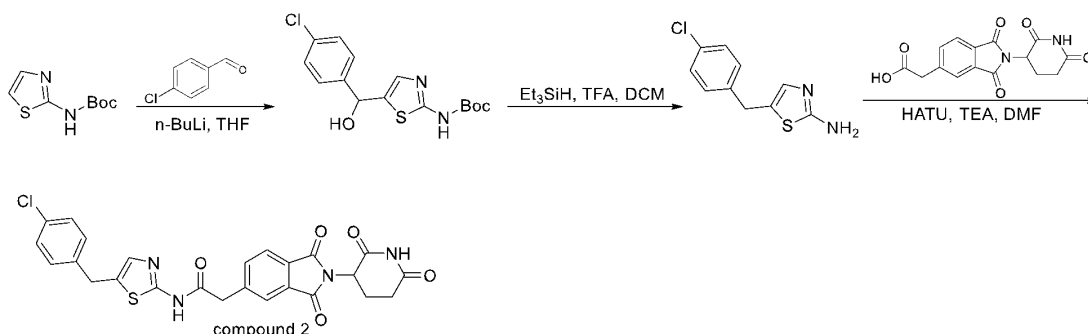
Step 3: Synthesis of N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide

5-benzyl-2-aminothiazole (173 mg, 0.9 mmol) was dissolved in 4 ml of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (183 mg, 1.8 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (275 mg, 0.9 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 500 mg, 1.3 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 10 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the

product *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 1) (176 mg, yield 40%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.15 (s, 1H), 10.98 (s, 1H), 7.74-7.64 (m, 1H), 7.54 (s, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.26-7.15 (m, 4H), 5.10 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.43 (d, *J* = 17.2 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.06 (s, 2H), 3.85 (s, 2H), 2.96-2.85 (m, 1H), 2.62-2.57 (m, 1H), 2.43-2.34 (m, 1H), 2.03-1.95 (m, 1H). Chemical Formula: C₂₅H₂₂N₄O₄S, MS Calcd.: 474.5; MS Found: 475.3 [M+1]⁺.

Example 2: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide (compound 2)



Step 1: Synthesis of *tert*-butyl (5-((4-chlorophenyl)(hydroxy)methyl)thiazol-2-yl)carbamate

N-Boc-2-aminothiazole (2 g, 10 mmol) was dissolved in tetrahydrofuran (20 mL) and the reaction was cooled to -70 °C, and *n*-butyllithium solution (10 mL, 2.5 N THF solution) was slowly added dropwise under argon protection. The reaction was allowed to continue at this temperature for 30 minutes. *p*-Chlorobenzaldehyde (1.7 g, 12 mmol) was dissolved in tetrahydrofuran (10 mL) and added dropwise to the above reaction and the reaction was allowed to continue at -70 °C for 30 minutes, and then the reaction was slowly heated to room temperature. After the reaction was complete, the reaction was quenched by adding saturated ammonium chloride solution thereto, and extracted with ethyl acetate. The organic phase was collected and washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to remove the solvent, and the concentrate was separated and purified by column chromatography to obtain the target product compound *tert*-butyl (5-((4-chlorophenyl)(hydroxy)methyl)thiazol-2-yl)carbamate (3.1 g, yield 91%) as off-white solid.

Step 2: Synthesis of 5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine

Compound *tert*-butyl (5-((4-chlorophenyl)(hydroxy)methyl)thiazol-2-yl)carbamate (2.04 g, 6 mmol) was dissolved in dichloromethane (36 mL) solvent, and triethylsilane (2.09 g, 18 mmol) and trifluoroacetic acid (6.83 g, 60 mmol) were sequentially added dropwise while stirring in an ice bath. The stirring of the reaction was continued at room temperature for about 5

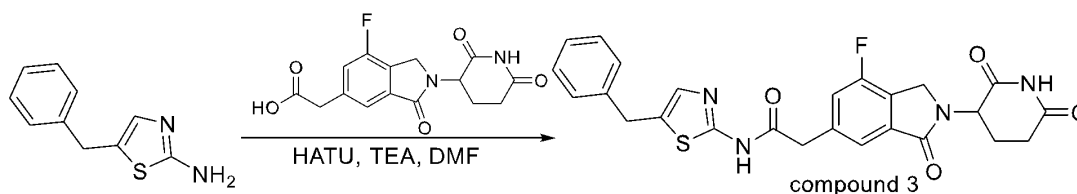
hours. After completion of the reaction, the reaction was concentrated to remove the solvent. Water was added and the pH was adjusted to about 7 with saturated sodium bicarbonate solution. The liquids were extracted and separated with dichloromethane. The organic phase was collected and washed with saturated brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to remove the solvent, and the concentrate was separated and purified by column chromatography to obtain the target product compound 5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (1.08 g, yield 80%) as an off-white solid.

Step 3: Synthesis of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide

5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (22 mg, 0.1 mmol) was dissolved in 2 mL of *N,N*-dimethylformamide (DMF), and triethylamine (Et₃N) (15 mg, 0.15 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetic acid (32 mg, 0.1 mmol) and 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 45 mg, 0.12 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 10 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide (compound 2) (18 mg, yield 35%) as an off-white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.32 (s, 1H), 11.12 (s, 1H), 7.88 (d, *J* = 6.8 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.32-7.20 (m, 3H), 5.14 (dd, *J* = 12.9, 5.3 Hz, 1H), 4.07 (s, 2H), 3.99 (s, 2H), 2.94-2.87 (m, 1H), 2.63-2.59 (m, 1H), 2.58-2.55 (m, 1H), 2.09-2.01 (m, 1H). Chemical Formula: C₂₅H₁₉ClN₄O₅S, MS Calcd.: 523.0; MS Found: 523.3 [M+1]⁺.

Example 3: Preparation of *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-7-fluoro-3-oxoisindolin-5-yl)acetamide (compound 3)

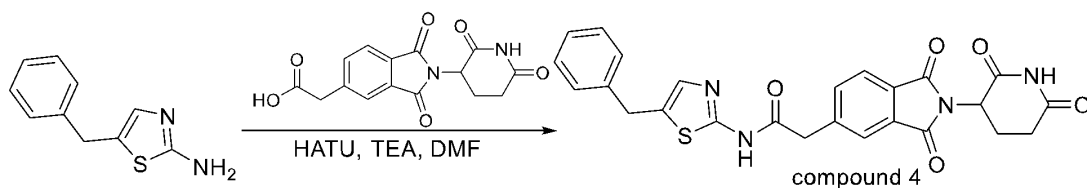


5-benzyl-2-aminothiazole (19 mg, 0.1 mmol) was dissolved in 2 ml of *N,N*-dimethylformamide (DMF), and triethylamine (Et₃N) (15 mg, 0.15 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-7-fluoro-3-oxoisindolin-5-yl)acetic acid (32 mg, 0.1 mmol) and 2-(7-

azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 45 mg, 0.12 mmol) were sequentially added while stirring at room temperature. After stirring the reaction at room temperature for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 10 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-7-fluoro-3-oxoisindolin-5-yl)acetamide (compound 3) (16 mg, yield 32%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.25 (s, 1H), 11.00 (s, 1H), 7.56 (s, 1H), 7.43 (d, *J* = 9.8 Hz, 1H), 7.30 (t, *J* = 6.9 Hz, 2H), 7.24 (q, *J* = 9.7, 9.0 Hz, 4H), 5.15-5.06 (m, 1H), 4.54 (d, *J* = 17.0 Hz, 1H), 4.37 (d, *J* = 17.3 Hz, 1H), 4.07 (s, 2H), 3.89 (s, 2H), 2.97-2.85 (m, 1H), 2.63-2.59 (m, 1H), 2.46-2.39 (m, 1H), 2.03 - 1.95 (m, 1H). Chemical Formula: C₂₅H₂₁FN₄O₄S, MS Calcd.: 492.5; MS Found: 493.4 [M+1]⁺.

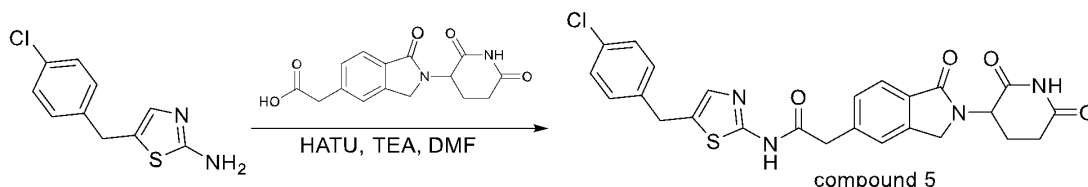
Example 4: Preparation of *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide (compound 4)



5-benzyl-2-aminothiazole (19 mg, 0.1 mmol) was dissolved in 2 ml of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (15 mg, 0.15 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetic acid (32 mg, 0.1 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 45 mg, 0.12 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 10 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)acetamide (compound 4) (14 mg, yield 29%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.30 (s, 1H), 11.12 (s, 1H), 7.88 (d, $J = 6.8$ Hz, 2H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.38-7.34 (m, 3H), 7.32-7.20 (m, 3H), 5.14 (dd, $J = 12.9, 5.3$ Hz, 1H), 4.07 (s, 2H), 3.97 (s, 2H), 2.94-2.87 (m, 1H), 2.62-2.58 (m, 1H), 2.56-2.53 (m, 1H), 2.09-2.01 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_5\text{S}$, MS Calcd.: 488.5; MS Found: 489.3 $[\text{M}+1]^+$.

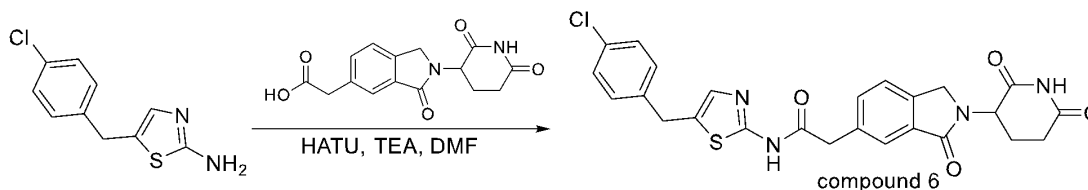
Example 5: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)acetamide (compound 5)



5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (11 mg, 0.05 mmol) was dissolved in 2 mL of *N,N*-dimethylformamide (DMF), and triethylamine (Et_3N) (10 mg, 0.10 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)acetic acid (15 mg, 0.05 mmol) and 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 23 mg, 0.06 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 8 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)acetamide (compound 5) (8 mg, yield 32%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.29 (s, 1H), 10.98 (s, 1H), 7.68 (d, $J = 7.8$ Hz, 1H), 7.52 (s, 1H), 7.43 (d, $J = 7.9$ Hz, 1H), 7.40-7.31 (m, 2H), 7.31-7.19 (m, 3H), 5.10 (dd, $J = 13.2, 5.1$ Hz, 1H), 4.44 (d, $J = 17.3$ Hz, 1H), 4.31 (d, $J = 17.3$ Hz, 1H), 4.07 (s, 2H), 3.87 (s, 2H), 2.97-2.86 (m, 1H), 2.62-2.57 (m, 1H), 2.44-2.35 (m, 1H), 2.03-1.94 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{21}\text{ClN}_4\text{O}_4\text{S}$, MS Calcd.: 509.0; MS Found: 509.3 $[\text{M}+1]^+$.

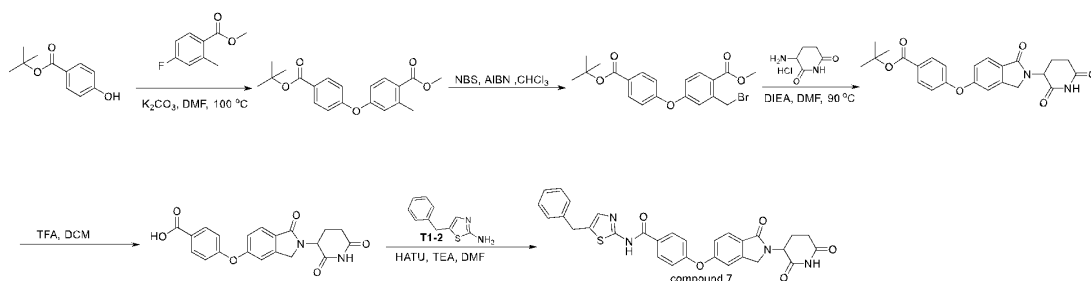
Example 6: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 6)



5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (11 mg, 0.05 mmol) was dissolved in 2 mL of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (10 mg, 0.10 mmol), 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (15 mg, 0.05 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 23 mg, 0.06 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 8 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 6) (7.6 mg, yield 30%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.27 (s, 1H), 10.98 (s, 1H), 7.69 (s, 1H), 7.55 (s, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 3H), 5.10 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.43 (d, *J* = 17.2 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.07 (s, 2H), 3.85 (s, 2H), 2.97-2.86 (m, 1H), 2.62-2.57 (m, 1H), 2.44-2.35 (m, 1H), 2.03-1.97 (m, 1H). Chemical Formula: C₂₅H₂₁ClN₄O₄S, MS Calcd.: 509.0; MS Found: 509.4 [M+1]⁺.

Example 7: Preparation of *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide (compound 7)



Step 1: Synthesis of methyl 4-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate

Tert-butyl 4-hydroxybenzoate (300 mg, 1.5 mmol), potassium carbonate (427 mg, 3.1 mmol) and methyl 4-fluoro-2-methylbenzoate (260 mg, 1.5 mmol) were dissolved in 10 mL of N,N-dimethylformamide (DMF). The reaction system was heated to 100 °C and stirred at this temperature for about 3 hours. LCMS detection showed that the starting materials had reacted completely. After the temperature of the reaction system was lowered to room temperature, it was filtered, and the filtrate was diluted by adding 20 ml of water thereto and extracted and separated by adding ethyl acetate (2 x 10 ml) thereto. The organic phases were combined and backwashed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under

reduced pressure to obtain a crude product. After column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/10), methyl 4-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate (317 mg, yield 60%) was obtained as a yellowish solid.

Step 2: Synthesis of methyl 2-(bromomethyl)-4-(4-(tert-butoxycarbonyl)phenoxy)benzoate

The intermediate methyl 4-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate (317 mg, 0.93 mmol) and N-bromosuccinimide (NBS) (247 mg, 1.39 mmol) were dissolved in 10 ml of chloroform and heated to 65 °C, then a catalytic amount of azobisisobutyronitrile (AIBN) (7 mg) was added to initiate the reaction and the reaction was allowed to continue with stirring at this temperature for about 4 hours. LCMS detection showed that the starting materials had reacted completely. The reaction was cooled to room temperature, and the insoluble matter was removed by suction filtration. The filtrate was diluted by adding 15 ml of water thereto and extracted and separated by adding dichloromethane (2 x 10 ml) thereto. The organic phases were combined and backwashed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/10), a yellowish liquid methyl 2-(bromomethyl)-4-(4-(tert-butoxycarbonyl)phenoxy)benzoate (311 mg, yield 80%) was obtained.

Step 3: Synthesis of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoate

The intermediate methyl 2-(bromomethyl)-4-(4-(tert-butoxycarbonyl)phenoxy)benzoate (311 mg, 0.74 mmol) and 3-aminopiperidin-2,6-dione hydrochloride (146 mg, 0.89 mmol) were dissolved in 5 ml of N,N-dimethylformamide (DMF), and diisopropylethylamine (DIEA) (239 mg, 1.85 mmol) was added at room temperature. The mixed system was heated to 90 °C and the reaction was allowed to stir at this temperature for about 4 hours. LCMS detection showed that the reaction was complete. The reaction was diluted by adding 20 mL of water thereto and extracted and separated by adding dichloromethane (3 x 10 mL) thereto. The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography (methanol/dichloromethane = 1/100 to 1/30), an off-white solid tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoate (145 mg, yield 45%) was obtained.

Step 4: Synthesis of compound 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoic acid

The intermediate tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoate (145 mg, 10 mmol) was dissolved in 3 ml of dichloromethane, 1 ml of trifluoroacetic acid (TFA) was added at room temperature and the temperature was raised to 40

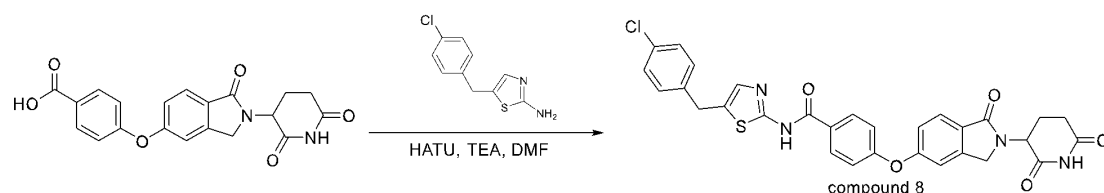
°C to initiate the reaction. After reacting for about 1 hour, LCMS detection showed that the starting materials had disappeared. Excess trifluoroacetic acid solution, by-products and solvent were removed by concentrating under reduced pressure to obtain crude 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoic acid (120 mg, yield 95%).

Step 5: Synthesis of *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide

5-benzyl-2-aminothiazole (5 mg, 0.026 mmol) was dissolved in 2 ml of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (7 mg, 0.066 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.026 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 3 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide (compound 7) (5 mg, yield 35%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 10.99 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.43-7.26 (m, 6H), 7.27-7.21 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.45 (d, *J* = 17.6 Hz, 1H), 4.32 (d, *J* = 17.5 Hz, 1H), 4.12 (s, 2H), 2.92-2.86 (m, 1H), 2.68-2.62 (m, 1H), 2.42-2.37 (m, 1H), 2.04-1.97 (m, 1H). Chemical Formula: C₃₀H₂₄N₄O₅S, MS Calcd.: 552.6; MS Found: 553.4 [M+1]⁺.

Example 8: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide (compound 8)

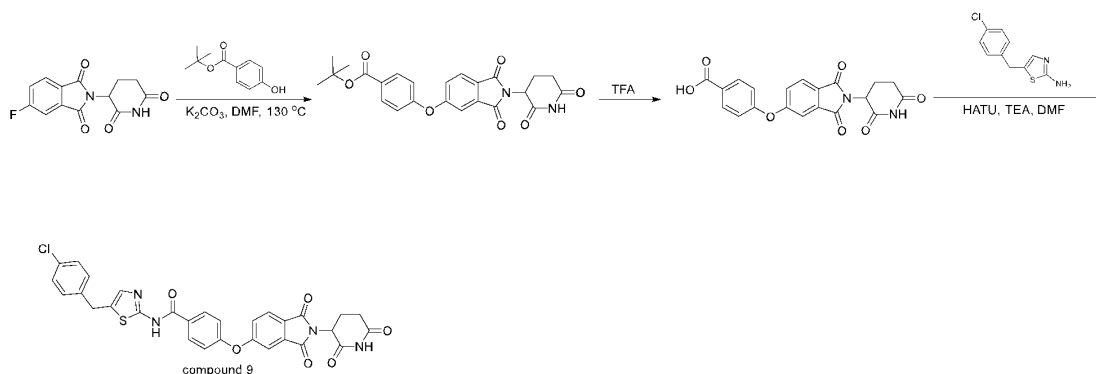


5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (T1-4) (6 mg, 0.026 mmol) was dissolved in 2 mL of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (7 mg, 0.066 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.026 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After

reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 10 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)oxy)benzamide (compound 8) (4.6 mg, yield 30%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.47 (s, 1H), 10.98 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.46-7.29 (m, 5H), 7.29-7.25 (m, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 5.16 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.48 (d, *J* = 17.6 Hz, 1H), 4.37 (d, *J* = 17.5 Hz, 1H), 4.15 (s, 2H), 2.94-2.86 (m, 1H), 2.68-2.61 (m, 1H), 2.45-2.37 (m, 1H), 2.06-1.99 (m, 1H). Chemical Formula: C₃₀H₂₃ClN₄O₅S, MS Calcd.: 587.0; MS Found: 587.4 [M+1]⁺.

Example 9: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide (compound 9)



Step 1: Synthesis of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoate

Tert-butyl 4-hydroxybenzoate (300 mg, 1.5 mmol), potassium carbonate (427 mg, 3.1 mmol) and 2-(2,6-dioxopiperidin-3-yl)-5-fluoroisindoline-1,3-dione (427 mg, 1.5 mmol) were dissolved in 10 mL of *N,N*-dimethylformamide (DMF), the mixed system was heated to 130 °C and the reaction was allowed to stir at this temperature for about 3 hours. LCMS detection showed that the starting materials had disappeared. After the mixed system was cooled to room temperature, it was filtered, and the filtrate was diluted by adding 15 ml of water thereto and extracted and separated by adding ethyl acetate (2 x 10 ml) thereto. The organic phases were combined and backwashed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography

(ethyl acetate/petroleum ether = 1/20 to 1/1), *tert-butyl* 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoate (383 mg, yield 55%) was obtained as a yellowish solid.

Step 2: Synthesis of 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoic acid

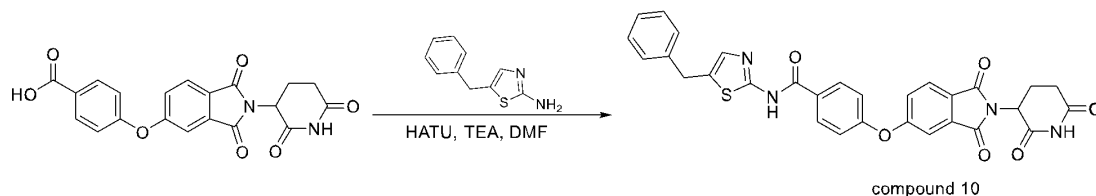
The intermediate *tert-butyl* 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoate (383 mg, 0.85 mmol) was dissolved in 5 ml of dichloromethane, 2 ml of trifluoroacetic acid (TFA) was added at room temperature and the temperature was raised to 40 °C to initiate the reaction. After reacting for about 1 hour, LCMS detection showed that the starting materials had disappeared. Excess trifluoroacetic acid solution and solvent were removed by concentrating under reduced pressure to obtain 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoic acid (322 mg, yield 96%).

Step 3: Synthesis of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide

5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (6 mg, 0.026 mmol) was dissolved in 2 mL of *N,N*-dimethylformamide (DMF), and triethylamine (Et₃N) (7 mg, 0.066 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.025 mmol) and 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 5 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the white solid product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide (compound 9) (5.2 mg, yield 34%).

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.52 (s, 1H), 11.13 (s, 1H), 8.16 (dd, *J* = 8.9, 2.3 Hz, 2H), 7.98 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.59-7.46 (m, 2H), 7.46-7.36 (m, 2H), 7.37-7.11 (m, 5H), 5.16 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.13 (s, 2H), 2.96-2.86 (m, 1H), 2.67-2.62 (m, 1H), 2.59-2.55 (m, 1H), 2.14-2.03 (m, 1H). Chemical Formula: C₃₀H₂₁ClN₄O₆S, MS Calcd.: 601.0; MS Found: 601.4 [M+1]⁺.

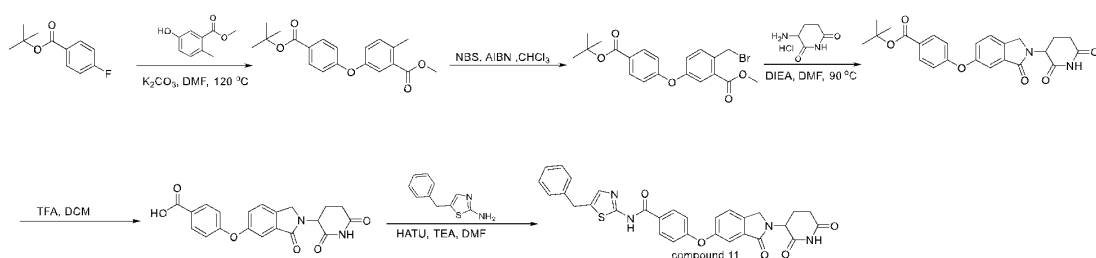
Example 10: Preparation of *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide (compound 10)



5-benzyl-2-aminothiazole (5.3 mg, 0.028 mmol) was dissolved in 2 ml of N,N-dimethylformamide (DMF), and triethylamine (Et_3N) (7 mg, 0.066 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.025 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 5 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)oxy)benzamide (compound 10) (4.3 mg, yield 30%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.51 (s, 1H), 11.13 (s, 1H), 8.16 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.40-7.18 (m, 8H), 5.16 (dd, J = 12.8, 5.3 Hz, 1H), 4.12 (s, 2H), 2.95-2.87 (m, 1H), 2.63-2.58 (m, 1H), 2.56-2.53 (m, 1H), 2.10-2.04 (m, 1H). Chemical Formula: $\text{C}_{30}\text{H}_{22}\text{N}_4\text{O}_6\text{S}$, MS Calcd.: 566.6; MS Found: 567.4 $[\text{M}+1]^+$.

Example 11: Preparation of *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide (compound 11)



Step 1: Synthesis of methyl 5-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate

Tert-butyl 4-fluorobenzoate (300 mg, 1.5 mmol), potassium carbonate (427 mg, 3.1 mmol) and methyl 4-fluoro-2-methylbenzoate (260 mg, 1.5 mmol) were dissolved in 10 mL of N,N-dimethylformamide (DMF). The mixed system was heated to 100 °C and the reaction was allowed to stir at this temperature for about 3 hours. LCMS detection showed that the starting materials had disappeared. After the mixed system was cooled to room temperature, it was filtered,

and the filtrate was diluted by adding 20 ml of water thereto and extracted and separated by adding ethyl acetate (2 x 10 ml) thereto. The organic phases were combined and backwashed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/10), a yellowish solid methyl 5-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate (277 mg, yield 53%) was obtained.

Step 2: Synthesis of methyl 2-(bromomethyl)-5-(4-(tert-butoxycarbonyl)phenoxy)benzoate

The intermediate methyl 5-(4-(tert-butoxycarbonyl)phenoxy)-2-methylbenzoate (277 mg, 0.81 mmol) and N-bromosuccinimide (NBS) (217 mg, 1.22 mmol) were dissolved in 10 ml of chloroform and heated to 65 °C, and then a catalytic amount of azobisisobutyronitrile (AIBN) (6 mg) was added and the reaction was allowed to continue with stirring at this temperature for about 4 hours. LCMS detection showed that the starting materials had disappeared. The reaction was cooled to room temperature, diluted by adding 15 mL of water thereto and extracted and separated by adding dichloromethane (2 x 10 mL) thereto. The organic phases were combined and backwashed with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/10), a yellowish liquid methyl 2-(bromomethyl)-5-(4-(tert-butoxycarbonyl)phenoxy)benzoate (255 mg, yield 75%) was obtained.

Step 3: Synthesis of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoate

The intermediate methyl 2-(bromomethyl)-5-(4-(tert-butoxycarbonyl)phenoxy)benzoate (255 mg, 0.61 mmol) and 3-aminopiperidin-2,6-dione hydrochloride (146 mg, 0.89 mmol) were dissolved in 5 ml of N,N-dimethylformamide (DMF), and diisopropylethylamine (DIEA) (239 mg, 1.85 mmol) was added at room temperature. The mixed system was heated to 90 °C and the reaction was allowed to stir at this temperature for about 4 hours. LCMS detection showed that the reaction was complete. The reaction was diluted by adding 10 mL of water thereto and extracted and separated by adding dichloromethane (3 x 10 mL) thereto. The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain a crude product. After column chromatography (methanol/dichloromethane = 1/100 to 1/30), an off-white solid tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoate (111 mg, yield 42%) was obtained.

Step 4: Synthesis of 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoic acid

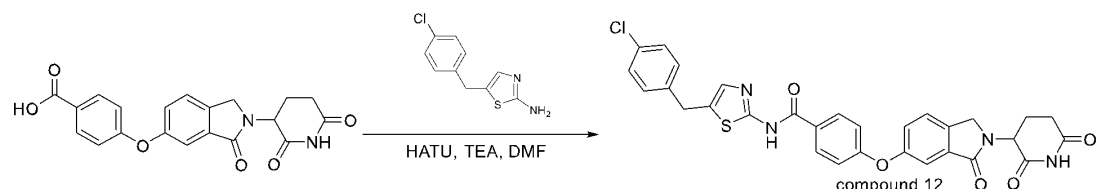
The intermediate *tert-butyl* 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoate (111 mg, 0.25 mmol) was dissolved in 3 ml of dichloromethane, 1 ml of trifluoroacetic acid (TFA) was added at room temperature and the temperature was raised to 40 °C to initiate the reaction. After reacting for about 1 hour, LCMS detection showed that the starting materials had disappeared. Excess trifluoroacetic acid solution and solvent were removed by concentrating under reduced pressure to obtain 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoic acid (106 mg, yield 95%).

Step 5: Synthesis of *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide

5-benzyl-2-aminothiazole (5 mg, 0.026 mmol) was dissolved in 2 ml of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (7 mg, 0.066 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.026 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After reacting at room temperature for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 6 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide (compound 11) (4.5 mg, yield 31%) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 12.11 (s, 1H), 10.85 (s, 1H), 8.03-7.98(m, 2H), 7.80 (d, *J* = 8.9 Hz, 2H), 7.51-7.44 (m, 2H), 7.42-7.32 (m, 3H), 7.23-7.04 (m, 4H), 5.15 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.39 (d, *J* = 17.2 Hz, 1H), 4.28 (d, *J* = 17.2 Hz, 1H), 4.03 (s, 2H), 2.95-2.85 (m, 1H), 2.61-2.55 (m, 1H), 2.40-2.33 (m, 1H), 2.03-1.97(m, 1H). Chemical Formula: C₃₀H₂₄N₄O₅S, MS Calcd.: 552.6; MS Found: 553.4 [M+1]⁺.

Example 12: Preparation of *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide (compound 12)

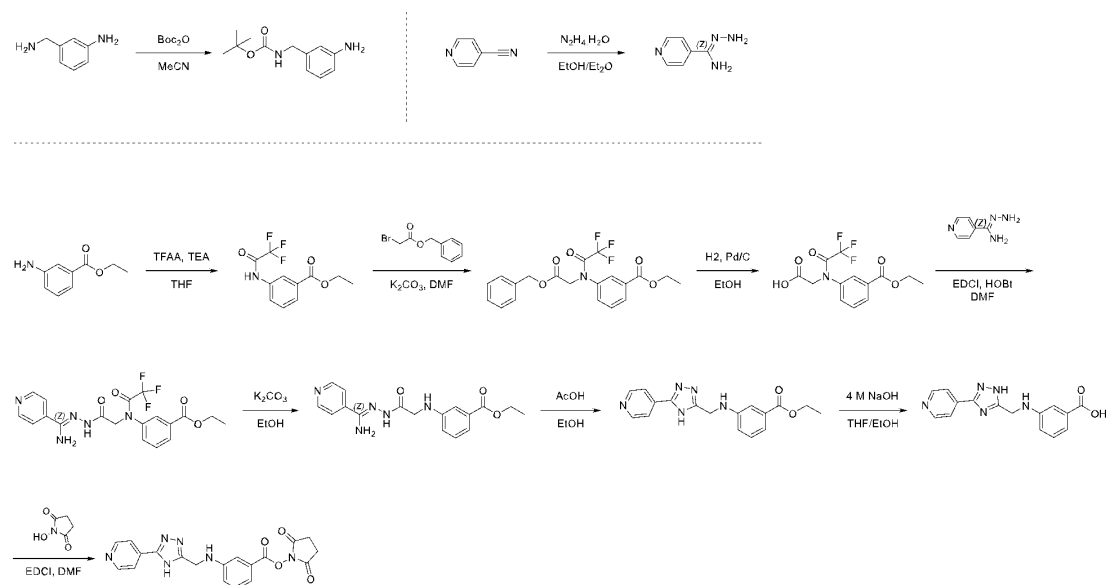


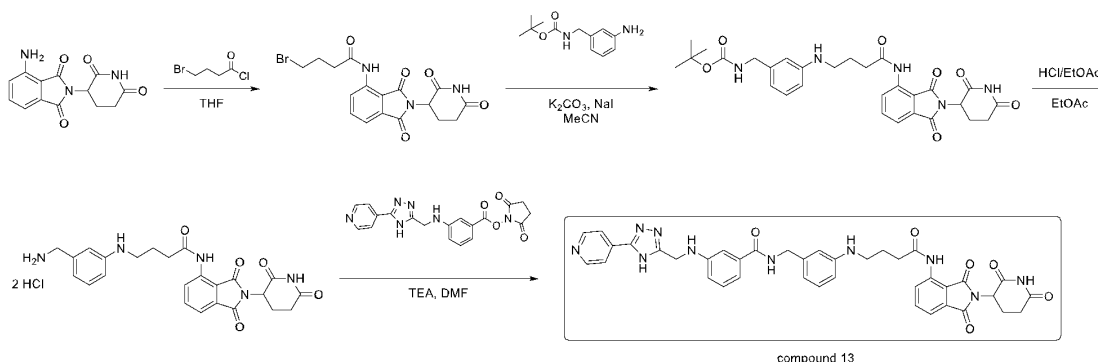
5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (6 mg, 0.026 mmol) was dissolved in 2 mL of N,N-dimethylformamide (DMF), and triethylamine (Et₃N) (7 mg, 0.066 mmol), 4-((2-(2,6-

dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzoic acid (10 mg, 0.026 mmol) and 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU, 12 mg, 0.03 mmol) were sequentially added while stirring at room temperature. After reacting for about 1 hour, LCMS detection showed that the starting materials had reacted completely. The reaction was quenched by adding 6 ml of distilled water thereto and ethyl acetate was added to extract and separate the liquids. The extraction was repeated for three times until the extraction was complete. The organic phases were combined and washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to obtain a crude yellowish concentrate. Then the concentrate was subject to column chromatography (methanol/dichloromethane = 1/100 to 1/30) to obtain the product *N*-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)oxy)benzamide (compound 12) (4.3 mg, yield 28%) as a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 12.31 (s, 1H), 10.97 (s, 1H), 8.07 (d, *J* = 8.9 Hz, 2H), 7.85 (s, 1H), 7.52-7.45 (m, 3H), 7.43-7.33 (m, 2H), 7.28-7.08 (m, 4H), 5.16 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.40 (d, *J* = 17.2 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 4.05 (s, 2H), 2.97-2.86 (m, 1H), 2.62-2.57 (m, 1H), 2.44-2.35 (m, 1H), 2.03-1.97 (m, 1H). Chemical Formula: C₃₀H₂₃ClN₄O₅S, MS Calcd.: 587.0; MS Found: 587.4 [M+1]⁺.

Example 13: Preparation of *N*-(3-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide (compound 13)





Step 1: Synthesis of tert-butyl (3-aminobenzyl)carbamate

3-(aminomethyl)aniline (60.0 g, 0.49 mol, 1.0 eq.) and MeCN (900 mL) were added to a 3 L four-necked flask, and a solution of Boc₂O (107 g, 0.49 mol, 1.0 eq.) in MeCN (300 mL) was added dropwise quickly. The reaction was allowed to stir at room temperature for 1 h, concentrated to dryness to obtain a crude product, which was purified by column (PE/EtOAc = 5:1) to obtain the product (110 g, 100% yield) as a yellow solid.

Step 2: Synthesis of (Z)-isonicotinohydrazonamide

Isonicotinonitrile (50.0 g, 0.48 mol, 1.0 eq.), EtOH (120 mL), Et₂O (120 mL) and 80% hydrazine hydrate (250 mL) were added sequentially to a 1L single-necked bottle, and the reaction was allowed to stir at 30 °C for 24 h, concentrated to remove most of ethanol and diethyl ether, stirred in an ice-water bath for 2 h, and filtered. The filter cake was vacuum-dried to obtain the product (60 g, 91.8% yield) as an off-white solid.

Step 3: Synthesis of ethyl 3-(2,2,2-trifluoroacetamido)benzoate

Ethyl 3-aminobenzoate (83.0 g, 0.50 mol, 1.0 eq.), THF (1.66 L) and TEA (76.0 g, 0.75 mol, 1.5 eq.) were added to a 3 L four-necked flask. The reaction was cooled to 0-5 °C in an ice-water bath, and TFAA (110.0 g, 0.53 mol, 1.05 eq.) was added dropwise while maintaining the temperature <10 °C. After dropping was complete, the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched by adding 1 N HCl (1 L) thereto. Water (1 L) and EtOAc (1 L) were added, and the reaction was stirred and then left to separate. The organic phase was washed successively with saturated sodium bicarbonate (1 L) and saturated brine (0.5 L), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (120 g, 91.4% yield) as a yellow solid, which was directly used in the next step.

Step 4: Synthesis of ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

Ethyl 3-(2,2,2-trifluoroacetamido)benzoate (120.0 g, 0.46 mol, 1.0 eq.), DMF (1.2 L), benzyl bromoacetate (116.0 g, 0.50 mol, 1.1 eq.) and K₂CO₃ (95.0 g, 0.69 mol, 1.5 eq.) were added sequentially to a 3L single-necked bottle. The reaction was allowed to stir at 25 °C for 16 h. Water

(5 L) and EtOAc (2.5 L) were added, and the reaction was stirred and then left to separate. The organic phase was washed with saturated brine (1.5 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (170 g, 90.4% yield) as an off-white solid, which was directly used in the next step.

Step 5: Synthesis of N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine

Ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (170.0 g, 0.42 mol, 1.0 eq.), EtOH (2.1 L) and 10% wet Pd/C (34.0 g, 57% water content) were added sequentially into a 5 L four-necked flask. The reaction was allowed to stir at 15°C for 4 h under H₂ (15 psi) condition. The reaction was filtered, and the filtrate was concentrated to obtain the product (132 g, 100% yield) as a slightly yellow transparent solid, which was directly used in the next step.

Step 6: Synthesis of ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine (132.0 g, 0.41 mol, 1.0 eq.), (Z)-isonicotinohydrazonamide (58.0 g, 0.43 mol, 1.04 eq.), DMF (1.4 L), HOBt (59.0 g, 0.44 mol, 1.06 eq.) and EDCI (136.0 g, 0.71 mol, 1.73 eq.) were added sequentially to a 2L single-necked bottle. The reaction was allowed to stir at 15°C for 4 h under N₂ protection. The reaction was quenched by pouring into water (6 L), and extracted with EtOAc (7 L). The organic phase was washed with saturated brine (2 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 190 g of crude product. The crude product was slurried in EtOAc (760 mL) at 70°C for 3 h, stirred in an ice-water bath for 2 h, filtered, and the filter cake was vacuum-dried to obtain the product (118 g, 65.2% yield) as a white solid.

Step 7: Synthesis of ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate

Ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (110.0 g, 0.25 mol, 1.0 eq.), K₂CO₃ (104.0 g, 0.75 mol, 3.0 eq.) and EtOH (2.2 L) were added to a 3 L single-necked bottle. The reaction was allowed to stir at 65°C for 2 h. The reaction was poured into stirred water (11 L), and a large amount of solid precipitated out. The reaction was filtered, and the filter cake was vacuum-dried to obtain the product (68 g, 79.2% yield) as a white solid, which was directly used in the next step.

