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(71) Applicant: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(72) Inventors: **GRAY, Nathanael S.**; 26 Greenview Avenue, Boston, Massachusetts 02130 (US). **DOBROVOLSKY, Dennis**; 70 Line Street, Somerville, Massachusetts 02143 (US). **HUANG, Hai-Tsang**; 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(74) Agent: **ERLACHER, Heidi** et al.; Cooley LLP, 1299 Pennsylvania Avenue, Suite 700, Washington, District of Columbia 20004 (US).

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(54) Title: DEGRADATION OF BRUTON'S TYROSINE KINASE (BTK) BY CONJUGATION OF BTK INHIBITORS WITH E3 LIGASE LIGAND AND METHODS OF USE

(57) Abstract: The present application provides bifunctional compounds of Formula (I), or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, which act as protein degradation inducing moieties for Bruton's tyrosine kinase (BTK). The present application also relates to methods for the targeted degradation of BTK through the use of the bifunctional compounds that link a ubiquitin ligase-binding moiety to a ligand that is capable of binding to BTK which can be utilized in the treatment of disorders modulated by BTK.

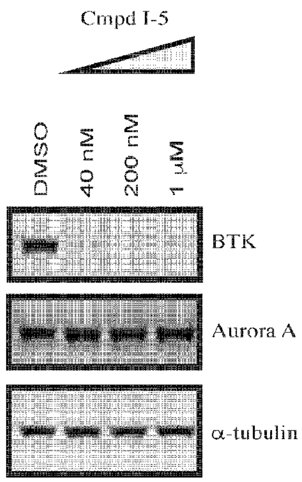
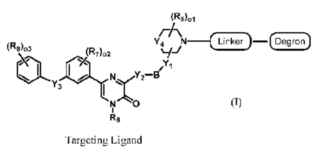


FIG. 1



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DEGRADATION OF BRUTON'S TYROSINE KINASE (BTK) BY CONJUGATION OF BTK INHIBITORS WITH E3 LIGASE LIGAND AND METHODS OF USE

RELATED APPLICATION

This application claims priority to, and the benefit of, U.S. Application No. 62/425,204, filed on November 22, 2016, the entire contents of which are incorporated herein by reference.

BACKGROUND

Ubiquitin-Proteasome Pathway (UPP) is a critical pathway that regulates proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases. These ligases comprise over 500 different proteins and are categorized into multiple classes defined by the structural element of their E3 functional activity. For example, cereblon (CRBN) interacts with damaged DNA binding protein 1 and forms an E3 ubiquitin ligase complex with Cullin 4 in which the proteins recognized by CRBN are ubiquitinated and degraded by proteasomes. Various immunomodulatory drugs (IMiDs), *e.g.*, thalidomide and lenalidomide, binds to CRBN and modulates CRBN's role in the ubiquitination and degradation of protein factors involved in maintaining regular cellular function.

Bifunctional compounds composed of a target protein-binding moiety and an E3 ubiquitin ligase-binding moiety have been shown to induce proteasome-mediated degradation of selected proteins. These drug-like molecules offer the possibility of temporal control over protein expression, and could be useful as biochemical reagents for the treatment of diseases.

Bruton's tyrosine kinase (BTK) is a member of the Tec family of tyrosine kinases and a key signaling enzyme expressed in B-cells and myeloid cells. BTK plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses, and is a key regulator of B-cell development, activation, signaling, and survival. Moreover, BTK plays a role in a number of other hematopoietic cell signaling pathways, including IgE receptor signaling in Mast cells, Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation.

Inhibition of BTK has been shown to affect cancer development (*e.g.*, B cell malignancies) and cell viability, and improve autoimmune diseases (*e.g.*, rheumatoid arthritis and lupus). Compounds which inhibit BTK via alternative strategies, such as through degradation of BTK, have the potential to be more potent than known inhibitors of BTK and are needed. The present application addresses the need.

SUMMARY

The present application relates to novel bifunctional compounds, which function to recruit targeted proteins to E3 ubiquitin ligase for degradation, and methods of preparation and uses thereof. The bifunctional compound is of Formula X:

(X),

wherein:

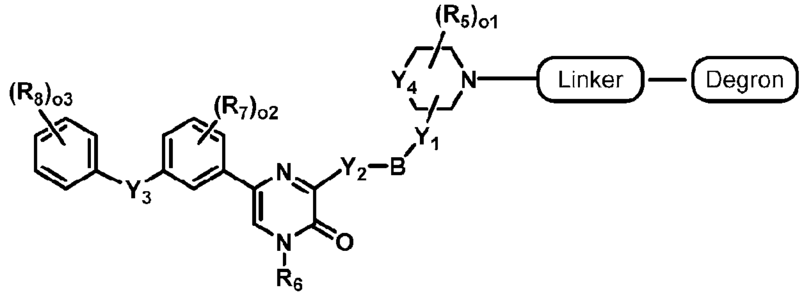
the Targeting Ligand is capable of binding to a targeted protein, such as a protein kinase (*e.g.*, BTK);

the Linker is a group that covalently binds to the Targeting Ligand and the Degron; and

the Degron is capable of binding to a ubiquitin ligase, such as an E3 ubiquitin ligase (*e.g.*, cereblon).

The present application also relates to targeted degradation of proteins through the use of bifunctional compounds, including bifunctional compounds that link an E3 ubiquitin ligase-binding moiety to a ligand that binds the targeted proteins.

The present application also relates to a bifunctional compound of Formula I:

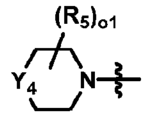


(I), or

Targeting Ligand

or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, wherein:

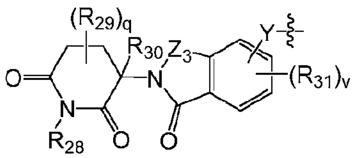
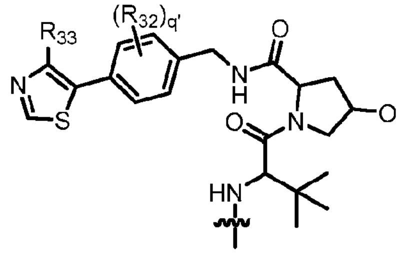
R_5, R_6, R_7, Y_1, Y_2, Y_3, Y_4, B, o1, o2, and o3 are each as defined herein;

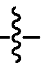
the Linker is a group that covalently binds to  and the Degron;

the Degron is capable of binding to a ubiquitin ligase, such as an E3 ubiquitin ligase (*i.e.*, cereblon); and

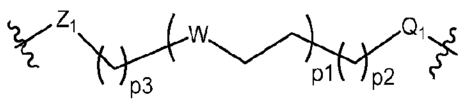
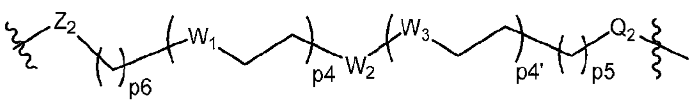
the Targeting Ligand is capable of binding to a targeted protein, such as BTK.

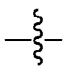
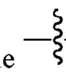
The present application further relates to a Degron of Formula D1 or D2:


(D1) or

(D2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein Y, Z_3, R_{28}, R_{29}, R_{30}, R_{31}, R_{32}, R_{33}, v, q, and q' are each as defined herein, and the Degron covalently binds to a Linker via .

The present application further relates to a Linker of Formula L1 or L2:


(L1) or

(L2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein p1, p2, p3, p4, p4', p5, p6, W, W_1, W_2, W_3, Q_1, Q_2, Z_1, and Z_2 are each as defined herein, the Linker is covalently bonded to a Degron via the  next to Q_1 or Q_2, and covalently bonded to a Targeting Ligand via the  next to Z_1 or Z_2.

The present application also relates to a pharmaceutical composition comprising a therapeutically effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Another aspect of the present application relates to a method of inhibiting BTK. The method comprises administering to a subject in need thereof an effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application.

Another aspect of the present application relates to a method of modulating (*e.g.*, decreasing) the amount of BTK. The method comprises administering to a subject in need thereof a therapeutically effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application.

Another aspect of the present application relates to a method of treating or preventing a disease (*e.g.*, a disease in which BTK plays a role). The method comprises administering to a subject in need thereof an effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application. In one aspect, the disease is BTK mediated disorder. In one aspect, the disease is a proliferative disease (*e.g.*, a proliferative disease in which BTK plays a role).

Another aspect of the present application relates to a method of treating or preventing cancer in a subject, wherein the cancer cell comprises an activated BTK or wherein the subject is identified as being in need of BTK inhibition for the treatment or prevention of cancer. The method comprises administering to the subject an effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable thereof, or a pharmaceutical composition of the application.

Another aspect of the present application relates to a kit comprising a bifunctional compound capable of inhibiting BTK activity, selected from a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof.

Another aspect of the present application relates to a kit comprising a bifunctional compound capable of modulating (*e.g.*, decreasing) the amount of BTK, selected from a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof.

Another aspect of the present application relates to use of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, in the manufacture of a medicament for inhibiting BTK or for modulating (*e.g.*, decreasing) the amount of BTK.

Another aspect of the present application relates to use of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, in the manufacture of a medicament for treating or preventing a disease (*e.g.*, a disease in which BTK plays a role). In one aspect, the disease is a BTK mediated disorder. In one aspect, the disease is a proliferative disease (*e.g.*, a proliferative disease in which BTK plays a role).

Another aspect of the present application relates to use of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, in the manufacture of a medicament for treating or preventing cancer in a subject, wherein the cancer cell comprises an activated BTK or wherein the subject is identified as being in need of BTK inhibition for the treatment or prevention of cancer.

Another aspect of the present application relates to a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, for inhibiting BTK or modulating (*e.g.*, decreasing) the amount of BTK.

Another aspect of the present application relates to a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, for treating or preventing a disease (*e.g.*, a disease in which BTK plays a role). In one aspect, the disease is BTK mediated disorder. In one aspect, the disease is a proliferative disease (*e.g.*, a proliferative disease in which BTK plays a role).

Another aspect of the present application relates to a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer, or pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the application, for treating or preventing cancer in a subject, wherein the cancer cell comprises an activated BTK or wherein the subject is identified as being in need of BTK inhibition for the treatment or prevention of cancer.

The present application provides inhibitors of BTK that are therapeutic agents in the treatment or prevention of diseases such as cancer and metastasis.

The present application further provides compounds and compositions with an improved efficacy and/or safety profile relative to known BTK inhibitors. The present application also provides agents with novel mechanisms of action toward BTK proteins in the treatment of various types of diseases including cancer and metastasis.

The compounds and methods of the present application address unmet needs in the treatment of diseases or disorders in which pathogenic or oncogenic endogenous proteins (*e.g.*, BTK) play a role, such as cancer.

The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present application, illustrative methods and materials are now described. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and are not intended to be limiting. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. The references cited herein are not admitted to be prior art to the application.

BRIEF DESCRIPTION OF THE DRAWINGS

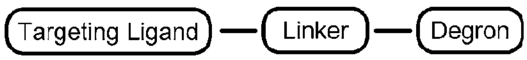
FIG. 1 is a Western blot showing the levels of BTK, Aurora A, and α-tubulin in Molm14 cells treated for 4 hours with DMSO or 40 nM, 200 nM, or 1 μM of Compound I-5.

DETAILED DESCRIPTION

<u>Compounds of the Application</u>

The present application relates to bifunctional compounds having utility as modulators of ubiquitination and proteosomal degradation of targeted proteins, especially compounds comprising a moiety capable of binding to a polypeptide or a protein that is degraded and/or otherwise inhibited by the bifunctional compounds of the present application. In particular, the present application is directed to compounds which contain a moiety, *e.g.*, a small molecule moiety (*i.e.*, having a molecular weight of below 2,000, 1,000, 500, or 200 Daltons), such as a thalidomide-like moiety, which is capable of binding to an E3 ubiquitin ligase, such as cereblon, and a ligand that is capable of binding to a target protein, in such a way that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and/or inhibition) of that protein.

In one embodiment, the present application provides a bifunctional compound of Formula X:



(X),

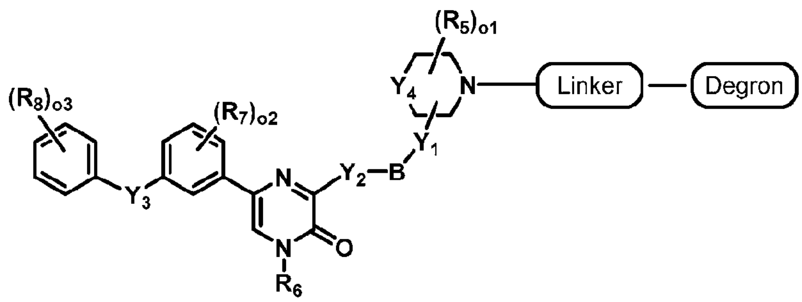
wherein:

the Targeting Ligand is capable of binding to a targeted protein, such as BTK;

the Linker is a group that covalently binds to the Targeting Ligand and the Degron; and

the Degron is capable of binding to a ubiquitin ligase, such as an E3 ubiquitin ligase (*e.g.*, cereblon).