Step 8: Synthesis of ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

Ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate (68.0 g, 0.20 mol, 1.0 eq.), EtOH (2.2 L) and AcOH (136 mL) were added sequentially into a 2 L single-necked flask. The reaction was allowed to stir at 90°C under

reflux for 6 h. The reaction was concentrated to dryness, EtOAc (600 mL) and 1 M sodium carbonate (600 mL) were added, the layers were separated, and the aqueous phase was extracted once more with EtOAc (400 mL). The organic phases were combined, washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 60 g of crude product. The crude product was slurried in ethyl acetate (420 mL) at 60°C for 1 h, stirred in an ice-water bath for 0.5 h, filtered, and the filter cake was vacuum-dried to obtain the product (60.3 g, 98.6% yield) as a white solid.

Step 9: Synthesis of 3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid

Ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (60.0 g, 0.19 mol, 1.0 eq.), EtOH (300 mL), THF (300 mL) and 4 M NaOH (450 mL, 1.8 mol, 9.7 eq.) were added sequentially to a 5 L single-necked flask. The reaction was allowed to stir at 15°C for 16 h. Concentrated hydrochloric acid was added to adjust the pH to 4-5. The reaction was concentrated to remove most of EtOH and THF, stirred in an ice-water bath for 0.5 h, and filtered. The filter cake was vacuum-dried to obtain the product (47.0 g, 85.8% yield) as a white solid, which was directly used in the next step.

Step 10: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid (46.8 g, 0.16 mol, 1.0 eq.), HOSu (20.1 g, 0.17 mol, 1.1 eq.), MeCN (500 mL) and DIC (22.0 g, 0.17 mol, 1.1 eq.) were added sequentially to a 1L single-necked flask. The reaction was allowed to stir at 15°C for 4h. The reaction was poured into water (2 L). A large amount of solid precipitated out. The solid was filtered, and the filter cake was vacuum-dried to give the product (53.7 g, 86.4% yield) as an off-white solid, which was directly used in the next step.

Step 11: Synthesis of 4-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)butanamide

4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (1.80 g, 6.6 mmol, 1.0 eq.), THF (36 mL) and 4-bromohexanoyl chloride (3.67 g, 19.8 mmol, 3.0 eq.) were added sequentially to a 100 mL single-necked flask. The reaction was allowed to stir at 70°C for 17 h under N₂ protection. The reaction was concentrated to dryness and purified by column (DCM/MeOH=60:1) to obtain the product (2.62 g, 83.7% yield) as a yellow solid.

Step 12: Synthesis of tert-butyl (3-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutyl)amino)benzyl)carbamate

4-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)butanamide (0.94 g, 2.22 mmol, 1.0 eq.), MeCN (20 mL), K₂CO₃ (0.61 g, 4.44 mmol, 2.0 eq.), NaI (0.33 g, 2.22 mmol,

1.0 eq.) and *tert*-butyl (3-aminobenzyl)carbamate (0.99 g, 4.44 mol, 2.0 eq.) were added sequentially to a 100 mL four-necked flask. The reaction was allowed to stir at 70 °C for 16 h under N₂ protection. The reaction was concentrated to dryness, EtOAc (100 mL) and water (100 mL) were added, and the layers were separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to obtain a crude product. The crude product was purified by column (PE/EtOAc = 1.3/1) to obtain the product (200 mg, 16.0% yield) as a yellow solid.

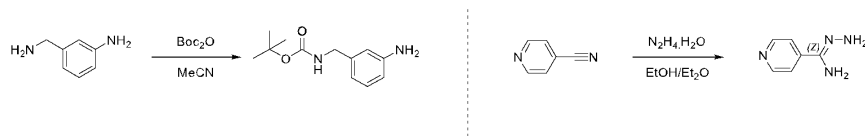
Step 13: Synthesis of 4-((3-(aminomethyl)phenyl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)butanamide

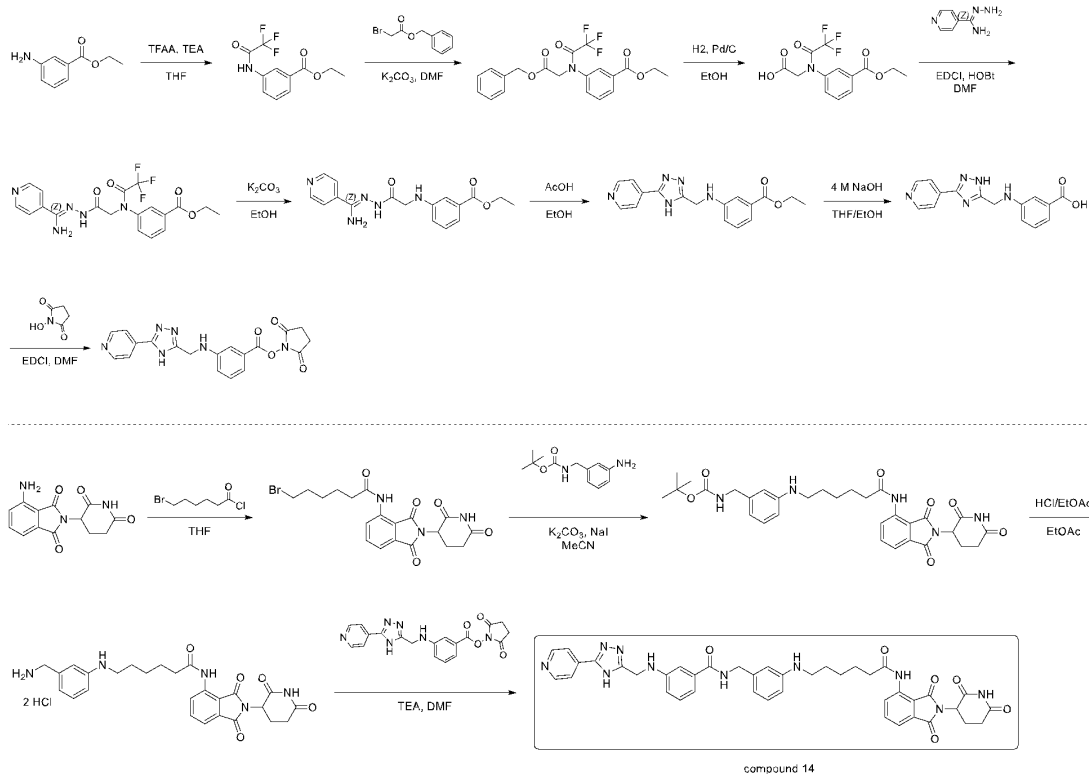
Tert-butyl (3-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutyl)amino)benzyl)carbamate (160 mg, 0.28 mmol, 1.0 eq.) and EtOAc (3.5 mL) were added to a 100 mL four-necked flask, and to which 3 M HCl/EtOAc (7 mL) was added under stirring. The reaction was allowed to stir at 15 °C for 2h under N₂ protection. The reaction was concentrated to obtain the product (160 mg, 100% yield) as a brownish yellow solid, which was directly used in the next step.

Step 14: Synthesis of N-(3-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide

4-((3-(aminomethyl)phenyl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)butanamide (160 mg, 0.28 mmol, 1.0 eq.), DMF (5.5 mL), TEA (113 mg, 1.12 mmol, 4.0 eq.) and 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (110 g, 0.28 mmol, 1.0 eq.) were added sequentially to a 100 mL four-necked flask. The reaction was allowed to stir at 30 °C for 16h under N₂ protection. The reaction was poured into 50 mL of water. The mixture was filtered, and the filter cake was vacuum-dried to obtain a crude product. The product was prepared and purified by HPLC to obtain the product (50 mg, 24.1% yield) as a yellow solid.

Example 14: Preparation of N-(3-(((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide (compound 14)





Step 1: Synthesis of tert-butyl (3-aminobenzyl)carbamate

3-(aminomethyl)aniline (60.0 g, 0.49 mol, 1.0 eq.) and MeCN (900 mL) were added to a 3 L four-necked flask, and a solution of Boc₂O (107 g, 0.49 mol, 1.0 eq.) in MeCN (300 mL) was added dropwise quickly. The reaction was allowed to stir at room temperature for 1 h, concentrated to dryness to obtain a crude product, which was purified by column (PE/EtOAc = 5:1) to obtain the product (110 g, 100% yield) as a yellow solid.

Step 2: Synthesis of (Z)-isonicotinohydrazonamide

Isonicotinonitrile (50.0 g, 0.48 mol, 1.0 eq.), EtOH (120 mL), Et₂O (120 mL) and 80% hydrazine hydrate (250 mL) were added sequentially to a 1L single-necked bottle, and the reaction was allowed to stir at 30 °C for 24 h, concentrated to remove most of ethanol and diethyl ether, stirred in an ice-water bath for 2 h, and filtered. The filter cake was vacuum-dried to obtain the product (60 g, 91.8% yield) as an off-white solid.

Step 3: Synthesis of ethyl 3-(2,2,2-trifluoroacetamido)benzoate

Ethyl 3-aminobenzoate (83.0 g, 0.50 mol, 1.0 eq.), THF (1.66 L) and TEA (76.0 g, 0.75 mol, 1.5 eq.) were added to a 3 L four-necked flask. The reaction was cooled to 0-5 °C in an ice-water bath, and TFAA (110.0 g, 0.53 mol, 1.05 eq.) was added dropwise while maintaining the temperature <10 °C. After dropping was complete, the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched by adding 1 N HCl (1 L) thereto. Water (1 L) and EtOAc (1 L) were added, and the reaction was stirred and then left to separate. The organic phase

was washed successively with saturated sodium bicarbonate (1 L) and saturated brine (0.5 L), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (120 g, 91.4% yield) as a yellow solid, which was directly used in the next step.

Step 4: Synthesis of ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

Ethyl 3-(2,2,2-trifluoroacetamido)benzoate (120.0 g, 0.46 mol, 1.0 eq.), DMF (1.2 L), benzyl bromoacetate (116.0 g, 0.50 mol, 1.1 eq.) and K₂CO₃ (95.0 g, 0.69 mol, 1.5 eq.) were added sequentially to a 3L single-necked bottle. The reaction was allowed to stir at 25 °C for 16 h. Water (5 L) and EtOAc (2.5 L) were added, and the reaction was stirred and then left to separate. The organic phase was washed with saturated brine (1.5 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (170 g, 90.4% yield) as an off-white solid, which was directly used in the next step.

Step 5: Synthesis of N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine

Ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (170.0 g, 0.42 mol, 1.0 eq.), EtOH (2.1 L) and 10% wet Pd/C (34.0 g, 57% water content) were added sequentially into a 5 L four-necked flask. The reaction was allowed to stir at 15 °C for 4 h under H₂ (15 psi) condition. The reaction was filtered, and the filtrate was concentrated to obtain the product (132 g, 100% yield) as a slightly yellow transparent solid, which was directly used in the next step.

Step 6: Synthesis of ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine (132.0 g, 0.41 mol, 1.0 eq.), (Z)-isonicotinohydrazonamide (58.0 g, 0.43 mol, 1.04 eq.), DMF (1.4 L), HOBt (59.0 g, 0.44 mol, 1.06 eq.) and EDCI (136.0 g, 0.71 mol, 1.73 eq.) were added sequentially to a 2L single-necked bottle. The reaction was allowed to stir at 15 °C for 4 h under N₂ protection. The reaction was quenched by pouring into water (6 L), and extracted with EtOAc (7 L). The organic phase was washed with saturated brine (2 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 190 g of crude product. The crude product was slurried in EtOAc (760 mL) at 70 °C for 3 h, stirred in an ice-water bath for 2 h, filtered, and the filter cake was vacuum-dried to obtain the product (118 g, 65.2% yield) as a white solid.

Step 7: Synthesis of ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate

Ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (110.0 g, 0.25 mol, 1.0 eq.), K₂CO₃ (104.0 g, 0.75 mol, 3.0 eq.) and EtOH (2.2 L) were added to a 3 L single-necked bottle. The reaction was allowed to stir at 65 °C

for 2 h. The reaction was poured into stirred water (11 L), and a large amount of solid precipitated out. The reaction was filtered, and the filter cake was vacuum-dried to obtain the product (68 g, 79.2% yield) as a white solid, which was directly used in the next step.

Step 8: Synthesis of ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

Ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate (68.0 g, 0.20 mol, 1.0 eq.), EtOH (2.2 L) and AcOH (136 mL) were added sequentially into a 2 L single-necked flask. The reaction was allowed to stir at 90°C under reflux for 6 h. The reaction was concentrated to dryness, EtOAc (600 mL) and 1 M sodium carbonate (600 mL) were added, the layers were separated, and the aqueous phase was extracted once more with EtOAc (400 mL). The organic phases were combined, washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 60 g of crude product. The crude product was slurried in ethyl acetate (420 mL) at 60°C for 1 h, stirred in an ice-water bath for 0.5 h, filtered, and the filter cake was vacuum-dried to obtain the product (60.3 g, 98.6% yield) as a white solid.

Step 9: Synthesis of 3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid

Ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (60.0 g, 0.19 mol, 1.0 eq.), EtOH (300 mL), THF (300 mL) and 4 M NaOH (450 mL, 1.8 mol, 9.7 eq.) were added sequentially to a 5 L single-necked flask. The reaction was allowed to stir at 15°C for 16 h. Concentrated hydrochloric acid was added to adjust the pH to 4-5. The reaction was concentrated to remove most of EtOH and THF, stirred in an ice-water bath for 0.5 h, and filtered. The filter cake was vacuum-dried to obtain the product (47.0 g, 85.8% yield) as a white solid, which was directly used in the next step.

Step 10: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid (46.8 g, 0.16 mol, 1.0 eq.), HOSu (20.1 g, 0.17 mol, 1.1 eq.), MeCN (500 mL) and DIC (22.0 g, 0.17 mol, 1.1 eq.) were added sequentially to a 1L single-necked flask. The reaction was allowed to stir at 15°C for 4h. The reaction was poured into water (2 L). A large amount of solid precipitated out. The solid was filtered, and the filter cake was vacuum-dried to give the product (53.7 g, 86.4% yield) as an off-white solid, which was directly used in the next step.

Step 11: Synthesis of 6-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)hexanamide

4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (100.0 g, 0.37 mol, 1.0 eq.), THF (2 L) and 6-bromohexanoyl chloride (218 g, 1.02 mol, 2.8 eq.) were added sequentially to a 3L single-necked flask. The reaction was allowed to stir at 70°C for 6h under N₂ protection. The reaction was concentrated to dryness and purified by column (DCM/MeOH=100:1) to obtain the product (162 g, 98.9% yield) as a yellow solid.

Step 12: Synthesis of tert-butyl (3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)amino)benzyl)carbamate

6-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)hexanamide (76.0 g, 0.17 mol, 1.0 eq.), MeCN (1.5 L), K₂CO₃ (46.6 g, 0.34 mol, 2.0 eq.), NaI (25.4 g, 0.17 mol, 2.0 eq.) and tert-butyl (3-aminobenzyl)carbamate (75.0 g, 0.34 mol, 2.0 eq.) were added sequentially to a 3L four-necked flask. The reaction was allowed to stir at 70°C for 48h under N₂ protection. The reaction was concentrated to dryness, and EtOAc (3 L) and water (3 L) were added. The liquids were separated, and the organic phase was concentrated to dryness to obtain 280 g of crude product, which was purified by column (DCM/EtOAc = 1/0.3) to obtain the product (65 g, 65.1% yield) as a yellow solid.

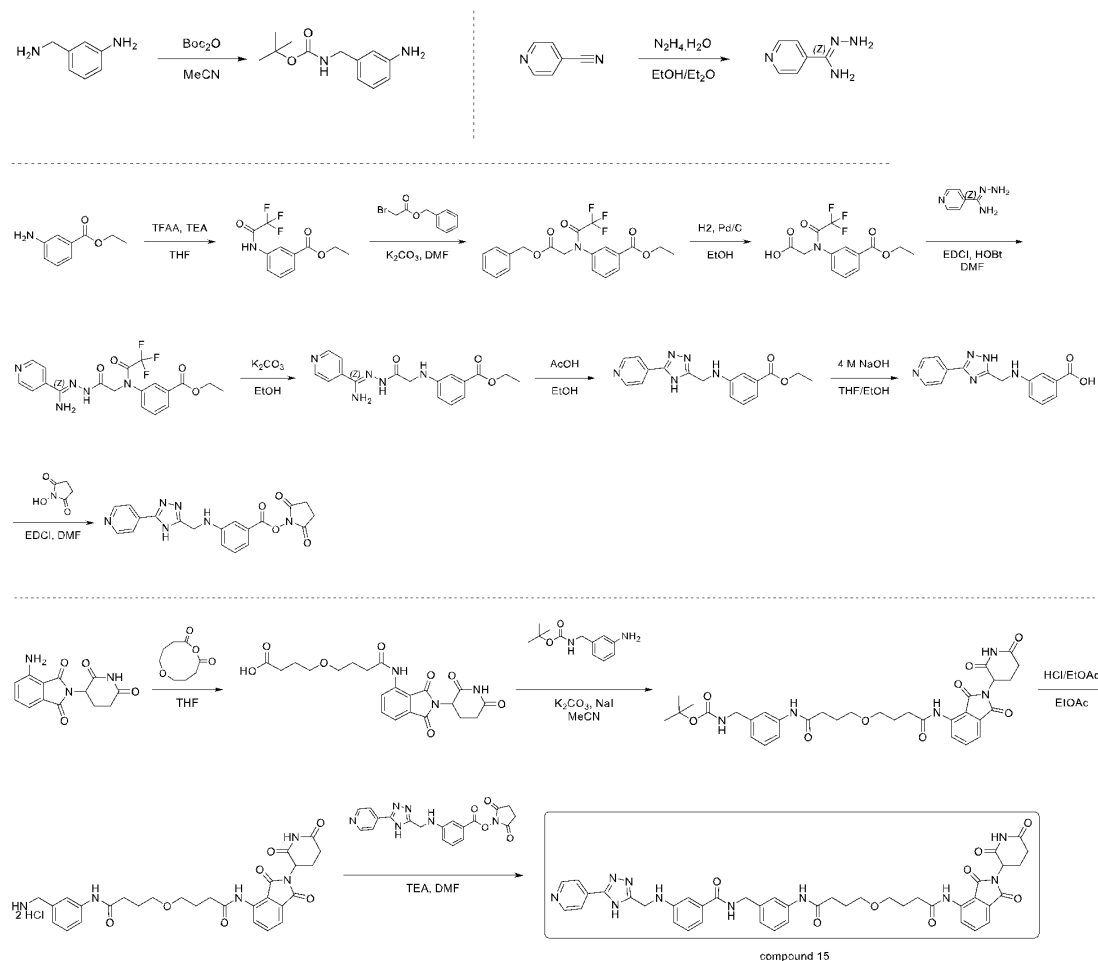
Step 13: Synthesis of 6-((3-(aminomethyl)phenyl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)hexanamide

Tert-butyl (3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)amino)benzyl)carbamate (60.0 g, 0.10 mol, 1.0 eq.) and EtOAc (600 mL) were added to a 2L four-necked flask, and 3 M HCl/EtOAc (600 mL) was added under stirring. The reaction was allowed to stir at 15°C for 2h under N₂ protection. The reaction was filtered, and the filter cake was vacuum-dried to obtain the product (51.7 g, 90.3% yield) as a gray-black solid.

Step 14: Synthesis of N-(3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-6-oxohexyl)amino)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide

6-((3-(aminomethyl)phenyl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)hexanamide (51.7 g, 91.6 mmol, 1.0 eq.), DMF (520 mL), TEA (37.1 g, 0.37 mol, 4.0 eq.) and 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (36.0 g, 91.6 mmol, 1.0 eq.) were added sequentially to a 2L four-necked flask. The reaction was allowed to stir at 30°C for 16h under N₂ protection. The reaction was poured into 2.5 L of water, filtered, and the filter cake was vacuum-dried to obtain 70 g of crude product. The product was purified by column (DCM/MeOH=20/1) to obtain the product (43.0 g, 61.1% yield) as a yellowish solid.

Example 15: Preparation of N-(3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamido)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide (compound 15)



Step 1: Synthesis of tert-butyl (3-aminobenzyl)carbamate

3-(aminomethyl)aniline (60.0 g, 0.49 mol, 1.0 eq.) and MeCN (900 mL) were added to a 3 L four-necked flask, and a solution of Boc_2O (107 g, 0.49 mol, 1.0 eq.) in MeCN (300 mL) was added dropwise quickly. The reaction was allowed to stir at room temperature for 1 h, concentrated to dryness to obtain a crude product, which was purified by column (PE/EtOAc = 5:1) to obtain the product (110 g, 100% yield) as a yellow solid.

Step 2: Synthesis of (Z)-isonicotinohydrazonamide

Isonicotinonitrile (50.0 g, 0.48 mol, 1.0 eq.), EtOH (120 mL), Et₂O (120 mL) and 80% hydrazine hydrate (250 mL) were added sequentially to a 1L single-necked bottle, and the reaction was allowed to stir at 30 °C for 24 h, concentrated to remove most of ethanol and diethyl ether,

stirred in an ice-water bath for 2 h, and filtered. The filter cake was vacuum-dried to obtain the product (60 g, 91.8% yield) as an off-white solid.

Step 3: Synthesis of ethyl 3-(2,2,2-trifluoroacetamido)benzoate

Ethyl 3-aminobenzoate (83.0 g, 0.50 mol, 1.0 eq.), THF (1.66 L) and TEA (76.0 g, 0.75 mol, 1.5 eq.) were added to a 3 L four-necked flask. The reaction was cooled to 0-5°C in an ice-water bath, and TFAA (110.0 g, 0.53 mol, 1.05 eq.) was added dropwise while maintaining the temperature <10°C. After dropping was complete, the reaction was allowed to stir at room temperature for 1 h. The reaction was quenched by adding 1 N HCl (1 L) thereto. Water (1 L) and EtOAc (1 L) were added, and the reaction was stirred and then left to separate. The organic phase was washed successively with saturated sodium bicarbonate (1 L) and saturated brine (0.5 L), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (120 g, 91.4% yield) as a yellow solid, which was directly used in the next step.

Step 4: Synthesis of ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

Ethyl 3-(2,2,2-trifluoroacetamido)benzoate (120.0 g, 0.46 mol, 1.0 eq.), DMF (1.2 L), benzyl bromoacetate (116.0 g, 0.50 mol, 1.1 eq.) and K₂CO₃ (95.0 g, 0.69 mol, 1.5 eq.) were added sequentially to a 3L single-necked bottle. The reaction was allowed to stir at 25°C for 16 h. Water (5 L) and EtOAc (2.5 L) were added, and the reaction was stirred and then left to separate. The organic phase was washed with saturated brine (1.5 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain the product (170 g, 90.4% yield) as an off-white solid, which was directly used in the next step.

Step 5: Synthesis of N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine

Ethyl 3-(N-(2-(benzyloxy)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (170.0 g, 0.42 mol, 1.0 eq.), EtOH (2.1 L) and 10% wet Pd/C (34.0 g, 57% water content) were added sequentially into a 5 L four-necked flask. The reaction was allowed to stir at 15°C for 4 h under H₂ (15 psi) condition. The reaction was filtered, and the filtrate was concentrated to obtain the product (132 g, 100% yield) as a slightly yellow transparent solid, which was directly used in the next step.

Step 6: Synthesis of ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate

N-(3-(ethoxycarbonyl)phenyl)-N-(2,2,2-trifluoroacetyl)glycine (132.0 g, 0.41 mol, 1.0 eq.), (Z)-isonicotinohydrazonamide (58.0 g, 0.43 mol, 1.04 eq.), DMF (1.4 L), HOBt (59.0 g, 0.44 mol, 1.06 eq.) and EDCI (136.0 g, 0.71 mol, 1.73 eq.) were added sequentially to a 2L single-necked bottle. The reaction was allowed to stir at 15°C for 4 h under N₂ protection. The reaction was quenched by pouring into water (6 L), and extracted with EtOAc (7 L). The organic phase

was washed with saturated brine (2 L*3), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 190 g of crude product. The crude product was slurried in EtOAc (760 mL) at 70°C for 3 h, stirred in an ice-water bath for 2 h, filtered, and the filter cake was vacuum-dried to obtain the product (118 g, 65.2% yield) as a white solid.

Step 7: Synthesis of ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate

Ethyl (Z)-3-(N-(2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)-2,2,2-trifluoroacetamido)benzoate (110.0 g, 0.25 mol, 1.0 eq.), K₂CO₃ (104.0 g, 0.75 mol, 3.0 eq.) and EtOH (2.2 L) were added to a 3 L single-necked bottle. The reaction was allowed to stir at 65°C for 2 h. The reaction was poured into stirred water (11 L), and a large amount of solid precipitated out. The reaction was filtered, and the filter cake was vacuum-dried to obtain the product (68 g, 79.2% yield) as a white solid, which was directly used in the next step.

Step 8: Synthesis of ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

Ethyl (Z)-3-((2-(2-(amino(pyridin-4-yl)methylene)hydrazineyl)-2-oxoethyl)amino)benzoate (68.0 g, 0.20 mol, 1.0 eq.), EtOH (2.2 L) and AcOH (136 mL) were added sequentially into a 2 L single-necked flask. The reaction was allowed to stir at 90°C under reflux for 6 h. The reaction was concentrated to dryness, EtOAc (600 mL) and 1 M sodium carbonate (600 mL) were added, the layers were separated, and the aqueous phase was extracted once more with EtOAc (400 mL). The organic phases were combined, washed with saturated brine (500 mL), dried over anhydrous sodium sulfate, filtered, and the filtrate was concentrated to dryness to obtain 60 g of crude product. The crude product was slurried in ethyl acetate (420 mL) at 60°C for 1 h, stirred in an ice-water bath for 0.5 h, filtered, and the filter cake was vacuum-dried to obtain the product (60.3 g, 98.6% yield) as a white solid.

Step 9: Synthesis of 3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid

Ethyl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (60.0 g, 0.19 mol, 1.0 eq.), EtOH (300 mL), THF (300 mL) and 4 M NaOH (450 mL, 1.8 mol, 9.7 eq.) were added sequentially to a 5 L single-necked flask. The reaction was allowed to stir at 15°C for 16 h. Concentrated hydrochloric acid was added to adjust the pH to 4-5. The reaction was concentrated to remove most of EtOH and THF, stirred in an ice-water bath for 0.5 h, and filtered. The filter cake was vacuum-dried to obtain the product (47.0 g, 85.8% yield) as a white solid, which was directly used in the next step.

Step 10: Synthesis of 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate

3-(((3-(pyridin-4-yl)-1H-1,2,4-triazol-5-yl)methyl)amino)benzoic acid (46.8 g, 0.16 mol, 1.0 eq.), HOSu (20.1 g, 0.17 mol, 1.1 eq.), MeCN (500 mL) and DIC (22.0 g, 0.17 mol, 1.1 eq.) were added sequentially to a 1L single-necked flask. The reaction was allowed to stir at 15°C for 4h. The reaction was poured into water (2 L). A large amount of solid precipitated out. The solid was filtered, and the filter cake was vacuum-dried to give the product (53.7 g, 86.4% yield) as an off-white solid, which was directly used in the next step.

Step 11: Synthesis of 4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanoic acid

4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (855 mg, 3.13 mmol, 1.0 eq.), THF (8.5 mL) and 5-oxazelaic anhydride (1.62 g, 9.39 mmol, 3.0 eq.) were sequentially added to a 50 mL single-necked flask. The reaction was allowed to stir at 70°C for 17h under N₂ protection. The reaction was concentrated to dryness and purified by column (DCM/MeOH=120:1) to obtain the product (75 mg, 5.4% yield) as a yellow solid.

Step 12: Synthesis of tert-butyl (3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamido)benzyl)carbamate

4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanoic acid (75 mg, 0.17 mmol, 1.0 eq.), MeCN (3 mL), tert-butyl (3-aminobenzyl)carbamate (38 mg, 0.17 mmol, 1.0 eq.), DIEA (44 mg, 0.34 mmol, 2.0 eq.) and HATU (96 mg, 0.25 mmol, 1.5 eq.) were sequentially added to a 10 mL thumb flask. The reaction was allowed to stir at 15°C for 2h under N₂ protection. The reaction was concentrated to dryness, and EtOAc (50 mL) and water (50 mL) were added, and the layers were separated. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated to dryness to obtain a crude product. The crude product was purified by column (DCM/MeOH = 20/1) to obtain the product (95 mg, 87.0% yield) as a yellow solid.

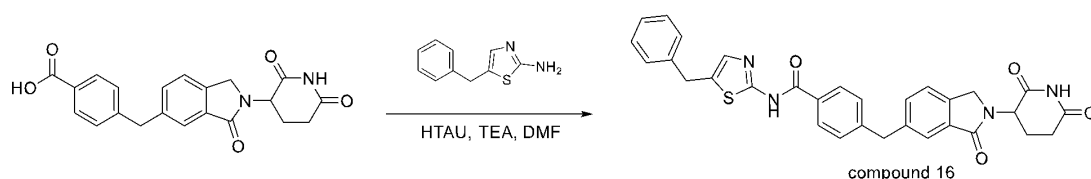
Step 13: Synthesis of N-(3-((λ²-azaneyl)methyl)phenyl)-4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamide

Tert-butyl (3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamido)benzyl)carbamate (95 mg, 0.15 mmol, 1.0 eq.) and EtOAc (4 mL) were added to a 10 mL thumb flask, and 3 M HCl/EtOAc (4 mL) was added while stirring. The reaction was allowed to stir at 15°C for 2h under N₂ protection. The reaction was concentrated to obtain the product (85 mg, 93.2% yield) as a brownish yellow solid, which was directly used in the next step.

Step 14: Synthesis of N-(3-(4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamido)benzyl)-3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzamide

N-(3-((λ²-azaneyl)methyl)phenyl)-4-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-4-oxobutoxy)butanamide (85 mg, 0.14 mmol, 1.0 eq.), DMF (3 mL), TEA (55 mg, 0.54 mmol, 4.0 eq.) and 2,5-dioxopyrrolidin-1-yl 3-(((5-(pyridin-4-yl)-4H-1,2,4-triazol-3-yl)methyl)amino)benzoate (54 g, 0.14 mmol, 1.0 eq.) were sequentially added to a 10 mL thumb flask. The reaction was allowed to stir at 30 °C for 16 h under N₂ protection. The reaction was poured into 50 mL of water, filtered, and the filter cake was vacuum-dried to obtain a crude product. The product was prepared and purified by HPLC to obtain the product (14 mg, 12.4% yield) as a yellow solid.

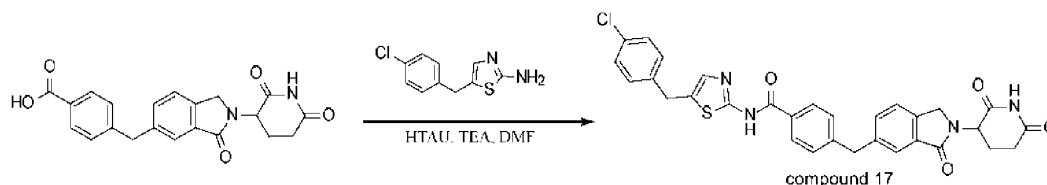
Example 16: Preparation of N-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide (compound 16)



To a solution of 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzoic acid (15 mg, 0.04 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-benzyl-2-aminothiazole (7.5 mg, 0.04 mmol) in DMF (3 mL), TEA (6 mg, 0.06 mmol) and HATU (18 mg, 0.048 mmol) were added. The solution was stirred at RT for 1 hour. Water (20 mL) was added and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide (4.4 mg, 20%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.09 (s, 1H), 10.83 (s, 1H), 8.03-7.98(m, 2H), 7.81-7.79 (m, 2H), 7.43-7.41 (m, 2H), 7.42-7.39 (m, 1H), 7.36-7.32 (m, 2H), 7.23-7.04 (m, 4H), 5.15 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.39 (d, *J* = 17.2 Hz, 1H), 4.28 (d, *J* = 17.2 Hz, 1H), 4.03 (s, 2H), 3.96 (s, 2H), 2.95-2.85 (m, 1H), 2.61-2.55 (m, 1H), 2.40-2.33 (m, 1H), 2.03-1.97(m, 1H). Chemical Formula: C₃₁H₂₆N₄O₄S, MS Calcd.: 550.6; MS Found: 551.4 [M+1]⁺.

Example 17: Preparation of N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide (compound 17)

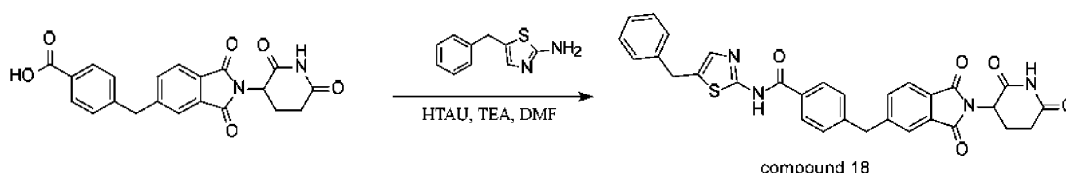


To a mixture of 4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzoic acid (20 mg, 0.053 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.)

and 5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (11.9 mg, 0.053 mmol) in DMF (3 mL), TEA (8 mg, 0.079 mmol) and HATU (18 mg, 0.048 mmol) were added. The solution was stirred at RT for 1 hour. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)methyl)benzamide (4.9 mg, 16%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.23 (s, 1H), 10.95 (s, 1H), 8.03-7.98(m, 1H), 7.85-7.83 (m, 2H), 7.51-7.49 (m, 2H), 7.42-7.39 (m, 1H), 7.36-7.32 (m, 2H), 7.29-7.25 (m, 2H), 7.15-7.12 (m, 2H), 5.15 (dd, *J*=13.4, 5.1 Hz, 1H), 4.39 (d, *J*=17.2 Hz, 1H), 4.32 (d, *J*=17.2 Hz, 1H), 4.05 (s, 2H), 3.96 (s, 2H), 2.92-2.89 (m, 1H), 2.61-2.55 (m, 1H), 2.40-2.36 (m, 1H), 2.03-1.97(m, 1H). Chemical Formula: C₃₁H₂₅ClN₄O₄S, MS Calcd. : 585.1; MS Found: 585.3 [M+1]⁺.

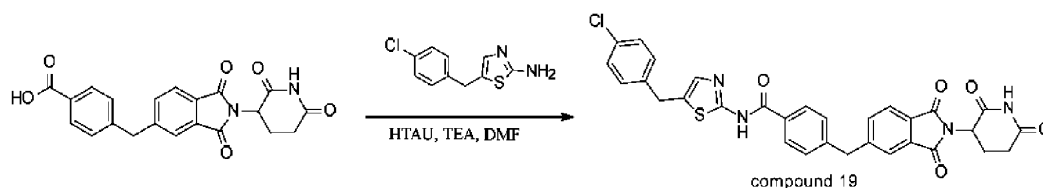
Example 18: Preparation of N-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide (compound 18)



To a mixture of 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzoic acid (20 mg, 0.051 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-benzyl-2-aminothiazole (9.7 mg, 0.051 mmol) in DMF (3 mL), TEA (7.7 mg, 0.077 mmol) and HATU (21.4 mg, 0.056 mmol) were added. The solution was stirred at RT for 1 hour. Water (20 mL) was added and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzylthiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide (4.9 mg, 17%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.42 (s, 1H), 11.12 (s, 1H), 8.02-7.95 (m, 2H), 7.90-7.83 (m, 2H), 7.79 (dd, *J*=7.6, 1.5 Hz, 1H), 7.47 (d, *J*=1.7 Hz, 1H), 7.45 (d, *J*=1.8 Hz, 1H), 7.35-7.31 (m, 2H), 7.31-7.29 (m, 2H), 7.29-7.26 (m, 1H), 7.25-7.19 (m, 1H), 5.13 (dd, *J*=12.8, 5.4 Hz, 1H), 4.25 (s, 2H), 4.11 (s, 2H), 2.93-2.83 (m, 1H), 2.62-2.55 (m, 1H), 2.47-2.41 (m, 1H), 2.07-2.00 (m, 1H). Chemical Formula: C₃₁H₂₄N₄O₅S, MS Calcd.: 564.6; MS Found: 565.5 [M+1]⁺.

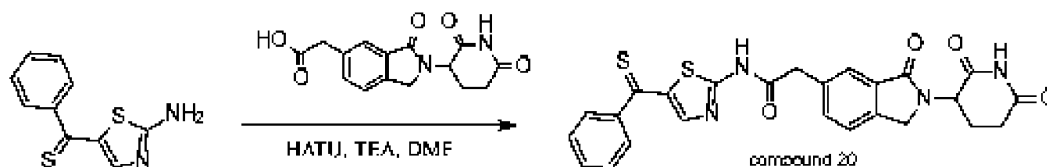
Example 19: Preparation of N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide (compound 19)



To a mixture of 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzoic acid (20 mg, 0.051 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-[(4-chlorophenyl)methyl]-1,3-thiazol-2-amine (11.4 mg, 0.051 mmol) in DMF (3 mL), TEA (7.7 mg, 0.077 mmol) and HATU (21.4 mg, 0.056 mmol) were added. The solution was stirred at RT for 1 hour. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-(4-chlorobenzyl)thiazol-2-yl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-5-yl)methyl)benzamide (4.6 mg, 16%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.28 (s, 1H), 11.00 (s, 1H), 8.04-7.98 (m, 2H), 7.94-7.90 (m, 1H), 7.87-7.83 (m, 1H), 7.73-7.71 (m, 1H), 7.54 (d, $J = 1.4$ Hz, 2H), 7.30-7.27 (m, 1H), 7.27-7.22 (m, 2H), 7.16-7.07 (m, 2H), 5.11 (dd, $J = 13.3, 5.0$ Hz, 1H), 4.06 (s, 2H), 3.85 (s, 2H), 2.95-2.86 (m, 1H), 2.63-2.55 (m, 1H), 2.47-2.32 (m, 1H), 2.03-1.94 (m, 1H). Chemical Formula: $\text{C}_{31}\text{H}_{23}\text{ClN}_4\text{O}_5\text{S}$, MS Calcd.: 599.1; MS Found: 599.4 $[\text{M}+1]^+$.

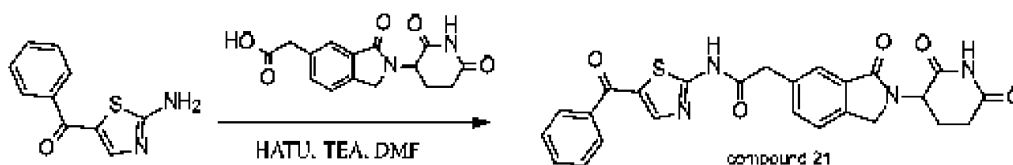
Example 20: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylcarbonothioyl)thiazol-2-yl)acetamide (compound 20)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (15 mg, 0.05 mmol) and (2-aminothiazol-5-yl)(phenyl)methanethione (10.9 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), TEA (8 mg, 0.08 mmol) and HATU (21 mg, 0.055 mmol) were added. The solution was stirred at RT for 5 hours. Water (20 mL) was added and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by silica gel column chromatography (MeOH/DCM=1/100 - 1/30) to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylcarbonothioyl)thiazol-2-yl)acetamide (5 mg, 20%) as a green solid.

^1H NMR (400 MHz, DMSO- d_6) δ 13.10 (s, 1H), 11.00 (s, 1H), 7.85 (s, 1H), 7.74 (d, J = 1.3 Hz, 1H), 7.68 (d, J = 1.2 Hz, 1H), 7.66 (d, J = 1.5 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.59 (d, J = 1.3 Hz, 2H), 7.48 (t, J = 7.7 Hz, 2H), 5.12 (dd, J = 13.3, 5.0 Hz, 1H), 4.46 (d, J = 17.2 Hz, 1H), 4.32 (d, J = 17.2 Hz, 1H), 4.00 (s, 2H), 2.92-2.87 (m, 1H), 2.64-2.57 (m, 1H), 2.43-2.34 (m, 1H), 2.04-1.97 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_4\text{S}_2$, MS Calcd.: 504.6; MS Found: 505.5 $[\text{M}+1]^+$.

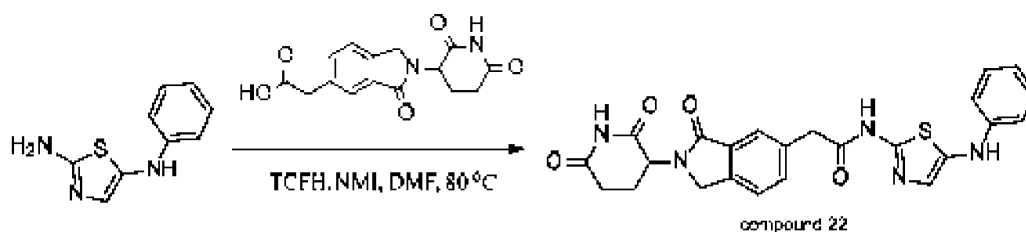
Example 21: Preparation of N-(5-benzoylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 21)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and (2-aminothiazol-5-yl)(phenyl)methanone (13.5 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), TEA (10 mg, 0.099 mmol) and HATU (27.7 mg, 0.073 mmol) were added. The solution was stirred at RT for 1 hour. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzoylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (4.8 mg, 15%) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 12.98 (s, 1H), 11.01 (s, 1H), 8.11 (s, 1H), 7.85 (t, J = 1.3 Hz, 1H), 7.86-7.84 (m, 1H), 7.74 (d, J = 1.2 Hz, 1H), 7.72-7.64 (m, 1H), 7.59 (t, J = 2.0 Hz, 2H), 7.59-7.53 (m, 2H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.45 (d, J = 17.3 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 3.99 (s, 2H), 2.98-2.84 (m, 1H), 2.64-2.56 (m, 1H), 2.45-2.34 (m, 1H), 2.04-1.97 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_5\text{S}$, MS Calcd.: 488.5; MS Found: 489.2 $[\text{M}+1]^+$.

Example 22: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylamino)thiazol-2-yl)acetamide (compound 22)

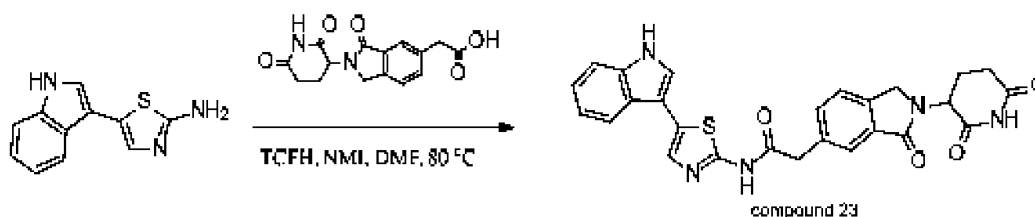


2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (30.2 mg, 0.1 mmol) and N^5 -phenylthiazole-2,5-diamine (19.1 mg, 0.1 mmol; commercially available from Chengdu

Fendi Pharmaceutical Co. Ltd.) were mixed with DMF (3 mL), 1-methylimidazole (24.6 mg, 0.3 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (33.6 mg, 0.12 mmol) were added. The solution was stirred at 80 °C for 3 hours. Then water (20 mL) was added and the mixture was extracted with DCM (10 mL x 3). The combined organic layer was dried by Na₂SO₄ and concentrated in *vacuo* and the residue was purified by silica gel column chromatography (MeOH/DCM=1/100 - 1/30) and *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylamino)thiazol-2-yl)acetamide (4.9 mg, 10%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.22 (s, 1H), 11.00 (s, 1H), 8.12 (s, 1H), 7.72 (d, *J* = 1.3 Hz, 1H), 7.57 (d, *J* = 1.2 Hz, 2H), 7.21-7.10 (m, 3H), 6.86-6.76 (m, 2H), 6.75-6.68 (m, 1H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.44 (d, *J* = 17.3 Hz, 1H), 4.31 (d, *J* = 17.2 Hz, 1H), 3.87 (s, 2H), 2.96-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.44-2.34 (m, 1H), 2.04-1.95 (m, 1H). Chemical Formula: C₂₄H₂₁N₅O₄S, MS Calcd.: 475.5; MS Found: 476.3 [M+1]⁺.

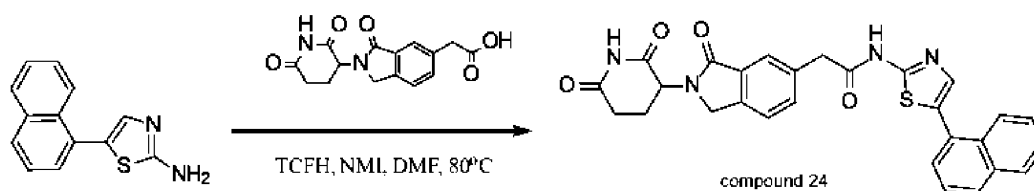
Example 23: Preparation of N-(5-(1H-indol-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 23)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-(1H-indol-3-yl)thiazol-2-amine (10.7 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (16.3 mg, 0.198 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (22.3 mg, 0.079 mmol) were added. The solution was stirred at 80 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-(1H-indol-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (5.9 mg, 18%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.36 (s, 1H), 11.43 (s, 1H), 11.00 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.71-7.64 (m, 2H), 7.64-7.55 (m, 2H), 7.46-7.40 (m, 1H), 7.19-7.14 (m, 1H), 7.12-7.08 (m, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.45 (d, *J* = 17.3 Hz, 1H), 4.32 (d, *J* = 17.2 Hz, 1H), 3.92 (s, 2H), 2.96-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.44-2.35 (m, 1H), 2.05-1.96 (m, 1H). Chemical Formula: C₂₆H₂₁N₅O₄S, MS Calcd.: 499.5; MS Found: 500.3 [M+1]⁺.

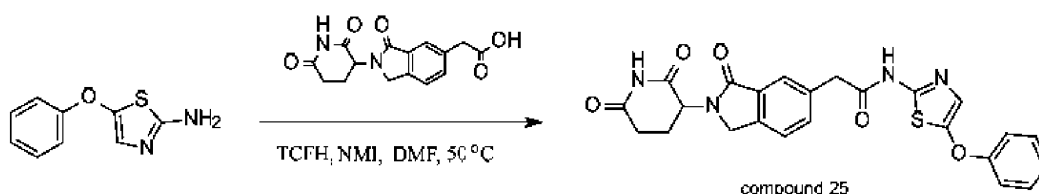
Example 24: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(naphthalen-1-yl)thiazol-2-yl)acetamide (compound 24)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-(naphthalen-1-yl)thiazol-2-amine (15 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (16.3 mg, 0.198 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (22.3 mg, 0.079 mmol) were added. The solution was stirred at 80 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(naphthalen-1-yl)thiazol-2-yl)acetamide (5.7 mg, 17%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.58 (s, 1H), 11.00 (s, 1H), 8.15-8.08 (m, 1H), 8.02-7.95 (m, 2H), 7.76 (s, 1H), 7.67 (s, 1H), 7.63-7.59 (m, 2H), 7.59-7.53 (m, 4H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.45 (d, *J* = 17.3 Hz, 1H), 4.32 (d, *J* = 17.3 Hz, 1H), 3.96 (s, 2H), 2.96-2.86 (m, 1H), 2.64-2.55 (m, 1H), 2.45-2.35 (m, 1H), 2.04-1.97 (m, 1H). Chemical Formula: C₂₈H₂₂N₄O₄S, MS Calcd.: 510.1; MS Found: 511.3 [M+1]⁺.

Example 25: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-phenoxythiazol-2-yl)acetamide (compound 25)

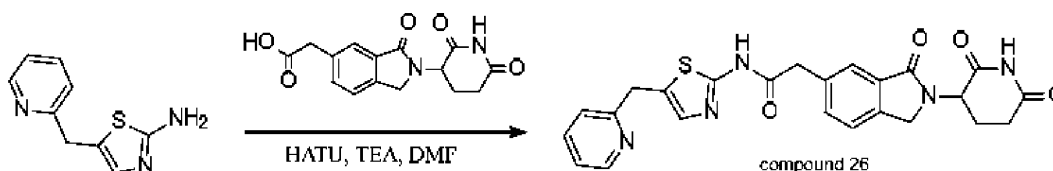


To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-phenoxythiazol-2-amine (12.7 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (16.3 mg, 0.198 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (22.3 mg, 0.079 mmol) were added. The solution was stirred at 50 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was

dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-phenoxythiazol-2-yl)acetamide (4.7 mg, 15%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.40 (s, 1H), 11.00 (s, 1H), 7.71 (d, $J = 1.2$ Hz, 1H), 7.57 (d, $J = 1.2$ Hz, 2H), 7.42-7.32 (m, 2H), 7.25 (s, 1H), 7.16-7.13 (m, 1H), 7.12-7.11 (m, 1H), 7.10-7.08 (m, 1H), 5.11 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.44 (d, $J = 17.3$ Hz, 1H), 4.31 (d, $J = 17.4$ Hz, 1H), 3.87 (s, 2H), 2.98-2.84 (m, 1H), 2.64-2.55 (m, 1H), 2.44-2.33 (m, 1H), 2.03-1.95 (m, 1H). Chemical Formula: $\text{C}_{24}\text{H}_{20}\text{N}_4\text{O}_5\text{S}$, MS Calcd.: 476.5; MS Found: 477.2 $[\text{M}+1]^+$.

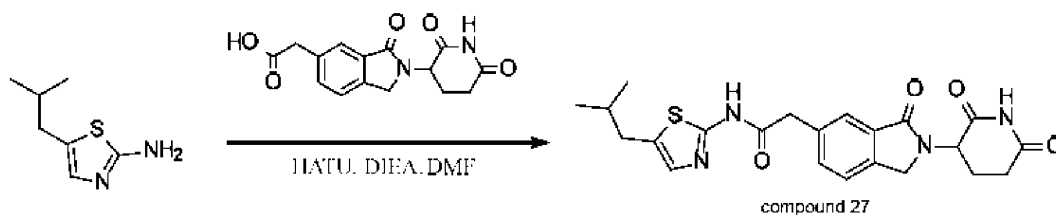
Example 26: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-picolinoylthiazol-2-yl)acetamide (compound 26)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-(pyridin-2-ylmethyl)thiazol-2-amine (12.6 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), TEA (10 mg, 0.099 mmol) and HATU (30.2 mg, 0.079 mmol) were added. The solution was stirred at RT for 4 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-picolinoylthiazol-2-yl)acetamide (5.3 mg, 17%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.24 (s, 1H), 10.99 (s, 1H), 8.50-8.48 (m, 1H), 7.76-7.70 (m, 1H), 7.69 (t, $J = 1.3$ Hz, 1H), 7.55 (d, $J = 1.3$ Hz, 2H), 7.31 (dt, $J = 7.8, 1.1$ Hz, 1H), 7.27 (d, $J = 1.1$ Hz, 1H), 7.25-7.19 (m, 1H), 5.11 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.43 (d, $J = 17.3$ Hz, 1H), 4.30 (d, $J = 17.1$ Hz, 1H), 4.20 (s, 2H), 3.85 (s, 2H), 2.95-2.85 (m, 1H), 2.63-2.55 (m, 1H), 2.44-2.34 (m, 1H), 2.02-1.94 (m, 1H). Chemical Formula: $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_4\text{S}$, MS Calcd.: 475.5; MS Found: 476.2 $[\text{M}+1]^+$.

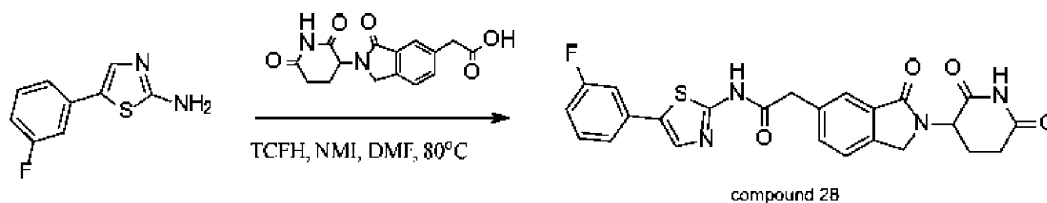
Example 27: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-isobutylthiazol-2-yl)acetamide (compound 27)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-isobutylthiazol-2-amine (10.3 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), DIEA (12.8 mg, 0.099 mmol) and HATU (27.7 mg, 0.073 mmol) were added. The solution was stirred at RT for 4 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-isobutylthiazol-2-yl)acetamide (6.1 mg, 21%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.24 (s, 1H), 11.01 (s, 1H), 7.71 (s, 1H), 7.57 (d, *J* = 1.1 Hz, 2H), 7.15 (d, *J* = 0.9 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.44 (d, *J* = 17.3 Hz, 1H), 4.31 (d, *J* = 17.2 Hz, 1H), 3.87 (s, 2H), 2.98-2.84 (m, 1H), 2.63-2.60 (m, 1H), 2.58 (d, *J* = 6.5 Hz, 2H), 2.45-2.35 (m, 1H), 2.03-1.91 (m, 1H), 1.80-1.71 (m, 1H), 0.88 (s, 3H), 0.86 (s, 3H). Chemical Formula: C₂₂H₂₄N₄O₄S, MS Calcd.: 440.5; MS Found: 441.2 [M+1]⁺.

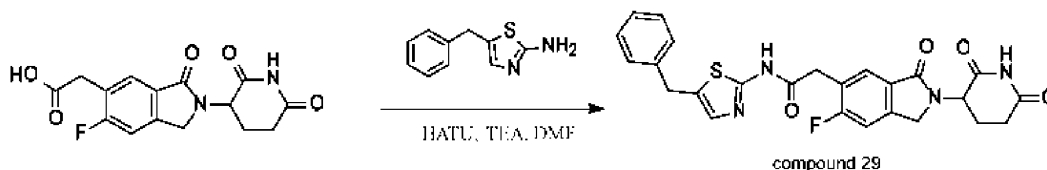
Example 28: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-fluorophenyl)thiazol-2-yl)acetamide (compound 28)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-(3-fluorophenyl)thiazol-2-amine (12.8 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (16.3 mg, 0.20 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (22.3 mg, 0.079 mmol) were added. The solution was stirred at 80 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-fluorophenyl)thiazol-2-yl)acetamide (6 mg, 19%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.48 (s, 1H), 11.01 (s, 1H), 7.99 (s, 1H), 7.74 (d, J = 1.3 Hz, 1H), 7.61-7.57 (m, 2H), 7.51 (dt, J = 10.4, 2.0 Hz, 1H), 7.48-7.42 (m, 1H), 7.42-7.37 (m, 1H), 7.17-7.08 (m, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.45 (d, J = 17.3 Hz, 1H), 4.32 (d, J = 17.3 Hz, 1H), 3.94 (s, 2H), 2.96-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.45-2.33 (m, 1H), 2.04-1.96 (m, 1H). Chemical Formula: $\text{C}_{24}\text{H}_{19}\text{FN}_4\text{O}_4\text{S}$, MS Calcd.: 478.5; MS Found: 479.2 $[\text{M}+1]^+$.

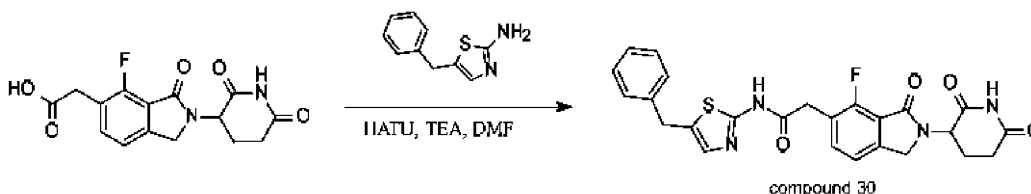
Example 29: Preparation of N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-oxoisindolin-5-yl)acetamide (compound 29)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-oxoisindolin-5-yl)acetic acid (16 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-benzyl-2-aminothiazole (9.5 mg, 0.05 mmol) in DMF (3 mL), TEA (8 mg, 0.08 mmol) and HATU (21 mg, 0.055 mmol) were added. The solution was stirred at RT for 4 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-6-fluoro-3-oxoisindolin-5-yl)acetamide (5.7 mg, 23%) as a white solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 12.29 (s, 1H), 11.00 (s, 1H), 7.77 (d, J = 6.8 Hz, 1H), 7.47 (d, J = 9.4 Hz, 1H), 7.33-7.29 (m, 1H), 7.28 (d, J = 1.3 Hz, 1H), 7.26-7.24 (m, 2H), 7.23-7.22 (m, 1H), 7.22-7.17 (m, 1H), 5.09 (dd, J = 13.3, 5.2 Hz, 1H), 4.44 (d, J = 17.6 Hz, 1H), 4.31 (d, J = 17.5 Hz, 1H), 4.07 (s, 2H), 3.92 (s, 2H), 2.94-2.85 (m, 1H), 2.64-2.55 (m, 1H), 2.45-2.33 (m, 1H), 2.05-1.95 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{21}\text{FN}_4\text{O}_4\text{S}$, MS Calcd.: 492.5; MS Found: 493.2 $[\text{M}+1]^+$.

Example 30: Preparation of N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-3-oxoisindolin-5-yl)acetamide (compound 30)

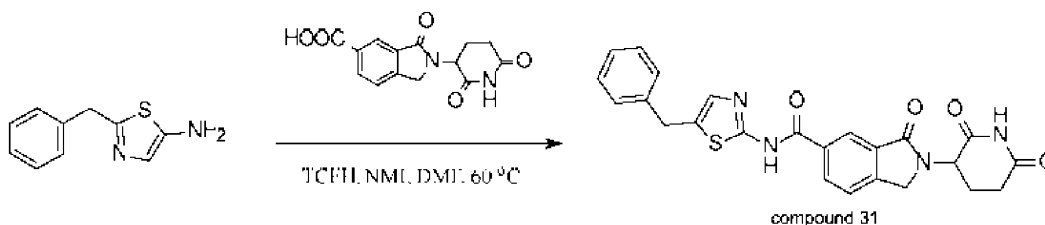


To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-3-oxoisindolin-5-yl)acetic acid (16 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-benzyl-2-aminothiazole (9.5 mg, 0.05 mmol) in DMF (3 mL), TEA (8 mg, 0.08 mmol) and

HATU (21 mg, 0.055 mmol) were added. The solution was stirred at RT for 4 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-4-fluoro-3-oxoisindolin-5-yl)acetamide (5.2 mg, 21%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.11 (s, 1H), 10.98 (s, 1H), 7.79-7.77 (m, 1H), 7.47 (d, *J* = 9.4 Hz, 1H), 7.32-7.28 (m, 1H), 7.28 (d, *J* = 1.3 Hz, 1H), 7.24-7.22 (m, 1H), 7.21-7.17 (m, 2H), 7.16-7.13 (m, 1H), 5.09 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.44 (d, *J* = 17.6 Hz, 1H), 4.31 (d, *J* = 17.5 Hz, 1H), 4.07 (s, 2H), 3.92 (s, 2H), 2.94-2.85 (m, 1H), 2.64-2.55 (m, 1H), 2.45-2.33 (m, 1H), 2.05-1.95 (m, 1H). Chemical Formula: C₂₅H₂₁FN₄O₄S, MS Calcd.: 492.5; MS Found: 493.2 [M+1]⁺.

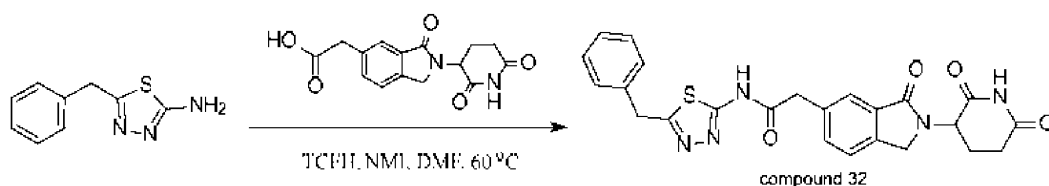
Example 31: Preparation of N-(5-benzylthiazol-2-yl)-2-(2,6-dioxopiperidin-3-yl)-3-oxoisindoline-5-carboxamide (compound 31)



2-(2,6-dioxopiperidin-3-yl)-3-oxoisindoline-5-carboxylic acid (28.8 mg, 0.1 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) and 5-benzyl-2-aminothiazole (19 mg, 0.1 mmol) were mixed with DMF (3 mL). To the resulting mixture, 1-methylimidazole (24.6 mg, 0.3 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (33.6 mg, 0.12 mmol) were added. The solution was stirred at 60 °C for 4 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (10 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzylthiazol-2-yl)-2-(2,6-dioxopiperidin-3-yl)-3-oxoisindoline-5-carboxamide (6 mg, 13%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.67 (s, 1H), 11.03 (s, 1H), 8.46-8.41 (m, 1H), 8.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 1.0 Hz, 1H), 7.34 (d, *J* = 1.7 Hz, 1H), 7.31 (dd, *J* = 4.0, 1.3 Hz, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.26-7.20 (m, 1H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.56 (d, *J* = 18.0 Hz, 1H), 4.42 (d, *J* = 18.0 Hz, 1H), 4.13 (s, 2H), 2.97-2.88 (m, 1H), 2.66-2.57 (m, 1H), 2.46-2.34 (m, 1H), 2.06-1.99 (m, 1H). Chemical Formula: C₂₄H₂₀N₄O₄S, MS Calcd.: 460.5; MS Found: 461.3 [M+1]⁺.

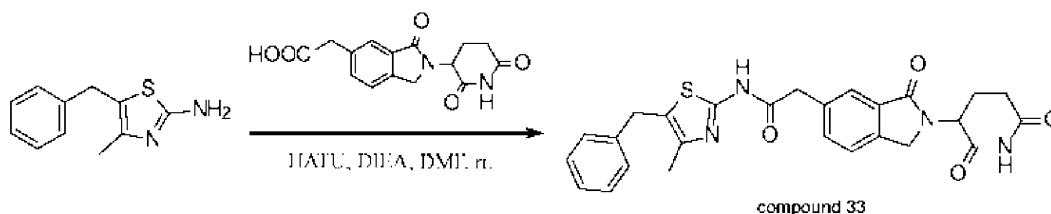
Example 32: Preparation of N-(5-benzyl-1,3,4-thiadiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 32)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 5-benzyl-1,3,4-thiadiazol-2-amine (12.6 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (16.3 mg, 0.20 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (22.3 mg, 0.079 mmol) were added. The solution was stirred at 80 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzyl-1,3,4-thiadiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (6.3 mg, 20%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 11.00 (s, 1H), 7.69 (s, 1H), 7.54 (d, *J* = 1.5 Hz, 2H), 7.36-7.32 (m, 1H), 7.31 (d, *J* = 1.8 Hz, 2H), 7.29 (d, *J* = 1.7 Hz, 1H), 7.27-7.22 (m, 1H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.43 (d, *J* = 17.3 Hz, 1H), 4.33 (s, 2H), 4.30 (d, *J* = 17.2 Hz, 1H), 3.91 (s, 2H), 2.95-2.86 (m, 1H), 2.64-2.54 (m, 1H), 2.44-2.34 (m, 1H), 2.03-1.93 (m, 1H). Chemical Formula: C₂₄H₂₁N₅O₄S, MS Calcd.: 475.5; MS Found: 476.3 [M+1]⁺.

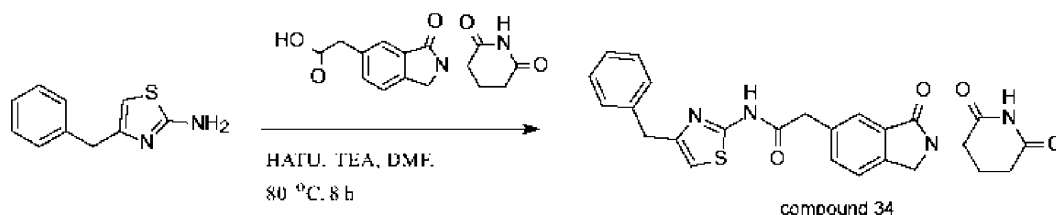
Example 33: Preparation of N-(5-benzyl-4-methylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 33)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (15 mg, 0.05 mmol) and 5-benzyl-4-methylthiazol-2-amine (10.1 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), DIEA (10.3 mg, 0.08 mmol) and HATU (21 mg, 0.055 mmol) were added. The solution was stirred at RT for 5 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(5-benzyl-4-methylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (5.5 mg, 23%) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 12.21 (s, 1H), 11.00 (s, 1H), 7.68 (s, 1H), 7.54 (d, J = 1.8 Hz, 2H), 7.32-7.24 (m, 2H), 7.22-7.20 (m, 1H), 7.19-7.16 (m, 2H), 5.11 (dd, J = 13.3, 5.1 Hz, 1H), 4.43 (d, J = 17.3 Hz, 1H), 4.30 (d, J = 17.3 Hz, 1H), 3.99 (s, 2H), 3.82 (s, 2H), 2.95-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.43-2.33 (m, 1H), 2.23 (s, 3H), 2.02-1.95 (m, 1H). Chemical Formula: $\text{C}_{26}\text{H}_{24}\text{N}_4\text{O}_4\text{S}$, MS Calcd.: 488.6; MS Found: 489.3 $[\text{M}+1]^+$.

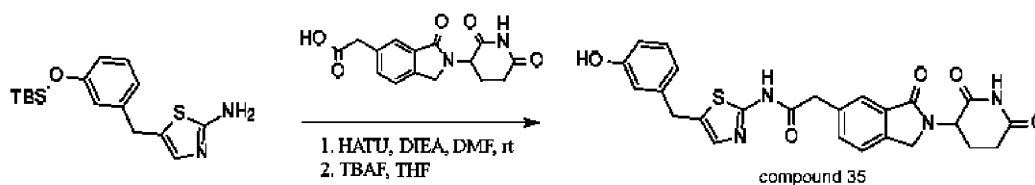
Example 34: Preparation of N-(4-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 34)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (20 mg, 0.066 mmol) and 4-benzylthiazol-2-amine (12.6 mg, 0.066 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), TEA (10 mg, 0.099 mmol) and HATU (27.7 mg, 0.073 mmol) were added. The solution was stirred at 80 °C for 3 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by *prep*-HPLC to obtain the product N-(4-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (4.7 mg, 15%) as a white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 12.45 (s, 1H), 11.00 (s, 1H), 7.72 (d, J = 1.4 Hz, 1H), 7.58 (d, J = 1.3 Hz, 2H), 7.44 (s, 2H), 7.43 (s, 2H), 7.39-7.33 (m, 1H), 7.34-7.24 (m, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 (d, J = 17.3 Hz, 1H), 4.31 (d, J = 17.3 Hz, 1H), 3.90 (s, 2H), 2.96-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.45-2.37 (m, 1H), 2.35 (s, 2H), 2.03-1.96 (m, 1H). Chemical Formula: $\text{C}_{25}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$, MS Calcd.: 474.5; MS Found: 475.3 $[\text{M}+1]^+$.

Example 35: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-hydroxybenzyl)thiazol-2-yl)acetamide (compound 35)

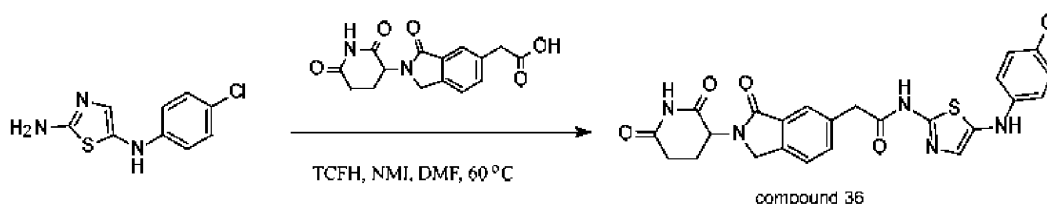


To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (30.2 mg, 0.1 mmol) and 5-(3-((tert-butyldimethylsilyl)oxy)benzyl)thiazol-2-amine (32 mg, 0.1 mmol);

commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), DIEA (39 mg, 0.3 mmol) and HATU (41.8 mg, 0.11 mmol) were added. After no 5-(3-((tert-butyldimethylsilyl)oxy)benzyl)thiazol-2-amine was detected by LCMS, TBAF (0.4 mL, 1M in THF) was added. The mixture was stirred at 60 °C for 3 hours. Then water (20 mL) was added to the residue and the mixture was extracted with DCM (10 mL x 4). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by silica gel column chromatography (MeOH/DCM=1/100 - 1/30) and *Prep*-HPLC to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-hydroxybenzyl)thiazol-2-yl)acetamide (5.4 mg, 11%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.12 (s, 1H), 11.03 (s, 1H), 8.05 (s, 1H), 7.75-7.73 (m, 1H), 7.59-7.57 (m, 1H), 7.46-7.43 (m, 2H), 7.43 (s, 2H), 7.39-7.33 (m, 1H), 7.34-7.24 (m, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.42 (d, *J* = 17.3 Hz, 1H), 4.33 (d, *J* = 17.3 Hz, 1H), 3.90 (s, 2H), 2.96-2.86 (m, 1H), 2.63-2.56 (m, 1H), 2.45-2.37 (m, 1H), 2.35 (s, 2H), 2.03-1.96 (m, 1H). Chemical Formula: C₂₅H₂₂N₄O₅S, MS Calcd.: 490.5; MS Found: 491.2 [M+1]⁺.

Example 36: Preparation of N-(5-((4-chlorophenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 36)

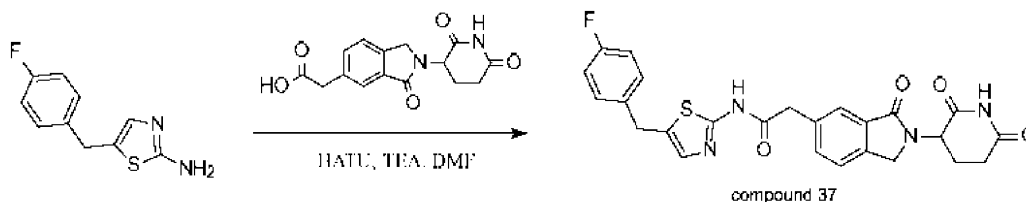


To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (30.2 mg, 0.1 mmol) and *N*⁵-(4-chlorophenyl)thiazole-2,5-diamine (22.5 mg, 0.1 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), 1-methylimidazole (24.6 mg, 0.3 mmol) and N,N,N',N'-tetramethylchloroformamidinium hexafluorophosphate (33.6 mg, 0.12 mmol) were added. The solution was stirred at 60 °C for 3 hours. Water (20 mL) was added to the reaction mixture and the mixture was extracted with DCM (10 mL x 3). The combined organic layer was dried by Na₂SO₄, concentrated in *vacuo* and the residue was purified by silica gel column chromatography (MeOH/DCM=1/100 - 1/30) and *Prep*-HPLC to obtain the product N-(5-((4-chlorophenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (6.1 mg, 12%) as a pale white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ 12.27 (s, 1H), 11.00 (s, 1H), 8.25 (s, 1H), 7.72 (d, *J* = 1.4 Hz, 1H), 7.57 (d, *J* = 1.2 Hz, 2H), 7.19 (d, *J* = 2.1 Hz, 1H), 7.18-7.13 (m, 2H), 6.81 (d, *J* = 2.2 Hz, 1H), 6.79 (d, *J* = 2.2 Hz, 1H), 5.11 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.44 (d, *J* = 17.3 Hz, 1H), 4.31

(d, $J = 17.3$ Hz, 1H), 3.87 (s, 2H), 2.95-2.87 (m, 1H), 2.63-2.57 (m, 1H), 2.44-2.37 (m, 1H), 2.03-1.96 (m, 1H). Chemical Formula: $C_{24}H_{20}ClN_5O_4S$, MS Calcd.: 510.0; MS Found: 510.3 $[M+1]^+$.

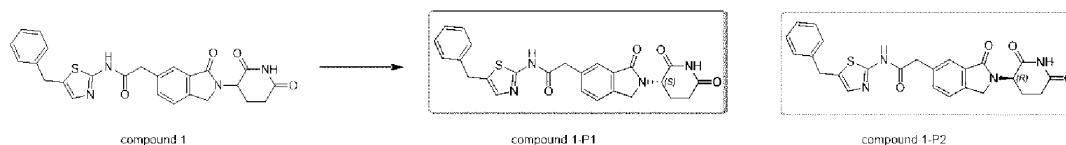
Example 37: Preparation of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4-fluorobenzyl)thiazol-2-yl)acetamide (compound 37)



To a mixture of 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetic acid (15 mg, 0.05 mmol) and 5-(4-fluorobenzyl)thiazol-2-amine (10.4 mg, 0.05 mmol; commercially available from Chengdu Fendi Pharmaceutical Co. Ltd.) in DMF (3 mL), TEA (8 mg, 0.08 mmol) and HATU (21 mg, 0.055 mmol) were added. The solution was stirred at RT for 5 hours. Water (20 mL) was added to the residue and the mixture was extracted with DCM (5 mL x 3). The combined organic layer was dried by Na_2SO_4 , concentrated in *vacuo* and the residue was purified by silica gel column chromatography (MeOH/DCM=1/100 - 1/30) to obtain the product 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4-fluorobenzyl)thiazol-2-yl)acetamide (4.9 mg, 20%) as a white solid.

1H NMR (400 MHz, $DMSO-d_6$) δ 12.28 (s, 1H), 11.12 (s, 1H), 7.71-7.69 (m, 1H), 7.53-7.51 (m, 2H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.24-7.21 (m, 1H), 7.19-7.17 (m, 2H), 5.10 (dd, $J = 13.4$, 5.1 Hz, 1H), 4.43 (d, $J = 17.2$ Hz, 1H), 4.30 (d, $J = 17.2$ Hz, 1H), 4.07 (s, 2H), 3.85 (s, 2H), 2.93-2.86 (m, 1H), 2.62-2.59 (m, 1H), 2.42-2.38 (m, 1H), 2.03-1.97 (m, 1H). Chemical Formula: $C_{25}H_{21}ClN_4O_4S$, MS Calcd.: 492.5; MS Found: 493.2 $[M+1]^+$.

Example 38: Preparation of stereoisomers of N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide (compound 1-P1 and compound 1-P2)



The compound 1 (3.0 g) was dissolved in MeCN/DCM/FA (200 mL) and then separated by SFC (conditions: column: Chiralpak AS-3 50×4.6mm I.D., 3 μ m mobile phase: phase A for CO_2 , and phase B for IPA+ACN(0.05%DEA); gradient elution: 40% IPA+ACN (0.05% DEA) in CO_2 ; flow rate: 3 mL/min; detector: PDA; column temperature: 35 $^{\circ}C$; back pressure: 100 bar) to obtain the products compound 1-P1 ((S)-N-(5-benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide) (1.05 g, purity: 99.14%) and compound 1-P2 ((R)-N-(5-

benzylthiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide) (1.46 g, purity: 98.93%) as white solids.

Compound 1-P1: ^1H NMR (400 MHz, DMSO- d_6) δ 12.25 (br s, 1H), 10.99 (br s, 1H), 7.69 (s, 1H), 7.54 (s, 2H), 7.39 - 7.14 (m, 6H), 5.10 (dd, , 1H), 4.48 - 4.38 (m, 1H), 4.36 - 4.22 (m, 1H), 4.05 (s, 2H), 3.85 (s, 2H), 2.99 - 2.83 (m, 1H), 2.59 (br dd, 1H), 2.06 - 1.91 (m, 1H).

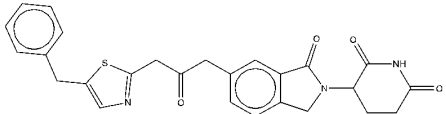
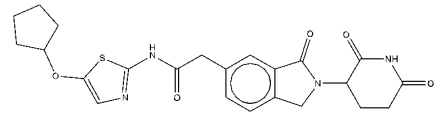
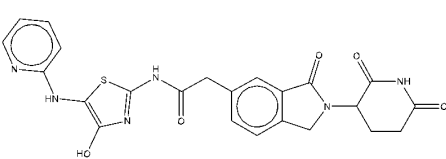
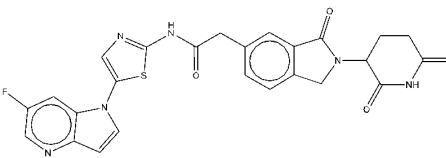
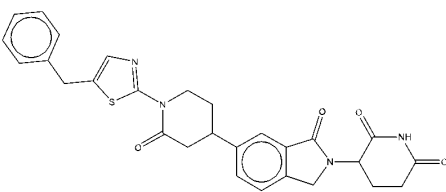
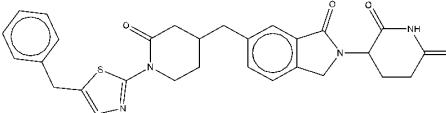
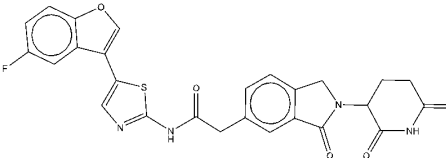
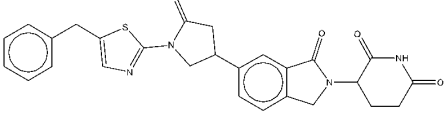
Compound 1-P2: ^1H NMR (400 MHz, DMSO- d_6) δ 12.59 - 11.87 (m, 1H), 10.99 (s, 1H), 7.69 (s, 1H), 7.54 (s, 2H), 7.35 - 7.11 (m, 5H), 5.10 (dd, 1H), 4.49 - 4.37 (m, 1H), 4.32 - 4.23 (m, 1H), 4.05 (s, 2H), 3.84 (s, 2H), 2.97 - 2.82 (m, 1H), 2.59 (br d, 1H), 2.38 (dq, 1H), 2.08 - 1.89 (m, 1H).