In one embodiment, the present application provides a compound of Formula I:

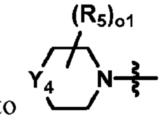


(I),

Targeting Ligand

or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, wherein:

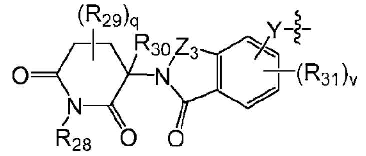
R_5, R_6, R_7, B, Y_1, Y_2, Y_3, o1, o2, and o3 are each as defined herein;

the Linker is a group that covalently binds to  and the Degron;

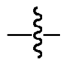
the Degron is capable of binding to a ubiquitin ligase, such as an E3 ubiquitin ligase (*e.g.*, cereblon); and

the Targeting Ligand is capable of binding to a targeted protein, such as BTK.

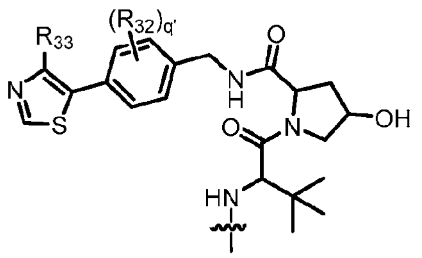
The present application further relates to a Degron of Formula D1:



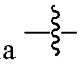
(D1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein Y, Z_3, R_{28}, R_{29}, R_{30}, R_{31}, q, and v are each as defined herein, and the Degron covalently binds to a Linker via .

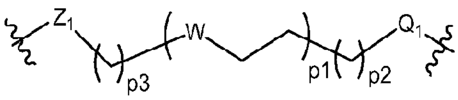
The present application further relates to a Degron of Formula D2:



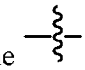
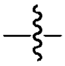
(D2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein R_{32}, R_{33}, and q' are each as defined herein, and the Degron covalently binds to a Linker via .

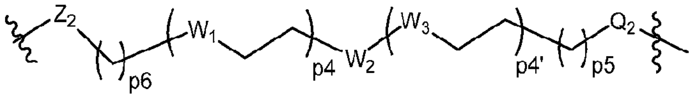
The present application further relates to a Linker of Formula L1:



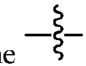
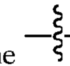
(L1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein p1, p2, p3, W, Q_1, and Z_1 are each as defined herein, the Linker is covalently bonded to a Degron via the  next to Q_1, and covalently bonded to a Targeting Ligand via the  next to Z_1.

The present application further relates to a Linker of Formula L2:



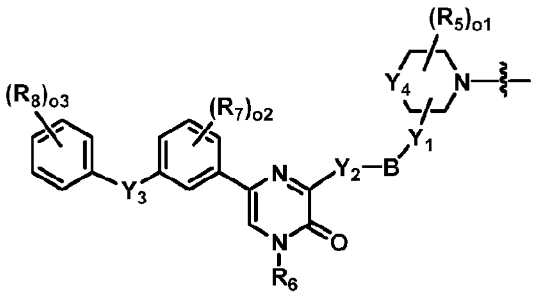
(L2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein p4, p4', p5, p6, W_1, W_2, W_3, Q_2, and Z_2 are each as defined herein, the Linker is covalently bonded to a Degron via the  next to Q_2, and covalently bonded to the Targeting Ligand via the  next to Z_2.

Targeting Ligand

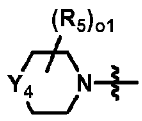
Targeting Ligand (TL) (or target protein moiety or target protein ligand or ligand) is a small molecule which is capable of binding to a target protein of interest, such BTK.

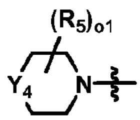
In one embodiment, a Targeting Ligand is a compound of Formula TL-I:



(TL-I),

or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, wherein:

B is phenyl or 5- or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, wherein the phenyl or heteroaryl is optionally substituted with 1 to 3 R_9, wherein when Y_1 is absent, B is bonded to a carbon atom or Y_4 in  ;

Y_1 is absent or C(O), wherein Y_1 is bonded to a carbon atom or Y_4 in  ;

Y_2 is NR_{10a} or O;

Y_3 is $C(O)NR_{10b}$ or $NR_{10b}C(O)$;

Y_4 is NR_5' or, when Y_1 is bonded to Y_4 or when Y_1 is absent and B is bonded to Y_4, Y_4 is N;

R_5' is H, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, or halogen;

each R_5 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, or oxo;

R_6 is H, (C_1-C_4) alkyl, or (C_1-C_4) haloalkyl;

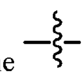
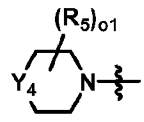
each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, (C_1-C_4) hydroxyalkyl, halogen, OH, or NH_2;

each R_8 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, OH, or NH_2;

each R_9 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, or halogen;

R_{10a} and R_{10b} are each independently H, (C_1-C_4) alkyl, or (C_1-C_4) haloalkyl; and

o1, o2, and o3 are each independently 0, 1, 2, or 3;

wherein the Targeting Ligand is bonded to the Linker via the  next to 

.

In some embodiments, B is phenyl optionally substituted with 1 to 3 R_9. In other embodiments, B is 5- or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, optionally substituted with 1 to 3 R_9. In other embodiments, B is 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, optionally substituted with 1 to 3 R_9. In other embodiments, B is 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, optionally substituted with 1 to 3 R_9. In other embodiments, B is 5- or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S. In other embodiments, B is 5-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S. In other embodiments, B is 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S. In other embodiments, B is pyridinyl optionally substituted with 1 to 3 R_9. In other embodiments, B is pyridinyl. In other embodiments, B is phenyl.

In some embodiments, Y_1 is absent. In other embodiments, Y_1 is C(O).

In some embodiments, Y_2 is NR_{10a}. In other embodiments, Y_2 is O.

In some embodiments, Y_3 is $C(O)NR_{10b}$. In other embodiments, Y_3 is $NR_{10b}C(O)$.

In some embodiments, Y_4 is NR_5'. In other embodiments, Y_4 is N.

In some embodiments, R_5' is (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, or halogen. In other embodiments, R_5' is (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, or (C_1-C_3) haloalkoxy. In other embodiments, R_5' is (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, or halogen. In other embodiments, R_5' is (C_1-C_3) alkyl or halogen. In other embodiments, R_5' is methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_5' is methyl or ethyl. In other embodiments, R_5' is methyl.

In some embodiments, each R_5 is independently (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, halogen, or oxo. In other embodiments, each R_5 is independently (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, or (C_1-C_3) haloalkoxy. In other embodiments, each R_5 is independently (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, halogen, or oxo. In other embodiments, each R_5 is independently (C_1-C_3) alkyl, halogen, or oxo. In other embodiments, each R_5 is independently (C_1-C_3) alkyl or oxo. In other embodiments, each R_5 is independently methyl, ethyl, n-propyl, i-propyl, or oxo. In other embodiments, each R_5 is independently methyl, ethyl, or oxo. In other embodiments, each R_5 is independently methyl or oxo.

In some embodiments, R_6 is H, (C_1-C_3) alkyl, or (C_1-C_3) haloalkyl. In other embodiments, R_6 is H or (C_1-C_4) alkyl. In other embodiments, R_6 is H or (C_1-C_3) alkyl. In other embodiments, R_6 is H, methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_6 is H, methyl, or ethyl. In other embodiments, R_6 is (C_1-C_4) alkyl. In other embodiments, R_6 is methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_6 is H. In other embodiments, R_6 is methyl or ethyl. In other embodiments, R_6 is methyl.

In some embodiments, each R_7 is independently (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_3) alkoxy, (C_1-C_3) haloalkoxy, (C_1-C_3) hydroxyalkyl, halogen, OH, or NH_2. In other embodiments, each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, (C_1-C_4) hydroxyalkyl, halogen, or OH. In other embodiments, each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, (C_1-C_4) hydroxyalkyl, or OH. In other embodiments, each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) hydroxyalkyl, halogen, or OH. In other embodiments, each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) hydroxyalkyl, or OH. In other embodiments, each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) hydroxyalkyl, or OH. In other embodiments, each R_7 is independently

$(C_1\text{-}C_4)$ alkyl or $(C_1\text{-}C_4)$ hydroxyalkyl. In other embodiments, each R_7 is independently $(C_1\text{-}C_3)$ alkyl or $(C_1\text{-}C_3)$ hydroxyalkyl. In other embodiments, each R_7 is independently $(C_1\text{-}C_3)$ alkyl. In other embodiments, each R_7 is independently $(C_1\text{-}C_3)$ hydroxyalkyl. In other embodiments, each R_7 is independently methyl, ethyl, n-propyl, i-propyl, or $(C_1\text{-}C_3)$ hydroxyalkyl. In other embodiments, each R_7 is independently methyl, ethyl, n-propyl, i-propyl, CH_2OH, CH_2CH_2OH, $CH_2CH_2CH_2OH$, $CH(OH)CH_3$, $CH(OH)CH_2CH_3$, or $CH_2CH(OH)CH_3$. In other embodiments, each R_7 is independently methyl, ethyl, CH_2OH, CH_2CH_2OH, or $CH(OH)CH_3$. In other embodiments, each R_7 is independently methyl, ethyl, CH_2OH, or CH_2CH_2OH. In other embodiments, each R_7 is independently methyl or CH_2OH. In other embodiments, each R_7 is independently methyl, ethyl, n-propyl, or i-propyl. In other embodiments, each R_7 is independently methyl or ethyl. In other embodiments, at least one R_7 is methyl.

In some embodiments, each R_8 is independently $(C_1\text{-}C_3)$ alkyl, $(C_1\text{-}C_3)$ haloalkyl, $(C_1\text{-}C_3)$ alkoxy, $(C_1\text{-}C_3)$ haloalkoxy, halogen, OH, or NH_2. In other embodiments, each R_8 is independently $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, $(C_1\text{-}C_4)$ alkoxy, $(C_1\text{-}C_4)$ haloalkoxy, or halogen. In other embodiments, each R_8 is independently $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, $(C_1\text{-}C_4)$ alkoxy, $(C_1\text{-}C_4)$ haloalkoxy, or halogen. In other embodiments, each R_8 is independently $(C_1\text{-}C_4)$ alkyl, $(C_1\text{-}C_4)$ haloalkyl, or halogen. In other embodiments, each R_8 is independently $(C_1\text{-}C_4)$ alkyl or halogen. In other embodiments, each R_8 is independently methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, F, or Cl. In other embodiments, each R_8 is independently n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, F, or Cl. In other embodiments, each R_8 is independently i-propyl, i-butyl, t-butyl, or F. In other embodiments, each R_8 is independently i-propyl, t-butyl, or F. In other embodiments, each R_8 is independently t-butyl or F. In other embodiments, at least one R_8 is F. In other embodiments, at least one R_8 is t-butyl.

In some embodiments, each R_9 is independently $(C_1\text{-}C_3)$ alkyl, $(C_1\text{-}C_3)$ haloalkyl, $(C_1\text{-}C_3)$ alkoxy, $(C_1\text{-}C_3)$ haloalkoxy, or halogen. In other embodiments, each R_9 is independently $(C_1\text{-}C_3)$ alkyl, $(C_1\text{-}C_3)$ haloalkyl, or halogen. In other embodiments, each R_9 is independently $(C_1\text{-}C_3)$ alkoxy, $(C_1\text{-}C_3)$ haloalkoxy, or halogen. In other embodiments, each R_9 is independently $(C_1\text{-}C_3)$ alkyl, $(C_1\text{-}C_3)$ alkoxy, or halogen. In other embodiments, each R_9 is independently $(C_1\text{-}C_3)$ alkyl, or halogen. In other embodiments, each R_9 is independently methyl, ethyl, n-propyl, i-propyl, F or Cl.

In some embodiments, R_{10a} is H, (C_1-C_3) alkyl, or (C_1-C_3) haloalkyl. In other embodiments, R_{10a} is (C_1-C_4) alkyl or (C_1-C_4) haloalkyl. In other embodiments, R_{10a} is H or (C_1-C_4) alkyl. In other embodiments, R_{10a} is H, methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_{10a} is H, methyl or ethyl. In other embodiments, R_{10a} is (C_1-C_4) alkyl. In other embodiments, R_{10a} is methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_{10a} is methyl or ethyl. In other embodiments, R_{10a} is H.

In some embodiments, R_{10b} is H, (C_1-C_3) alkyl, or (C_1-C_3) haloalkyl. In other embodiments, R_{10b} is (C_1-C_4) alkyl or (C_1-C_4) haloalkyl. In other embodiments, R_{10b} is H or (C_1-C_4) alkyl. In other embodiments, R_{10b} is H, methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_{10b} is H, methyl or ethyl. In other embodiments, R_{10b} is (C_1-C_4) alkyl. In other embodiments, R_{10b} is methyl, ethyl, n-propyl, or i-propyl. In other embodiments, R_{10b} is methyl or ethyl. In other embodiments, R_{10b} is H.