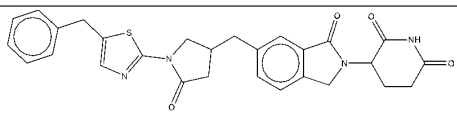
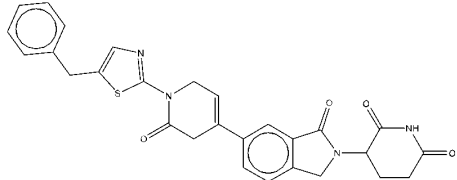
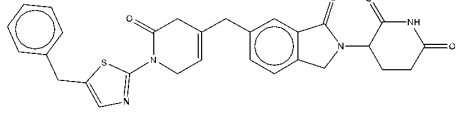
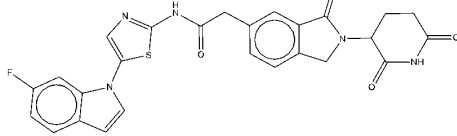
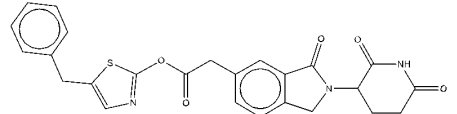
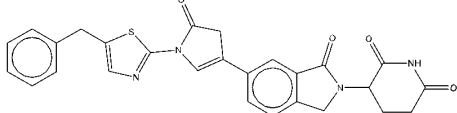
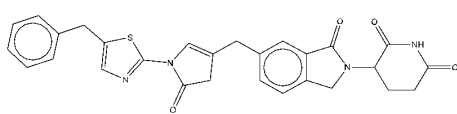
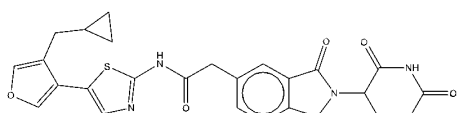
Example 39: Preparation of additional example compounds

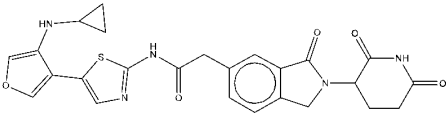
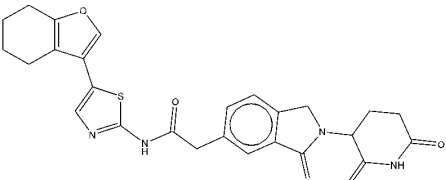
The following example compounds were made by following procedures analogous to the above Examples 1-37 starting from appropriate intermediates and reacting with the appropriate reagents under similar conditions.

WO 2024/165075	Structure	Name PCT/CN2024/077138	
38		N-(5-(difluoro(4-fluorophenyl)methyl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	528.5081
39		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(3-hydroxybenzyl)thiazol-2-yl)acetamide	490.5368
40		N-(5-((4-chloro-3-hydroxyphenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	525.97
41		N-(5-(cycloheptyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	496.5842
42		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(indolin-1-yl)thiazol-2-yl)acetamide	501.5637
43		N-(5-((4-chlorophenyl)amino)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	509.971
44		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4-fluorobenzyl)thiazol-2-yl)acetamide	492.5279
45		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-((isopropylthio)methyl)thiazol-2-yl)acetamide	472.5856

No.	Structure	Name	MW
46		N-(5-(cyclohexyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	482.5574
47		N-(5-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	502.5518
48		N-(5-(1H-indol-1-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	499.5479
49		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phenylthio)thiazol-2-yl)acetamide	492.576
50		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(phthalazin-1-yl)thiazol-2-yl)acetamide	512.547
51		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(4-hydroxy-5-(phenylamino)thiazol-2-yl)acetamide	491.5249
52		N-(5-(1H-benzo[d]imidazol-1-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	500.536
53		3-(6-(3-(5-benzylthiazol-2-yl)-2-oxopropyl)-1-	473.5497

No.	Structure	Name	MW
		oxoisindolin-2-yl)piperidine-2,6-dione	
54		N-(5-(cyclopentyloxy)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	468.5306
55		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(4-hydroxy-5-(pyridin-2-ylamino)thiazol-2-yl)acetamide	492.513
56		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(6-fluoro-1H-pyrrolo[3,2-b]pyridin-1-yl)thiazol-2-yl)acetamide	518.5261
57		3-(6-(1-(5-benzylthiazol-2-yl)-2-oxopiperidin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	514.6024
58		3-(6-((1-(5-benzylthiazol-2-yl)-2-oxopiperidin-4-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	528.6292
59		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(5-fluorobenzofuran-3-yl)thiazol-2-yl)acetamide	518.5221
60		3-(6-(1-(5-benzylthiazol-2-yl)-5-oxopyrrolidin-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	500.5756
61		3-(6-((1-(5-benzylthiazol-2-yl)-5-oxopyrrolidin-3-	514.6024

No.	Structure	Name	MW
		yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	
62		3-(6-((1-(5-benzylthiazol-2-yl)-2-oxo-1,2,3,6-tetrahydropyridin-4-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	512.5866
63		3-(6-((1-(5-benzylthiazol-2-yl)-2-oxo-1,2,3,6-tetrahydropyridin-4-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	526.6134
64		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(6-fluoro-1H-indol-1-yl)thiazol-2-yl)acetamide	517.538
65		5-benzylthiazol-2-yl 2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetate	475.5219
66		3-(6-((1-(5-benzylthiazol-2-yl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	498.5598
67		3-(6-((1-(5-benzylthiazol-2-yl)-5-oxo-4,5-dihydro-1H-pyrrol-3-yl)methyl)-1-oxoisindolin-2-yl)piperidine-2,6-dione	512.5866
68		N-(5-(4-(cyclopropylmethyl)furan-3-yl)thiazol-2-yl)-2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	504.5636
69		N-(5-(4-(cyclopropylamino)furan-3-yl)thiazol-2-yl)-2-(2-	505.5517

No.	Structure	Name	MW
		(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)acetamide	
70		2-(2-(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)-N-(5-(4,5,6,7-tetrahydrobenzofuran-3-yl)thiazol-2-yl)acetamide	504.5636

Pharmacological Examples

Example 40: *In vitro* GRK2 degradation assay (Part I)

In this example, the primary human, mouse and rat pulmonary artery smooth muscle cells (PASMCs, purchased from iCell Bioscience, Inc. (shanghai)) were treated under hypoxic condition (oxygen content: 3%) for 24 hours to establish a hypoxic model. Afterwards, a Western blotting assay was used to observe the change in the expression level of GRK2 relative to that of β -actin used as a reference protein. Meanwhile, the the degradative effects of various concentrations of compound 1 on GRK2 in PASMCs induced under hypoxic condition were investigated. Lastly, MG132 (a known inhibitor of proteasome) was administrated to PASMCs alone or in combination with compound 1 under the same experimental conditions to explore the possible mechanism of the degradative effect of compound 1 on GRK2.

1. Hypoxic Treatment of PASMCs and Stimulation of the Same with Compound 1

PASMCs originated from human, mouse and rat were treated under hypoxic conditions (oxygen content: 3%) and then stimulated with different concentrations of compound 1 that were serially diluted (0.1 nM, 1 nM, 10 nM, 100 nM, 1 μ M, and optionally 10 μ M and 20 μ M), MG132 (a known inhibitor of proteasome) (1 μ M) or the combination thereof (1 μ M MG132 plus 0.1 nM, 1 nM, 10 nM, 100 nM, 1 μ M, 10 μ M or 20 μ M compound 1) for 24 hours, respectively.

2. Extraction of Cellular Proteins from PASMCs

After hypoxic treatment of PASMCs, an appropriate amount of cell lysis buffer was added to the cells, then the proteins released therefrom were scraped with a cell scraper, put into a pre-cooled 1.5 mL centrifuge tube (EP tube), and placed onto ice to continue lysing for 30 min. The EP tube was transferred to a low-temperature high-speed centrifuge, centrifuged at 12000 rpm at 4°C for 15 min. The supernatant obtained by centrifugation was the whole protein extract of PASMCs, which was drawn into a new pre-cooled centrifuge tube. A BCA (bicinchoninic acid) working solution was prepared according to the number of samples to be

tested. The samples to be tested and the protein standard were prepared in turn, then transferred to a 37°C incubator and incubated for 30 minutes. After taking out, they were subject to Vortex. The concentrations of the protein standard in each group were measured, and a standard curve was plotted according to the results of the measurements. The protein concentrations corresponding to the measured samples were measured according to the standard curve, and the proteins were aliquoted according to the loading amounts.

3. Electrophoretic Separation and Imaging of the Proteins

The proteins obtained from the previous step were separated by electrophoresis in 10% Precast-gel (SDS - PAGE gel), then transferred to a PVDF membrane, and then blocked with bovine serum albumin (BSA) at room temperature for 1 hour. A GRK2 primary antibody (purchased from Santa Cruz Biotechnology, Inc.) was added, then the membrane was cultured overnight at 4°C. On the next day, a GRK2 secondary antibody (purchased from Santa Cruz Biotechnology, Inc.) was added, then the membrane was cultured at room temperature for 2 hours. An imaging system was used to detect the resulting signals.

4. Results and Discussion

As shown in the images of Figures 1, 2, 4, 5, 7 and 8, the expression of β -actin in PASMCs was almost unchanged under various treatment conditions. This fact indicates that β -actin is eligible as a reference protein in relation to GRK2, because the expression of β -actin in PASMCs is very stable and is hardly influenced by the variations in different stimulating conditions. In contract, the expression of GRK2 protein was significantly elevated in hypoxically treated PASMCs originated from human (see Figure 1 and Figure 2), mouse (see Figure 4 and Figure 5) and rat (see Figure 7 and Figure 8), indicating that hypoxic condition resulted in significant induction of the expression of GRK2 protein in PASMCs. The above facts were also confirmed by the significantly elevated ratios of GRK2/ β -actin in hypoxically treated PASMCs originated from human and mouse (see Figure 3 and Figure 6). Unexpectedly, the expression level of GRK2 in hypoxically treated PASMCs was significantly reduced after treatment with various concentrations of compound 1, exhibiting a concentration-dependent manner. The above result indicates that compound 1 is a potent GRK2 degrader. Besides, as shown in Figures 2, 5 and 8, it was found that the degradative effect of compound 1 on GRK2 was significantly reduced in the presence of MG132. This fact indicates that compound 1 may degrade GRK2 via the ubiquitin-proteasome pathway.

Example 41: *In vivo* study on the therapeutic effect against PAH

Pulmonary hypertension (PH) refers to a group of serious medical conditions characterized by increased blood pressure in the arteries of the lungs. Typical symptoms of PH include fainting, tiredness, chest pain, shortness of breath, swelling of the legs and a fast heartbeat.

Pulmonary arterial hypertension (PAH) is a common subtype of PH, which affects the heart and lungs and it is specifically characterized by abnormally high blood pressure (hypertension) in the pulmonary artery, i.e., the blood vessel that carries blood from the heart to the lungs. PAH can be life-threatening if it is not well-controlled. The main existing commercially available drugs for treating PAH target a pathway selected from the group consisting of endothelin receptor, NO, prostacyclin and TGF- β , and include but not limited to ambrisentan, tadalafil and beraprost. However, according to the inventors' knowledge, no relationship between PAH and GRK2 has been reported and no GRK2 degrader has been suggested to be useful in preventing or treating PAH till now.

Based on the findings of *in vitro* GRK2 degradation assay, it was found that the compound of the present disclosure (e.g., compound 1) is a potent GRK2 degrader which may degrade GRK2 via the ubiquitin-proteasome pathway. It was known that GRK2 is an upstream central regulatory molecule of endothelin, NO, prostacyclin and TGF, and has a wide range of functions. Therefore, it is speculated, for the first time, that the compound of the present disclosure, functioned as GRK2 degrader, might be useful in preventing or treating PAH. Therefore in the present Example, an *in vivo* study was further conducted to investigate the effectiveness of compound 1 on alleviating PAH in mice.

1. General Experimental Protocol

Male C57BL/6 mice aged 6-8 weeks (purchased from Hangzhou Ziyuan Experimental Animal Technology Co., Ltd.) were selected to construct a hypoxia-induced pulmonary artery hypertension (PAH) mouse model.

Briefly, after one week of adaptive feeding (1w), the mice were randomly divided into 3 groups, including:

(1) normoxia group (control group): raised in normal air environment (FiO_2 : 0.21 ± 0.05 ; temperature: 22 ± 2 °C, humidity: $55 \pm 5\%$) for four weeks;

(2) hypoxia group (PH model group): raised in an animal hypoxic incubator (FiO_2 : 0.1 ± 0.01 ; temperature: 22 ± 2 °C, humidity: $55 \pm 5\%$) for four weeks, during which period Sugen 5416 (a known VEGF receptor inhibitor) was subcutaneously injected into the neck every week at a dose of 20 mg/kg to induce modeling;

(3) hypoxia + compound 1 group (compound 1 group): raised in the animal hypoxic incubator (FiO_2 : 0.1 ± 0.01 ; temperature: 22 ± 2 °C, humidity: $55 \pm 5\%$) for four weeks, during which period Sugen 5416 was subcutaneously injected into the neck every week at a dose of 20 mg/kg to induce modeling and compound 1 was administrated orally (10 mg/kg, bid) for three weeks.

The body weight of the mice from each of the three experimental groups was measured two weeks post modeling (2w).

Besides, the mice from each of the three experimental groups were subject to M-mode cardiac color Doppler ultrasonography (VisualSonics Vevo 2100 system) two weeks (2w) and four weeks (4w) post modeling in the Animal Experiment Center of Nanjing Medical University. The specific operation steps were as follows:

(1) the mice were put into a gas anesthesia chamber, and anesthetized by injection of 5% isoflurane to the chamber;

(2) the limbs of the mice were evenly spread with gel and then fixed onto electrode sheets; meanwhile, a nose cone with 1.5% isoflurane was used to maintain anesthesia during examination; during the period of measurement, the body temperature of the mice was maintained at 36-37°C and the heart rate was maintained within 400-450 times/min;

(3) the hairs on the mice's chest area were gently shaved off, and a gelatinous ultrasonic coupling agent was evenly spread onto this area; then, an ultrasonic probe (frequency: 30MHz) was used to detect the mice's chest area and images were collected therefrom;

(4) the following indices were sequentially detected by color Doppler ultrasound: pulmonary artery acceleration time (PAT), pulmonary artery ejection time (PET), blood flow velocity of tricuspid valve orifice E peak (TVE), blood flow velocity of tricuspid valve orifice A peak (TVA), right ventricle internal dimension in systole (RVID; s), right ventricle internal dimension in diastole (RVID; d) and right ventricular anterior wall (RVAW) thickness; besides, the ratios of PAT/PET and TV E/A (i.e., TVE/TVA) were calculated;

(5) for each index of each mouse, the data from 5-6 cardiac cycles were selected, averaged and subject to statistical analysis. Moreover, the right ventricular systolic pressure (RVSP) of the mice was measured four weeks (4w) post modeling, according to the experimental protocol described hereinafter. Briefly, the mice were anesthetized by intraperitoneal injection of pentobarbital sodium (50 mg/kg), then fixed onto the processing table in supine position. The mice's neck skins were incised layer by layer to expose the trachea, which was then carefully incised for the placement of a tracheal cannula and connected to a ventilator for small animals. After confirming that the breathings of the mice were stable, the mice's precordial tissues were bluntly dissected layer by layer with tweezers until the heart was exposed. Afterwards, the tip of a venous indwelling needle was slowly inserted into the right ventricle, which was then connected to a multi-lead physiological recorder. The waveforms were observed, and the pressures of the right ventricle were recorded.

Finally, the mice were sacrificed four weeks (4w) post modelling. The heart of each of the mice was then dissected, and the right ventricle (RV) was separated from the left ventricle +

ventricular septum (LV+S) under a microscope. The RVs were suck-dried with absorbent paper to remove their surface moisture and weighed respectively. The right ventricular hypertrophy index (RVHI) of the mice, expressed as the ratio of the weights of the two (i.e., $RVHI = RV/(LV + S)$), was calculated.

2. Results and Discussion

In case of PAH, due to pulmonary artery remodeling, vascular resistance is increased, which leads to increased pulmonary artery pressure and right ventricular afterload that can eventually lead to right heart failure. Based on this recognition, cardiac color Doppler ultrasonography was performed to evaluate the changes in the structure and function of the right ventricle of the mice from the three experimental groups two weeks (2w) and four weeks (4w) post modeling, respectively. Besides, at the end of the study (i.e., four weeks (4w) post modeling), the RVSP and RVHI values of the mice from the three experimental groups were obtained to further validate the above findings. The results are summarized hereinafter.

First, it was found that the right ventricular internal dimension (RVID) of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 11B), and that the right ventricular anterior wall (RVAW) thickness of the mice from hypoxia group was significantly higher than that of normoxia group (see Figure 11C) two weeks after hypoxic treatment. However, oral administration of compound 1 for one week effectively alleviated the reduction of RVID and elevation of RVAW caused by hypoxia (see Figure 11B and Figure 11C), indicating that compound 1 could potentially improve pathological ventricular remodeling.

Second, it was found that the ratio of PAT/PET of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 13) two weeks after hypoxic treatment, indicating that the mice from hypoxia group had reduced right heart function. However, oral administration of compound 1 for one week effectively improved right heart dysfunction caused by hypoxia (see Figure 13).

Third, it was found that the ratio of TVE/TVA (i.e., TV E/A) of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 15) two weeks after hypoxic treatment, indicating that the mice from hypoxia group had reduced right heart function. However, oral administration of compound 1 for one week effectively improved right heart dysfunction caused by hypoxia (see Figure 15).

Fourth, it was found that the RVSP of the mice from hypoxia group was significantly higher than that of normoxia group (see Figure 17A) four weeks after hypoxic treatment. Besides, the RVHI of mice from hypoxia group was significantly elevated (see Figure 17B). However, oral administration of compound 1 for three weeks effectively reduced the RVSP and RVHI values

(see Figure 17A and Figure 17B). The above results confirmed that compound 1 can potentially alleviate pulmonary artery hypertension and right heart remodeling induced by hypoxia.

Fifth, it was found that the right ventricular internal dimension (RVID) of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 19A), and that the right ventricular anterior wall (RVAW) thickness of the mice from hypoxia group was significantly higher than that of normoxia group (See Figure 19B) four weeks after hypoxic treatment. However, oral administration of compound 1 for three weeks effectively alleviated the reduction of RVID and elevation of RVAW caused by hypoxia (see Figure 19A and Figure 19B), further confirming that compound 1 could potentially improve pathological ventricular remodeling.

Six, it was found that the ratio of PAT/PET of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 21) four weeks after hypoxic treatment, indicating that the mice from hypoxia group had reduced right heart function. However, oral administration of compound 1 for three weeks effectively improved right heart dysfunction caused by hypoxia (see Figure 21).

Lastly, it was found that the ratio of TVE/TVA (i.e., TV E/A) of the mice from hypoxia group was significantly lower than that of normoxia group (see Figure 23) four weeks after hypoxic treatment, indicating that the mice from hypoxia group had reduced right heart function. However, oral administration of compound 1 for three weeks effectively improved right heart dysfunction caused by hypoxia (see Figure 23).

To sum up, the above results demonstrated that compound 1 significantly inhibited right ventricular remodeling and elevation of pulmonary artery pressure. It is therefore indicated that compound 1 is a promising agent for the prevention or treatment of PAH.

Example 42: *In vitro* GRK2 degradation assay (Part II)

In this example, the degradative effects of additional compounds disclosed herein on GRK2 were investigated using the same *in vitro* hypoxic model as mentioned above in Example 40. Briefly, the hypoxic model was established by treating primary human pulmonary artery smooth muscle cells (h-PASMCs, purchased from iCell Bioscience, Inc. (shanghai)) under hypoxic condition (oxygen content: 3%) for 24 hours. Afterwards, a Western blotting assay was used to observe the change in the expression level of GRK2 relative to that of β -actin. Meanwhile, the degradative effects of various tested additional compounds on GRK2 in h-PASMCs induced under hypoxic condition were similarly investigated. Again, MG132 was administrated to h-PASMCs alone or in combination with various tested additional compounds under the same experimental conditions to validate the mechanisms of the degradative effects of these tested additional compounds on GRK2.

1. Hypoxic Treatment of h-PASMCs and Stimulation of the Same with tested Compounds

The h-PASMCs were treated under hypoxic conditions (oxygen content: 3%) and then stimulated with indicated concentrations of various tested compounds (compounds 2, 3, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 33, 34, 35, 37, 1-P1 and 1-P2), MG132 (1 μ M) or the combination thereof (1 μ M MG132 plus 20 μ M of compounds 2, 3, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 33, 34, 35 and 37) for 24 hours, respectively.

2. Extraction of Cellular Proteins from h-PASMCs

After hypoxic treatment of h-PASMCs, an appropriate amount of cell lysis buffer was added to the cells, then the proteins released therefrom were scraped with a cell scraper, put into a pre-cooled 1.5 mL centrifuge tube (EP tube), and placed onto ice to continue lysing for 30 min. The EP tube was transferred to a low-temperature high-speed centrifuge, centrifuged at 12000 rpm at 4°C for 15 min. The supernatant obtained by centrifugation was the whole protein extract of h-PASMCs, which was drawn into a new pre-cooled centrifuge tube. A BCA working solution was prepared according to the number of samples to be tested. The samples to be tested and the protein standard were prepared in turn, then transferred to a 37°C incubator and incubated for 30 minutes. After taking out, they were subject to Vortex. The concentrations of the protein standard in each group were measured, and a standard curve was plotted according to the results of the measurements. The protein concentrations corresponding to the measured samples were measured according to the standard curve, and the proteins were aliquoted according to the loading amounts.

3. Electrophoretic Separation and Imaging of the Proteins

The proteins obtained from the previous step were separated by electrophoresis in 10% Precast-gel (SDS - PAGE gel), then transferred to a PVDF membrane, and then blocked with bovine serum albumin (BSA) at room temperature for 1 hour. A GRK2 primary antibody (purchased from Santa Cruz Biotechnology, Inc.) was added, then the membrane was cultured overnight at 4°C. On the next day, a GRK2 secondary antibody (purchased from Santa Cruz Biotechnology, Inc.) was added, then the membrane was cultured at room temperature for 2 hours. An imaging system was used to detect the resulting signals.

4. Results and Discussion

The images of Figures 24-41 further indicated that compounds 2, 3, 20, 21, 22, 23, 25, 26, 27, 28, 29, 30, 33, 34, 35, 37, 1-P1 and 1-P2 are potent GRK2 degraders as well. In brief, the expression of β -actin in h-PASMCs remained almost constant under various treatment conditions. In contract, the expression of GRK2 protein in h-PASMCs was significantly triggered under the hypoxic condition. Like the results observed for compound 1, treatment with each of these tested additional compounds resulted in the reduction of the expression level of GRK2 in hypoxically treated h-PASMCs.

OTHER EMBODIMENTS

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (1):

GBM-DT

(1)

or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof;

wherein:

GBM is a GRK2 binding moiety; and

DT is a degradation tag having E3 ligase binding capacity.

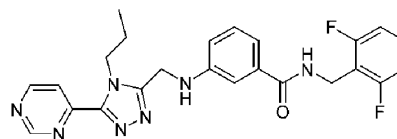
2. The compound according to claim 1, wherein the GBM is a moiety derived from polyanionic and polycationic compounds.

3. The compound according to claim 2, wherein the polyanionic and polycationic compounds is selected from heparin and dextran sulfate.

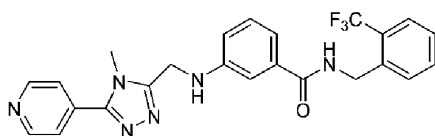
4. The compound according to claim 1, wherein the GBM is a moiety derived from balanol, or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

5. The compound according to claim 1, wherein the GBM is a moiety derived from

Takeda inhibitors selected from

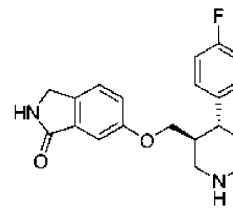
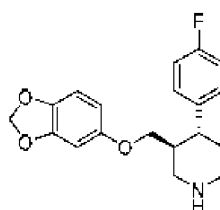


and

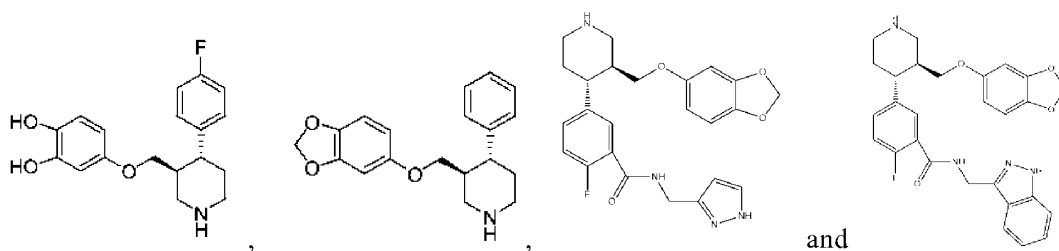


, or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

6. The compound according to claim 1, wherein the GBM is a moiety derived from

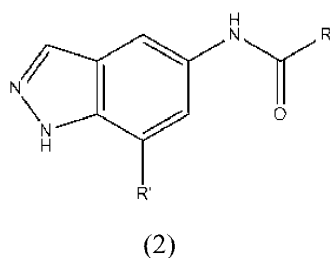


paroxetine series selected from



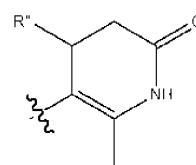
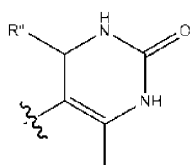
, or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof.

7. The compound according to claim 1, wherein the GBM is a moiety derived from indazole or dihydropyrimidine series represented by Formula (2), or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof

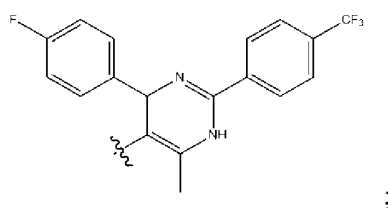


wherein

R is selected from



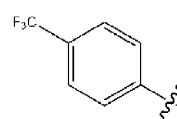
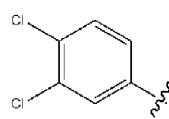
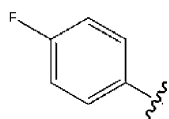
and



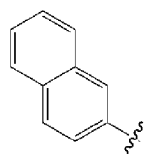
;

R' is selected from H and halogen; and

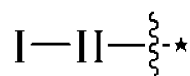
R'' is selected from



and



8. The compound according to claim 1, wherein the GBM is represented by Formula (3):



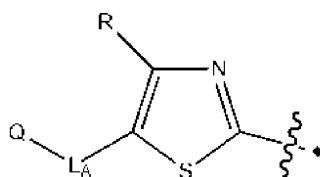
(3)

wherein $\star$ denotes the point of attachment with the DT;

the Formula I is a moiety covalently linked to the Formula II, wherein the Formula I comprises a thiazole ring or triazole ring in its backbone and is capable of binding to GRK2 by itself or along with the Formula II; and

the Formula II is a moiety covalently linked to both the Formula I and the DT, wherein the Formula II comprises an acyclic or cyclic saturated or unsaturated carbon, ethylene glycol group, amide group, ester group, amino group, oxy group, thio group, ether group, urea group, carbamate group, aromatic group, heteroaromatic group, heterocyclic group, carbonyl group or the combination thereof.

9. The compound according to claim 8, wherein the Formula I is represented by Formula (4):



(4)

wherein:

◆ denotes the point of attachment with the Formula II;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally

substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that a + b ≤ 5; and

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

10. The compound according to claim 9, wherein Q is selected from optionally substituted C₁₋₆ alkyl, -OR_a, -SR_a, -NR_bR_c and Cy.

11. The compound according to claim 9, wherein Q is selected from C₁₋₆ alkyl, -SR_a, and Cy.

12. The compound according to claim 9, wherein Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

13. The compound according to claim 9, wherein Q is selected from isopropyl, isopropylthio and Cy.

14. The compound according to claim 9, wherein Q is Cy.

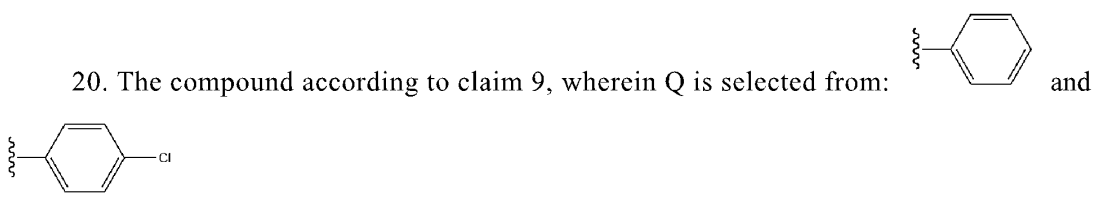
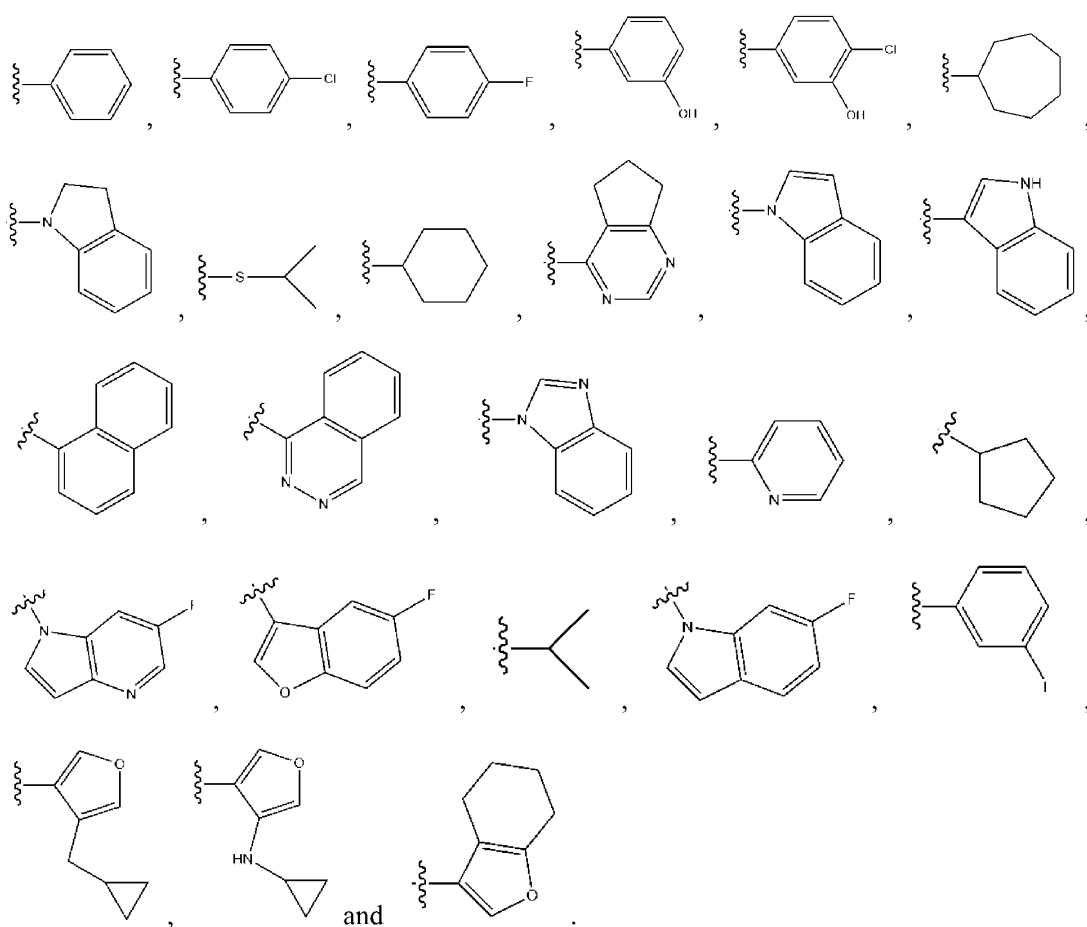
15. The compound according to claim 9, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

16. The compound according to claim 9, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranal, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

17. The compound according to claim 9, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

18. The compound according to claim 9, wherein Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.

19. The compound according to claim 9, wherein Q is selected from:



21. The compound according to claim 9, wherein L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

22. The compound according to claim 9, wherein L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

23. The compound according to claim 9, wherein L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

24. The compound according to claim 9, wherein L_A is $-CH_2-$.

25. The compound according to claim 9, wherein R is selected from H, halogen, $-CN$, $-NO_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

26. The compound according to claim 9, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

27. The compound according to claim 9, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

28. The compound according to claim 9, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

29. The compound according to claim 9, wherein R is selected from H and -OH.

30. The compound according to claim 9, wherein R is H.

31. The compound according to claim 9, wherein each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C_{1-C6} alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

32. The compound according to claim 9, wherein each of R₁ and R₂ is independently selected from H, halogen, C_{1-C6} alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

33. The compound according to claim 9, wherein each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

34. The compound according to claim 9, wherein each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

35. The compound according to claim 9, wherein each of R₁ and R₂ is independently selected from H and F.

36. The compound according to claim 9, wherein both of R₁ and R₂ are H.

37. The compound according to claim 9, wherein both of R₁ and R₂ are F.

38. The compound according to claim 9, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

39. The compound according to claim 9, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

40. The compound according to claim 9, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

41. The compound according to claim 9, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

42. The compound according to claim 9, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

43. The compound according to claim 9, wherein R' is Cl.

44. The compound according to claim 9, wherein each R_a is independently selected from H and C₁₋₆alkyl.

45. The compound according to claim 9, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

46. The compound according to claim 9, wherein each R_a is independently H or isopropyl.

47. The compound according to claim 9, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

48. The compound according to claim 9, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

49. The compound according to claim 9, wherein R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

50. The compound according to claim 9, wherein each R_d is independently selected from H and C₁₋₆alkyl.

51. The compound according to claim 9, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

52. The compound according to claim 9, wherein each R_d is independently H or methyl.

53. The compound according to claim 9, wherein a is selected from 0 and 1 and b is selected from 0 and 1.

54. The compound according to claim 9, wherein a is 0 and b is 0.

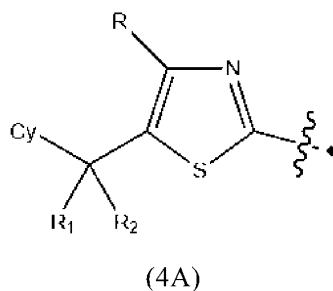
55. The compound according to claim 9, wherein the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical

group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

56. The compound according to claim 9, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

57. The compound according to claim 9, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

58. The compound according to claim 8, wherein the Formula I is represented by Formula (4A):



wherein:

◆ denotes the point of attachment with the Formula II;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted

C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; and

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

59. The compound according to claim 58, wherein each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

60. The compound according to claim 58, wherein each of R₁ and R₂ is independently selected from H, halogen, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

61. The compound according to claim 58, wherein each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally

substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

62. The compound according to claim 58, wherein each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

63. The compound according to claim 58, wherein each of R₁ and R₂ is independently selected from H and F.

64. The compound according to claim 58, wherein both of R₁ and R₂ are H.

65. The compound according to claim 58, wherein R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

66. The compound according to claim 58, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

67. The compound according to claim 58, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

68. The compound according to claim 58, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

69. The compound according to claim 58, wherein R is selected from H and -OH.

70. The compound according to claim 58, wherein R is H.

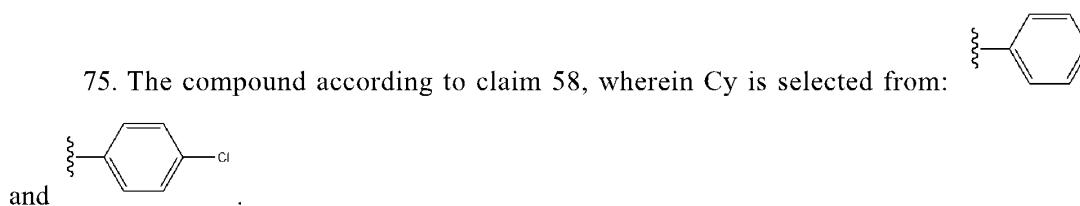
71. The compound according to claim 58, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

72. The compound according to claim 58, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl,

benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

73. The compound according to claim 58, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

74. The compound according to claim 58, wherein Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.



76. The compound according to claim 58, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

77. The compound according to claim 58, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

78. The compound according to claim 58, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

79. The compound according to claim 58, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

80. The compound according to claim 58, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

81. The compound according to claim 58, wherein R' is Cl.

82. The compound according to claim 58, wherein each R_a is independently selected from H and C₁₋₆alkyl.

83. The compound according to claim 58, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

84. The compound according to claim 58, wherein each of R_b and R_c is independently selected from H, C_{1-6} alkyl and C_{3-6} cycloalkyl.

85. The compound according to claim 58, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

86. The compound according to claim 58, wherein each R_d is independently selected from H and C_{1-6} alkyl.

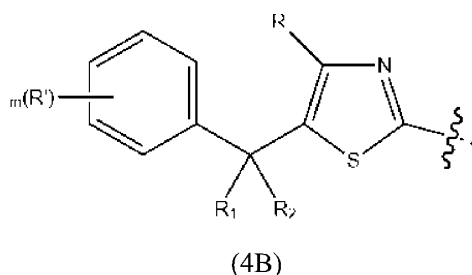
87. The compound according to claim 58, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

88. The compound according to claim 58, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl, -OH, -NH₂, -NO₂, -CN and C_{3-6} cycloalkyl.

89. The compound according to claim 58, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

90. The compound according to claim 58, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

91. The compound according to claim 58, wherein the Formula I is represented by Formula (4B):



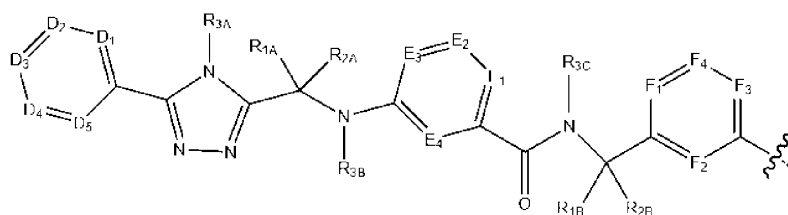
wherein

m is selected from 0, 1, 2, 3, 4 and 5.

92. The compound according to claim 91, wherein m is selected from 0, 1 and 2.

93. The compound according to claim 91, wherein m is 0 or 1.

94. The compound according to claim 8, wherein the Formula I is represented by Formula (5):



(5)

wherein:

◆ denotes the point of attachment with the Formula II;

each of R_{1A} , R_{2A} , R_{1B} and R_{2B} is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-C(=O)NR_bR_c$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-S(=O)_2NR_bR_c$, optionally substituted C_{3-6} carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R_{1A} and R_{2A} or R_{1B} and R_{2B} may be taken together along with the atom to which they are attached to form an optionally substituted C_{3-12} carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

each of R_{3A} , R_{3B} and R_{3C} is independently selected from H, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-C(=O)R_a$, $-C(=S)R_a$, $-C(=O)OR_a$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-C(=O)NR_bR_c$, $-S(=O)NR_bR_c$, $-S(=O)_2NR_bR_c$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of D_1 , D_2 , D_3 , D_4 and D_5 is independently N or CR_{4A} ;

each of E_1 , E_2 , E_3 and E_4 is independently N or CR_{4B} ;

each of F_1 , F_2 , F_3 and F_4 is independently N or CR_{4C} ;

each of R_{4A} , R_{4B} and R_{4C} is independently selected from H, halogen, $-CN$, $-N(=O)$, $-NO_2$, $-ON(=O)$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-C(=O)R_a$, $-C(=S)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-SR_a$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-NR_bR_c$, $-C(=O)NR_bR_c$, $-S(=O)NR_bR_c$, $-S(=O)_2NR_bR_c$, $-NR_dC(=O)R_a$, $-NR_dC(=O)OR_a$, $-NR_dC(=O)NR_bR_c$, $-NR_dS(=O)R_a$, $-NR_dS(=O)_2R_a$, $-NR_dS(=O)NR_bR_c$, $-NR_dS(=O)_2NR_bR_c$, $-SN(=O)$, $-NR_dN(=O)$, optionally

substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

95. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

96. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H, halogen, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

97. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

98. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

99. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently selected from H and F.