In some embodiments, o1 is 0. In other embodiments, o1 is 1. In other embodiments, o1 is 2. In other embodiments, o1 is 3. In other embodiments, o1 is 0 or 1. In other embodiments, o1 is 1 or 2. In other embodiments, o1 is 2 or 3. In other embodiments, o1 is 0, 1 or 2. In other embodiments, o1 is 1, 2, or 3.

In some embodiments, o2 is 0. In other embodiments, o2 is 1. In other embodiments, o2 is 2. In other embodiments, o2 is 3. In other embodiments, o2 is 0 or 1. In other embodiments, o2 is 1 or 2. In other embodiments, o2 is 2 or 3. In other embodiments, o2 is 0, 1 or 2. In other embodiments, o2 is 1, 2, or 3.

In some embodiments, o3 is 0. In other embodiments, o3 is 1. In other embodiments, o3 is 2. In other embodiments, o3 is 3. In other embodiments, o3 is 0 or 1. In other embodiments, o3 is 1 or 2. In other embodiments, o3 is 2 or 3. In other embodiments, o3 is 0, 1 or 2. In other embodiments, o3 is 1, 2, or 3.

Any of the groups described herein for any of B, Y_1, Y_2, Y_3, Y_4, R_5, R_5', R_6, R_7, R_8, R_9, R_{10a}, R_{10b}, o1, o2, and o3 can be combined with any of the groups described herein for one or more of the remainder of B, Y_1, Y_2, Y_3, Y_4, R_5, R_5', R_6, R_7, R_8, R_9, R_{10a}, R_{10b}, o1, o2, and o3, and may further be combined with any of the groups described herein for the Linker.

For a Targeting Ligand of Formula TL-I:

(1) In one embodiment, B is phenyl and Y_2 is NR_{10a}.

(2) In one embodiment, B is phenyl, Y_2 is NR_{10a}, and Y_1 is C(O).

(3) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(4) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(5) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(6) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(7) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(8) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and Y_3 is C(O)NR_{10b}.

(9) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(10) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(11) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(12) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently halogen.

(13) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(14) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(15) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently halogen.

(16) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(17) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(18) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently halogen.

(19) In one embodiment, B is phenyl, Y_2 is NR_{10a}, and Y_1 is absent.

(20) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, and R_6 is (C_1-C_4) alkyl.

(21) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(22) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(23) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(24) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(25) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and Y_3 is C(O)NR_{10b}.

(26) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(27) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(28) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(29) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(30) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(31) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl.

(32) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(33) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(34) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl.

(35) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(36) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(37) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(38) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(39) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(40) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(41) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(42) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(43) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(44) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(45) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(46) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(47) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(48) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(49) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(50) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(51) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(52) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(53) In one embodiment, B is phenyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(54) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(53), and R_{10a} is H.

(55) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(53), and R_{10b} is H.

(56) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(53), R_{10a} is H, and R_{10b} is H.

(57) In one embodiment, B is pyridinyl and Y_2 is NR_{10a}.

(58) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, and Y_1 is absent.

(59) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, and R_6 is (C_1-C_4) alkyl.

(60) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(61) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(62) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(63) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and Y_3 is $C(O)NR_{10b}$.

(64) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and Y_3 is $C(O)NR_{10b}$.

(65) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and Y_3 is $C(O)NR_{10b}$.

(66) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(67) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl.

(68) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(69) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(70) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl.

(71) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(72) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(73) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently (C_1-C_4) alkyl.

(74) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(75) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(76) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(77) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(78) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(79) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(80) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(81) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(82) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(83) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(84) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, and Y_1 is C(O).

(85) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(86) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(87) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(88) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(89) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(90) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and Y_3 is C(O)NR_{10b}.

(91) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and Y_3 is C(O)NR_{10b}.

(92) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(93) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(94) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently halogen.

(95) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(96) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(97) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently halogen.

(98) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(99) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is C(O)NR_{10b}, and each R_8 is independently (C_1-C_4) alkyl.

(100) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, Y_3 is $C(O)NR_{10b}$, and each R_8 is independently halogen.

(101) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(102) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(103) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(104) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(105) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(106) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(107) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(108) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(109) In one embodiment, B is pyridinyl, Y_2 is NR_{10a}, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(110) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (57)-(109), and R_{10a} is H.

(111) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (57)-(109), and R_{10b} is H.

(112) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (57)-(109), R_{10a} is H, and R_{10b} is H.

(113) In one embodiment, B is pyridinyl and R_6 is methyl.

(114) In one embodiment, B is phenyl and R_6 is methyl.

(115) In one embodiment, R_6 is methyl and Y_2 is NR_{10a}.

(116) In one embodiment, B is pyridinyl and Y_1 is absent.

(117) In one embodiment, B is phenyl and Y_1 is absent.

(118) In one embodiment, B is pyridinyl and Y_1 is C(O).

(119) In one embodiment, B is phenyl and Y_1 is C(O).

(120) In one embodiment, B is pyridinyl and Y_3 is $C(O)NR_{10b}$.

(121) In one embodiment, B is phenyl and Y_3 is $C(O)NR_{10b}$.

(122) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 0.

(123) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 1.

(124) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 2.

(125) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 2, and R_5 is (C_1-C_4) alkyl or oxo.

(126) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o2 is 1.

(127) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o2 is 2.

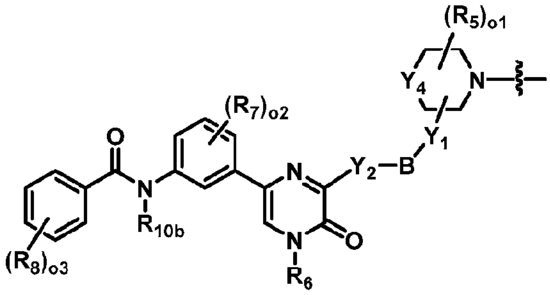
(128) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 0 and o2 is 1.

(129) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is1 and o2 is 1.

(130) In one embodiment, B, Y_1, Y_2, Y_3, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(121), o1 is 2 and o2 is 1.

(131) In one embodiment, B, Y_1, Y_2, Y_3, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, and o2 are each as defined, where applicable, in any one of (1)-(130), and Y_1 is bonded to Y_4.

In one embodiment, the compound of Formula TL-I is of Formula TL-Ia:



(TL-Ia),

wherein B, Y_1, Y_2, Y_4, R_5, R_6, R_7, R_8, R_{10b}, o1, o2, and o3 are each as defined above in Formula TL-I.

For a Targeting Ligand of Formula TL-Ia:

(1) In one embodiment, B is phenyl.

(2) In one embodiment, B is phenyl, and Y_1 is C(O).

(3) In one embodiment, B is phenyl, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(4) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(5) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(6) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(7) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(8) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(9) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(10) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(11) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(12) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(13) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(14) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(15) In one embodiment, B is phenyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(16) In one embodiment, B is phenyl, and Y_1 is absent.

(17) In one embodiment, B is phenyl, Y_1 is absent, and R_6 is (C_1-C_4) alkyl.

(18) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(19) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(20) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(21) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(22) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(23) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(24) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(25) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(26) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(27) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(28) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(29) In one embodiment, B is phenyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(30) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(29), and Y_2 is NR_{10a}.

(31) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(29), and Y_2 is O.

(32) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(29), and R_{10a} is H.

(33) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(29), and R_{10b} is H.

(34) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(29), and Y_2 is NR_{10a} and R_{10a} is H.

(35) In one embodiment, B is pyridinyl.

(36) In one embodiment, B is pyridinyl, and Y_1 is C(O).

(37) In one embodiment, B is pyridinyl, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(38) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(39) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(40) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(41) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(42) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(43) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(44) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(45) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(46) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(47) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(48) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(49) In one embodiment, B is pyridinyl, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(50) In one embodiment, B is pyridinyl, and Y_1 is absent.

(51) In one embodiment, B is pyridinyl, Y_1 is absent, and R_6 is (C_1-C_4) alkyl.

(52) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(53) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(54) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(55) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(56) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(57) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(58) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(59) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(60) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(61) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(62) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(63) In one embodiment, B is pyridinyl, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(64) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (35)-(63), and Y_2 is NR_{10a}.

(65) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (35)-(63), and Y_2 is O.

(66) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (35)-(63), and R_{10a} is H.

(67) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (35)-(63), and R_{10b} is H.

(68) In one embodiment, B, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (35)-(63), and Y_2 is NR_{10a} and R_{10a} is H.

(69) In one embodiment, B is pyridinyl and R_6 is methyl.

(70) In one embodiment, B is phenyl and R_6 is methyl.

(71) In one embodiment, R_6 is methyl and Y_1 is absent.

(72) In one embodiment, R_6 is methyl and Y_1 is C(O).

(73) In one embodiment, R_6 is methyl and Y_2 is NR_{10a}.

(74) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 0.

(75) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 1.

(76) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 2.

(77) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o3 is 1.

(78) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o3 is 1.

(79) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 0 and o2 is 1.

(80) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o2 is 1 and o3 is 1.

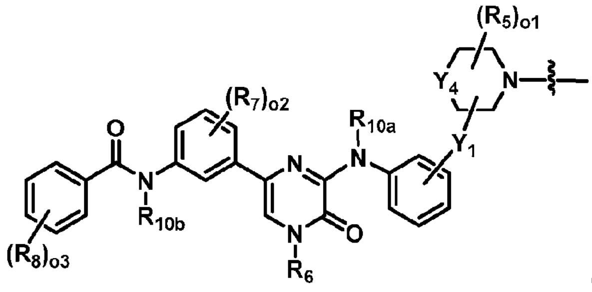
(81) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 0, o2 is 1, and o3 is 1.

(82) In one embodiment, B, Y_1, Y_2, R_6, R_7, R_8, R_{10a},and R_{10b} are each as defined, where applicable, in any one of (1)-(73), o1 is 2, and R_5 is (C_1-C_4) alkyl or oxo.

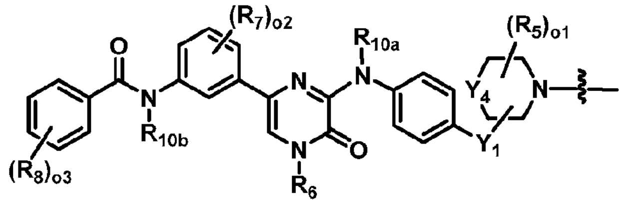
(83) In one embodiment, B, Y_1, Y_2, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, and o2 are each as defined, where applicable, in any one of (1)-(82), and Y_1 is bonded to Y_4.

B, Y_1, Y_2, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, o2, and o3 can each be selected from any of the groups and combined as described above in Formula TL-I or TL-Ia.

In one embodiment, the compound of Formula TL-I is of Formula TL-Ib or TL-Ic:



(TL-Ib), or



(TL-Ic),

wherein Y_1, Y_4, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, o2, and o3 are each as defined above in Formula TL-I.

For a Targeting Ligand of Formula TL-Ib and TL-Ic:

(1) In one embodiment, Y_1 is C(O).

(2) In one embodiment, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(3) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(4) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(5) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(6) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(7) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(8) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(9) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(10) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(11) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(12) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(13) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(14) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(15) In one embodiment, Y_1 is absent.

(16) In one embodiment, Y_1 is absent and R_6 is (C_1-C_4) alkyl.

(17) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(18) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(19) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(20) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(21) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(22) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(23) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(24) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(25) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(26) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(27) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(28) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(29) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(28), and R_{10a} is H.

(30) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(28), and R_{10b} is H.

(31) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(28), and Y_2 is NR_{10a} and R_{10a} is H.

(32) In one embodiment, R_6 is methyl.

(33) In one embodiment, R_6 is methyl and Y_1 is absent.

(34) In one embodiment, R_6 is methyl and Y_1 is C(O).

(35) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 0.

(36) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 1.

(37) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 2.

(38) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o3 is 1.

(39) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o3 is 1.

(40) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 0 and o2 is 1.

(41) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o2 is 1 and o3 is 1.

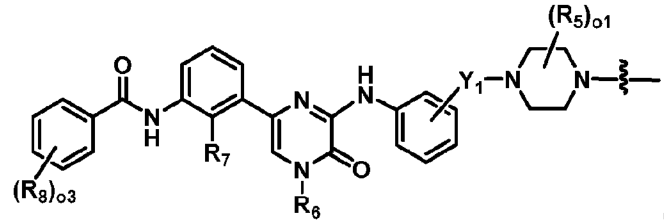
(42) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 0, o2 is 1, and o3 is 1.

(43) In one embodiment, Y_1, R_6, R_7, R_8, R_{10a}, and R_{10b} are each as defined, where applicable, in any one of (1)-(34), o1 is 2, and R_5 is (C_1-C_4) alkyl or oxo.

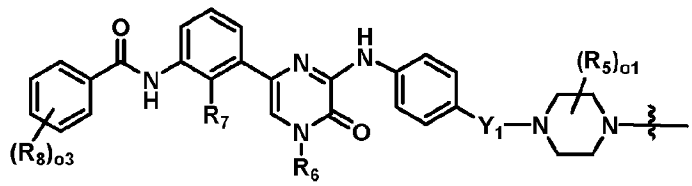
(44) In one embodiment, Y_1, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, o2, and o3 are each as defined, where applicable, in any one of (1)-(43), and Y_1 is bonded to Y_4.

Y_1, R_5, R_6, R_7, R_8, R_{10a}, R_{10b}, o1, o2, and o3 can each be selected from any of the groups and combined as described above in Formula TL-I, TL-Ib, or TL-Ic.

In one embodiment, the compound of Formula TL-I is of Formula TL-Id or TL-Ie:



(TL-Id), or



(TL-Ie),

wherein Y_1, R_5, R_6, R_7, R_8, o1, and o3 are each as defined above in Formula TL-I.

For a Targeting Ligand of Formula TL-Id and TL-Ie:

(1) In one embodiment, Y_1 is C(O).

(2) In one embodiment, Y_1 is C(O), and R_6 is (C_1-C_4) alkyl.

(3) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(4) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(5) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(6) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(7) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(8) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(9) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(10) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(11) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(12) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(13) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(14) In one embodiment, Y_1 is C(O), R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(15) In one embodiment, Y_1 is absent.

(16) In one embodiment, Y_1 is absent and R_6 is (C_1-C_4) alkyl.

(17) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

(18) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) alkyl.

(19) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, and each R_7 is independently (C_1-C_4) hydroxyalkyl.

(20) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(21) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(22) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(23) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(24) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently (C_1-C_4) alkyl.

(25) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) alkyl, and each R_8 is independently halogen.

(26) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl or halogen.

(27) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently (C_1-C_4) alkyl.

(28) In one embodiment, Y_1 is absent, R_6 is (C_1-C_4) alkyl, each R_7 is independently (C_1-C_4) hydroxyalkyl, and each R_8 is independently halogen.

(29) In one embodiment, R_6 is methyl.

(30) In one embodiment, R_6 is methyl and Y_1 is absent.

(31) In one embodiment, R_6 is methyl and Y_1 is C(O).

(32) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o1 is 0.

(33) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o1 is 1.

(34) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o3 is 1.

(35) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o3 is 1.

(36) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o1 is 0 and o3 is 1.

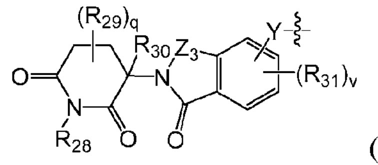
(37) In one embodiment, Y_1, R_6, R_7, and R_8 are each as defined, where applicable, in any one of (1)-(31), o1 is 2, and R_5 is (C_1-C_4) alkyl or oxo.

Y_1, R_5, R_6, R_7, R_8, o1, and o3 can each be selected from any of the groups and combined as described above in Formula TL-I, TL-Id, or TL-Ie.

Degron

The Degron serves to link a targeted protein, through a Linker and a Targeting Ligand, to a ubiquitin ligase for proteosomal degradation. In one embodiment, the Degron is capable of binding to a ubiquitin ligase, such as an E3 ubiquitin ligase. In one embodiment, the Degron is capable of binding to cereblon.

In one embodiment, the Degron is of Formula D1:



(D1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

Y is a bond, $(CH_2)_{1-6}$, $(CH_2)_{0-6}$-O, $(CH_2)_{0-6}$-C(O)NR_{26}, $(CH_2)_{0-6}$-NR_{26}C(O), $(CH_2)_{0-6}$-NH, or $(CH_2)_{0-6}$-NR_{27};

Z_3 is C(O) or $C(R_{28})_2$;

R_{26} is H or C_1-C_6 alkyl;

R_{27} is C_1-C_6 alkyl or C(O)-C_1-C_6 alkyl;

each R_{28} is independently H or C_1-C_3 alkyl;

each R_{29} is independently C_1-C_3 alkyl;

R_{30} is H, deuterium, C_1-C_3 alkyl, F, or Cl;

each R_{31} is independently halogen, OH, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q is 0, 1, or 2; and

v is 0, 1, 2, or 3,

wherein the Degron is covalently bonded to the Linker via $\sim$.

In one embodiment, Z_3 is C(O).

In one embodiment, Z_3 is C(O) or CH_2.

In one embodiment, Z_3 is $C(R_{28})_2$; and each R_{28} is H. In one embodiment, Z_3 is $C(R_{28})_2$; and one of R_{28} is H, and the other is C_1-C_3 alkyl selected from methyl, ethyl, and propyl. In one embodiment, Z_3 is $C(R_{28})_2$; and each R_{28} is independently selected from methyl, ethyl, and propyl.

In one embodiment, Y is a bond.

In one embodiment, Y is a bond, O, or NH.

In one embodiment, Y is $(CH_2)_1$, $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2)_5$, or $(CH_2)_6$. In one embodiment, Y is $(CH_2)_1$, $(CH_2)_2$, or $(CH_2)_3$. In one embodiment, Y is $(CH_2)_1$ or $(CH_2)_2$.

In one embodiment, Y is O, CH_2-O, $(CH_2)_2$-O, $(CH_2)_3$-O, $(CH_2)_4$-O, $(CH_2)_5$-O, or $(CH_2)_6$-O. In one embodiment, Y is O, CH_2-O, $(CH_2)_2$-O, or $(CH_2)_3$-O. In one embodiment, Y is O or CH_2-O. In one embodiment, Y is O.

In one embodiment, Y is C(O)NR_{26}, CH_2-C(O)NR_{26}, $(CH_2)_2$-C(O)NR_{26}, $(CH_2)_3$-C(O)NR_{26}, $(CH_2)_4$-C(O)NR_{25}, $(CH_2)_5$-C(O)NR_{26}, or $(CH_2)_6$-C(O)NR_{26}. In one embodiment, Y is C(O)R_{26}, CH_2-C(O)NR_{26}, $(CH_2)_2$-C(O)NR_{26}, or $(CH_2)_3$-C(O)NR_{26}. In one embodiment, Y is C(O)NR_{26} or CH_2-C(O)NR_{26}. In one embodiment, Y is C(O)NR_{26}.

In one embodiment, Y is NR_{26}C(O), CH_2-NR_{26}C(O), $(CH_2)_2$-NR_{26}C(O), $(CH_2)_3$-NR_{26}C(O), $(CH_2)_4$-NR_{26}C(O), $(CH_2)_5$-NR_{26}C(O), or $(CH_2)_6$-NR_{26}C(O). In one embodiment, Y is NR_{26}C(O), CH_2-NR_{26}C(O), $(CH_2)_2$-NR_{26}C(O), or $(CH_2)_3$-NR_{26}C(O). In one embodiment, Y is NR_{26}C(O) or CH_2-NR_{26}C(O). In one embodiment, Y is NR_{26}C(O).

In one embodiment, R_{26} is H. In one embodiment, R_{26} is selected from methyl, ethyl, propyl, butyl, i-butyl, t-butyl, pentyl, i-pentyl, and hexyl. In one embodiment, R_{26} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, Y is NH, CH_2-NH, $(CH_2)_2$-NH, $(CH_2)_3$-NH, $(CH_2)_4$-NH, $(CH_2)_5$-NH, or $(CH_2)_6$-NH. In one embodiment, Y is NH, CH_2-NH, $(CH_2)_2$-NH, or $(CH_2)_3$-NH. In one embodiment, Y is NH or CH_2-NH. In one embodiment, Y is NH.

In one embodiment, Y is NR_{27}, CH_2-NR_{27}, $(CH_2)_2$-NR_{27}, $(CH_2)_3$-NR_{27}, $(CH_2)_4$-NR_{27}, $(CH_2)_5$-NR_{27}, or $(CH_2)_6$-NR_{27}. In one embodiment, Y is N R_{27}, CH_2-NR_{27}, $(CH_2)_2$-NR_{27}, or $(CH_2)_3$-NR_{27}. In one embodiment, Y is NR_{27} or CH_2-NR_{27}. In one embodiment, Y is NR_{27}.

In one embodiment, R_{27} is selected from methyl, ethyl, propyl, butyl, i-butyl, t-butyl, pentyl, i-pentyl, and hexyl. In one embodiment, R_{27} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, R_{27} is selected from C(O)-methyl, C(O)-ethyl, C(O)-propyl, C(O)-butyl, C(O)-i-butyl, C(O)-t-butyl, C(O)-pentyl, C(O)-i-pentyl, and C(O)-hexyl. In one embodiment, R_{27} is C(O)-C_1-C_3 alkyl selected from C(O)-methyl, C(O)-ethyl, and C(O)-propyl.

In one embodiment, R_{28} is H.

In one embodiment, R_{28} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl. In one embodiment, R_{28} is methyl.

In one embodiment, q is 0.

In one embodiment, q is 1.

In one embodiment, q is 2.

In one embodiment, each R_{29} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, v is 0.

In one embodiment, v is 1.

In one embodiment, v is 2.

In one embodiment, v is 3.

In one embodiment, each R_{31} is independently selected from halogen (*e.g.*, F, Cl, Br, and I), OH, C_1-C_6 alkyl (*e.g.*, methyl, ethyl, propyl, butyl, i-butyl, t-butyl, pentyl, i-pentyl, and hexyl), and C_1-C_6 alkoxy (*e.g.*, methoxy, ethoxy, propoxy, butoxy, i-butoxy, t-butoxy, and pentoxy). In a further embodiment, each R_{31} is independently selected from F, Cl, OH, methyl, ethyl, propyl, butyl, i-butyl, t-butyl, methoxy, and ethoxy.

In one embodiment, R_{30} is H, deuterium, or C_1-C_3 alkyl. In another embodiment, R_{30} is H or C_1-C_3 alkyl. In a further embodiment, R_{30} is in the (*S*) or (*R*) configuration. In a further embodiment, R_{30} is in the (*S*) configuration. In one embodiment, the compound comprises a racemic mixture of (*S*)-R_{30} and (*R*)-R_{30}.

In one embodiment, R_{30} is H.

In one embodiment, R_{30} is deuterium.

In one embodiment, R_{30} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl. In one embodiment, R_{30} is methyl.

In one embodiment, R_{30} is F or Cl. In a further embodiment, R_{30} is in the (*S*) or (*R*) configuration. In a further embodiment, R_{30} is in the (*R*) configuration. In one embodiment, the compound comprises a racemic mixture of (*S*)-R_{30} and (*R*)-R_{30}. In one embodiment, R_{30} is F.

Any of the groups described herein for any of Y, Z_3, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, q and v can be combined with any of the groups described herein for one or more of the remainder of Y, Z_3, R_{26}, R_{27}, R_{28}, R_{29}, R_{30}, R_{31}, q and v, and may further be combined with any of the groups described herein for the Linker.

For a Degron of Formula D1:

(1) In one embodiment, Z_3 is C(O) and Y is a bond.

(2) In one embodiment, Z_3 is C(O) and Y is NH.

(3) In one embodiment, Z_3 is C(O) and Y is $(CH_2)_{0\text{-}6}$-O. In a further embodiment, Y is O.

(4) In one embodiment, Z_3 is C(O); Y is a bond; and q and v are each 0.

(5) In one embodiment, Z_3 is C(O); Y is NH; and q and v are each 0.

(6) In one embodiment, Z_3 is C(O); Y is $(CH_2)_{0-6}$-O; and q and v are each 0. In a further embodiment, Y is O.

(7) In one embodiment, Z_3 is C(O); Y is a bond; and R_{28} is H.

(8) In one embodiment, Z_3 is C(O); Y is a bond; and R_{28} is H.

(9) In one embodiment, Z_3 is C(O); Y is NH; and R_{28} is H.

(10) In one embodiment, Z_3 is C(O); Y is NH; and R_{30} is H.

(11) In one embodiment, Z_3 is C(O); Y is a bond; R_{28} is H; and R_{30} is H.

(12) In one embodiment, Z_3 is C(O); Y is NH; R_{28} is H; and R_{30} is H.

(13) In one embodiment, Z_3 is C(O); Y is $(CH_2)_{0-6}$-O; and R_{28} is H. In a further embodiment, Y is O.

(14) In one embodiment, Z_3 is C(O); Y is $(CH_2)_{0-6}$-O; and R_{30} is H. In a further embodiment, Y is O.

(15) In one embodiment, Z_3 is C(O); Y is $(CH_2)_{0-6}$-O; R_{28} is H; and R_{30} is H. In a further embodiment, Y is O.

(16) In one embodiment, q and v are each 0; and Y, Z_3, R_{28}, R_{30}, and R_{31} are each as defined in any of (1) – (3) and (7) – (15).

(17) In one embodiment, Z_3 is CH_2 and Y is a bond.

(18) In one embodiment, Z_3 is CH_2 and Y is NH.

(19) In one embodiment, Z_3 is CH_2 and Y is $(CH_2)_{0-6}$-O. In a further embodiment, Y is O.

(20) In one embodiment, Z_3 is CH_2; Y is a bond; and q and v are each 0.

(21) In one embodiment, Z_3 is CH_2; Y is NH; and q and v are each 0.