100. The compound according to claim 94, wherein each of R_{1A}, R_{2A}, R_{1B} and R_{2B} is independently H.

101. The compound according to claim 94, wherein each of R_{3A}, R_{3B} and R_{3C} is independently selected from H, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl and optionally substituted C₂₋₆ alkynyl.

102. The compound according to claim 94, wherein each of R_{3A}, R_{3B} and R_{3C} is independently selected from H, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen and C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen.

103. The compound according to claim 94, wherein each of R_{3A}, R_{3B} and R_{3C} is independently selected from H, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen and propyl optionally substituted by 1, 2 or 3 halogen.

104. The compound according to claim 94, wherein each of R_{3A}, R_{3B} and R_{3C} is independently selected from H, methyl, ethyl and propyl.

105. The compound according to claim 94, wherein each of R_{3A}, R_{3B} and R_{3C} is independently selected from H.

106. The compound according to claim 94, wherein at least one of D₁, D₂, D₃, D₄ and D₅ is N, and the others are CR_A.

107. The compound according to claim 94, wherein one of D₁, D₂, D₃, D₄ and D₅ is N, and the others are CR_A.

108. The compound according to claim 94, wherein D₃ is N, and the others are CR_{4A}.

109. The compound according to claim 94, wherein each of E₁, E₂, E₃ and E₄ is independently CR_{4B}.

110. The compound according to claim 94, wherein each of F₁, F₂, F₃ and F₄ is independently CR_{4C}.

111. The compound according to claim 94, wherein each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

112. The compound according to claim 94, wherein each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

113. The compound according to claim 94, wherein each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or

3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

114. The compound according to claim 94, wherein each of R_{4A}, R_{4B} and R_{4C} is independently selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

115. The compound according to claim 94, wherein each of R_{4A}, R_{4B} and R_{4C} is independently H.

116. The compound according to claim 94, wherein each R_a is independently selected from H and C₁₋₆alkyl.

117. The compound according to claim 94, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

118. The compound according to claim 94, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

119. The compound according to claim 94, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

120. The compound according to claim 94, wherein each R_d is independently selected from H and C₁₋₆alkyl.

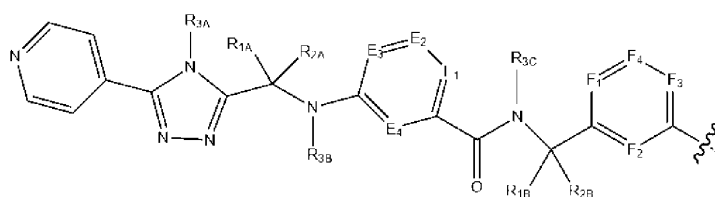
121. The compound according to claim 94, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

122. The compound according to claim 94, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

123. The compound according to claim 94, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

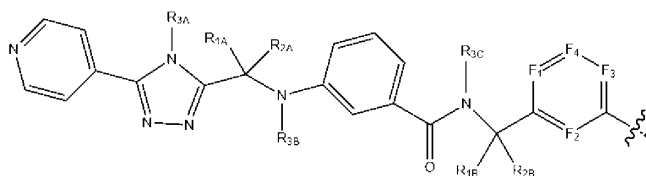
124. The compound according to claim 94, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

125. The compound according to claim 94, wherein the Formula I is represented by Formula (5A):



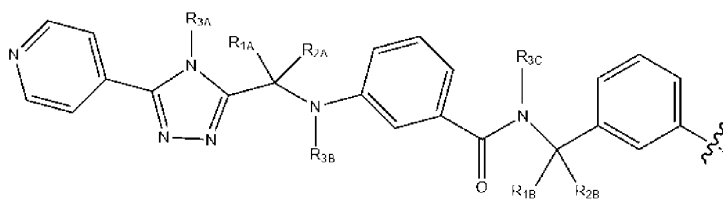
(5A)

126. The compound according to claim 94, wherein the Formula I is represented by Formula (5B):



(5B)

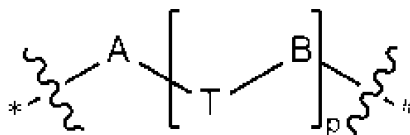
127. The compound according to claim 94, wherein the Formula I is represented by Formula (5C):



(5C)

128. The compound according to claim 8, wherein the Formula II comprises an amide group or an ester group.

129. The compound according to claim 8, wherein the Formula II is represented by Formula (6):



(6)

wherein

* denotes the point of attachment with the Formula I;

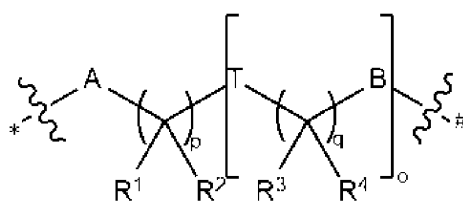
denotes the point of attachment with the DT;

A, T, and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR¹-, -C(=S)NR¹-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR¹-, -NR¹-, -NR¹C(=O)-, -NR¹C(=O)NR²-, -NR¹C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

R¹ and R² are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl; and

p is 0 to 15.

130. The compound according to claim 8, wherein the Formula II is represented by Formula (6A):



(6A)

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

R¹, R², R³, and R⁴, at each occurrence, are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl,

optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

A, T, and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR⁵-, -C(=S)NR⁵-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR⁵-, -NR⁵-, -NR⁵C(=O)-, -NR⁵C(=O)NR⁶-, -NR⁵C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

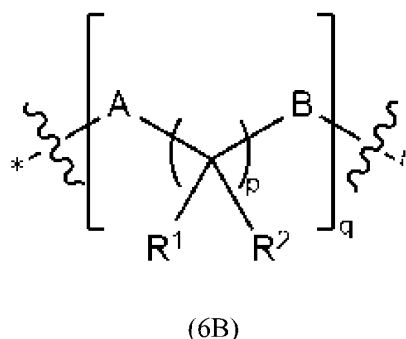
R⁵ and R⁶ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

p is 0 to 15;

each q is 0 to 15; and

o is 0 to 15.

131. The compound according to claim 8, wherein the Formula II is represented by Formula (6B):



wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

each R^1 , and each R^2 are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, and optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, or C₁-C₆alkylaminoC₁-C₆alkyl;

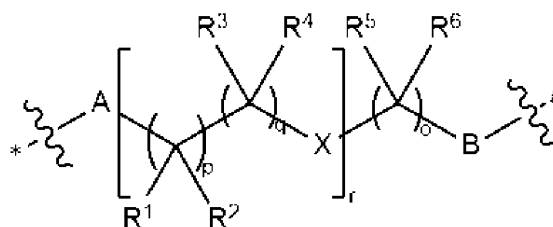
each A and each B are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR³-, -C(=S)NR³-, -O-, -S-, -S(=O)-, -S(=O)₂NR³-, -NR³-, -NR³C(=O)-, -NR³C(=O)NR⁴-, -NR³C(=S)-, and optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, or C₃-C₁₃ spiro heterocyclyl, wherein

R^3 and R^4 are independently selected from hydrogen, and optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, or C₁-C₆alkylaminoC₁-C₆alkyl;

each p is 0 to 15; and

q is 0 to 15.

132. The compound according to claim 8, wherein the Formula II is represented by Formula (6C):



(6C),

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

X is selected from -O-, -NH-, and -NR⁷-;

R¹, R², R³, R⁴, R⁵, and R⁶, at each occurrence, are independently selected from hydrogen, halogen, -CN, -OH, -NH₂, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

A and B, at each occurrence, are independently selected from null, -C(=O)-, -C(=O)O-, -C(=O)NR⁷-, -C(=S)NR⁷-, -O-, -S-, -S(=O)-, -S(=O)₂-, -S(=O)₂NR⁷-, -NR⁷-, -NR⁷C(=O)-, -NR⁷C(=O)NR⁸-, -NR⁷C(=S)-, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈ alkoxy, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₂-C₈ alkenyl, optionally substituted C₂-C₈ alkynyl, optionally substituted C₃-C₈ cycloalkyl, optionally substituted C₃-C₈ cycloalkoxy, optionally substituted 3-8 membered heterocyclyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C₃-C₁₃ fused cycloalkyl, optionally substituted C₃-C₁₃ fused heterocyclyl, optionally substituted C₃-C₁₃ bridged cycloalkyl, optionally substituted C₃-C₁₃ bridged heterocyclyl, optionally substituted C₃-C₁₃ spiro cycloalkyl, and optionally substituted C₃-C₁₃ spiro heterocyclyl, wherein

R⁷ and R⁸ are independently selected from hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₃-C₆ cycloalkyl, optionally substituted C₃-C₆ cycloalkoxy, optionally substituted 3-6 membered heterocyclyl, optionally substituted C₁-C₆ alkoxy, optionally substituted C₁-C₆ alkoxyalkyl, optionally substituted C₁-C₆ haloalkyl, optionally substituted C₁-C₆ hydroxyalkyl, optionally substituted C₁-C₆ alkylamino, and optionally substituted C₁-C₆alkylaminoC₁-C₆alkyl;

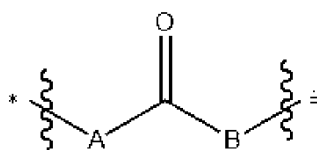
each p is 0 to 15;

each q is 0 to 15;

o is 0 to 15; and

r is 0 to 15.

133. The compound according to claim 8, wherein the Formula II is represented by Formula (7A):



(7A)

wherein * denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

A is selected from C₁₋₂₀alkylene, -O-, -S-, -N(R_c)- and -N(R_c)-C₁₋₂₀alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₂₀alkylene group is independently replaced with a group selected from -O-, -S-, -N(R_c)-, -C(=O)- and -C(=S)-;

B is a bond or is selected from arylene, C₃₋₁₂ carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

R_c is selected from H and optionally substituted C₁₋₆ alkyl; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

134. The compound according to claim 133, wherein A is selected from C₁₋₈alkylene, -O-, -NH-, -N(CH₃)-, -N(C₂H₅)-, -NH-C₁₋₈alkylene, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₈alkylene group is independently replaced with a group selected from -O- and -C(=O)-.

135. The compound according to claim 133, wherein A is selected from -CH₂-, -O-, -NH-, -NH-(CH₂)₃-, -NH-(CH₂)₅- and -NH-C(=O)-(CH₂)₃-O-(CH₂)₃-.

136. The compound according to claim 133, wherein A is selected from -CH₂-, -O- and -NH-.

137. The compound according to claim 133, wherein A is -NH-.

138. The compound according to claim 133, wherein B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

139. The compound according to claim 133, wherein B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolylene, imidazolylene, oxazolylene, isoxazolylene, oxadiazolylene, thiazolylene, isothiazolylene, thiadiazolylene, pyridinylen, pyranylene, pyrazinylen, pyrimidinylen, pyrazinylen, triazolylene, tetrazolylene and triazinylen, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

140. The compound according to claim 133, wherein B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

141. The compound according to claim 133, wherein B is a bond or phenylene.

142. The compound according to claim 133, wherein each R_a is independently selected from H and C₁₋₆alkyl.

143. The compound according to claim 133, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

144. The compound according to claim 133, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

145. The compound according to claim 133, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

146. The compound according to claim 133, wherein R_e is H.

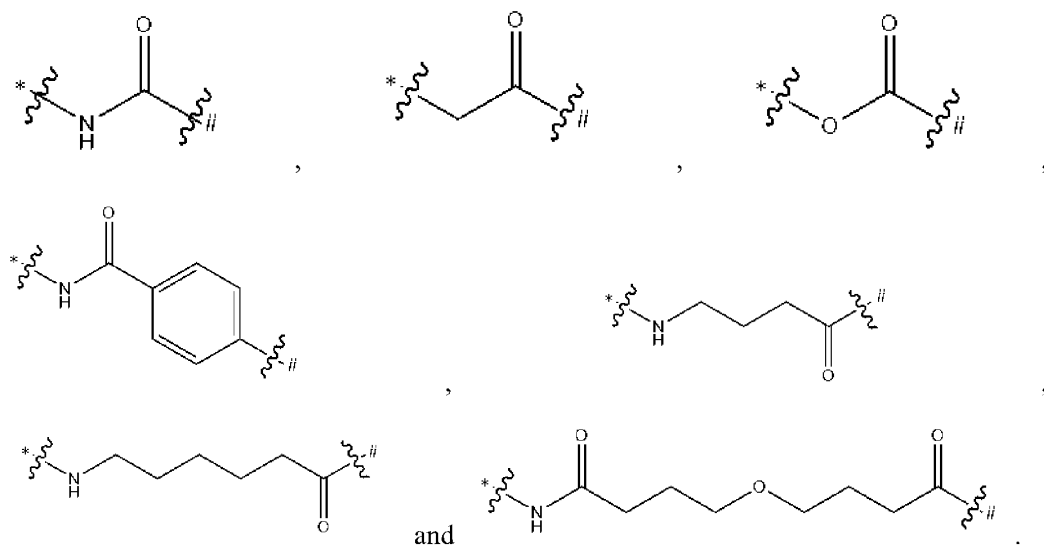
147. The compound according to claim 133, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

148. The compound according to claim 133, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical

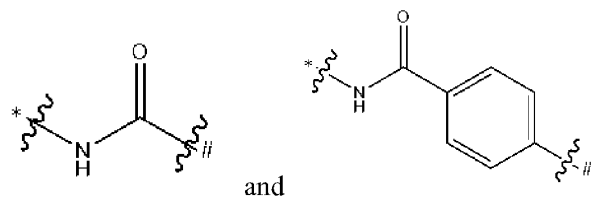
group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

149. The compound according to claim 133, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

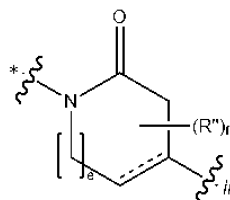
150. The compound according to claim 133, wherein Formula (7A) is a moiety selected from:



151. The compound according to claim 133, wherein Formula (7A) is a moiety selected from:



152. The compound according to claim 8, wherein the Formula II is represented by Formula (7B):



(7B)

wherein

* denotes the point of attachment with the Formula I;

denotes the point of attachment with the DT;

--- is a single bond or a double bond;

R'' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

e is 0 or 1;

f is selected from 0, 1, 2 and 3; and

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

153. The compound according to claim 152, wherein --- is a single bond.

154. The compound according to claim 152, wherein --- is a double bond.

155. The compound according to claim 152, wherein R'' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

156. The compound according to claim 152, wherein R'' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally

substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c.

157. The compound according to claim 152, wherein R'' is selected from halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

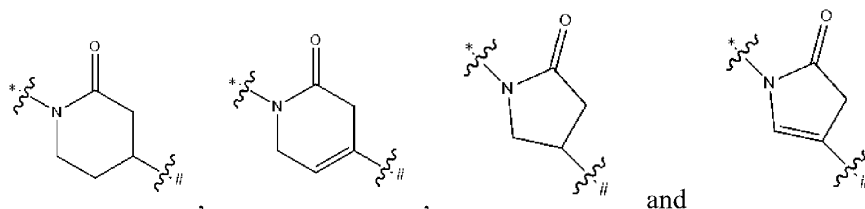
158. The compound according to claim 152, wherein R'' is selected from F, Cl, Br, methyl, ethyl, propyl, -OH and -NH₂.

159. The compound according to claim 152, wherein e is 0.

160. The compound according to claim 152, wherein e is 1.

161. The compound according to claim 152, wherein f is 0.

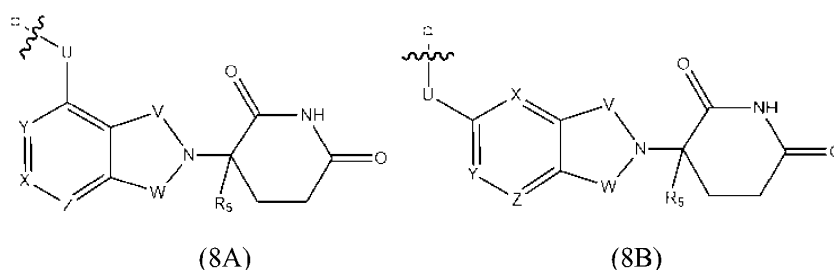
162. The compound according to claim 152, wherein Formula (7B) is a moiety selected from:

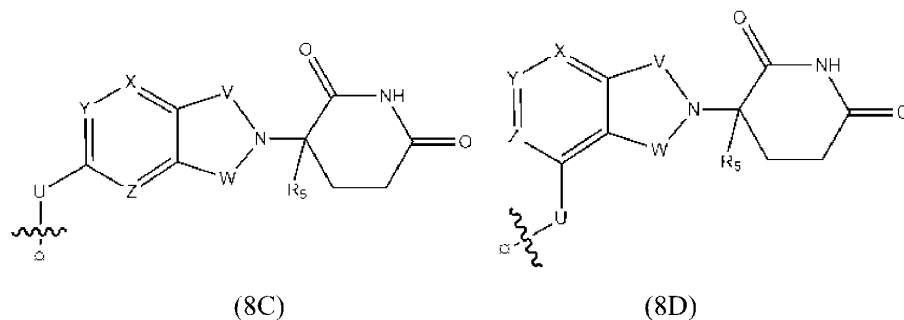


163. The compound according to claim 1, wherein the DT is capable of binding to an E3 ligase for recruitment of the corresponding ubiquitination machinery to GRK2, leading to the subsequent degradation of GRK2 in or near the proteasome and/or loss of function of GRK2.

164. The compound according to claim 1, wherein the DT is selected from the group consisting of cereblon ligands, VHL ligands, MDM2 ligands, TRIM24 ligands, TRIM21 ligands, KEAP1 ligands, RNF114 ligands, IAP ligands, DCAF16 ligands, DCAF15 ligands, FEM1B ligands, and ligands of arylhydrocarbon receptors.

165. The compound according to claim 1, wherein the DT is a moiety represented by Formula (8A), (8B), (8C) or (8D):





wherein,

$\square$ denotes the point of attachment with the Formula II;

U is independently selected from $-\text{CH}_2-$, $-\text{NH}-$ and $-\text{O}-$;

each of V and W is independently selected from $-\text{C}(=\text{O})-$ and $-\text{CH}_2-$;

each of X, Y, and Z is independently selected from CR_6 and N;

R_5 is selected from H, halogen and optionally substituted C_1 - C_6 alkyl; and

R_6 is selected from H, halogen and optionally substituted C_1 - C_6 alkyl.

166. The compound according to claim 165, wherein U is $-\text{CH}_2-$.

167. The compound according to claim 165, wherein U is $-\text{O}-$.

168. The compound according to claim 165, wherein U is $-\text{NH}-$.

169. The compound according to claim 165, wherein V is $-\text{C}(=\text{O})-$ and W is $-\text{CH}_2-$.

170. The compound according to claim 165, wherein V is $-\text{CH}_2-$ and W is $-\text{C}(=\text{O})-$.

171. The compound according to claim 165, wherein both of V and W are $-\text{C}(=\text{O})-$.

172. The compound according to claim 165, wherein each of X, Y, and Z is independently selected from CR_6 .

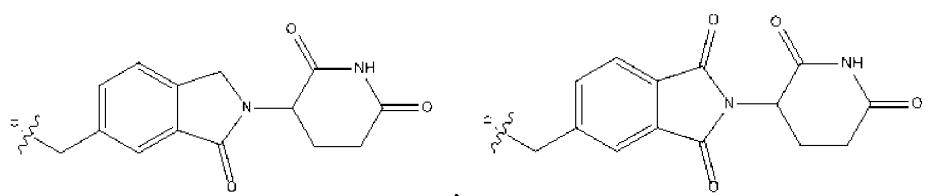
173. The compound according to claim 165, wherein R_5 is selected from H, F, Cl and Br.

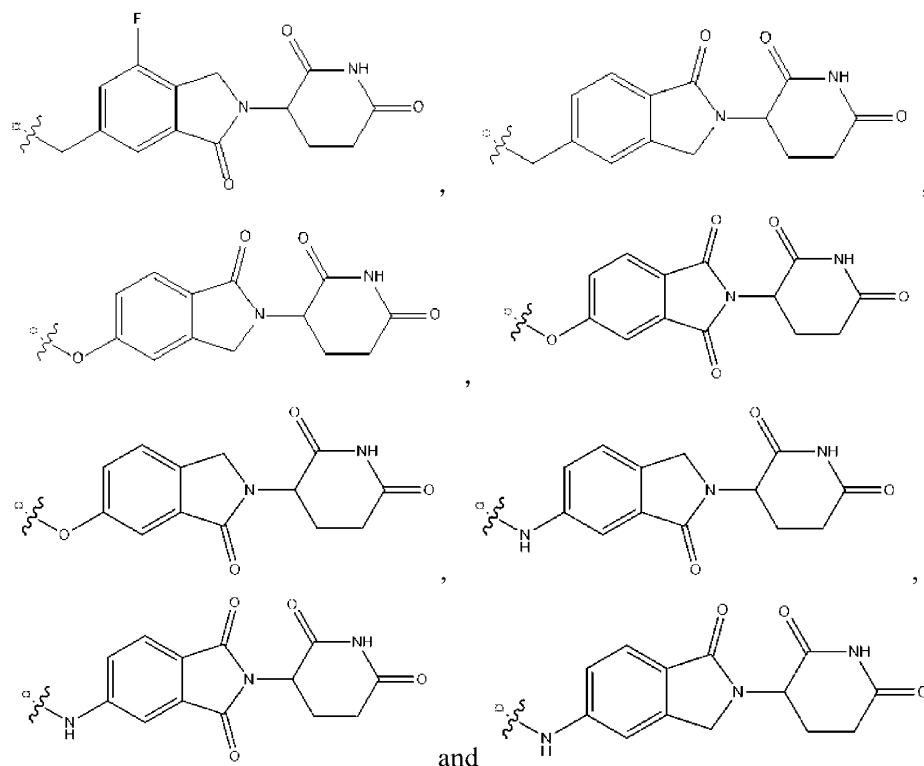
174. The compound according to claim 165, wherein R_5 is H.

175. The compound according to claim 165, wherein R_6 is selected from H, F, Cl and Br.

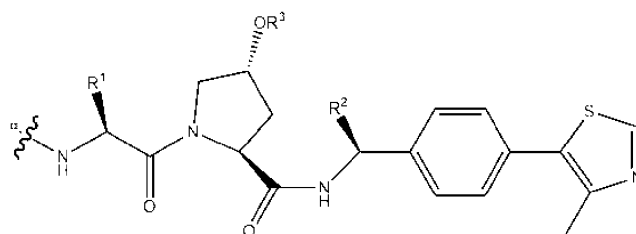
176. The compound according to claim 165, wherein R_6 is H or F.

177. The compound according to claim 165, wherein the DT is a moiety selected from:





178. The compound according to claim 1, wherein the DT is a moiety represented by Formula (9):



(9),

wherein

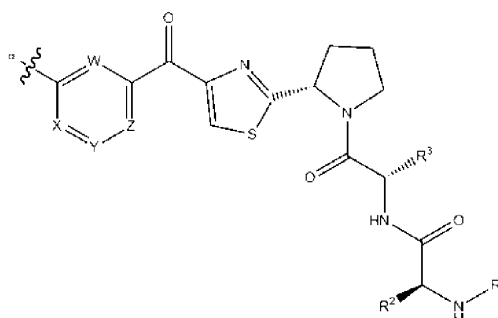
□ denotes the point of attachment with the Formula II;

R^1 and R^2 are independently selected from hydrogen, optionally substituted C_1 - C_8 alkyl, optionally substituted C_1 - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted C_1 - C_8 haloalkyl, optionally substituted C_1 - C_8 hydroxyalkyl, optionally substituted C_1 - C_8 aminoalkyl, optionally substituted C_1 - C_8 alkylamino C_1 - C_8 alkyl, optionally substituted C_3 - C_7 cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C_2 - C_8 alkenyl, and optionally substituted C_2 - C_8 alkynyl;

R^3 is hydrogen, optionally substituted $-C(=O)C_1$ - C_8 alkyl, optionally substituted $-C(=O)C_1$ - C_8 alkoxy C_1 - C_8 alkyl, optionally substituted $-C(=O)C_1$ - C_8 haloalkyl, optionally substituted -

C(=O)C₁-C₈ hydroxyalkyl, optionally substituted -C(=O)C₁-C₈ aminoalkyl, optionally substituted -C(=O)C₁-C₈alkylaminoC₁-C₈alkyl, optionally substituted -C(=O)C₃-C₇ cycloalkyl, optionally substituted -C(=O)(3-7 membered heterocyclyl), optionally substituted -C(=O)C₂-C₈ alkenyl, optionally substituted -C(=O)C₂-C₈ alkynyl, optionally substituted -C(=O)OC₁-C₈alkoxyC₁-C₈alkyl, optionally substituted -C(=O)OC₁-C₈ haloalkyl, optionally substituted -C(=O)OC₁-C₈ hydroxyalkyl, optionally substituted -C(=O)OC₁-C₈ aminoalkyl, optionally substituted -C(=O)OC₁-C₈alkylaminoC₁-C₈alkyl, optionally substituted -C(=O)OC₃-C₇ cycloalkyl, optionally substituted -C(=O)O(3-7 membered heterocyclyl), optionally substituted -C(=O)OC₂-C₈ alkenyl, optionally substituted -C(=O)OC₂-C₈ alkynyl, optionally substituted -C(=O)NC₁-C₈alkoxyC₁-C₈alkyl, optionally substituted -C(=O)NC₁-C₈ haloalkyl, optionally substituted -C(=O)NC₁-C₈ hydroxyalkyl, optionally substituted -C(=O)NC₁-C₈ aminoalkyl, optionally substituted -C(=O)NC₁-C₈alkylaminoC₁-C₈alkyl, optionally substituted -C(=O)NC₃-C₇ cycloalkyl, optionally substituted -C(=O)N(3-7 membered heterocyclyl), optionally substituted -C(=O)NC₂-C₈ alkenyl, optionally substituted -C(=O)NC₂-C₈ alkynyl, optionally substituted -P(=O)(OH)₂, optionally substituted -P(=O)(OC₁-C₈ alkyl)₂, and optionally substituted -P(=O)(OC₁-C₈ aryl)₂.

179. The compound according to claim 1, wherein the DT is a moiety represented by Formula (10):



(10),

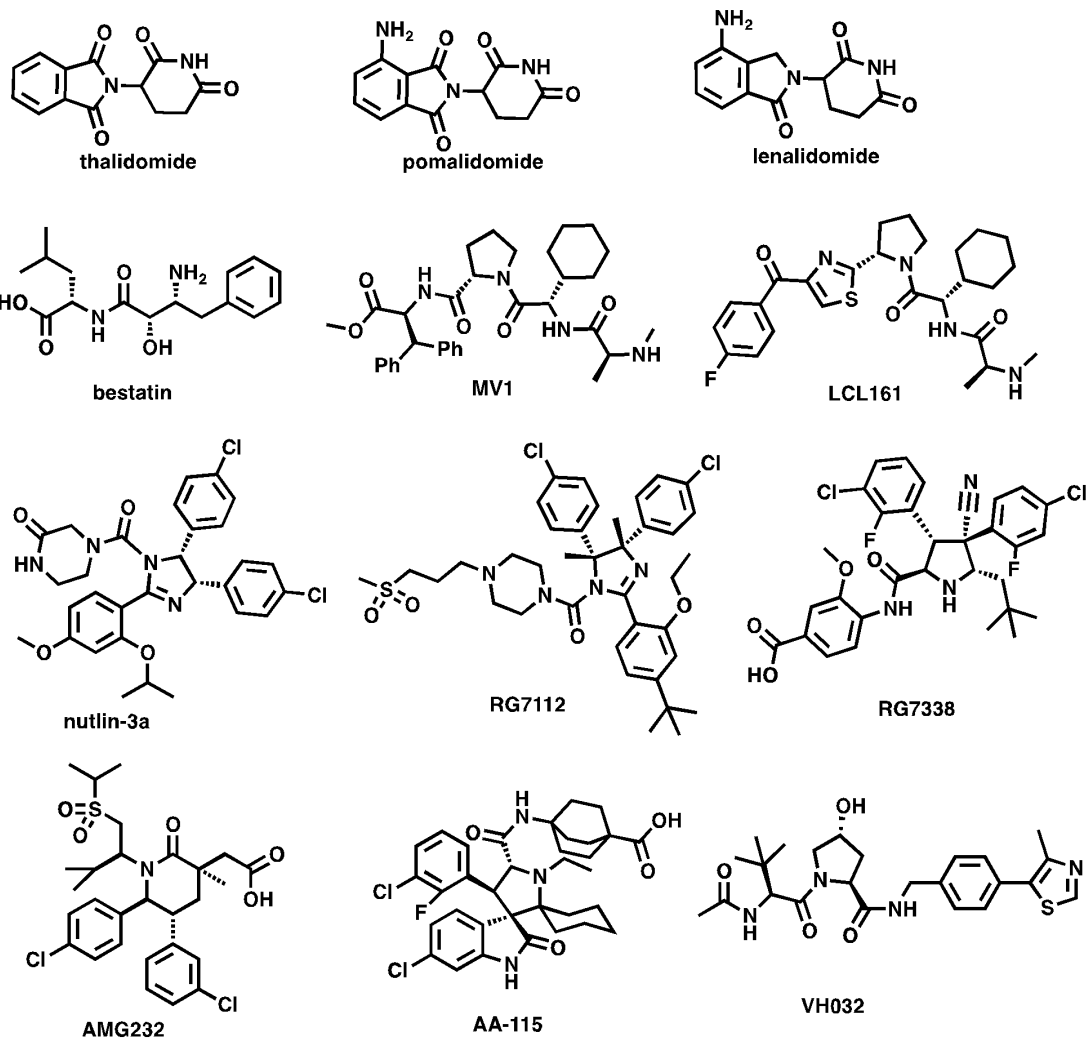
wherein

⧻ denotes the point of attachment with the Formula II;

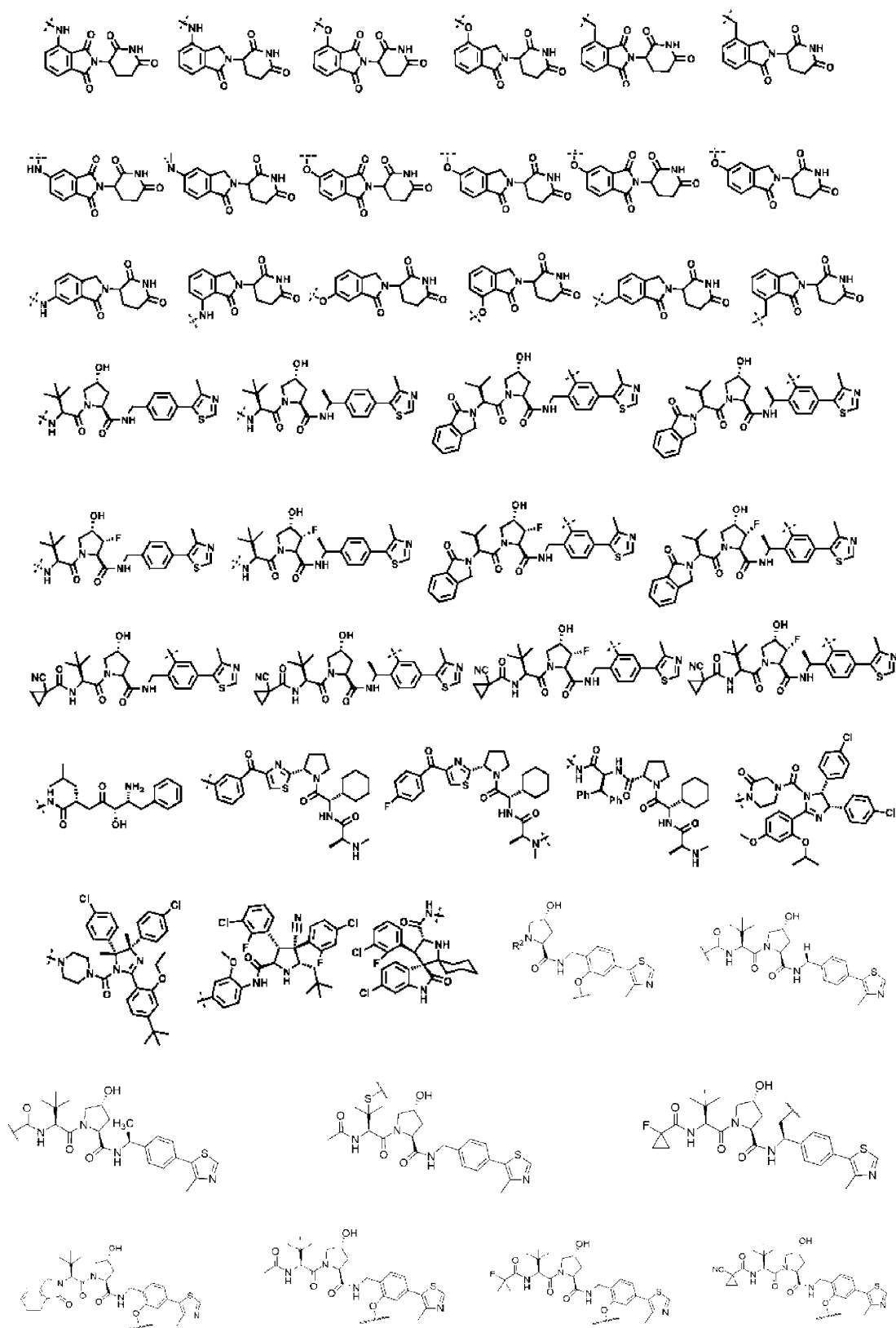
V, W, X, and Z are independently selected from CR⁴ and N;

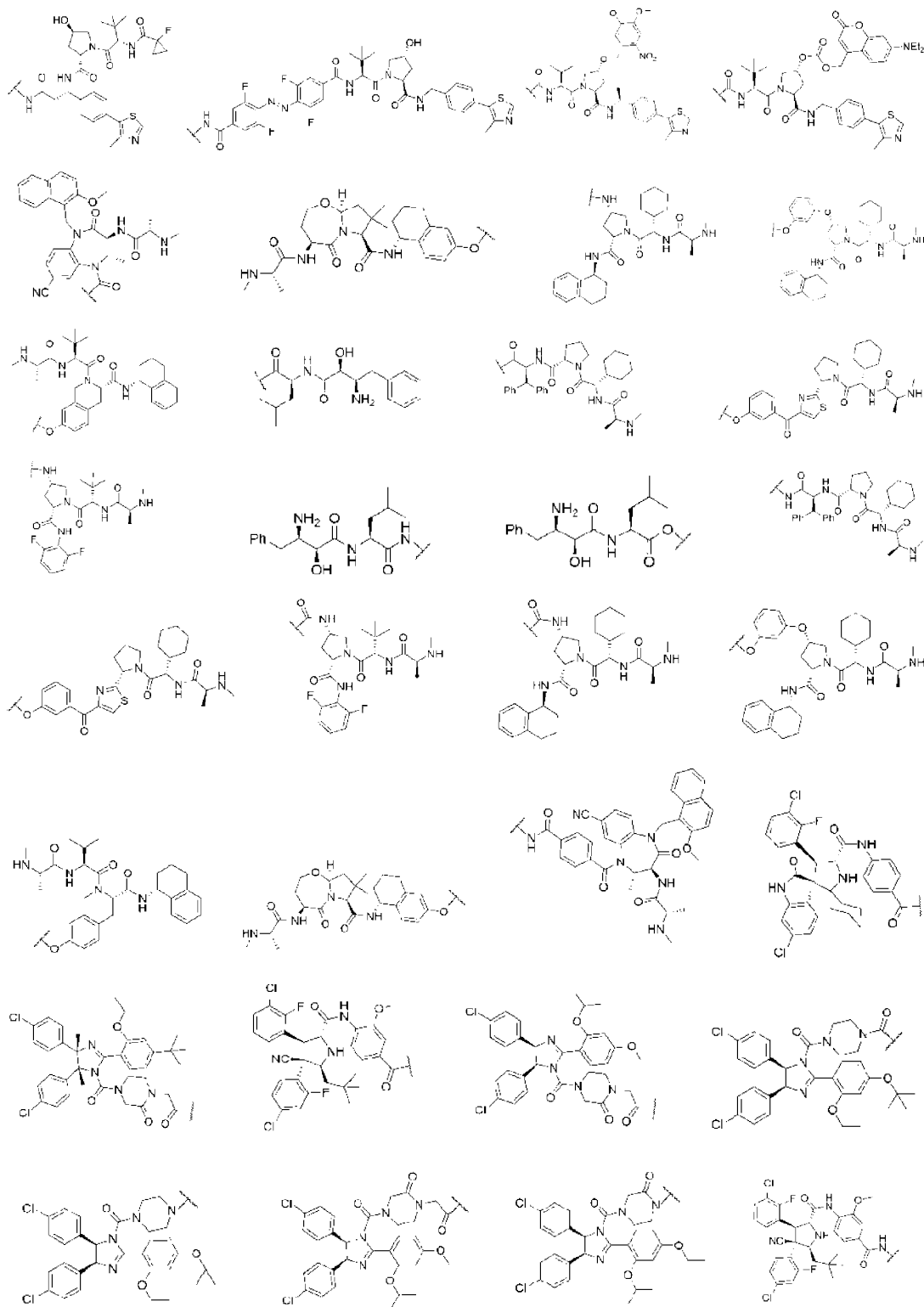
R¹, R², R³, and R⁴ are independently selected from hydrogen, optionally substituted C₁-C₈ alkyl, optionally substituted C₁-C₈alkoxyC₁-C₈alkyl, optionally substituted C₁-C₈ haloalkyl, optionally substituted C₁-C₈ hydroxyalkyl, optionally substituted C₃-C₇ cycloalkyl, optionally substituted 3-7 membered heterocyclyl, optionally substituted C₂-C₈ alkenyl, and optionally substituted C₂-C₈ alkynyl.