(22) In one embodiment, Z_3 is CH_2; Y is $(CH_2)_{0-6}$-O; and q and v are each 0. In a further embodiment, Y is O.

(23) In one embodiment, Z_3 is CH_2; Y is a bond; and R_{28} is H.

(24) In one embodiment, Z_3 is CH_2; Y is a bond; and R_{30} is H.

(25) In one embodiment, Z_3 is CH_2; Y is NH; and R_{28} is H.

(26) In one embodiment, Z_3 is CH_2; Y is NH; and R_{30} is H.

(27) In one embodiment, Z_3 is CH_2; Y is a bond; R_{28} is H; and R_{30} is H.

(28) In one embodiment, Z_3 is CH_2; Y is NH; R_{28} is H; and R_{30} is H.

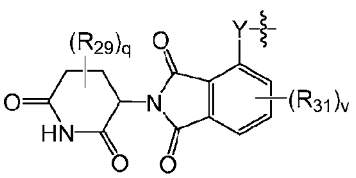
(29) In one embodiment, Z_3 is CH_2; Y is $(CH_2)_{0\text{-}6}$-O; and R_{28} is H. In a further embodiment, Y is O.

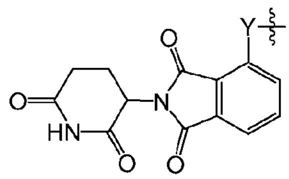
(30) In one embodiment, Z_3 is CH_2; Y is $(CH_2)_{0\text{-}6}$-O; and R_{30} is H. In a further embodiment, Y is O.

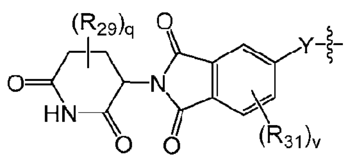
(31) In one embodiment, Z_3 is CH_2; Y is $(CH_2)_{0\text{-}6}$-O; R_{28} is H; and R_{30} is H. In a further embodiment, Y is O.

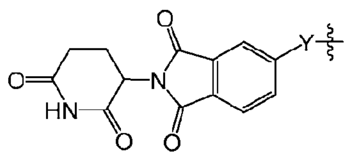
(32) In one embodiment, q and v are each 0; and Y, Z_3, R_{28}, R_{30}, and R_{31} are each as defined in any of (17) – (19) and (23) – (31).

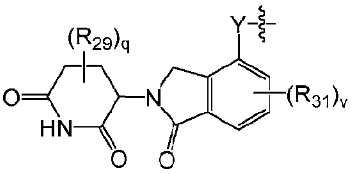
In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l:

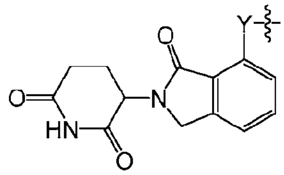

(D1a),

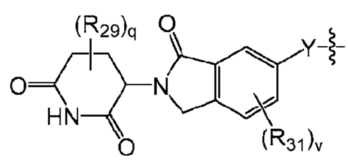

(D1b),

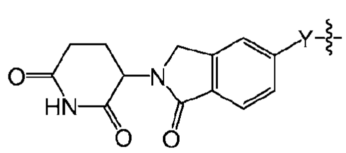

(D1c),

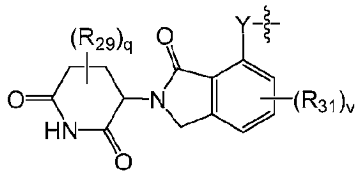

(D1d),

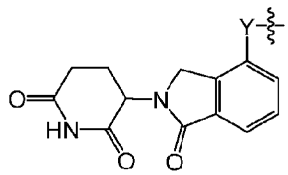

(D1e),

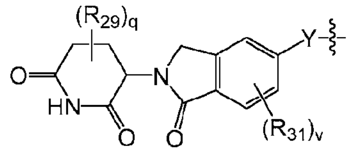
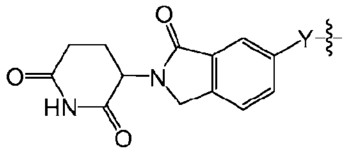

(D1f),


(D1g)


(D1h),


(D1i),

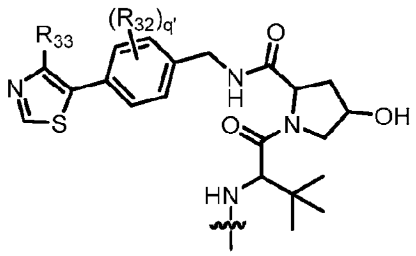

(D1j),

 (D1k) or  (D1l).

or an enantiomer, diastereomer, or stereoisomer thereof, wherein Y, R_{29}, R_{31}, q, and v are each as defined above in Formula D1, and can be selected from any moieties or combinations thereof described above.

In one embodiment, Y is a bond, O, or NH. In one embodiment, Y is a bond. In one embodiment, Y is O. In one embodiment, Y is NH.

In one embodiment, the Degron is of Formula D2:

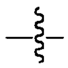
 (D2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

each R_{32} is independently C_1-C_3 alkyl;

q' is 0, 1, 2, 3 or 4; and

R_{33} is H or C_1-C_3 alkyl,

wherein the Degron is covalently bonded to another moiety (*e.g.*, a compound, or a Linker) via .

In one embodiment, q' is 0.

In one embodiment, q' is 1.

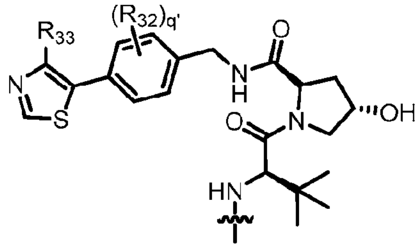
In one embodiment, q' is 2.

In one embodiment, q' is 3.

In one embodiment, each R_{32} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, R_{33} is methyl, ethyl, or propyl. In one embodiment, R_{33} is methyl.

In one embodiment, the Degron is of Formula D2a:



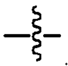
(D2a),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

each R_{32} is independently C_1-C_3 alkyl;

q' is 0, 1, 2, 3 or 4; and

R_{33} is H or C_1-C_3 alkyl,

wherein the Degron is covalently bonded to another moiety (*e.g.*, a compound, or a Linker) via .

In one embodiment, q' is 0.

In one embodiment, q' is 1.

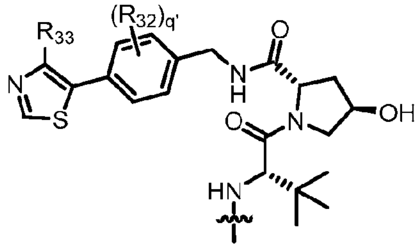
In one embodiment, q' is 2.

In one embodiment, q' is 3.

In one embodiment, each R_{32} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, R_{33} is methyl, ethyl, or propyl. In one embodiment, R_{33} is methyl.

In one embodiment, the Degron is of Formula D2b:



(D2b),

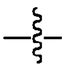
or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

each R_{32} is independently C_1-C_3 alkyl;

q' is 0, 1, 2, 3 or 4; and

R_{33} is H or C_1-C_3 alkyl,

wherein the Degron is covalently bonded to another moiety (*e.g.*, a compound, or a Linker) via

.

In one embodiment, q' is 0.

In one embodiment, q' is 1.

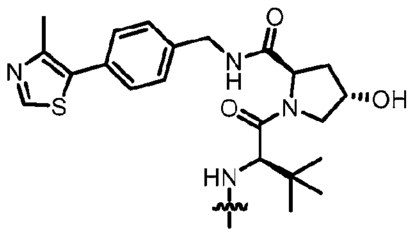
In one embodiment, q' is 2.

In one embodiment, q' is 3.

In one embodiment, each R_{32} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

In one embodiment, R_{33} is methyl, ethyl, or propyl. In one embodiment, R_{33} is methyl.

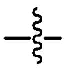
In one embodiment, the Degron is of Formula D2c:



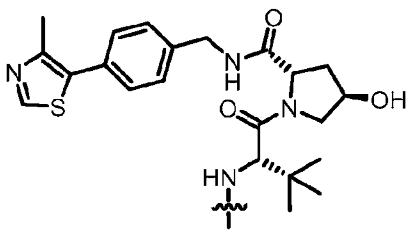
(D2c),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

wherein the Degron is covalently bonded to another moiety (*e.g.*, a compound, or a Linker) via

.

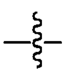
In one embodiment, the Degron is of Formula D2d:



(D2d),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

wherein the Degron is covalently bonded to another moiety (*e.g.*, a compound, or a Linker) via

.

Linker

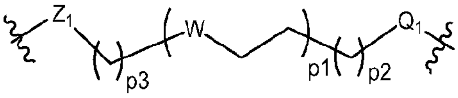
The Linker is a bond, a carbon chain, carbocyclic ring, or heterocyclic ring that serves to link a Targeting Ligand with a Degron. In one embodiment, the carbon chain optionally comprises one, two, three, or more heteroatoms selected from N, O, and S. In one embodiment, the carbon chain comprises only saturated chain carbon atoms. In one embodiment, the carbon chain optionally comprises two or more unsaturated chain carbon atoms (*e.g.*, $C{=}C$ or $C{\equiv}C$). In one embodiment, one or more chain carbon atoms in the carbon chain are optionally substituted with one or more substituents (*e.g.*, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_3 alkoxy, OH, halogen, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl$)_2$, CN, C_3-C_8 cycloalkyl, heterocyclyl, phenyl, and heteroaryl).

In one embodiment, the Linker comprises at least 5 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises less than 25 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises less than 20 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 5, 7, 9, 11, 13, 15, 17, or 19 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 5, 7, 9, or 11 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 11, 13, 15, 17, or 19 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 11, 13, 15, 17, 19, 21, or 23 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 6, 8, 10, 12, 14, 16, 18, 20, 22, or 24 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 6, 8, 10, 12, 14, 16, 18, or 20 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 6, 8, 10, or 12 chain atoms (*e.g.*, C, O, N, and S). In one embodiment, the Linker comprises 12, 14, 16, 18, or 20 chain atoms (*e.g.*, C, O, N, and S).

In one embodiment, the Linker comprises from 11 to 19 chain atoms (*e.g.*, C, O, N, and S).

In one embodiment, the Linker is a carbon chain optionally substituted with non-bulky substituents (*e.g.*, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_3 alkoxy, OH, halogen, NH_2, $NH(C_1$-C_3 alkyl), $N(C_1$-C_3 alkyl$)_2$, and CN). In one embodiment, the non-bulky substitution is located on the chain carbon atom proximal to the Degron (*i.e.*, the carbon atom is separated from the carbon atom to which the Degron is bonded by at least 3, 4, or 5 chain atoms in the Linker). In one embodiment, the non-bulky substitution is located on the chain carbon atom proximal to the Targeting Ligand (*i.e.*, the carbon atom is separated from the carbon atom to which the Degron is bonded by at least 3, 4, or 5 chain atoms in the Linker).

In one embodiment, the Linker is of Formula L1:



(L1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein

p1 is an integer selected from 0 to 12;

p2 is an integer selected from 0 to 12;

p3 is an integer selected from 1 to 6;

each W is independently absent, CH_2, O, S, or NR_{24};

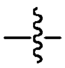
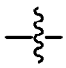
Z_1 is absent, C(O), CH_2, O, $(CH_2)_jNR_{24}$, $O(CH_2)_jC(O)NR_{24}$, $C(O)NR_{24}$, $(CH_2)_jC(O)NR_{24}$, $NR_{24}C(O)$, $(CH_2)_jNR_{24}C(O)$, $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$, or $NR_{24}(CH_2)_jC(O)NR_{24}$;

each R_{24} is independently H or C_1-C_3 alkyl;

j is 1, 2, or 3;

k is 1, 2, or 3; and

Q_1 is absent, C(O), $NHC(O)CH_2$, $OCH_2C(O)$, or $O(CH_2)_{1\text{-}2}$;

wherein the Linker is covalently bonded to a Degron via the  next to Q_1, and covalently bonded to a Targeting Ligand via the  next to Z_1.

In one embodiment, the total number of chain atoms in the Linker is less than 30. In a further embodiment, the total number of chain atoms in the Linker is less than 20.

For a Linker of Formula L1:

(1) In one embodiment, p1 is an integer selected from 0 to 10.

(2) In one embodiment, p1 is an integer selected from 1 to 10.

(3) In one embodiment, p1 is selected from 1, 2, 3, 4, 5, and 6.

(4) In one embodiment, p1 is 0, 1, 3, or 5.

(5) In one embodiment, p1 is 0, 1, 2, or 3.

(6) In one embodiment, p1 is 0.

(7) In one embodiment, p1 is 1.

(8) In one embodiment, p1 is 2.

(9) In one embodiment, p1 is 3.

(10) In one embodiment, p1 is 4.

(11) In one embodiment, p1 is 5.

(12) In one embodiment, p2 is an integer selected from 0 to 10.

(13) In one embodiment, p2 is selected from 0, 1, 2, 3, 4, 5, and 6.

(14) In one embodiment, p2 is 0, 1, 2, or 3.

(15) In one embodiment, p2 is 0.