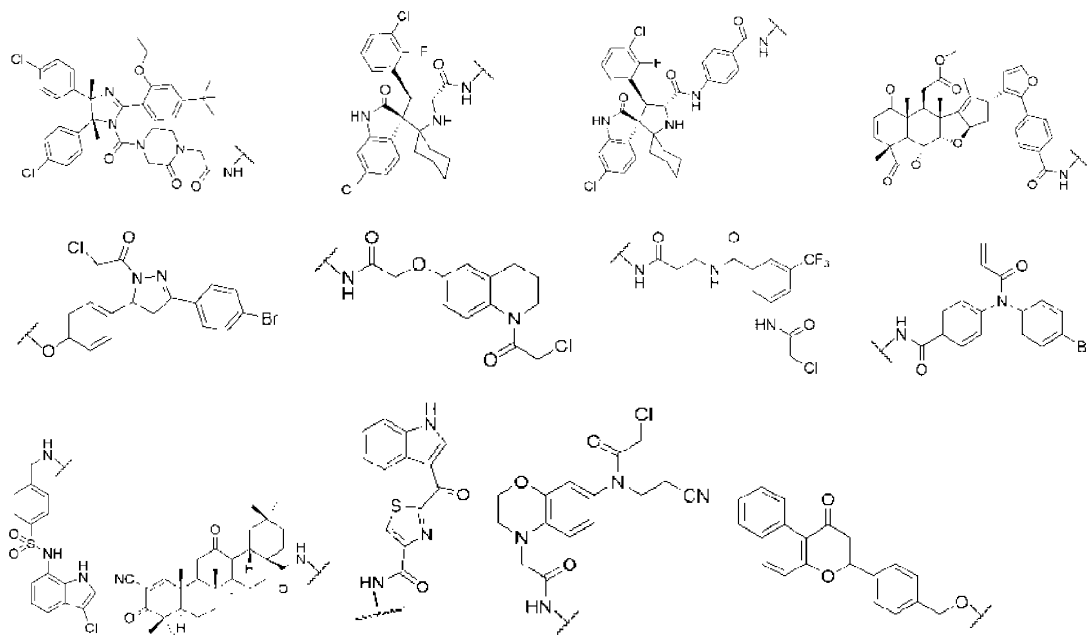
180. The compound according to claim 1, wherein the DT is a moiety derived from any of the following:



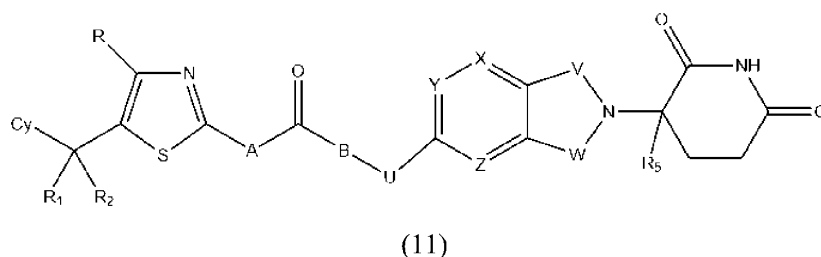
181. The compound according to claim 1, wherein the DT is selected from the group consisting of:







182. The compound according to claim 1, wherein the compound is represented by Formula (11)



wherein:

A is selected from C_{1-20} alkylene, -O-, -S-, -N(R_e)- and -N(R_e)- C_{1-20} alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C_{1-20} alkylene group is independently replaced with a group selected from -O-, -S-, -N(R_e)-, -C(=O)- and -C(=S)-;

B is a bond or is selected from arylene, C_{3-12} carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c;

U is independently selected from -CH₂-, -NH- and -O-;

each of V and W is independently selected from -C(=O)- and -CH₂-;

each of X, Y, and Z is independently selected from CR₆ and N;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R₅ is selected from H, halogen and optionally substituted C₁-C₆ alkyl;

R₆ is selected from H, halogen and optionally substituted C₁-C₆ alkyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆ cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆ cycloalkyl;

R_c is selected from H and optionally substituted C_{1-6} alkyl; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl.

183. The compound according to claim 182, wherein A is selected from C_{1-8} alkylene, $-O-$, $-NH-$, $-N(CH_3)-$, $-N(C_2H_5)-$, $-NH-C_{1-8}$ alkylene, and optionally wherein 1, 2, 3 or more methylene in the C_{1-8} alkylene group is independently replaced with a group selected from $-O-$ and $-C(=O)-$.

184. The compound according to claim 182, wherein A is selected from $-CH_2-$, $-O-$, $-NH-$, $-NH-(CH_2)_3-$, $-NH-(CH_2)_5-$ and $-NH-C(=O)-(CH_2)_3-O-(CH_2)_3-$.

185. The compound according to claim 182, wherein A is selected from $-CH_2-$, $-O-$ and $-NH-$.

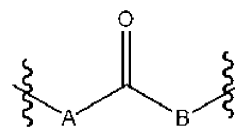
186. The compound according to claim 182, wherein A is $-NH-$.

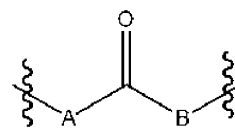
187. The compound according to claim 182, wherein B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, $-CN$, $-NO_2$, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

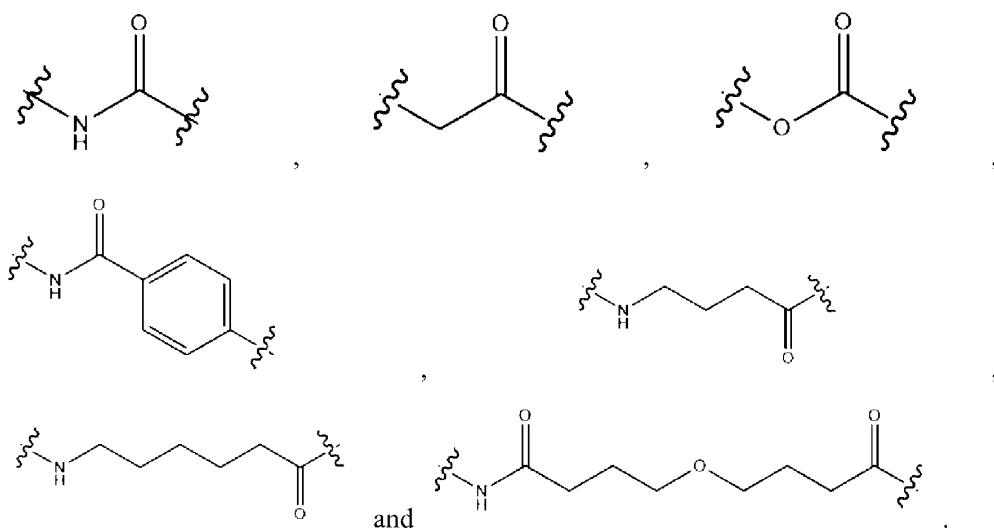
188. The compound according to claim 182, wherein B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolyene, imidazolyene, oxazolyene, isoxazolyene, oxadiazolyene, thiazolyene, isothiazolyene, thiadiazolyene, pyridinyne, pyranlyne, pyrazinyne, pyrimidinyne, pyrazinyne, triazolyene, tetrazolyene and triazinyne, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

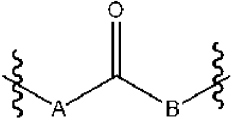
189. The compound according to claim 182, wherein B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

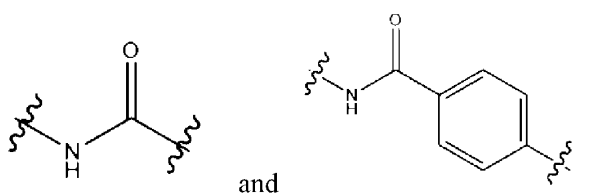
190. The compound according to claim 182, wherein B is a bond or phenylene.



191. The compound according to claim 182, wherein  is a moiety selected from:



192. The compound according to claim 182, wherein  is a moiety selected from:



193. The compound according to claim 182, wherein U is -CH₂-.

194. The compound according to claim 182, wherein U is -O-.

195. The compound according to claim 182, wherein U is -NH-.

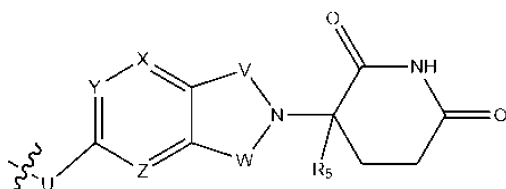
196. The compound according to claim 182, wherein V is -C(=O)- and W is -CH₂-.

197. The compound according to claim 182, wherein V is -CH₂- and W is -C(=O)-.

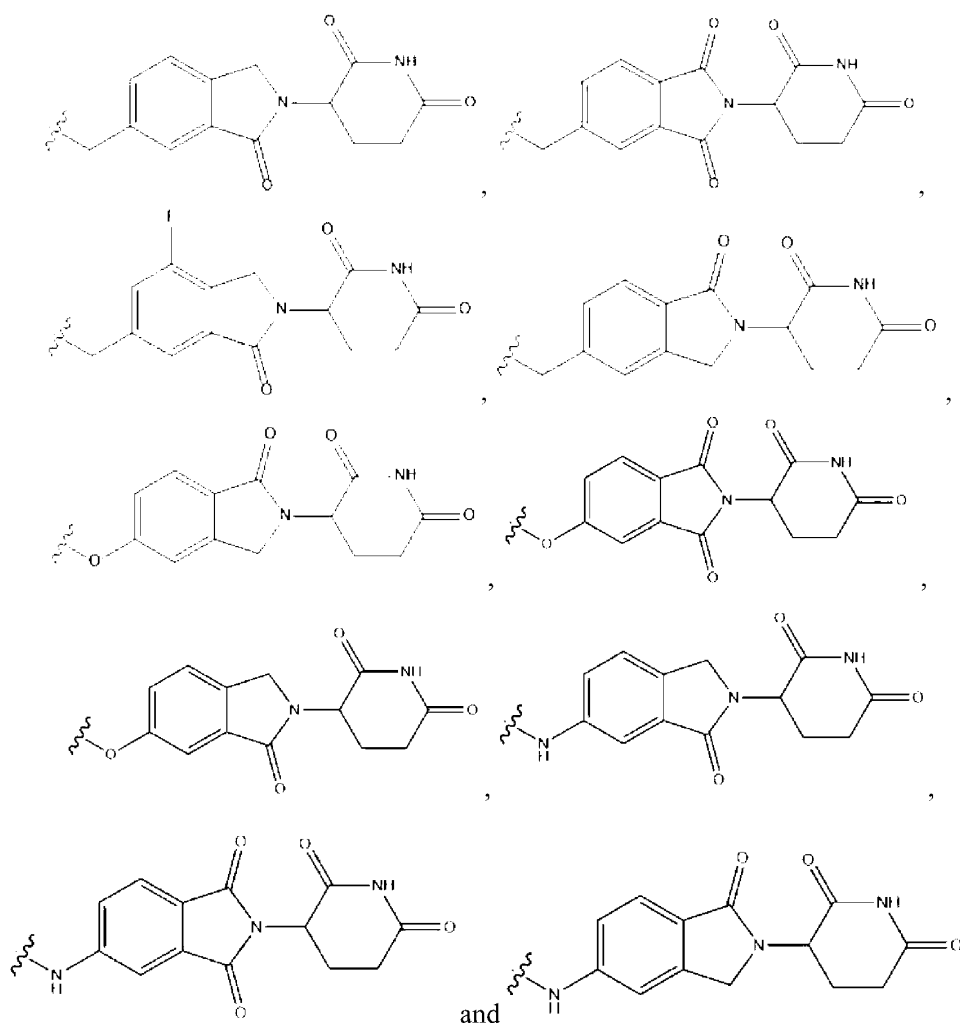
198. The compound according to claim 182, wherein both of V and W are -C(=O)-.

199. The compound according to claim 182, wherein each of X, Y, and Z is independently selected from CR₆.

200. The compound according to claim 182, wherein



is a moiety selected from:



201. The compound according to claim 182, wherein each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

202. The compound according to claim 182, wherein each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

203. The compound according to claim 182, wherein each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

204. The compound according to claim 182, wherein each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

205. The compound according to claim 182, wherein each of R₁ and R₂ is independently selected from H and F.

206. The compound according to claim 182, wherein both of R₁ and R₂ are H.

207. The compound according to claim 182, wherein R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

208. The compound according to claim 182, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

209. The compound according to claim 182, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

210. The compound according to claim 182, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

211. The compound according to claim 182, wherein R is selected from H and -OH.

212. The compound according to claim 182, wherein R is H.

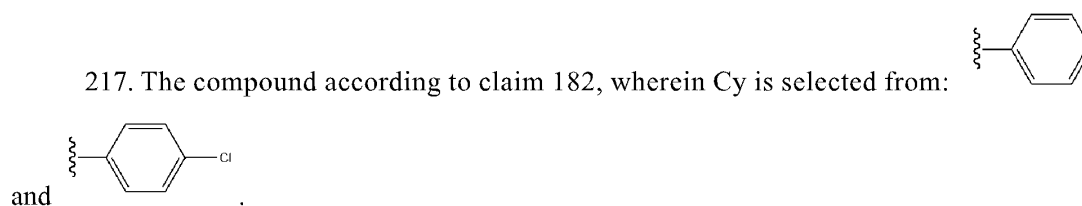
213. The compound according to claim 182, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

214. The compound according to claim 182, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl,

naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

215. The compound according to claim 182, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

216. The compound according to claim 182, wherein Cy is phenyl which is optionally substituted by 1, 2, 3 or more R'.



218. The compound according to claim 182, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

219. The compound according to claim 182, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

220. The compound according to claim 182, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

221. The compound according to claim 182, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

222. The compound according to claim 182, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

223. The compound according to claim 182, wherein R' is Cl.

224. The compound according to claim 182, wherein R₅ is selected from H, F, Cl and Br.

225. The compound according to claim 182, wherein R₅ is H.

226. The compound according to claim 182, wherein R₆ is selected from H, F, Cl and Br.

227. The compound according to claim 182, wherein R₆ is H or F.

228. The compound according to claim 182, wherein each R_a is independently selected from H and C_{1-6} alkyl.

229. The compound according to claim 182, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

230. The compound according to claim 182, wherein each of R_b and R_c is independently selected from H, C_{1-6} alkyl and C_{3-6} cycloalkyl.

231. The compound according to claim 182, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

232. The compound according to claim 182, wherein each R_d is independently selected from H and C_{1-6} alkyl.

233. The compound according to claim 182, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

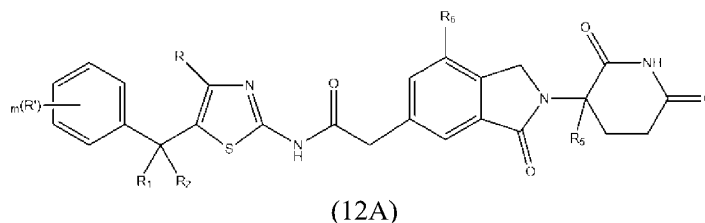
234. The compound according to claim 182, wherein R_e is H.

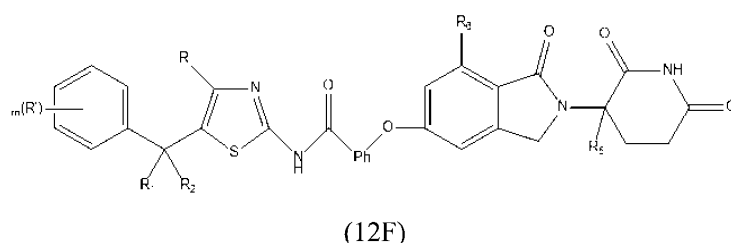
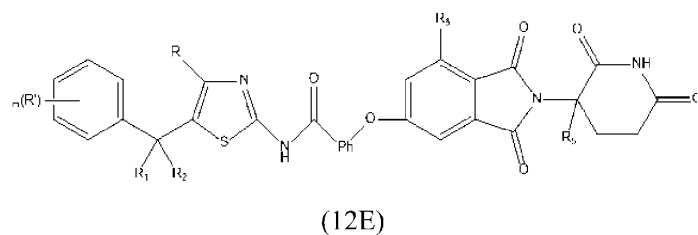
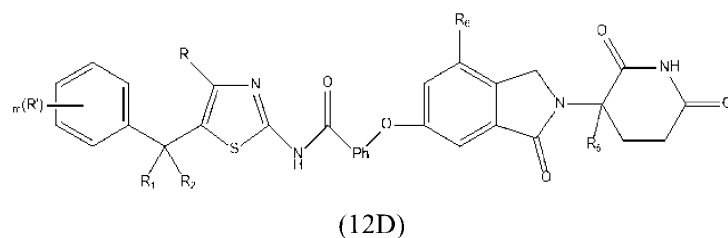
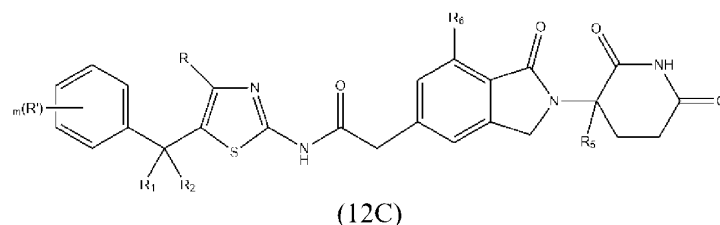
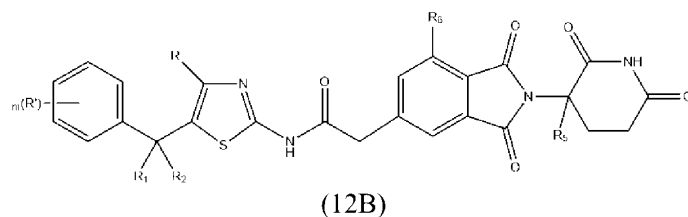
235. The compound according to claim 182, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl, -OH, -NH₂, -NO₂, -CN and C_{3-6} cycloalkyl.

236. The compound according to claim 182, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

237. The compound according to claim 182, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

238. The compound according to claim 1, wherein the compound is represented by Formula (12A), (12B), (12C), (12D), (12E) or (12F)





each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -

$S(=O)_2R_a$, $-NR_bR_c$, $-C(=O)NR_bR_c$, $-S(=O)NR_bR_c$, $-S(=O)_2NR_bR_c$, $-NR_dC(=O)R_a$, $-NR_dC(=O)OR_a$, $-NR_dC(=O)NR_bR_c$, $-NR_dS(=O)R_a$, $-NR_dS(=O)_2R_a$, $-NR_dS(=O)NR_bR_c$, $-NR_dS(=O)_2NR_bR_c$, $-SN(=O)$, $-NR_dN(=O)$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, $-CN$, $-N(=O)$, $-NO_2$, $-ON(=O)$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-C(=O)R_a$, $-C(=S)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-SR_a$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-NR_bR_c$, $-C(=O)NR_bR_c$, $-S(=O)NR_bR_c$, $-S(=O)_2NR_bR_c$, $-NR_dC(=O)R_a$, $-NR_dC(=O)OR_a$, $-NR_dC(=O)NR_bR_c$, $-NR_dS(=O)R_a$, $-NR_dS(=O)_2R_a$, $-NR_dS(=O)NR_bR_c$, $-NR_dS(=O)_2NR_bR_c$, $-SN(=O)$, $-NR_dN(=O)$, optionally substituted aryl, optionally substituted C_{3-12} carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R_5 is selected from H, halogen and optionally substituted C_1-C_6 alkyl;

R_6 is selected from H, halogen and optionally substituted C_1-C_6 alkyl;

each R_a is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

each of R_b and R_c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl;

Ph represents phenylene; and

m is selected from 0, 1, 2, 3, 4 and 5.

239. The compound according to claim 238, wherein each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

240. The compound according to claim 238, wherein each of R_1 and R_2 is independently selected from H, halogen, C_1-C_6 alkyl optionally substituted by 1, 2 or 3

halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

241. The compound according to claim 238, wherein each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

242. The compound according to claim 238, wherein each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

243. The compound according to claim 238, wherein each of R₁ and R₂ is independently selected from H and F.

244. The compound according to claim 238, wherein both of R₁ and R₂ are H.

245. The compound according to claim 238, wherein R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

246. The compound according to claim 238, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

247. The compound according to claim 238, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

248. The compound according to claim 238, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

249. The compound according to claim 238, wherein R is selected from H and -OH.

250. The compound according to claim 238, wherein R is H.

251. The compound according to claim 238, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

252. The compound according to claim 238, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

253. The compound according to claim 238, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

254. The compound according to claim 238, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

255. The compound according to claim 238, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

256. The compound according to claim 238, wherein R' is Cl.

257. The compound according to claim 238, wherein R₅ is selected from H, F, Cl and Br.

258. The compound according to claim 238, wherein R₅ is H.

259. The compound according to claim 238, wherein R₆ is selected from H, F, Cl and Br.

260. The compound according to claim 238, wherein R₆ is H or F.

261. The compound according to claim 238, wherein each R_a is independently selected from H and C₁₋₆alkyl.

262. The compound according to claim 238, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

263. The compound according to claim 238, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

264. The compound according to claim 238, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

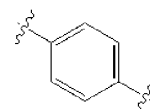
265. The compound according to claim 238, wherein each R_d is independently selected from H and C₁₋₆alkyl.

266. The compound according to claim 238, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

267. The compound according to claim 238, wherein the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

268. The compound according to claim 238, wherein the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

269. The compound according to claim 238, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

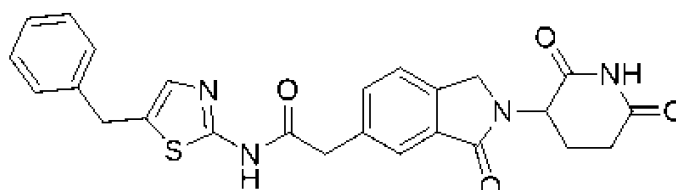


270. The compound according to claim 238, wherein Ph represents

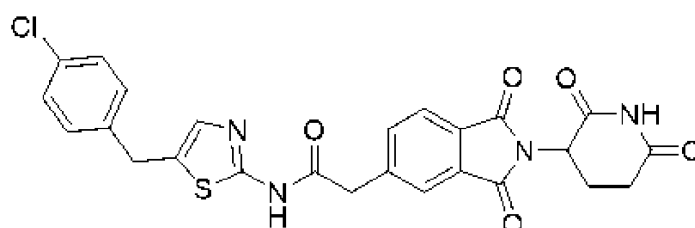
271. The compound according to claim 238, wherein m is selected from 0, 1 and 2.

272. The compound according to claim 238, wherein m is 0 or 1.

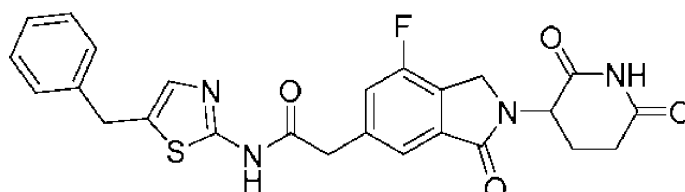
273. The compound according to claim 1, wherein the compound is selected from the group consisting of



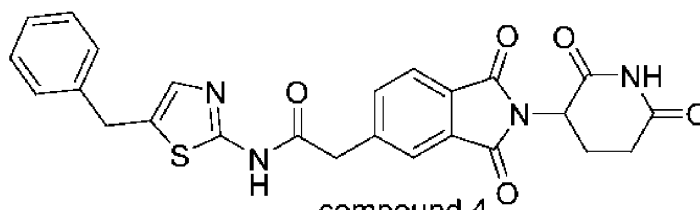
compound 1



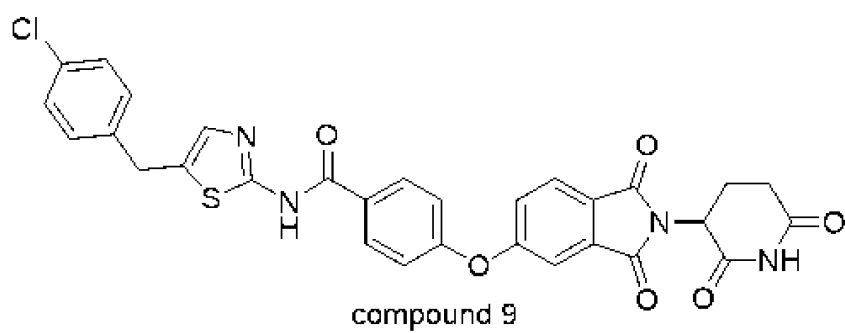
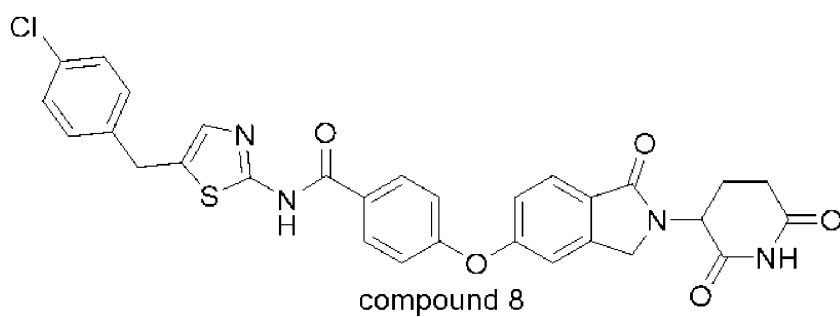
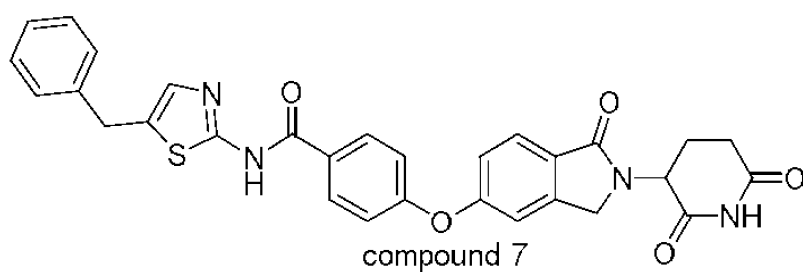
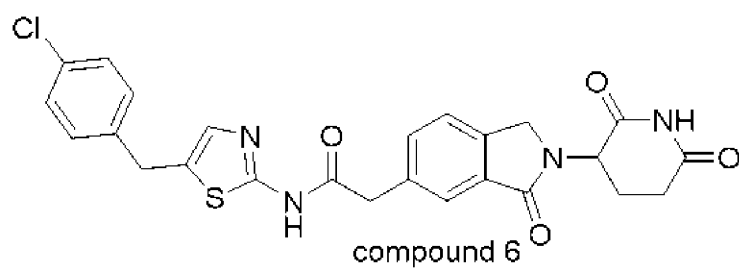
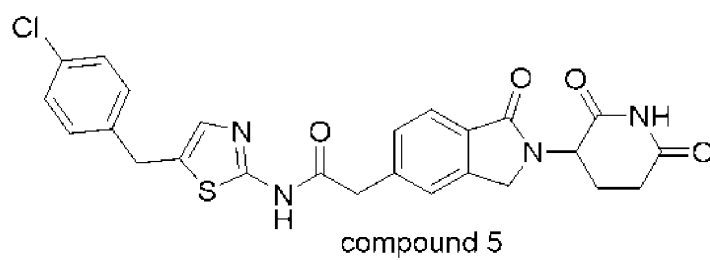
compound 2

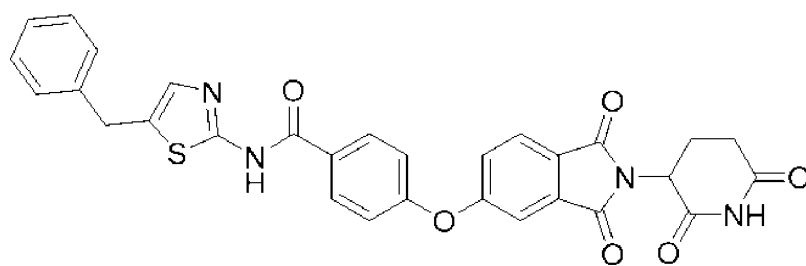


compound 3

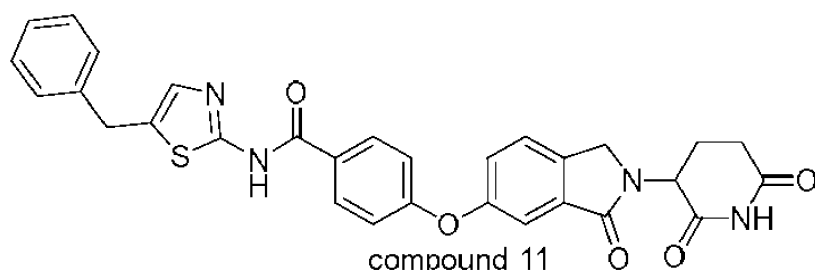


compound 4

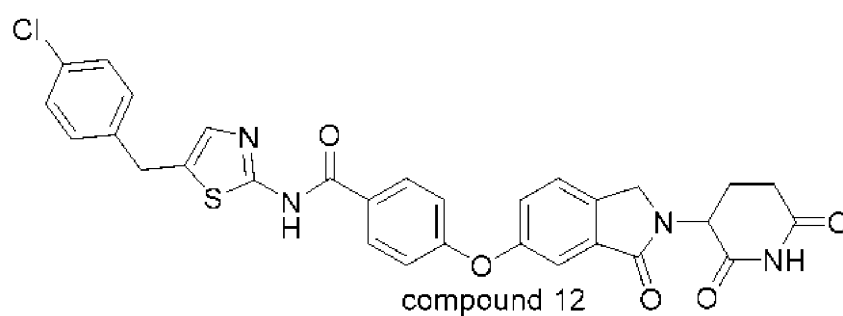




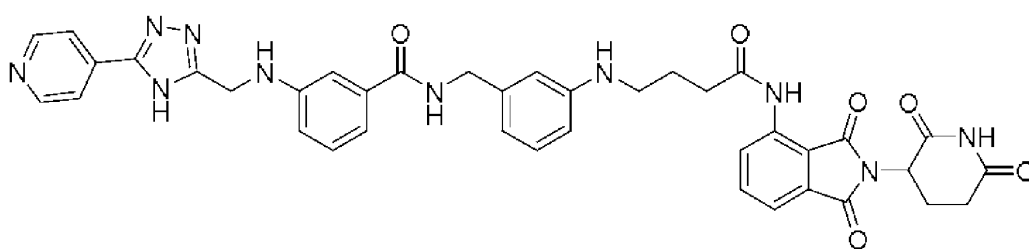
compound 10



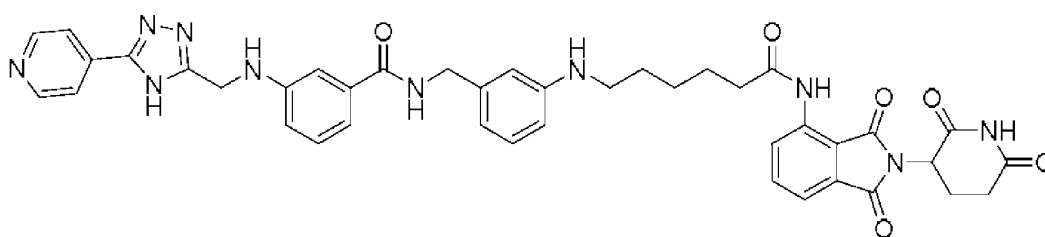
compound 11



compound 12

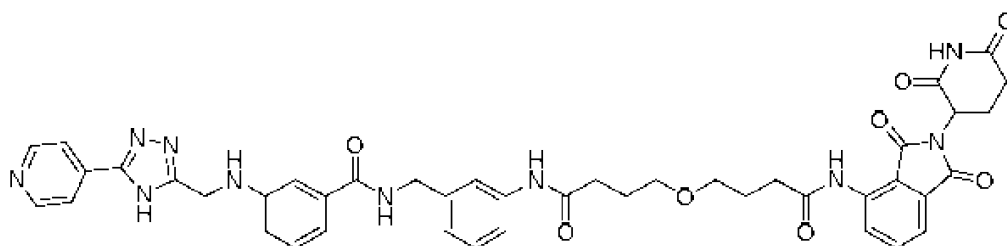


compound 13



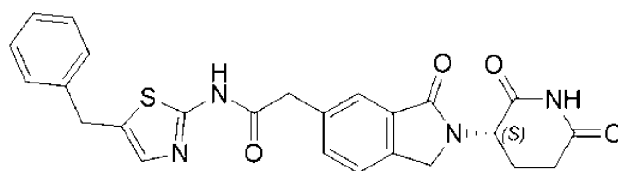
compound 14

, and



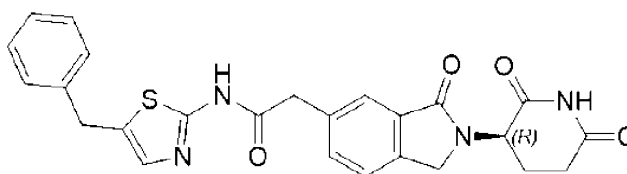
compound 15

274. The compound according to claim 1, wherein the compound is selected from the group consisting of



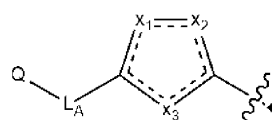
compound 1-P1

and



compound 1-P2

275. The compound according to claim 8, wherein the Formula I is represented by Formula (13):



(13)

wherein:

◆ denotes the point of attachment with the Formula II;

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

X₁, X₂ and X₃ are each independently selected from CR, S or N;

with the proviso that at least one of X₁, X₂ and X₃ is N and one of X₁, X₂ and X₃ is S;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally

substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -NO₂, =O, -CN and C₃₋₆cycloalkyl.

276. The compound according to claim 275, wherein Q is selected from optionally substituted C₁₋₆ alkyl, -OR_a, -SR_a, -NR_bR_c and Cy.

277. The compound according to claim 275, wherein Q is selected from C₁₋₆ alkyl, -SR_a, and Cy.

278. The compound according to claim 275, wherein Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

279. The compound according to claim 275, wherein Q is selected from isopropyl, isopropylthio and Cy.

280. The compound according to claim 275, wherein Q is Cy.

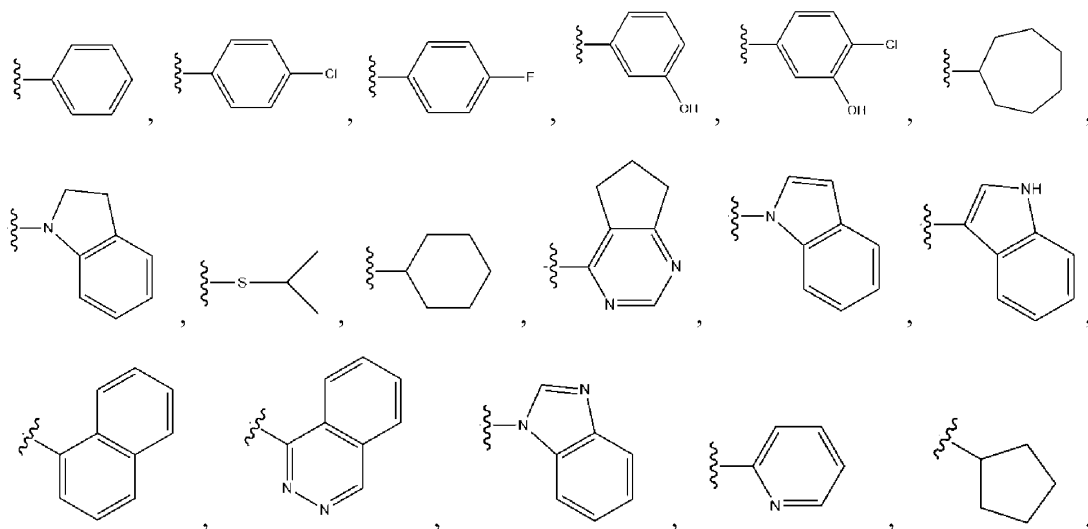
281. The compound according to claim 275, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

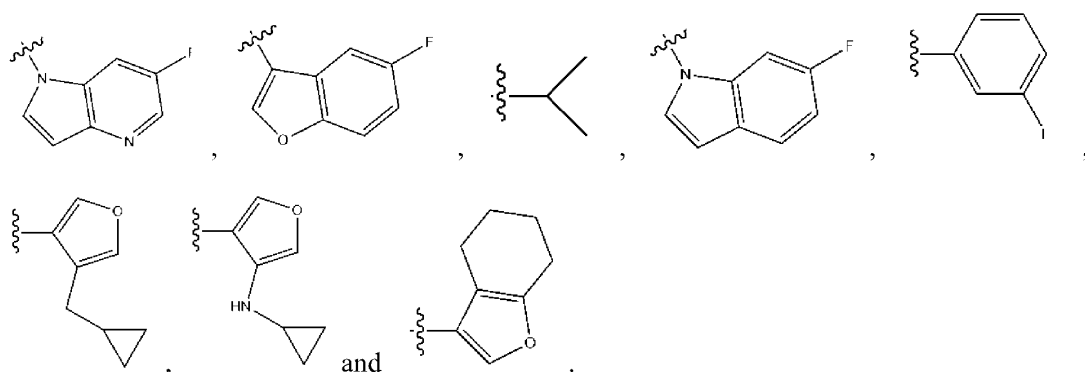
282. The compound according to claim 275, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5*H*-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

283. The compound according to claim 275, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5*H*-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

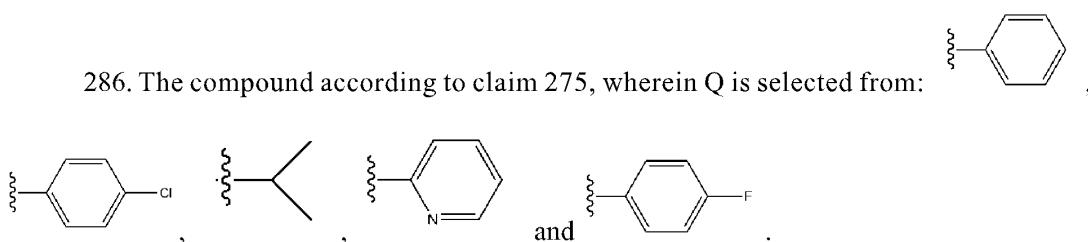
284. The compound according to claim 275, wherein Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

285. The compound according to claim 275, wherein Q is selected from:





286. The compound according to claim 275, wherein Q is selected from:



287. The compound according to claim 275, wherein L_A is selected from a bond, -C(R₁)(R₂)-, -N(R₁)-, -O-, -S-, -C(=O)- and -C(=S)-.

288. The compound according to claim 275, wherein L_A is selected from a bond, -CH₂-, -CF₂-, -CCl₂-, -CBr₂-, -CFCl-, -CFBr-, -CClBr-, -NH-, -O-, -S-, -C(=O)- and -C(=S)-.

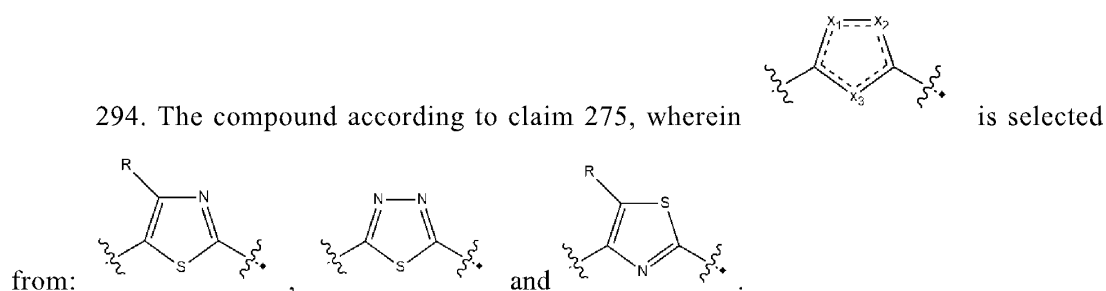
289. The compound according to claim 275, wherein L_A is selected from a bond, -CH₂-, -CF₂-, -NH-, -O-, -S-, -C(=O)- and -C(=S)-.

290. The compound according to claim 275, wherein L_A is -CH₂-.

291. The compound according to claim 275, wherein X₁ is CR or N.

292. The compound according to claim 275, wherein X₂ is S or N.

293. The compound according to claim 275, wherein X₃ is S or N.



294. The compound according to claim 275, wherein R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c.

296. The compound according to claim 275, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

297. The compound according to claim 275, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

298. The compound according to claim 275, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

299. The compound according to claim 275, wherein R is selected from H, methyl and -OH.

300. The compound according to claim 275, wherein R is H.

301. The compound according to claim 275, wherein each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

302. The compound according to claim 275, wherein each of R₁ and R₂ is independently selected from H, halogen, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

303. The compound according to claim 275, wherein each of R₁ and R₂ is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

304. The compound according to claim 275, wherein each of R₁ and R₂ is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

305. The compound according to claim 275, wherein each of R₁ and R₂ is independently selected from H and F.

306. The compound according to claim 275, wherein both of R₁ and R₂ are H.

307. The compound according to claim 275, wherein both of R₁ and R₂ are F.

308. The compound according to claim 275, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

309. The compound according to claim 275, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

310. The compound according to claim 275, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

311. The compound according to claim 275, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

312. The compound according to claim 275, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

313. The compound according to claim 275, wherein R' is Cl or F.

314. The compound according to claim 275, wherein each R_a is independently selected from H and C₁₋₆alkyl.

315. The compound according to claim 275, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

316. The compound according to claim 275, wherein each R_a is independently H or isopropyl.

317. The compound according to claim 275, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

318. The compound according to claim 275, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

319. The compound according to claim 275, wherein R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

320. The compound according to claim 275, wherein each R_d is independently selected from H and C₁₋₆alkyl.

321. The compound according to claim 275, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

322. The compound according to claim 275, wherein each R_d is independently H or methyl.

323. The compound according to claim 275, wherein a is selected from 0 and 1 and b is selected from 0 and 1.

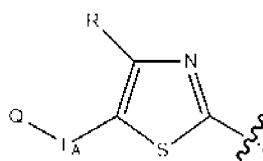
324. The compound according to claim 275, wherein a is 0 and b is 0.

325. The compound according to claim 275, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

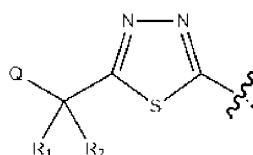
326. The compound according to claim 275, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

327. The compound according to claim 275, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

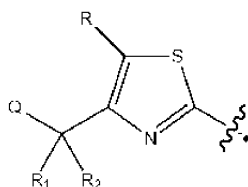
328. The compound according to claim 8, wherein the Formula I is represented by Formula (14A), (14B) or (14C):



(14A)



(14B)



(14C)

wherein:

◆ denotes the point of attachment with the Formula II;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c, optionally substituted C₃₋₆ carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R₁ and R₂ may be taken together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

Q is selected from optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, -NR_bR_c, -C(=O)R_a, -C(=O)OR_a, -OC(=O)R_a, -C(=O)NR_bR_c, -S(=O)R_a, -S(=O)₂R_a, -S(=O)₂NR_bR_c and Cy;

Cy is selected from aryl, C₃₋₁₂ carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -(CH₂)_aC(R₁)(R₂)(CH₂)_b-, -N(R₁)-, -O-, -S-, -C(=O)-, -C(=S)-, -S(=O)- and -S(=O)₂-;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl.

329. The compound according to claim 328, wherein each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

330. The compound according to claim 328, wherein each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$ and $-NR_bR_c$.

331. The compound according to claim 328, wherein each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-CN$, $-NO_2$, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

332. The compound according to claim 328, wherein each of R_1 and R_2 is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

333. The compound according to claim 328, wherein each of R_1 and R_2 is independently selected from H and F.

334. The compound according to claim 328, wherein both of R_1 and R_2 are H.

335. The compound according to claim 328, wherein both of R_1 and R_2 are F.

336. The compound according to claim 328, wherein R is selected from H, halogen, $-CN$, $-NO_2$, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, and $-NR_bR_c$.

337. The compound according to claim 328, wherein R is selected from H, halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

338. The compound according to claim 328, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

339. The compound according to claim 328, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

340. The compound according to claim 328, wherein R is selected from H, methyl and -OH.

341. The compound according to claim 328, wherein R is H.

342. The compound according to claim 328, wherein Q is selected from optionally substituted C₁₋₆ alkyl, -OR_a, -SR_a, -NR_bR_c and Cy.

343. The compound according to claim 328, wherein Q is selected from C₁₋₆ alkyl, -SR_a, and Cy.

344. The compound according to claim 328, wherein Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

345. The compound according to claim 328, wherein Q is selected from isopropyl, isopropylthio and Cy.

346. The compound according to claim 328, wherein Q is Cy.

347. The compound according to claim 328, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R'.

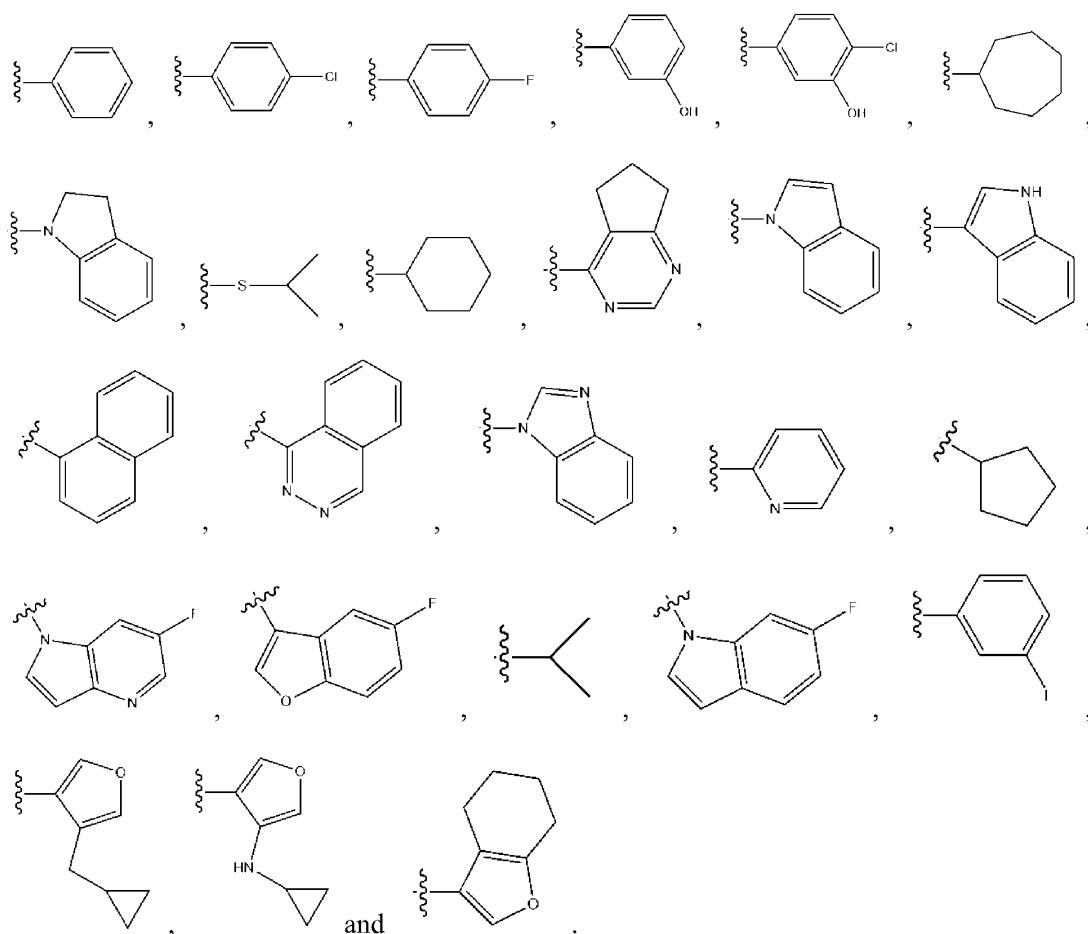
348. The compound according to claim 328, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl,

phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

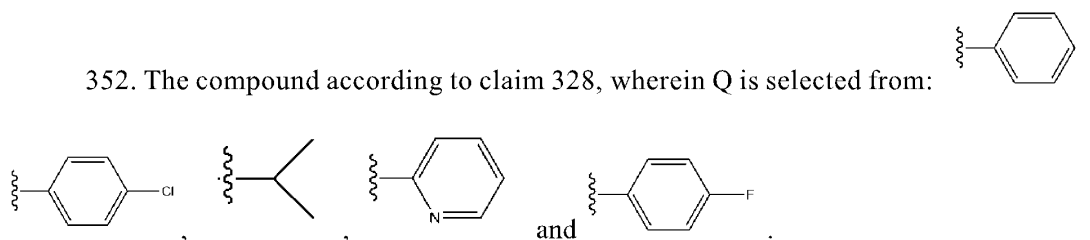
349. The compound according to claim 328, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

350. The compound according to claim 328, wherein Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

351. The compound according to claim 328, wherein Q is selected from:



352. The compound according to claim 328, wherein Q is selected from:



353. The compound according to claim 328, wherein L_A is selected from a bond, -C(R₁)(R₂)-, -N(R₁)-, -O-, -S-, -C(=O)- and -C(=S)-.

354. The compound according to claim 328, wherein L_A is selected from a bond, -CH₂-, -CF₂-, -CCl₂-, -CBr₂-, -CFCl-, -CFBr-, -CClBr-, -NH-, -O-, -S-, -C(=O)- and -C(=S)-.

355. The compound according to claim 328, wherein L_A is selected from a bond, -CH₂-, -CF₂-, -NH-, -O-, -S-, -C(=O)- and -C(=S)-.

356. The compound according to claim 328, wherein L_A is -CH₂-.

357. The compound according to claim 328, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

358. The compound according to claim 328, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

359. The compound according to claim 328, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

360. The compound according to claim 328, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

361. The compound according to claim 328, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

362. The compound according to claim 328, wherein R' is Cl or F.

363. The compound according to claim 328, wherein each R_a is independently selected from H and C₁₋₆alkyl.

364. The compound according to claim 328, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

365. The compound according to claim 328, wherein each R_a is independently H or isopropyl.

366. The compound according to claim 328, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

367. The compound according to claim 328, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

368. The compound according to claim 328, wherein R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

369. The compound according to claim 328, wherein each R_d is independently selected from H and C₁₋₆alkyl.

370. The compound according to claim 328, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

371. The compound according to claim 328, wherein each R_d is independently H or methyl.

372. The compound according to claim 328, wherein a is selected from 0 and 1 and b is selected from 0 and 1.

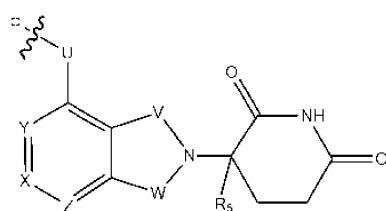
373. The compound according to claim 328, wherein a is 0 and b is 0.

374. The compound according to claim 328, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

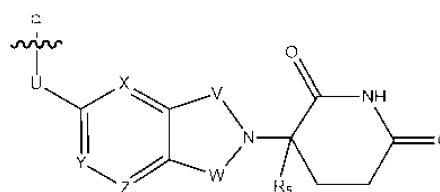
375. The compound according to claim 328, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

376. The compound according to claim 328, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

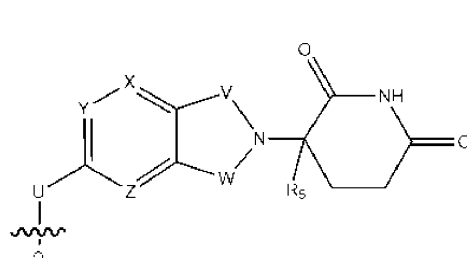
377. The compound according to claim 1, wherein the DT is a moiety represented by Formula (15A), (15B), (15C) or (15D):



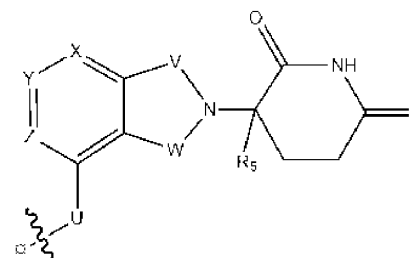
(15A)



(15B)



(15C)



(15D)

wherein,

⊗ denotes the point of attachment with the Formula II;

U is independently selected from a bond, -CH₂-, -NH- and -O-;

each of V and W is independently selected from -C(=O)- and -CH₂-;

each of X, Y, and Z is independently selected from CR₆ and N;

R₅ is selected from H, halogen and optionally substituted C₁-C₆ alkyl; and

R₆ is selected from H, halogen and optionally substituted C₁-C₆ alkyl.

378. The compound according to claim 377, wherein U is a bond.

379. The compound according to claim 377, wherein U is -CH₂-.

380. The compound according to claim 377, wherein V is -C(=O)- and W is -CH₂-.

381. The compound according to claim 377, wherein V is -CH₂- and W is -C(=O)-.

382. The compound according to claim 377, wherein both of V and W are -C(=O)-.

383. The compound according to claim 377, wherein each of X, Y, and Z is independently selected from CR₆.

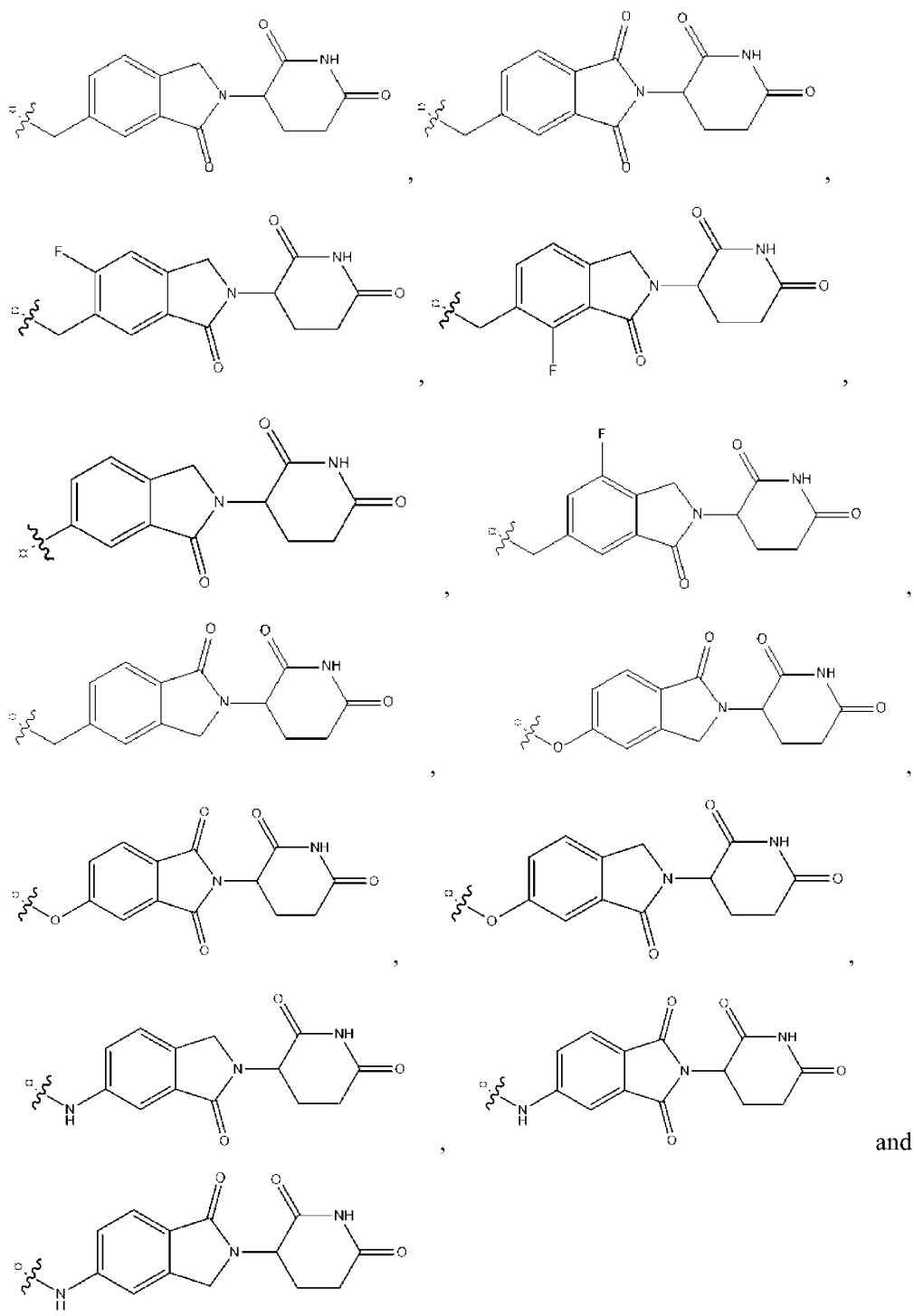
384. The compound according to claim 377, wherein R₅ is selected from H, F, Cl and Br.

385. The compound according to claim 377, wherein R₅ is H.

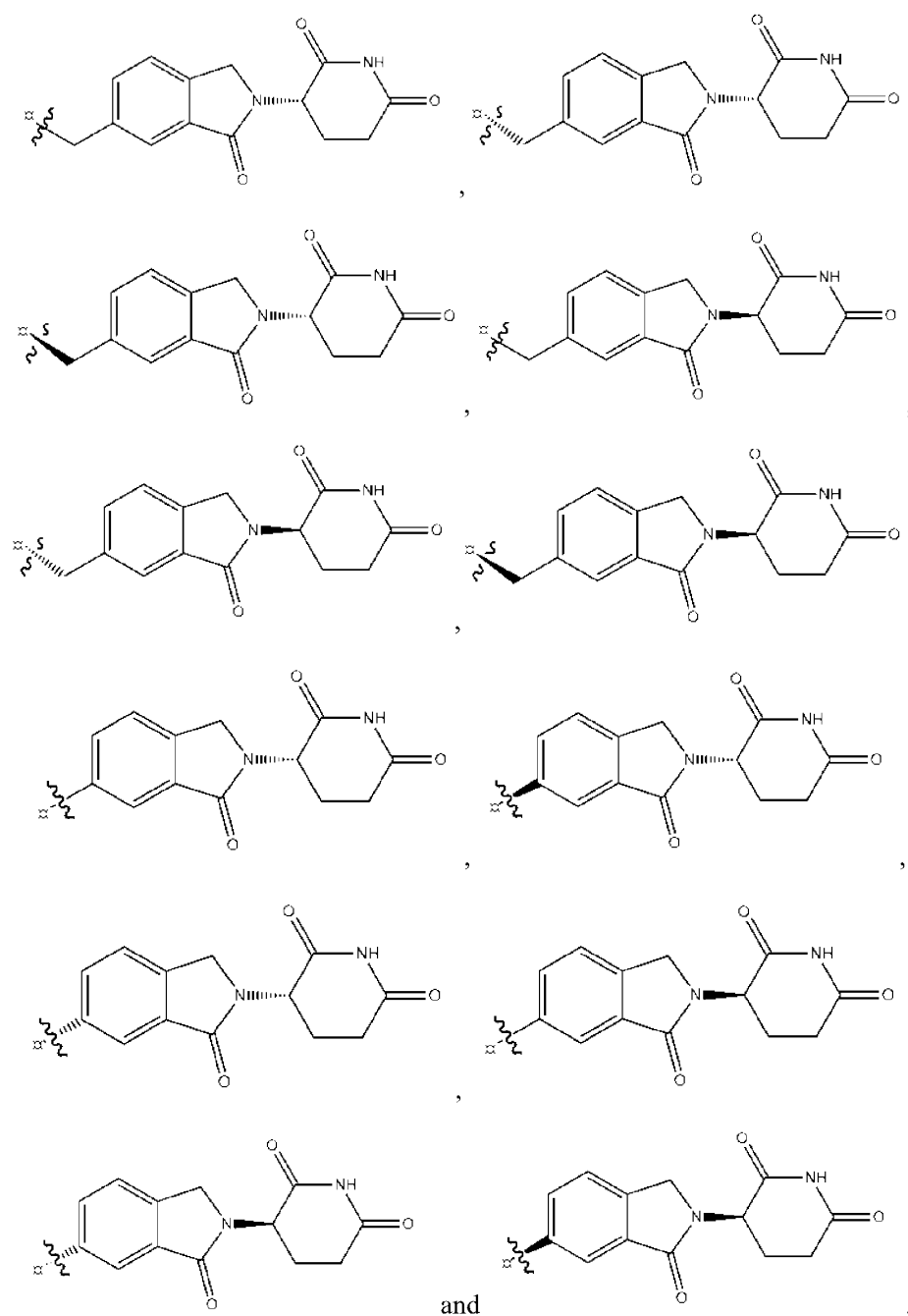
386. The compound according to claim 377, wherein R₆ is selected from H, F, Cl and Br.

387. The compound according to claim 377, wherein R₆ is H or F.

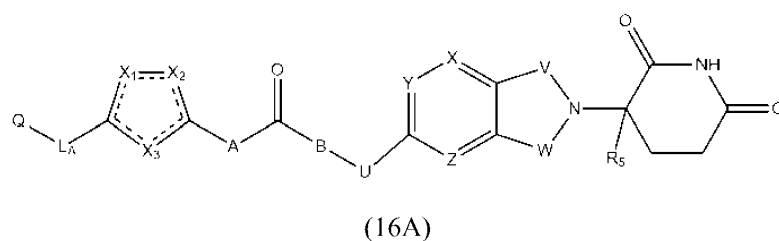
388. The compound according to claim 377, wherein the DT is a moiety selected from:

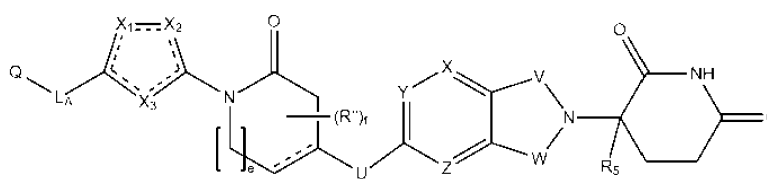


389. The compound according to claim 377, wherein the DT is a moiety selected from:



390. The compound according to claim 1, wherein the compound is represented by Formula (16A) or (16B)





(16B)

wherein:

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-OR_a$, $-SR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-C(=O)NR_bR_c$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-S(=O)_2NR_bR_c$ and Cy;

Cy is selected from aryl, C_{3-12} carbocyclyl, 5- to 12-membered heteroaryl and 3- to 12-membered heterocyclyl, each of which is optionally substituted by 1, 2, 3 or more R' ;

L_A is selected from a bond, $-(CH_2)_aC(R_1)(R_2)(CH_2)_b-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$, $-C(=S)-$, $-S(=O)-$ and $-S(=O)_2-$;

X_1 , X_2 and X_3 are each independently selected from CR, S or N;

with the proviso that at least one of X_1 , X_2 and X_3 is N and one of X_1 , X_2 and X_3 is S;

A is selected from C_{1-20} alkylene, $-O-$, $-S-$, $-N(R_e)-$ and $-N(R_e)-C_{1-20}$ alkylene-, and optionally wherein 1, 2, 3 or more methylene in the C_{1-20} alkylene group is independently replaced with a group selected from $-O-$, $-S-$, $-N(R_e)-$, $-C(=O)-$ and $-C(=S)-$;

B is a bond or is selected from arylene, C_{3-12} carbocyclylene, 5- to 12-membered heteroarylene and 3- to 12-membered heterocyclylene, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, $-CN$, $-NO_2$, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, $-OR_a$, $-SR_a$ and $-NR_bR_c$;

U is independently selected from a bond, $-CH_2-$, $-NH-$ and $-O-$;

each of V and W is independently selected from $-C(=O)-$ and $-CH_2-$;

each of X, Y, and Z is independently selected from CR_6 and N;

each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, $-CN$, $-NO_2$, $-OR_a$, $-SR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-C(=O)NR_bR_c$, $-S(=O)R_a$, $-S(=O)_2R_a$, $-S(=O)_2NR_bR_c$, optionally substituted C_{3-6} carbocyclyl and optionally substituted 3- to 6-membered heterocyclyl, or R_1 and R_2 may be taken

together along with the atom to which they are attached to form an optionally substituted C₃₋₁₂ carbocyclyl or optionally substituted 3- to 12-membered heterocyclyl;

R is selected from H, halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R'' is selected from halogen, -CN, -N(=O), -NO₂, -ON(=O), optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -C(=O)R_a, -C(=S)R_a, -C(=O)OR_a, -OC(=O)R_a, -SR_a, -S(=O)R_a, -S(=O)₂R_a, -NR_bR_c, -C(=O)NR_bR_c, -S(=O)NR_bR_c, -S(=O)₂NR_bR_c, -NR_dC(=O)R_a, -NR_dC(=O)OR_a, -NR_dC(=O)NR_bR_c, -NR_dS(=O)R_a, -NR_dS(=O)₂R_a, -NR_dS(=O)NR_bR_c, -NR_dS(=O)₂NR_bR_c, -SN(=O), -NR_dN(=O), optionally substituted aryl, optionally substituted C₃₋₁₂ carbocyclyl, optionally substituted 5- to 12-membered heteroaryl and optionally substituted 3- to 12-membered heterocyclyl;

R₅ is selected from H, halogen and optionally substituted C₁₋₆ alkyl;

R₆ is selected from H, halogen and optionally substituted C₁₋₆ alkyl;

each R_a is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆haloalkyl and C₃₋₆cycloalkyl; or an R_b and an R_c may be taken together along with the nitrogen atom to which they are attached to form an optionally substituted 3- to 12-membered heterocyclyl;

each R_d is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl and C_{3-6} cycloalkyl;

R_e is selected from H and optionally substituted C_{1-6} alkyl;

a is selected from 0, 1, 2, 3, 4 and 5, b is selected from 0, 1, 2, 3, 4 and 5, with the proviso that $a + b \leq 5$;

e is 0 or 1;

f is selected from 0, 1, 2 and 3; and

the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, $-OR_a$, $-NR_bR_c$, $-C(=O)R_a$, $-C(=O)OR_a$, $-OC(=O)R_a$, $-NO_2$, $=O$, $-CN$ and C_{3-6} cycloalkyl.

391. The compound according to claim 390, wherein Q is selected from optionally substituted C_{1-6} alkyl, $-OR_a$, $-SR_a$, $-NR_bR_c$ and Cy.

392. The compound according to claim 390, wherein Q is selected from C_{1-6} alkyl, $-SR_a$, and Cy.

393. The compound according to claim 390, wherein Q is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio, tert-butylthio and Cy.

394. The compound according to claim 390, wherein Q is selected from isopropyl, isopropylthio and Cy.

395. The compound according to claim 390, wherein Q is Cy.

396. The compound according to claim 390, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C_{3-8} carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R' .

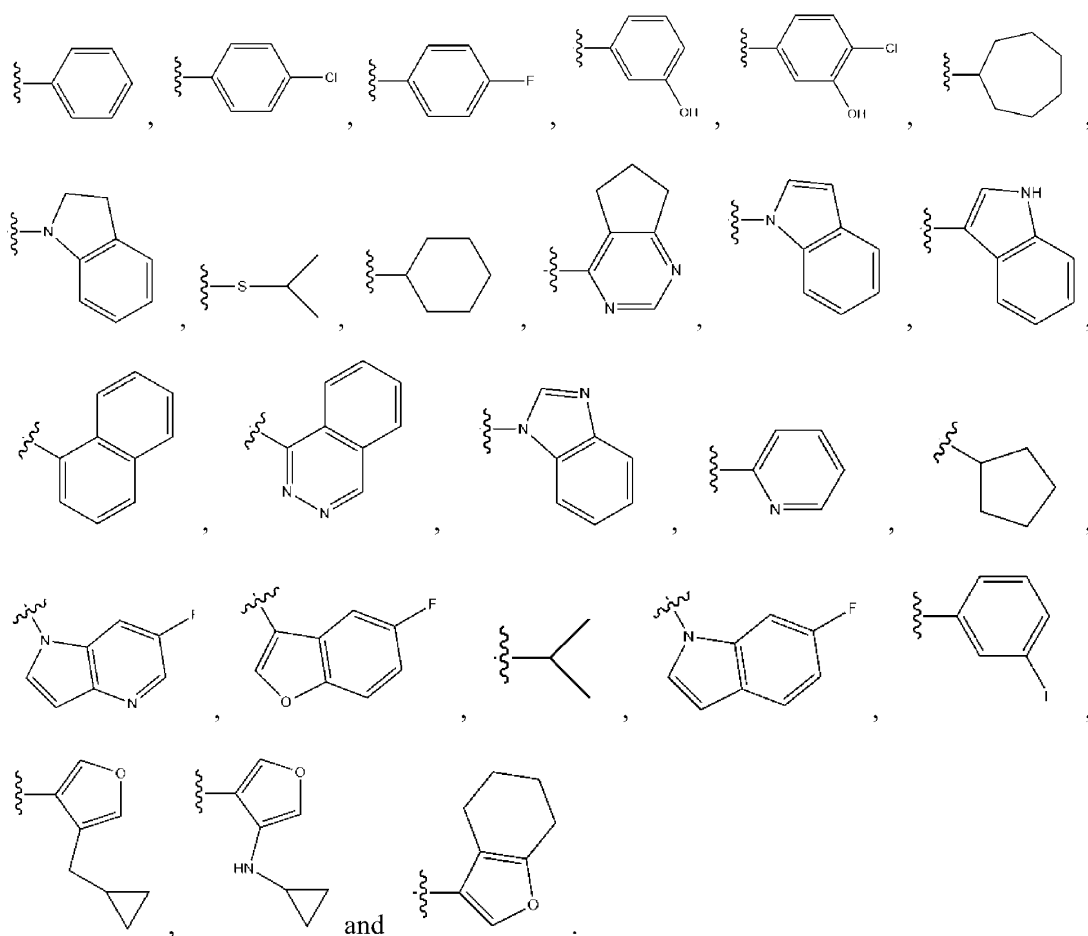
397. The compound according to claim 390, wherein Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, pyrrolyl, furyl, thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridinyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, carbazolyl, acridinyl, phenothiazinyl, phenazinyl, pteridinyl, purinyl, triazolyl, tetrazolyl, triazinyl, cinnolinyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl, tetrahydrobenzofuryl, benzoxazolyl, benzothienyl, imidazopyridinyl, benzothiazolyl, quinazolinyl, quinoxalinyl,

naphthyridinyl, furopyridinyl and indazolyl, each of which is optionally substituted by 1, 2, 3 or more R'.

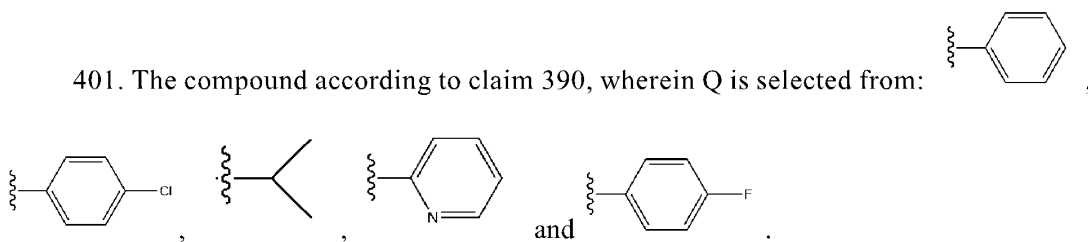
398. The compound according to claim 390, wherein Cy is selected from phenyl, naphthyl, cyclopentyl, cyclohexyl, cycloheptyl, furyl, pyridinyl, indolinyl, indolyl, 6,7-dihydro-5H-cyclopenta[d]pyrimidinyl, phthalazinyl, benzoimidazolyl, pyrrolopyridinyl, benzofuryl and tetrahydrobenzofuryl, each of which is optionally substituted by 1, 2, 3 or more R'.

399. The compound according to claim 390, wherein Cy is phenyl or pyridinyl which is optionally substituted by 1, 2, 3 or more R'.

400. The compound according to claim 390, wherein Q is selected from:



401. The compound according to claim 390, wherein Q is selected from:



402. The compound according to claim 390, wherein L_A is selected from a bond, $-C(R_1)(R_2)-$, $-N(R_1)-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

403. The compound according to claim 390, wherein L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-CCl_2-$, $-CBr_2-$, $-CFCl-$, $-CFBr-$, $-CClBr-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

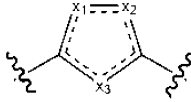
404. The compound according to claim 390, wherein L_A is selected from a bond, $-CH_2-$, $-CF_2-$, $-NH-$, $-O-$, $-S-$, $-C(=O)-$ and $-C(=S)-$.

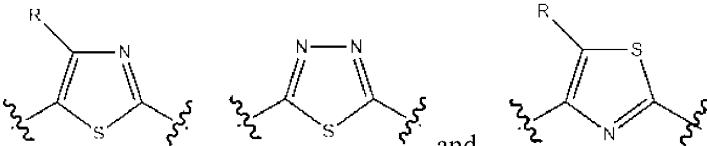
405. The compound according to claim 390, wherein L_A is $-CH_2-$.

406. The compound according to claim 390, wherein X_1 is CR or N.

407. The compound according to claim 390, wherein X_2 is S or N.

408. The compound according to claim 390, wherein X_3 is S or N.

409. The compound according to claim 390, wherein  is selected

from: , and

410. The compound according to claim 390, wherein A is selected from C_{1-8} alkylene, $-O-$, $-NH-$, $-N(CH_3)-$, $-N(C_2H_5)-$, $-NH-C_{1-8}$ alkylene, and optionally wherein 1, 2, 3 or more methylene in the C_{1-8} alkylene group is independently replaced with a group selected from $-O-$ and $-C(=O)-$.

411. The compound according to claim 390, wherein A is selected from $-CH_2-$, $-O-$, $-NH-$, $-NH-(CH_2)_3-$, $-NH-(CH_2)_5-$ and $-NH-C(=O)-(CH_2)_3-O-(CH_2)_3-$.

412. The compound according to claim 390, wherein A is selected from $-CH_2-$, $-O-$ and $-NH-$.

413. The compound according to claim 390, wherein A is $-NH-$.

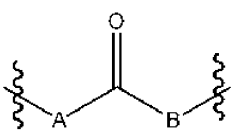
414. The compound according to claim 390, wherein B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, $-CN$, $-NO_2$, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, $-OH$, $-O(CH_3)$, $-NH_2$, $-NH(CH_3)$ and $-N(CH_3)_2$.

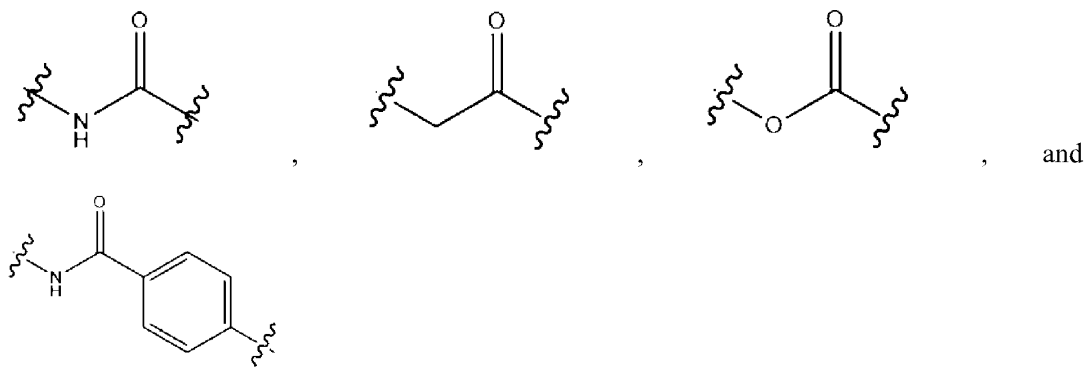
415. The compound according to claim 390, wherein B is a bond or is selected from phenylene, pyrrolylene, furylene, thienylene, pyrazolylene, imidazolylene, oxazolylene,

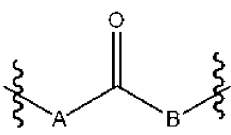
isoxazolylenes, oxadiazolylenes, thiazolylenes, isothiazolylenes, thiadiazolylenes, pyridinylenes, pyranilylenes, pyrazinylenes, pyrimidinylenes, pyrazinylenes, triazolylenes, tetrazolylenes and triazinylenes, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and propyl.

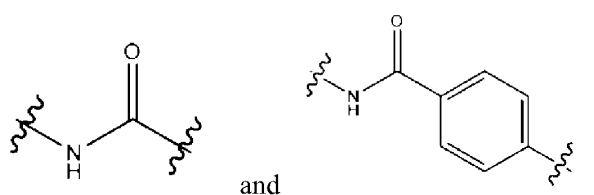
416. The compound according to claim 390, wherein B is a bond or phenylene which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of F, Cl and Br.

417. The compound according to claim 390, wherein B is a bond or phenylene.

418. The compound according to claim 390, wherein  is a moiety selected from:



419. The compound according to claim 390, wherein  is a moiety selected from:



420. The compound according to claim 390, wherein U is a bond.

421. The compound according to claim 390, wherein U is -CH₂-.

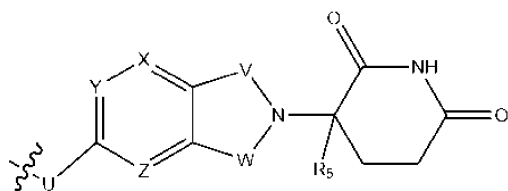
422. The compound according to claim 390, wherein V is -C(=O)- and W is -CH₂-.

423. The compound according to claim 390, wherein V is -CH₂- and W is -C(=O)-.

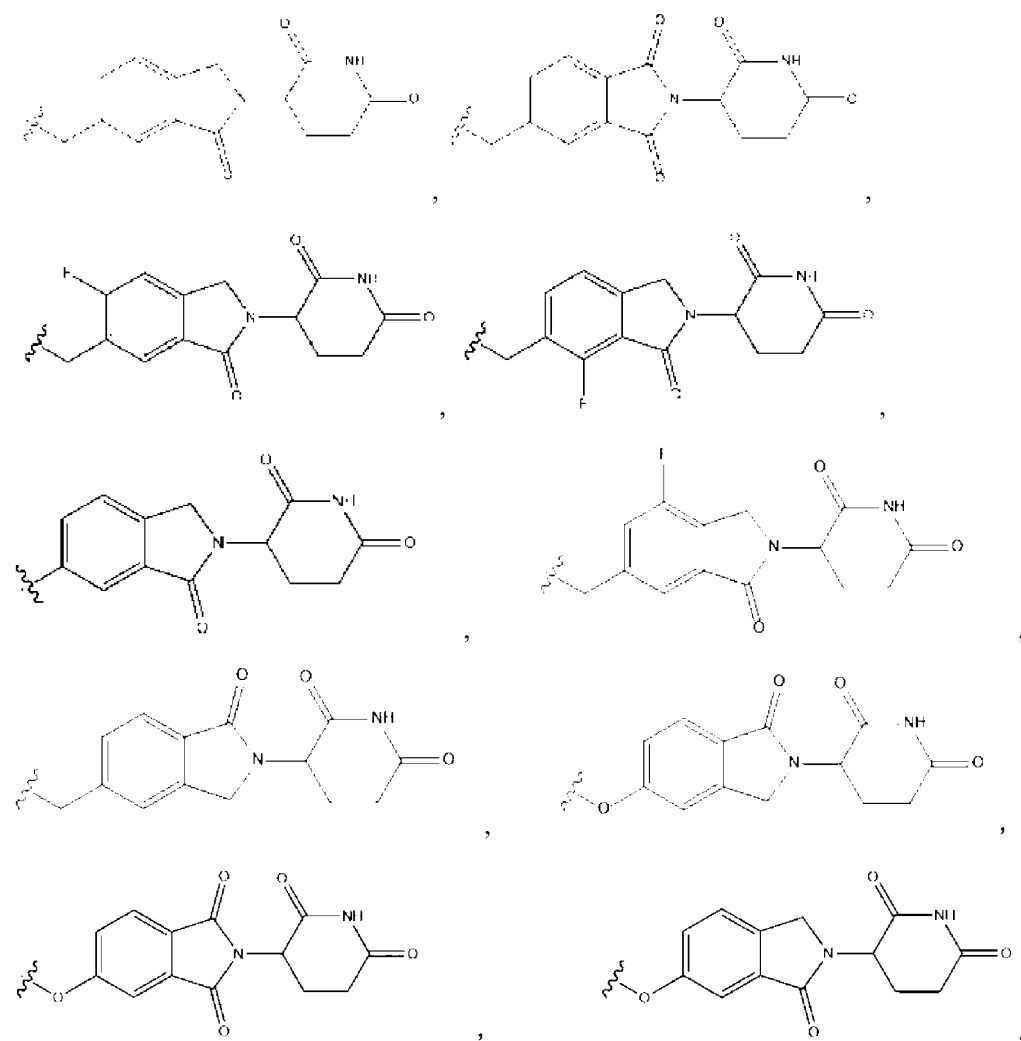
424. The compound according to claim 390, wherein both of V and W are -C(=O)-.