(16) In one embodiment, p2 is 1.

(17) In one embodiment, p2 is 2.

(18) In one embodiment, p2 is 3.

(19) In one embodiment, p3 is an integer selected from 1 to 5.

(20) In one embodiment, p3 is 2, 3, 4, or 5.

(21) In one embodiment, p3 is 0, 1, 2, or 3.

(22) In one embodiment, p3 is 0.

(23) In one embodiment, p3 is 1.

(24) In one embodiment, p3 is 2.

(25) In one embodiment, p3 is 3.

(26) In one embodiment, p3 is 4.

(27) In one embodiment, at least one W is CH_2.

(28) In one embodiment, at least one W is O.

(29) In one embodiment, at least one W is S.

(30) In one embodiment, at least one W is NH.

(31) In one embodiment, at least one W is NR_{24}; and each R_{24} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(32) In one embodiment, each W is O.

(33) In one embodiment, each W is CH_2.

(34) In one embodiment, j is 1, 2, or 3.

(35) In one embodiment, j is 1.

(36) In one embodiment, j is 2.

(37) In one embodiment, j is 3.

(38) In one embodiment, j is 2 or 3.

(39) In one embodiment, j is 1 or 2.

(40) In one embodiment, k is 1, 2, or 3.

(41) In one embodiment, k is 1.

(42) In one embodiment, k is 2.

(43) In one embodiment, k is 3.

(44) In one embodiment, k is 2 or 3.

(45) In one embodiment, k is 1 or 2.

(46) In one embodiment, Q_1 is absent.

(47) In one embodiment, Q_1 is $NHC(O)CH_2$.

(48) In one embodiment, Q_1 is $O(CH_2)_{1-2}$.

(49) In one embodiment, Q_1 is OCH_2.

(50) In one embodiment, Q_1 is OCH_2CH_2.

(51) In one embodiment, Q_1 is $OCH_2C(O)$.

(52) In one embodiment, Q_1 is $C(O)$.

(53) In one embodiment, Z_1 is absent.

(54) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; and R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(55) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; and R_{24} is H.

(56) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1.

(57) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 1.

(58) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2.

(59) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 2.

(60) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3.

(61) In one embodiment, Z_1 is $O(CH_2)_jC(O)NR_{24}$; and R_{24} is H; and j is 3.

(62) In one embodiment, Z_1 is $C(O)NR_{24}$; and R_{24} is H.

(63) In one embodiment, Z_1 is $C(O)NR_{24}$; and R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(64) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; and R_{24} is H.

(65) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; and R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(66) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 1.

(67) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1

(68) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 2.

(69) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; $R_{24}$is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2.

(70) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 3.

(71) In one embodiment, Z_1 is $(CH_2)_jC(O)NR_{24}$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3.

(72) In one embodiment, Z_1 is $NR_{24}C(O)$; and R_{24} is H.

(73) In one embodiment, Z_1 is $NR_{24}C(O)$; and R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(74) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; and R_{24} is H.

(75) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; and R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(76) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is H; and j is 1.

(77) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1

(78) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is H; and j is 2.

(79) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2.

(80) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is H; and j is 3.

(81) In one embodiment, Z_1 is $(CH_2)_jNR_{24}C(O)$; R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3.

(82) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; and each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(83) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; and one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl. In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NH$.

(84) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1.

(85) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 1.

(86) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; j is 1; and k is 1.

(87) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1. In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)C(O)NH$.

(88) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 1. In one embodiment, Z_1 is $(CH_2)NR_{24}(CH_2)_jC(O)NH$.

(89) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; j is 1; and k is 1. In one embodiment, Z_1 is $(CH_2)NR_{24}(CH_2)C(O)NH$. In one embodiment, Z_1 is $(CH_2)N(CH_3)(CH_2)C(O)NH$.

(90) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2.

(91) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 2.

(92) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2. In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_2C(O)NH$.

(93) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 2. In one embodiment, Z_1 is $(CH_2)_2NR_{24}(CH_2)_jC(O)NH$.

(94) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3.

(95) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 3.

(96) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3. In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_3C(O)NH$.

(97) In one embodiment, Z_1 is $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k is 3. In one embodiment, Z_1 is $(CH_2)_3NR_{24}(CH_2)_jC(O)NH$.

(98) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; and each R_{24} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(99) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; and each R_{24} is H.

(100) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 1.

(101) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 1.

(102) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 2.

(103) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; R_{24} is H; and j is 2.

(104) In one embodiment, Z_1 is $NR_{24}(CH_2)_jC(O)NR_{24}$; one of R_{24} is H and one of R_{24} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j is 3.

(105) In one embodiment, Z_1 is absent and p3 is 1.

(106) In one embodiment, Z_1 is absent and p3 is 2.

(107) In one embodiment, Z_1 is absent and p3 is 3.

(108) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 1-8.

(109) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 1.

(110) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 2.

(111) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 3.

(112) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 4.

(113) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 5.

(114) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 6.

(115) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 7.

(116) In one embodiment, Z_1 is absent, p3 is 1, and p1 is 8.

(117) In one embodiment, Z_1 is absent, p3 is 1, and W is O.

(118) In one embodiment, Z_1 is absent, p3 is 1, p1 is 1, and W is O.

(119) In one embodiment, Z_1 is absent, p3 is 1, p1 is 2, and W is O.

(120) In one embodiment, Z_1 is absent, p3 is 1, p1 is 3, and W is O.

(121) In one embodiment, Z_1 is absent, p3 is 1, p1 is 4, and W is O.

(122) In one embodiment, Z_1 is absent, p3 is 1, p1 is 5, and W is O.

(123) In one embodiment, Z_1 is absent, p3 is 1, p1 is 6, and W is O.

(124) In one embodiment, Z_1 is absent, p3 is 1, p1 is 7, and W is O.

(125) In one embodiment, Z_1 is absent, p3 is 1, p1 is 8, and W is O.

(126) In one embodiment, Z_1 is absent, p3 is 1, p1 is 1, and W is CH_2.

(127) In one embodiment, Z_1 is absent, p3 is 1, p1 is 2, and W is CH_2.

(128) In one embodiment, Z_1 is absent, p3 is 1, p1 is 3, and W is CH_2.

(129) In one embodiment, Z_1 is absent, p3 is 1, p1 is 4, and W is CH_2.

(130) In one embodiment, Z_1 is absent, p3 is 1, p1 is 5, and W is CH_2.

(131) In one embodiment, Z_1 is absent, p3 is 1, p1 is 6, and W is CH_2.

(132) In one embodiment, Z_1 is absent, p3 is 1, p1 is 7, and W is CH_2.

(133) In one embodiment, Z_1 is absent, p3 is 1, p1 is 8, and W is CH_2.

(134) In one embodiment, Z_1 is absent, p3 is 2, p1 is 1, and W is O.

(135) In one embodiment, Z_1 is absent, p3 is 2, p1 is 2, and W is O.

(136) In one embodiment, Z_1 is absent, p3 is 2, p1 is 3, and W is O.

(137) In one embodiment, Z_1 is absent, p3 is 2, p1 is 4, and W is O.

(138) In one embodiment, Z_1 is absent, p3 is 2, p1 is 5, and W is O.

(139) In one embodiment, Z_1 is absent, p3 is 2, p1 is 6, and W is O.

(140) In one embodiment, Z_1 is absent, p3 is 2, p1 is 7, and W is O.

(141) In one embodiment, Z_1 is absent, p3 is 2, p1 is 8, and W is O.

(142) In one embodiment, Z_1 is absent, p3 is 2, p1 is 1, and W is CH_2.

(143) In one embodiment, Z_1 is absent, p3 is 2, p1 is 2, and W is CH_2.

(144) In one embodiment, Z_1 is absent, p3 is 2, p1 is 3, and W is CH_2.

(145) In one embodiment, Z_1 is absent, p3 is 2, p1 is 4, and W is CH_2.

(146) In one embodiment, Z_1 is absent, p3 is 2, p1 is 5, and W is CH_2.

(147) In one embodiment, Z_1 is absent, p3 is 2, p1 is 6, and W is CH_2.

(148) In one embodiment, Z_1 is absent, p3 is 2, p1 is 7, and W is CH_2.

(149) In one embodiment, Z_1 is absent, p3 is 2, p1 is 8, and W is CH_2.

(150) In one embodiment, Z_1 is absent, p3 is 3, p1 is 1, and W is O.

(151) In one embodiment, Z_1 is absent, p3 is 3, p1 is 2, and W is O.

(152) In one embodiment, Z_1 is absent, p3 is 3, p1 is 3, and W is O.

(153) In one embodiment, Z_1 is absent, p3 is 3, p1 is 4, and W is O.

(154) In one embodiment, Z_1 is absent, p3 is 3, p1 is 5, and W is O.

(155) In one embodiment, Z_1 is absent, p3 is 3, p1 is 6, and W is O.

(156) In one embodiment, Z_1 is absent, p3 is 3, p1 is 7, and W is O.

(157) In one embodiment, Z_1 is absent, p3 is 3, p1 is 8, and W is O.

(158) In one embodiment, Z_1 is absent, p3 is 3, p1 is 1, and W is CH_2.

(159) In one embodiment, Z_1 is absent, p3 is 3, p1 is 2, and W is CH_2.

(160) In one embodiment, Z_1 is absent, p3 is 3, p1 is 3, and W is CH_2.

(161) In one embodiment, Z_1 is absent, p3 is 3, p1 is 4, and W is CH_2.

(162) In one embodiment, Z_1 is absent, p3 is 3, p1 is 5, and W is CH_2.

(163) In one embodiment, Z_1 is absent, p3 is 3, p1 is 6, and W is CH_2.

(164) In one embodiment, Z_1 is absent, p3 is 3, p1 is 7, and W is CH_2.

(165) In one embodiment, Z_1 is absent, p3 is 3, p1 is 8, and W is CH_2.

(166) In one embodiment, p1, Z_1, p3, and W are each as defined, where applicable, in any one of (1)-(165), and p2 is 0.

(167) In one embodiment, p1, Z_1, p3, and W are each as defined, where applicable, in any one of (1)-(165), and p2 is 1.

(168) In one embodiment, p1, Z_1, p3, and W are each as defined, where applicable, in any one of (1)-(165), and p2 is 2.

(169) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is absent.

(170) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is $NHC(O)CH_2$.

(171) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is $O(CH_2)_{1-2}$.

(172) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is $O(CH_2)$.

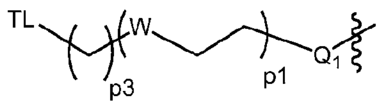
(173) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is $O(CH_2CH_2)$.

(174) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is C(O).

(175) In one embodiment, p1, Z_1, p3, p2, and W are each as defined, where applicable, in any one of (1)-(168), and Q_1 is $OCH_2C(O)$.

In one embodiment, the Linker–Targeting Ligand (TL) has the structure selected from Table L:

Table L:



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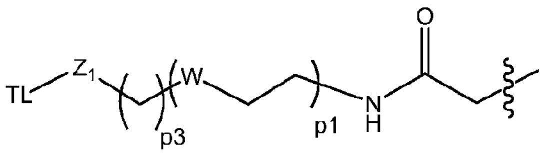

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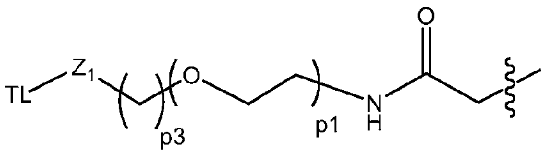

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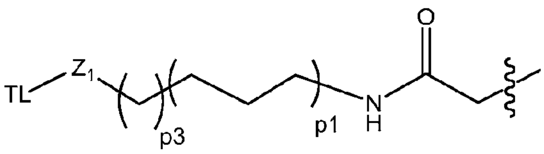

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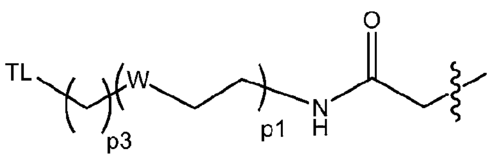

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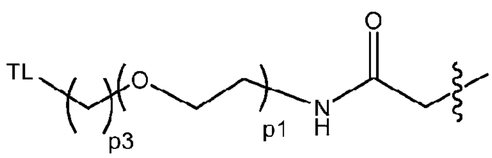
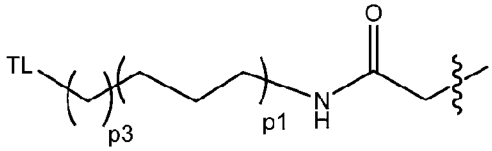
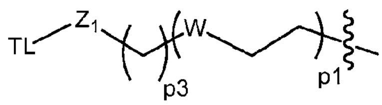


(L1f),


(L1g),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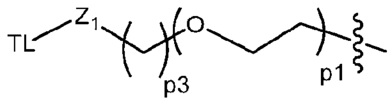
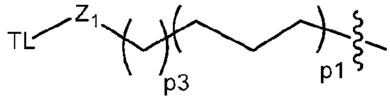