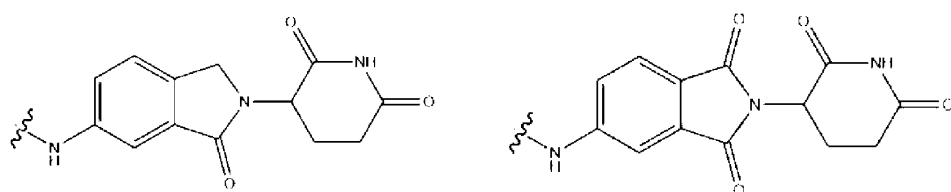
425. The compound according to claim 390, wherein each of X, Y, and Z is independently selected from CR₆.

426. The compound according to claim 390, wherein

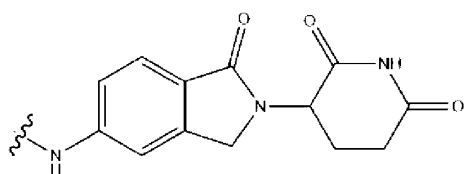


is a moiety selected from:

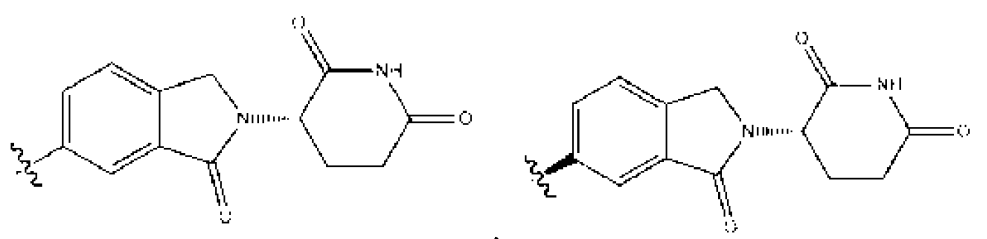
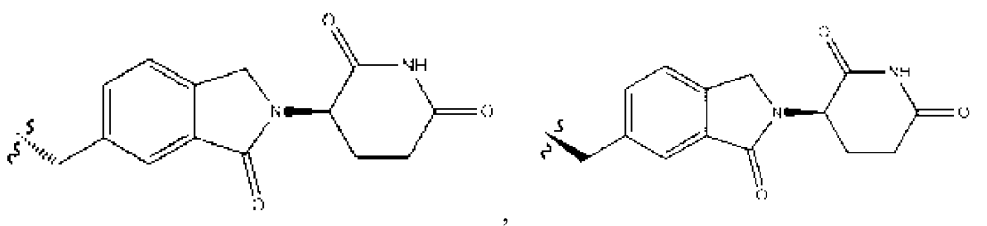
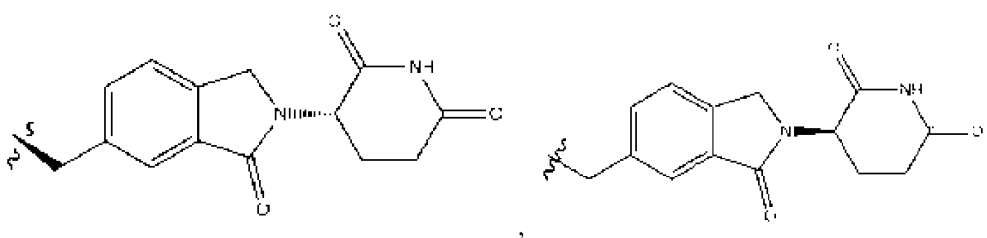
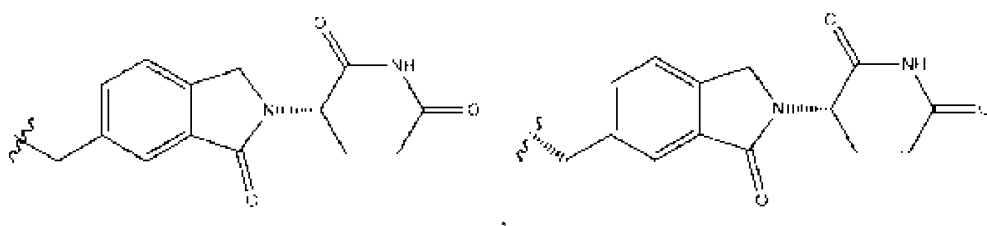
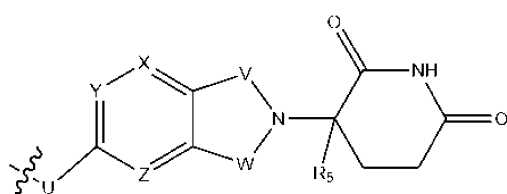


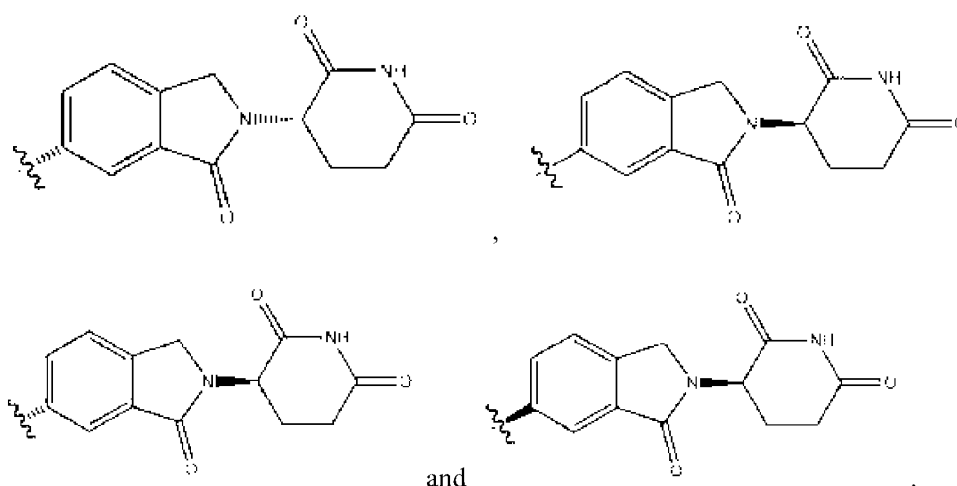


and



427. The compound according to claim 390, wherein





428. The compound according to claim 390, wherein each of R_1 and R_2 is independently selected from H, halogen, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

429. The compound according to claim 390, wherein each of R_1 and R_2 is independently selected from H, halogen, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkenyl optionally substituted by 1, 2 or 3 halogen, C_{2-6} alkynyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c.

430. The compound according to claim 390, wherein each of R_1 and R_2 is independently selected from H, halogen, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -CN, -NO₂, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

431. The compound according to claim 390, wherein each of R_1 and R_2 is independently selected from H, F, Cl, Br, methyl, ethyl and propyl.

432. The compound according to claim 390, wherein each of R_1 and R_2 is independently selected from H and F.

433. The compound according to claim 390, wherein both of R_1 and R_2 are H.

434. The compound according to claim 390, wherein both of R_1 and R_2 are F.

435. The compound according to claim 390, wherein R is selected from H, halogen, -CN, -NO₂, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} heteroalkyl, optionally substituted C_{2-6} alkenyl, optionally substituted C_{2-6} alkynyl, -OR_a, -SR_a, and -NR_bR_c.

436. The compound according to claim 390, wherein R is selected from H, halogen, -CN, -NO₂, C_{1-6} alkyl optionally substituted by 1, 2 or 3 halogen, C_{1-6} heteroalkyl optionally

substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a, and -NR_bR_c.

437. The compound according to claim 390, wherein R is selected from H, halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

438. The compound according to claim 390, wherein R is selected from H, F, Cl, Br, methyl, ethyl, propyl, -OH, -O(CH₃) and -NH₂.

439. The compound according to claim 390, wherein R is selected from H, methyl and -OH.

440. The compound according to claim 390, wherein R is H.

441. The compound according to claim 390, wherein R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

442. The compound according to claim 390, wherein R' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen or C₃₋₆cycloalkyl, -OR_a, -SR_a and -NR_bR_c.

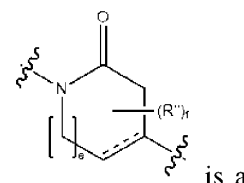
443. The compound according to claim 390, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH, -O(CH₃), -O(C₃₋₆cycloalkyl), -NH₂, -NH(CH₃), -N(CH₃)₂ and -NH(C₃₋₆cycloalkyl).

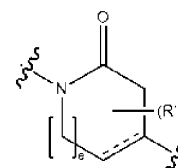
444. The compound according to claim 390, wherein R' is selected from halogen, -CH₂(C₃₋₆cycloalkyl), -OH and -NH(C₃₋₆cycloalkyl).

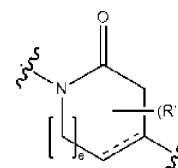
445. The compound according to claim 390, wherein R' is selected from F, Cl, cyclopropylmethyl, -OH and cyclopropylamino.

446. The compound according to claim 390, wherein R' is Cl or F.

447. The compound according to claim 390, wherein  in single bond.





448. The compound according to claim 390, wherein --- in  is a double bond.

449. The compound according to claim 390, wherein R'' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c.

450. The compound according to claim 390, wherein R'' is selected from halogen, -CN, -NO₂, C₁₋₆ alkyl optionally substituted by 1, 2 or 3 halogen, C₁₋₆ heteroalkyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkenyl optionally substituted by 1, 2 or 3 halogen, C₂₋₆ alkynyl optionally substituted by 1, 2 or 3 halogen, -OR_a, -SR_a and -NR_bR_c.

451. The compound according to claim 390, wherein R'' is selected from halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂.

452. The compound according to claim 390, wherein R'' is selected from F, Cl, Br, methyl, ethyl, propyl, -OH and -NH₂.

453. The compound according to claim 390, wherein R₅ is selected from H, F, Cl and Br.

454. The compound according to claim 390, wherein R₅ is H.

455. The compound according to claim 390, wherein R₆ is selected from H, F, Cl and Br.

456. The compound according to claim 390, wherein R₆ is H or F.

457. The compound according to claim 390, wherein each R_a is independently selected from H and C₁₋₆alkyl.

458. The compound according to claim 390, wherein each R_a is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

459. The compound according to claim 390, wherein each R_a is independently H or isopropyl.

460. The compound according to claim 390, wherein each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl.

461. The compound according to claim 390, wherein each of R_b and R_c is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

462. The compound according to claim 390, wherein R_b is H and R_c is cyclopropyl, or R_b is cyclopropyl and R_c is H.

463. The compound according to claim 390, wherein each R_d is independently selected from H and C_{1-6} alkyl.

464. The compound according to claim 390, wherein each R_d is independently selected from H, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

465. The compound according to claim 390, wherein R_e is H.

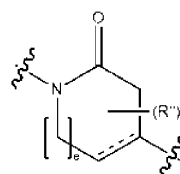
466. The compound according to claim 390, wherein a is selected from 0 and 1 and b is selected from 0 and 1.

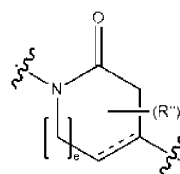
467. The compound according to claim 390, wherein a is 0 and b is 0.

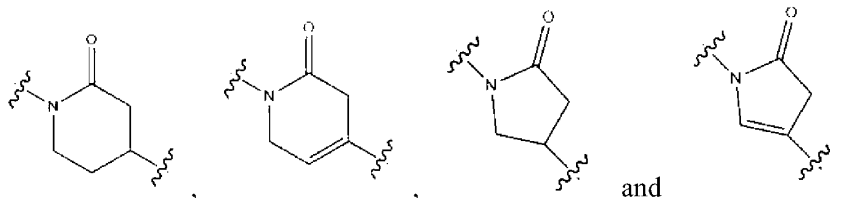
468. The compound according to claim 390, wherein c is 0.

469. The compound according to claim 390, wherein c is 1.

470. The compound according to claim 390, wherein f is 0.



471. The compound according to claim 390, wherein  is a moiety selected from:



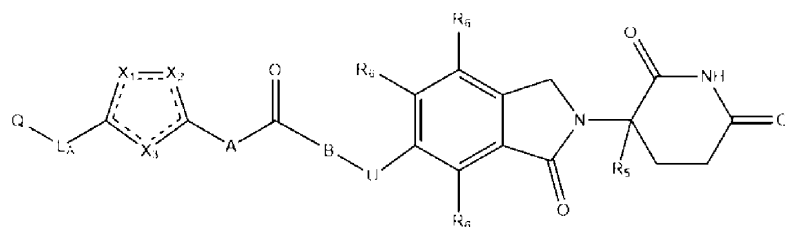
472. The compound according to claim 390, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C_{1-6} alkyl, -OH, -NH₂, -NO₂, -CN and C_{3-6} cycloalkyl.

473. The compound according to claim 390, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl, n-propyl, isopropyl, -OH, -NH₂, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

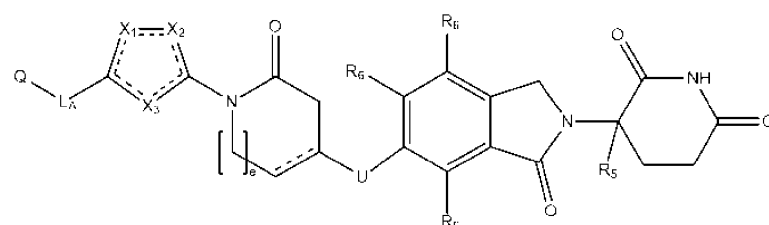
474. The compound according to claim 390, wherein the term “optionally substituted” before a chemical group without specifying the substituents(s) thereof indicates that said chemical

group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of F, Cl, Br, methyl, ethyl and cyclopropyl.

475. The compound according to claim 1, wherein the compound is represented by Formula (17A) or (17B)



(17A)



(17B)

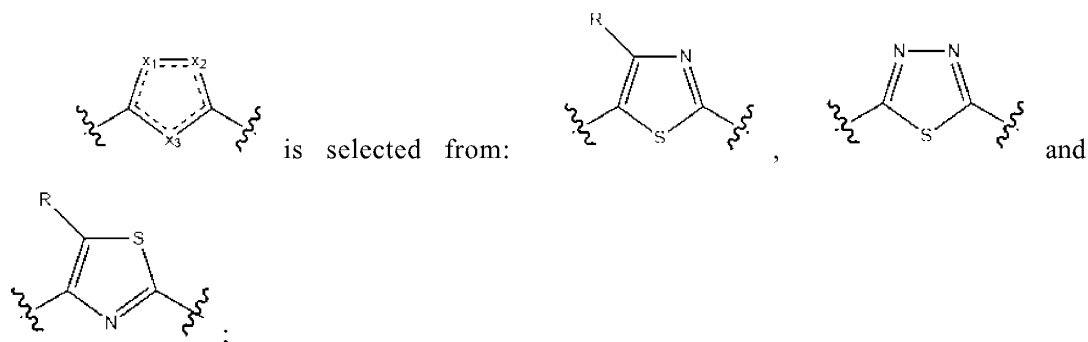
wherein:

each of --- is independently a single bond or a double bond;

Q is selected from optionally substituted C₁₋₆ alkyl, -OR_a, -SR_a, -NR_bR_c and Cy;

Cy is selected from phenyl, naphthyl, anthranyl, phenanthryl, C₃₋₈ carbocyclyl, 5- to 10-membered heteroaryl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S and 5- to 10-membered heterocyclyl comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more R';

L_A is selected from a bond, -C(R₁)(R₂)-, -N(R₁)-, -O-, -S-, -C(=O)- and -C(=S)-;



A is selected from C₁₋₈alkylene, -O-, -NH-, -N(CH₃)-, -N(C₂H₅)-, -NH-C₁₋₈alkylene, and optionally wherein 1, 2, 3 or more methylene in the C₁₋₈alkylene group is independently replaced with a group selected from -O- and -C(=O)-;

B is a bond or is selected from arylene and 5 or 6-membered heteroarylene comprising 1, 2, 3 or 4 heteroatoms selected from N, O and S, each of which is optionally substituted by 1, 2, 3 or more substituents selected from the group consisting of halogen, -CN, -NO₂, methyl optionally substituted by 1, 2 or 3 halogen, ethyl optionally substituted by 1, 2 or 3 halogen, propyl optionally substituted by 1, 2 or 3 halogen, -OH, -O(CH₃), -NH₂, -NH(CH₃) and -N(CH₃)₂;

U is independently selected from a bond, -CH₂-, -NH- and -O-;

each of R₁ and R₂ is independently selected from H, halogen, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -CN, -NO₂, -OR_a, -SR_a and -NR_bR_c;

R is selected from H, halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a, and -NR_bR_c;

R' is selected from halogen, -CN, -NO₂, optionally substituted C₁₋₆ alkyl, optionally substituted C₁₋₆ heteroalkyl, optionally substituted C₂₋₆ alkenyl, optionally substituted C₂₋₆ alkynyl, -OR_a, -SR_a and -NR_bR_c;

R₅ is selected from H, F, Cl and Br;

R₆ is selected from H, F, Cl and Br;

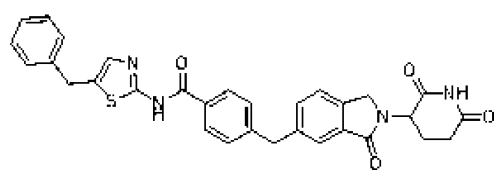
each R_a is independently selected from H and C₁₋₆alkyl;

each of R_b and R_c is independently selected from H, C₁₋₆alkyl and C₃₋₆cycloalkyl;

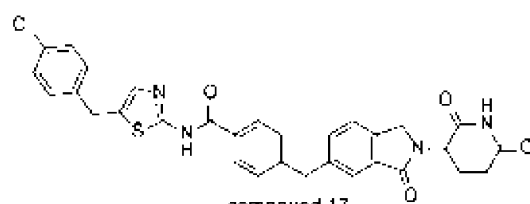
e is 0 or 1; and

wherein the term "optionally substituted" before a chemical group without specifying the substituents(s) thereof indicates that said chemical group is optionally substituted by 1, 2 or 3 substituents selected from the group consisting of halogen, C₁₋₆alkyl, -OH, -NH₂, -NO₂, -CN and C₃₋₆cycloalkyl.

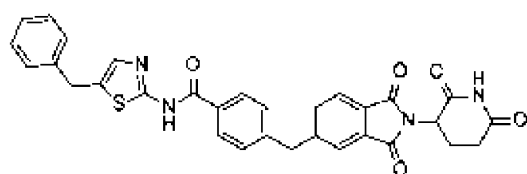
476. The compound according to claim 1, wherein the compound is selected from the group consisting of



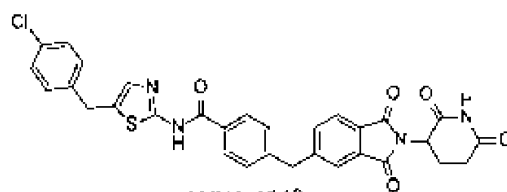
compound 16



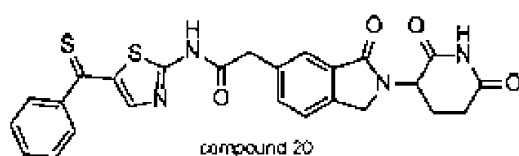
compound 17



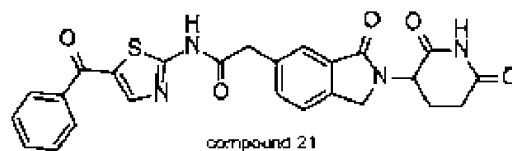
compound 18



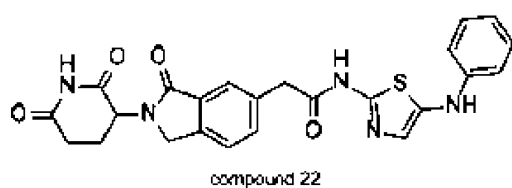
compound 19



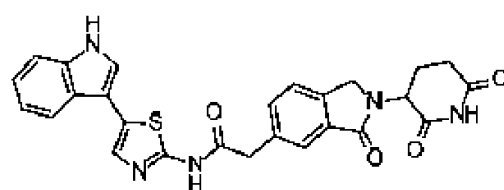
compound 20



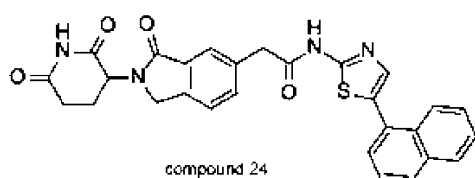
compound 21



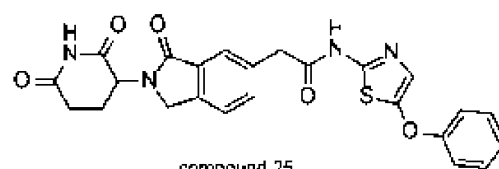
compound 22



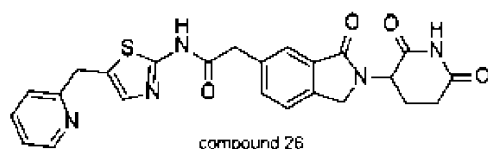
compound 23



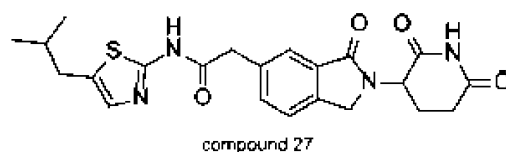
compound 24



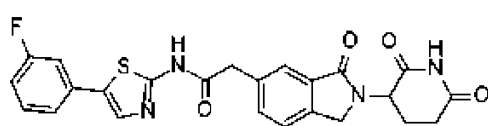
compound 25



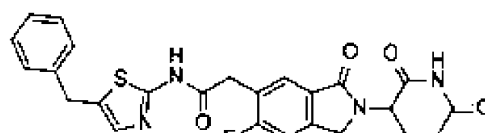
compound 26



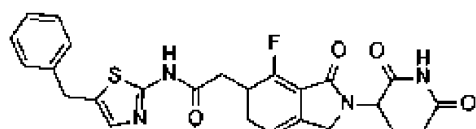
compound 27



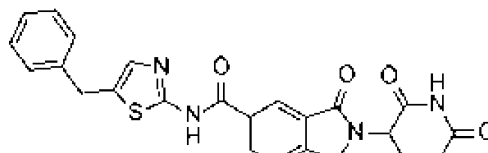
compound 28



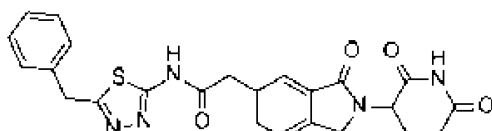
compound 29



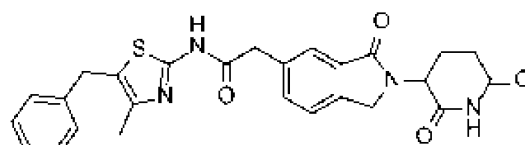
compound 30



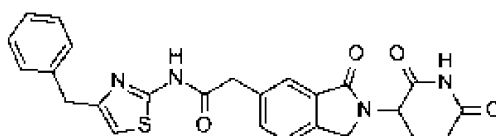
compound 31



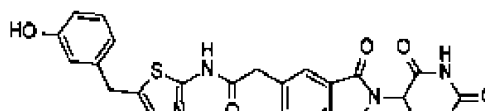
compound 32



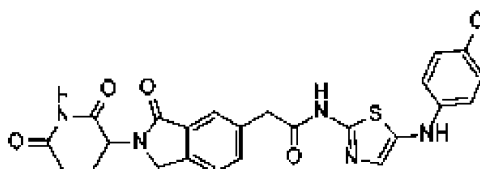
compound 33



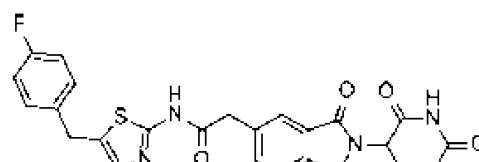
compound 34



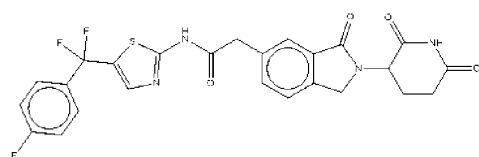
compound 35



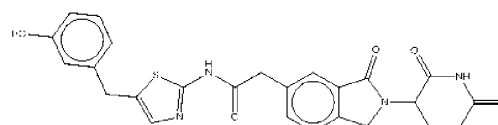
compound 36



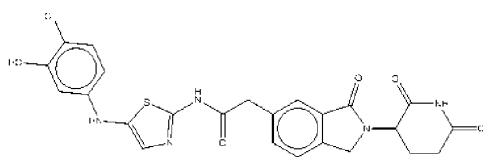
compound 37



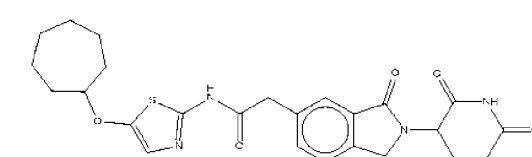
compound 38



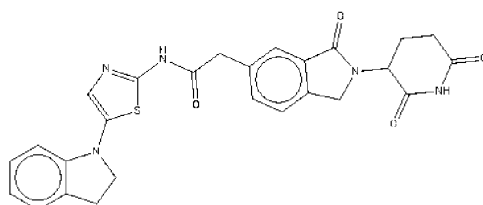
compound 39



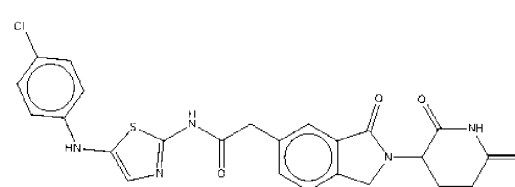
compound 40



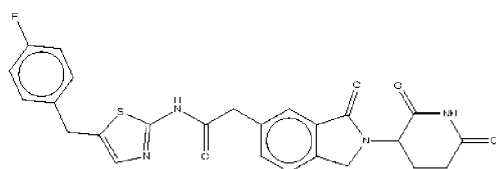
compound 41



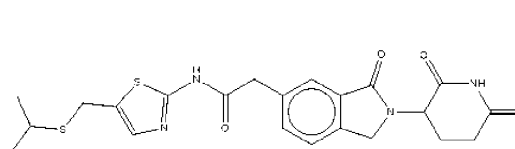
compound 42



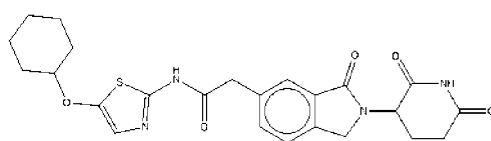
compound 43



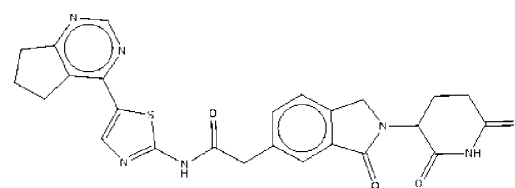
compound 44



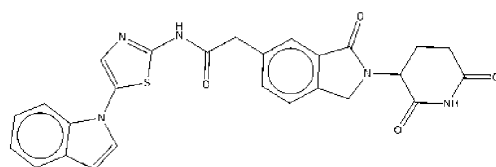
compound 45



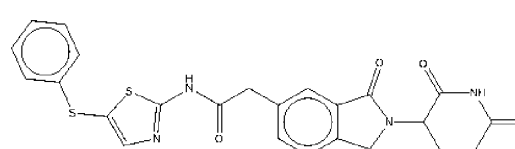
compound 46



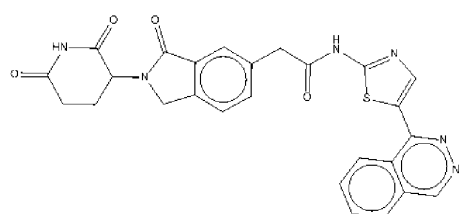
compound 47



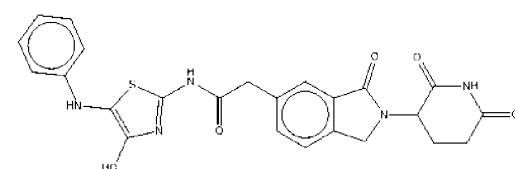
compound 48



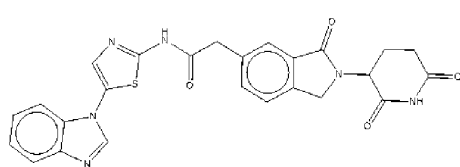
compound 49



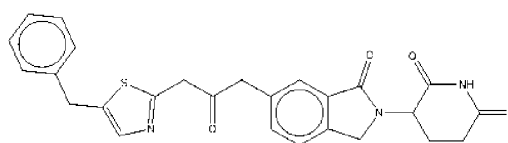
compound 50



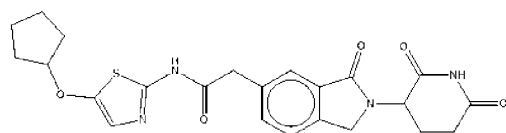
compound 51



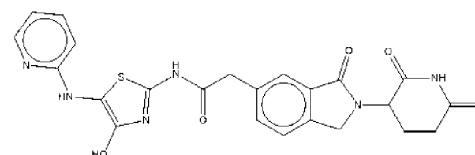
compound 52



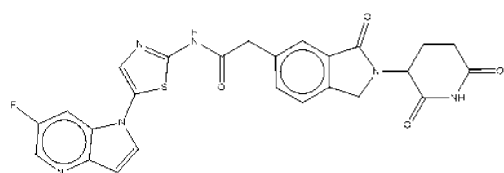
compound 53



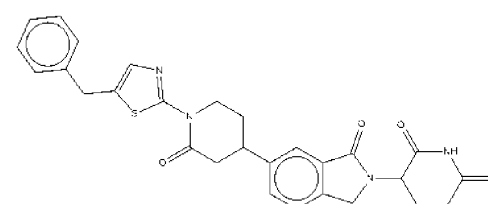
compound 54



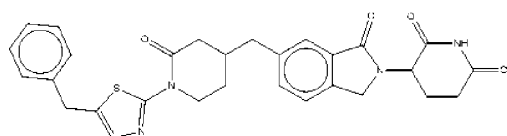
compound 55



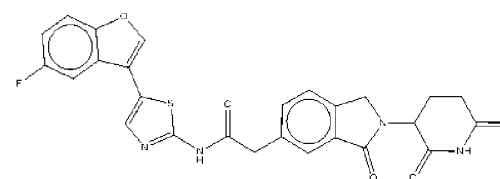
compound 56



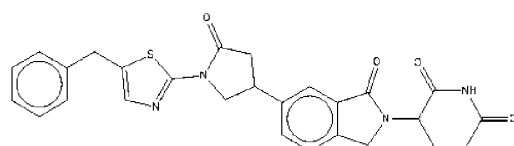
compound 57



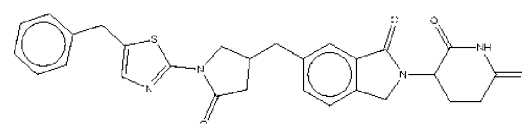
compound 58



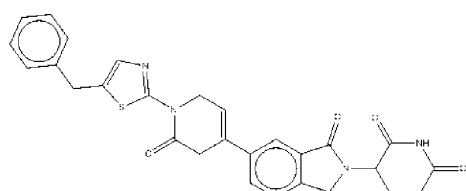
compound 59



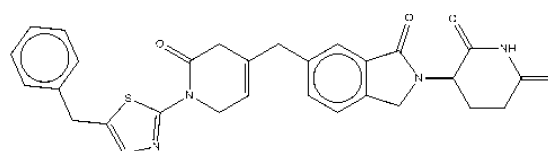
compound 60



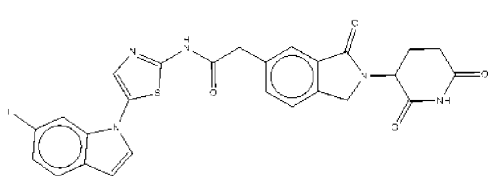
compound 61



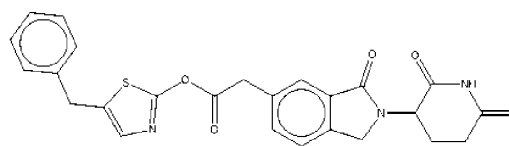
compound 62



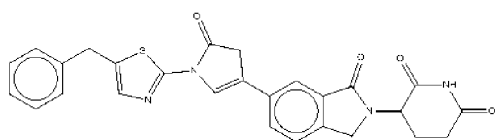
compound 63



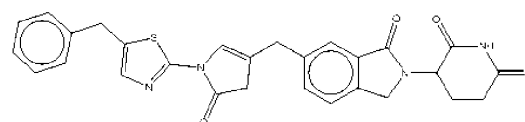
compound 64



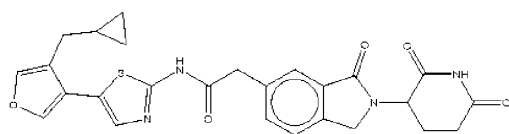
compound 65



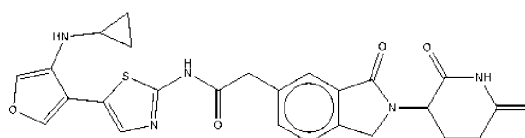
compound 66



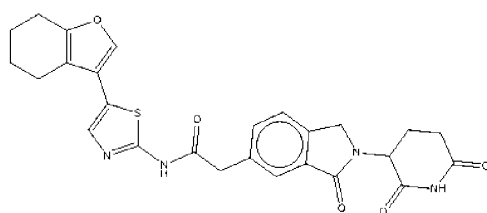
compound 67



compound 68



compound 69



compound 70

and

477. A pharmaceutical composition comprising the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof and one or more pharmaceutically acceptable excipients.

478. A kit comprising the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 and optionally an instruction for use.

479. A method for preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject, comprising administering an effective amount of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 to a subject in need thereof.

480. The method according to claim 479, wherein the disease or the condition is selected from a hyperproliferative disease, a cardiovascular disease, a hematological disease, an infective disease, an endocrinological disease, a metabolic disease, a gastroenterological disease, a respiratory disease, an inflammation, opioid addiction and a urological disease.

481. The method according to claim 479, wherein the disease or the condition is a hyperproliferative disease.

482. The method according to claim 481, wherein the hyperproliferative disease is a tumor.

483. The method according to claim 482, wherein the tumor is a cancer or a sarcoma.

484. The method according to claim 483, wherein the cancer is a hematopoietic cancer or a solid tumor.

485. The method according to claim 484, wherein the hematopoietic cancer is selected from a leukemia, a lymphoma, heavy chain disease, a myeloproliferative disorder, a multiple myeloma, a plasma cell neoplasia, a familial hypereosinophilia, an inflammatory myofibroblastic tumor and an immunocytic amyloidosis.

486. The method according to claim 484, wherein the solid tumor is selected from a nervous system cancer, an exocrine cancer, a musculoskeletal cancer, a gastrointestinal cancer, a respiratory cancer, a genitourinary cancer, a gynecological cancer, a skin cancer, a soft tissue cancer, an oral cancer, a head and neck cancer, an esophageal cancer, a liver cancer and a pancreatic cancer.

487. The method according to claim 479, wherein the disease or the condition is a cardiovascular disease.

488. The method according to claim 487, wherein the cardiovascular disease is selected from atherosclerosis, cardiac hypertrophy, hypertension, a coronary arterial disease, myocarditis, pericarditis, a cardiac valvular disease, stenosis, restenosis, in-stent-stenosis, angina pectoris, myocardial infarction, acute coronary syndromes, coronary artery bypass grafting, a cardio-pulmonary bypass procedure, endotoxemia, ischemia-reperfusion injury, cerebrovascular ischemia, renal reperfusion injury, embolism and myocardial ischemia.

489. The method according to claim 479, wherein the disease or the condition is pulmonary hypertension.

490. The method according to claim 489, wherein the disease or the condition is pulmonary arterial hypertension.

491. The method according to claim 490, wherein the disease or the condition is selected from idiopathic pulmonary arterial hypertension, heritable pulmonary arterial hypertension, drug- or toxin-induced pulmonary arterial hypertension, idiopathic pulmonary veno-occlusive disease, heritable pulmonary veno-occlusive disease, drug, toxin or radiation-induced pulmonary veno-

occlusive disease, idiopathic pulmonary capillary hemangiomatosis, heritable pulmonary capillary hemangiomatosis, drug, toxin or radiation-induced pulmonary capillary hemangiomatosis and persistent pulmonary hypertension of the newborn.

492. A method for inhibiting the growth or preventing the relapse of a tumor in a subject, comprising administering an effective amount of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 to a subject in need thereof.

493. A method for degrading GRK2 or inhibiting the activity of GRK2 in a subject, comprising administering an effective amount of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 to a subject in need thereof.

494. The compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477, for use in therapy.

495. The compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477, for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

496. The compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 and one or more pharmaceutically acceptable excipients, for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

497. The compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477, for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.

498. Use of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 for the preparation of a medicament for use in preventing or treating a disease or a condition for which the degradation of GRK2 is beneficial in a subject.

499. Use of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 for the preparation of a medicament for use in inhibiting the growth or preventing the relapse of a tumor in a subject.

500. Use of the compound according to anyone of claims 1-476 or a pharmaceutically acceptable salt, an isomer, an isotope, a prodrug, a solvate, or a polymorph thereof or the pharmaceutical composition according to claim 477 for the preparation of a medicament for use in degrading GRK2 or inhibiting the activity of GRK2 in a subject.