(L1i),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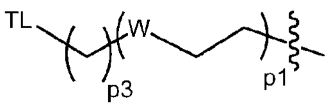
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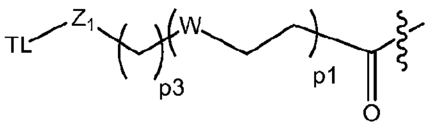
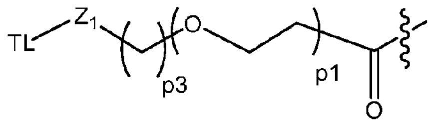
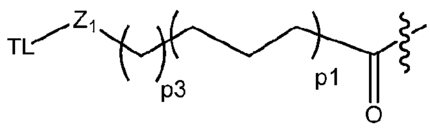
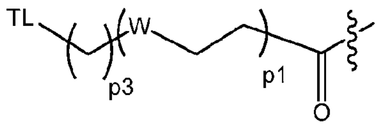

(L1l),


(L1m),


(L1n), and


(L1o)

wherein Z_1, W, Q_1, TL, p1, and p3 are each as described above.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L1a – L1o. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L1a. In one embodiment, the Degron is of Formula D1, and the

Linker is selected from L1b – L1d. In one embodiment, the Degron is of Formula D1, and the Linker is selected from L1e-L1g. In one embodiment, the Degron is of Formula D1, and the Linker is L1h-L1j. In one embodiment, the Degron is of Formula D1, and the Linker is L1p or L1q. In one embodiment, the Degron is of Formula D1, and the Linker is L1a, L1b, L1e, L1h, L1k, L1l or L1o. In one embodiment, the Degron is of Formula D1, and the Linker is L1c, L1d, L1f, L1g, L1i, L1j, L1m, or L1n. In one embodiment, the Degron is of Formula D1, and the Linker is L1k. In one embodiment, the Degron is of Formula D1, and the Linker is L1l or L1o. In one embodiment, the Degron is of Formula D1, and the Linker is L1c or L1d. In one embodiment, the Degron is of Formula D1, and the Linker is L1f or L1g. In one embodiment, the Degron is of Formula D1, and the Linker is L1i or L1j. In one embodiment, the Degron is of Formula D1, and the Linker is L1m or L1n.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L1a – L1o. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L1a. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L1b – L1d. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L1e-L1g. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1h-L1j. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1p or L1q. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1a, L1b, L1e, L1h, L1k, L1l or L1o. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1c, L1d, L1f, L1g, L1i, L1j, L1m, or L1n. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1k. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1l or L1o. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1c or L1d. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1f or L1g. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1i or L1j. In one embodiment, the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is L1m or L1n.

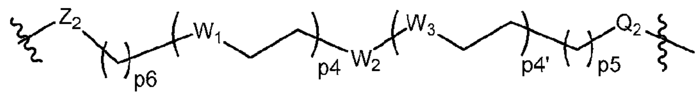
In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L1a – L1o. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L1a. In one embodiment, the Degron is of Formula D2, and the Linker is selected from L1b – L1d. In one embodiment, the Degron is of Formula D2, and the Linker is selected from L1e-L1g. In one embodiment, the Degron is of Formula D2, and the Linker is L1h-L1j. In one embodiment, the Degron is of Formula D2, and the Linker is L1p or L1q. In one embodiment, the Degron is of Formula D2, and the Linker is L1a, L1b, L1e, L1h, L1k, L1l or L1o. In one embodiment, the Degron is of Formula D2, and the Linker is L1c, L1d, L1f, L1g, L1i, L1j, L1m, or L1n. In one embodiment, the Degron is of Formula D2, and the Linker is L1k. In one embodiment, the Degron is of Formula D2, and the Linker is L1l or L1o. In one embodiment, the Degron is of Formula D2, and the Linker is L1c or L1d. In one embodiment, the Degron is of Formula D2, and the Linker is L1f or L1g. In one embodiment, the Degron is of Formula D2, and the Linker is L1i or L1j. In one embodiment, the Degron is of Formula D2, and the Linker is L1m or L1n.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L1a – L1o. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L1a. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is selected from L1b – L1d. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is selected from L1e-L1g. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1h-L1j. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1p or L1q. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1a, L1b, L1e, L1h, L1k, L1l or L1o. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1c, L1d, L1f, L1g, L1i, L1j, L1m, or L1n. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1k. In one embodiment, the Degron is of Formula D2a or D2b, and the

Linker is L1l or L1o. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1c or L1d. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1f or L1g. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1i or L1j. In one embodiment, the Degron is of Formula D2a or D2b, and the Linker is L1m or L1n.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L1a – L1o. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L1a. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is selected from L1b – L1d. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is selected from L1e-L1g. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1h-L1j. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1p or L1q. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1a, L1b, L1e, L1h, L1k, L1l or L1o. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1c, L1d, L1f, L1g, L1i, L1j, L1m, or L1n. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1k. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1l or L1o. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1c or L1d. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1f or L1g. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1i or L1j. In one embodiment, the Degron is of Formula D2c or D2d, and the Linker is L1m or L1n.

In one embodiment, the Linker is of Formula L2:



(L2),

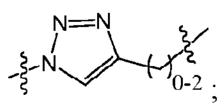
or an enantiomer, diastereomer, or stereoisomer thereof, wherein

p4 and p4' are each independently an integer selected from 0 to 12;

p5 is an integer selected from 0 to 12;

p6 is an integer selected from 1 to 6;

each W_1 is independently absent, CH_2, O, S, or NR_{25};

W_2 is $NR_{25}C(O)(CH_2)_{0-2}$ or 

;

each W_3 is independently absent, CH_2, O, S, or NR_{25};

Z_2 is absent, C(O), CH_2, O, $(CH_2)_{j1}NR_{25}$, $O(CH_2)_{j1}C(O)NR_{25}$, $C(O)NR_{25}$, $(CH_2)_{j1}C(O)NR_{25}$, $NR_{25}C(O)$, $(CH_2)_{j1}NR_{25}C(O)$, $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$,or $NR_{25}(CH_2)_{j1}C(O)NR_{25}$;

each R_{25} is independently H or C_1-C_3 alkyl;

j1 is 1, 2, or 3;

k1 is 1, 2, or 3; and

Q_2 is absent, C(O), $NHC(O)CH_2$, or $O(CH_2)_{1\text{-}2}$;

wherein the Linker is covalently bonded to a Degron via the $-\xi-$ next to Q_2, and covalently bonded to a Targeting Ligand via the $-\xi-$ next to Z_2.

For a Linker of Formula L2:

(1) In one embodiment, p4 is an integer selected from 0 to 10

(2) In one embodiment, p4 is an integer selected from 1 to 10.

(3) In one embodiment, p4 is selected from 1, 2, 3, 4, 5, and 6.

(4) In one embodiment, p4 is 0, 1, 3, or 5.

(5) In one embodiment, p4 is 0, 1, 2, or 3.

(6) In one embodiment, p4 is 0.

(7) In one embodiment, p4 is 1.

(8) In one embodiment, p4 is 2.

(9) In one embodiment, p4 is 3.

(10) In one embodiment, p4 is 4.

(11) In one embodiment, p4 is 5.

(12) In one embodiment, p4' is an integer selected from 0 to 10.

(13) In one embodiment, p4' is an integer selected from 1 to 10.

(14) In one embodiment, p4' is selected from 1, 2, 3, 4, 5, and 6.

(15) In one embodiment, p4' is 0, 1, 3, or 5.

(16) In one embodiment, p4' is 0, 1, 2, or 3.

(17) In one embodiment, p4' is 0.

(18) In one embodiment, p4' is 1.

(19) In one embodiment, p4' is 2.

(20) In one embodiment, p4' is 3.

(21) In one embodiment, p4' is 4.

(22) In one embodiment, p4' is 5.

(23) In one embodiment, p5 is an integer selected from 0 to 10.

(24) In one embodiment, p5 is selected from 0, 1, 2, 3, 4, 5, and 6.

(25) In one embodiment, p5 is 0, 1, 2, or 3.

(26) In one embodiment, p5 is 0.

(27) In one embodiment, p5 is 1.

(28) In one embodiment, p5 is 2.

(29) In one embodiment, p5 is 3.

(30) In one embodiment, p6 is an integer selected from 1 to 5.

(31) In one embodiment, p6 is 2, 3, 4, or 5.

(32) In one embodiment, p6 is 0, 1, 2, or 3.

(33) In one embodiment, p6 is 0.

(34) In one embodiment, p6 is 1.

(35) In one embodiment, p6 is 2.

(36) In one embodiment, p6 is 3.

(37) In one embodiment, p6 is 4.

(38) In one embodiment, at least one W_1 is CH_2.

(39) In one embodiment, at least one W_1 is O.

(40) In one embodiment, at least one W_1 is S.

(41) In one embodiment, at least one W_1 is NH.

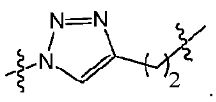
(42) In one embodiment, at least one W_1 is NR_{25}; and each R_{25} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

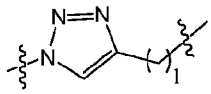
(43) In one embodiment, each W_1 is O.

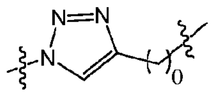
(44) In one embodiment, each W_1 is CH_2.

(45) In one embodiment, W_2 is $NR_{25}C(O)CH_2$-; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(46) In one embodiment, W_2 is $NR_{25}C(O)CH_2$-; and R_{25} is H.

(47) In one embodiment, W_2 is .

(48) In one embodiment, W_2 is  .

(49) In one embodiment, W_2 is  .

(50) In one embodiment, at least one W_3 is CH_2.

(51) In one embodiment, at least one W_3 is O.

(52) In one embodiment, at least one W_3 is S.

(53) In one embodiment, at least one W_3 is NH.

(54) In one embodiment, at least one W_3 is NR_{25}; and each R_{25} is independently C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(55) In one embodiment, each W_3 is O.

(56) In one embodiment, each W_3 is CH_2.

(57) In one embodiment, j1 is 1, 2, or 3.

(58) In one embodiment, j1 is 1.

(59) In one embodiment, j1 is 2.

(60) In one embodiment, j1 is 3.

(61) In one embodiment, j1 is 2 or 3.

(62) In one embodiment, j1 is 1 or 2.

(63) In one embodiment, k1 is 1, 2, or 3.

(64) In one embodiment, k1 is 1.

(65) In one embodiment, k1 is 2.

(66) In one embodiment, k1 is 3.

(67) In one embodiment, k1 is 2 or 3.

(68) In one embodiment, k1 is 1 or 2.

(69) In one embodiment, Q_2 is absent.

(70) In one embodiment, Q_2 is $NHC(O)CH_2$.

(71) In one embodiment, Q_2 is $O(CH_2)_{1\text{-}2}$.

(72) In one embodiment, Q_2 is OCH_2.

(73) In one embodiment, Q_2 is OCH_2CH_2.

(74) In one embodiment, Q_2 is $OCH_2C(O)$.

(75) In one embodiment, Q_2 is C(O).

(76) In one embodiment, Z_2 is absent.

(77) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(78) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; and R_{25} is H.

(79) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1.

(80) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 1.

(81) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2.

(82) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 2.

(83) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3.

(84) In one embodiment, Z_2 is $O(CH_2)_{j1}C(O)NR_{25}$; and R_{25} is H; and j1 is 3.

(85) In one embodiment, Z_2 is $C(O)NR_{25}$; and R_{25} is H.

(86) In one embodiment, Z_2 is $C(O)NR_{25}$; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(87) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; and R_{25} is H.

(88) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(89) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 1.

(90) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1

(91) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 2.

(92) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2.

(93) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 3.

(94) In one embodiment, Z_2 is $(CH_2)_{j1}C(O)NR_{25}$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3.

(95) In one embodiment, Z_2 is $NR_{25}C(O)$; and R_{25} is H.

(96) In one embodiment, Z_2 is $NR_{25}C(O)$; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(97) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; and R_{25} is H.

(98) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; and R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(99) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is H; and j1 is 1.

(100) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1

(101) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is H; and j1 is 2.

(102) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2.

(103) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is H; and j1 is 3.

(104) In one embodiment, Z_2 is $(CH_2)_{j1}NR_{25}C(O)$; R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3.

(105) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; and each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(106) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; and one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl. In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NH$.

(107) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1.

(108) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 1.

(109) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; j1 is 1; and k1 is 1.

(110) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1. In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)C(O)NH$.

(111) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 1. In one embodiment, Z_2 is $(CH_2)NR_{25}(CH_2)_{j1}C(O)NH$.

(112) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; j1 is 1; and k1 is 1. In one

embodiment, Z_2 is $(CH_2)NR_{25}(CH_2)C(O)NH$. In one embodiment, Z_2 is $(CH_2)N(CH_3)(CH_2)C(O)NH$.

(113) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2.

(114) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 2.

(115) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2. In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_2C(O)NH$.

(116) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 2. In one embodiment, Z_2 is $(CH_2)_2NR_{25}(CH_2)_{j1}C(O)NH$.

(117) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3.

(118) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 3.

(119) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3. In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_3C(O)NH$.

(120) In one embodiment, Z_2 is $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and k1 is 3. In one embodiment, Z_2 is $(CH_2)_3NR_{25}(CH_2)_{j1}C(O)NH$.

(121) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; and each R_{25} is independently H or C_1-C_3 alkyl selected from methyl, ethyl, and propyl.

(122) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; and each R_{25} is H.

(123) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 1.

(124) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 1.

(125) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 2.

(126) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; R_{25} is H; and j1 is 2.

(127) In one embodiment, Z_2 is $NR_{25}(CH_2)_{j1}C(O)NR_{25}$; one of R_{25} is H and one of R_{25} is C_1-C_3 alkyl selected from methyl, ethyl, and propyl; and j1 is 3.

(128) In one embodiment, Z_2 is absent and p6 is 1.

(129) In one embodiment, Z_2 is absent and p6 is 2.

(130) In one embodiment, Z_2 is absent and p6 is 3.

(131) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 1-5.

(132) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 1.

(133) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 2.

(134) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 3.

(135) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 4.

(136) In one embodiment, Z_2 is absent, p6 is 1, and p4 is 5.

(137) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 1-5.

(138) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 1.

(139) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 2.

(140) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 3.

(141) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 4.

(142) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 5.

(143) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 1-5.

(144) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 1.

(145) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 2.

(146) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 3.

(147) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 4.

(148) In one embodiment, Z_2 is absent, p6 is 2, and p4 is 5.

(149) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, and p4' is 1.

(150) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, and p4' is 2.

(151) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, and p4' is 3.

(152) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, and p4' is 4.

(153) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, and p4' is 5.

(154) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, and p4' is 1.

(155) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, and p4' is 2.

(156) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, and p4' is 3.

(157) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, and p4' is 4.

(158) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, and p4' is 5.

(159) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, and p4' is 1.

(160) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, and p4' is 2.

(161) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, and p4' is 3.

(162) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, and p4' is 4.

(163) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, and p4' is 5.

(164) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, and p4' is 1.

(165) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, and p4' is 2.

(166) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, and p4' is 3.

(167) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, and p4' is 4.

(168) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, and p4' is 5.

(169) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, and p4' is 1.

(170) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, and p4' is 2.

(171) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, and p4' is 3.

(172) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, and p4' is 4.

(173) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, and p4' is 5.

(174) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, and p4' is 1.

(175) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, and p4' is 2.

(176) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, and p4' is 3.

(177) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, and p4' is 4.

(178) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, and p4' is 5.

(179) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, and p4' is 1.

(180) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, and p4' is 2.

(181) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, and p4' is 3.

(182) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, and p4' is 4.

(183) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, and p4' is 5.

(184) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, and p4' is 1.

(185) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, and p4' is 2.

(186) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, and p4' is 3.

(187) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, and p4' is 4.

(188) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, and p4' is 5.

(189) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, and p4' is 1.

(190) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, and p4' is 2.

(191) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, and p4' is 3.

(192) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, and p4' is 4.

(193) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, and p4' is 5.

(194) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, and p4' is 1.

(195) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, and p4' is 2.

(196) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, and p4' is 3.

(197) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, and p4' is 4.

(198) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, and p4' is 5.

(199) In one embodiment, Z_2 is absent, p6 is 1, and W_1 is O.

(200) In one embodiment, Z_2 is absent, p6 is 2, and W_1 is O.

(201) In one embodiment, Z_2 is absent, p6 is 3, and W_1 is O.

(202)

(203) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 1, and W_1 is O.

(204) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 2, and W_1 is O.

(205) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 3, and W_1 is O.

(206) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 4, and W_1 is O.

(207) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 5, and W_1 is O.

(208) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 1, and W_1 is O.

(209) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 2, and W_1 is O.

(210) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 3, and W_1 is O.

(211) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 4, and W_1 is O.

(212) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 5, and W_1 is O.

(213) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 1, and W_1 is O.

(214) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 2, and W_1 is O.

(215) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 3, and W_1 is O.

(216) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 4, and W_1 is O.

(217) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 5, and W_1 is O.

(218) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 1, and W_1 is O.

(219) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 2, and W_1 is O.

(220) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 3, and W_1 is O.

(221) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 4, and W_1 is O.

(222) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 5, and W_1 is O.

(223) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 1, and W is O.

(224) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 2, and W is O.

(225) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 3, and W is O.

(226) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 4, and W is O.

(227) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 5, and W is O.

(228) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 1, and W_1 is CH_2.

(229) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 2, and W_1 is CH_2.

(230) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 3, and W_1 is CH_2.

(231) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 4, and W_1 is CH_2.

(232) In one embodiment, Z_2 is absent, p6 is 1, p4 is 1, p4' is 5, and W_1 is CH_2.

(233) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 1, and W_1 is CH_2.

(234) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 2, and W_1 is CH_2.

(235) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 3, and W_1 is CH_2.

(236) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 4, and W_1 is CH_2.

(237) In one embodiment, Z_2 is absent, p6 is 1, p4 is 2, p4' is 5, and W_1 is CH_2.

(238) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 1, and W_1 is CH_2.

(239) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 2, and W_1 is CH_2.

(240) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 3, and W_1 is CH_2.

(241) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 4, and W_1 is CH_2.

(242) In one embodiment, Z_2 is absent, p6 is 1, p4 is 3, p4' is 5, and W_1 is CH_2.

(243) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 1, and W_1 is CH_2.

(244) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 2, and W_1 is CH_2.

(245) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 3, and W_1 is CH_2.

(246) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 4, and W_1 is CH_2.

(247) In one embodiment, Z_2 is absent, p6 is 1, p4 is 4, p4' is 5, and W_1 is CH_2.

(248) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 1, and W is CH_2.

(249) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 2, and W is CH_2.

(250) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 3, and W is CH_2.

(251) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 4, and W is CH_2.

(252) In one embodiment, Z_2 is absent, p6 is 1, p4 is 5, p4' is 5, and W is CH_2.

(253) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 1, and W_1 is O.

(254) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 2, and W_1 is O.

(255) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 3, and W_1 is O.

(256) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 4, and W_1 is O.

(257) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 5, and W_1 is O.

(258) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 1, and W_1 is O.

(259) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 2, and W_1 is O.

(260) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 3, and W_1 is O.

(261) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 4, and W_1 is O.

(262) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 5, and W_1 is O.

(263) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 1, and W_1 is O.

(264) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 2, and W_1 is O.

(265) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 3, and W_1 is O.

(266) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 4, and W_1 is O.

(267) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 5, and W_1 is O.

(268) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 1, and W_1 is O.

(269) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 2, and W_1 is O.

(270) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 3, and W_1 is O.

(271) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 4, and W_1 is O.

(272) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 5, and W_1 is O.

(273) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 1, and W is O.

(274) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 2, and W is O.

(275) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 3, and W is O.

(276) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 4, and W is O.

(277) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 5, and W is O.

(278) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 1, and W_1 is CH_2.

(279) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 2, and W_1 is CH_2.

(280) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 3, and W_1 is CH_2.

(281) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 4, and W_1 is CH_2.

(282) In one embodiment, Z_2 is absent, p6 is 2, p4 is 1, p4' is 5, and W_1 is CH_2.

(283) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 1, and W_1 is CH_2.

(284) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 2, and W_1 is CH_2.

(285) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 3, and W_1 is CH_2.

(286) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 4, and W_1 is CH_2.

(287) In one embodiment, Z_2 is absent, p6 is 2, p4 is 2, p4' is 5, and W_1 is CH_2.

(288) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 1, and W_1 is CH_2.

(289) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 2, and W_1 is CH_2.

(290) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 3, and W_1 is CH_2.

(291) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 4, and W_1 is CH_2.

(292) In one embodiment, Z_2 is absent, p6 is 2, p4 is 3, p4' is 5, and W_1 is CH_2.

(293) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 1, and W_1 is CH_2.

(294) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 2, and W_1 is CH_2.

(295) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 3, and W_1 is CH_2.

(296) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 4, and W_1 is CH_2.

(297) In one embodiment, Z_2 is absent, p6 is 2, p4 is 4, p4' is 5, and W_1 is CH_2.

(298) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 1, and W is CH_2.

(299) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 2, and W_1 is CH_2.

(300) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 3, and W_1 is CH_2.

(301) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 4, and W_1 is CH_2.

(302) In one embodiment, Z_2 is absent, p6 is 2, p4 is 5, p4' is 5, and W_1 is CH_2.

(303) In one embodiment, p4, p4', Z_2, p6, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(302), and p5 is 0.

(304) In one embodiment, p4, p4', Z_2, p6, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(302), and p5 is 1.

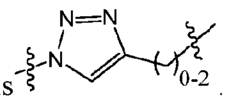
(305) In one embodiment, p4, p4', Z_2, p6, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(302), and p5 is 2.

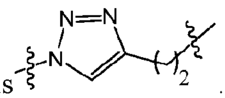
(306) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_3 are each as defined, where applicable, in any one of (1)-(44) and (50)-(305), and W_2 is O.

(307) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_3 are each as defined, where applicable, in any one of (1)-(44) and (50)-(305), and W_2 is CH_2.

(308) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_2 are each as defined, where applicable, in any one of (1)-(49) and (57)-(307), and W_3 is $NR_{25}C(O)CH_2$.

(309) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_2 are each as defined, where applicable, in any one of (1)-(49) and (57)-(307), and W_3 is $NHC(O)CH_2$.

(310) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_2 are each as defined, where applicable, in any one of (1)-(49) and (57)-(307), and W_3 is  .

(311) In one embodiment, p4, p4', Z_2, p6, p5, W_1, and W_2 are each as defined, where applicable, in any one of (1)-(49) and (57)-(307), and W_3 is  .

(312) In one embodiment, p4, p4', Z_2, p6, p5, and W_1 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is absent.

(313) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is $NHC(O)CH_2$.

(314) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is $O(CH_2)_{1-2}$.

(315) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is $O(CH_2)$.

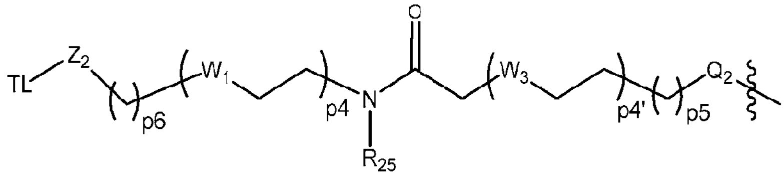
(316) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is $O(CH_2CH_2)$.

(317) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is C(O).

(318) In one embodiment, p4, p4', Z_2, p6, p5, W_1, W_2, and W_3 are each as defined, where applicable, in any one of (1)-(311), and Q_2 is $OCH_2C(O)$.

In one embodiment, the Linker–Targeting Ligand (TL) has the structure selected from Table M:

Table M:



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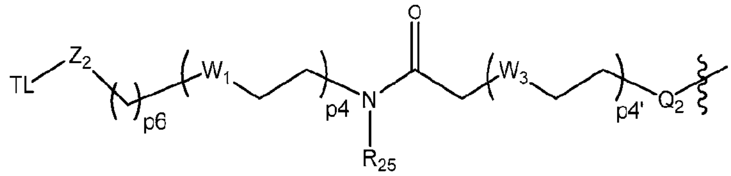

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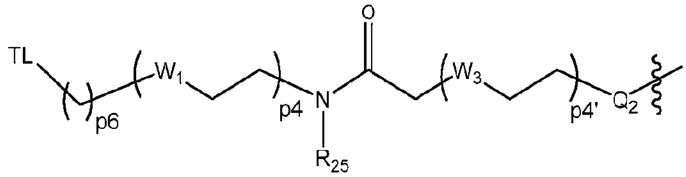

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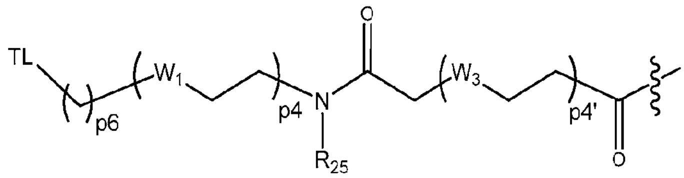

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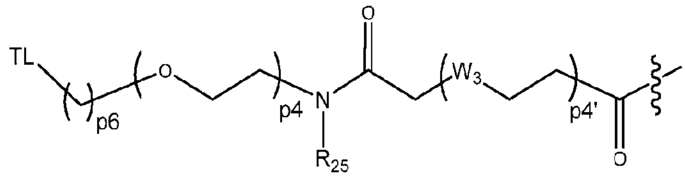

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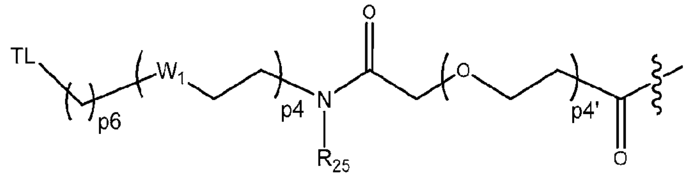

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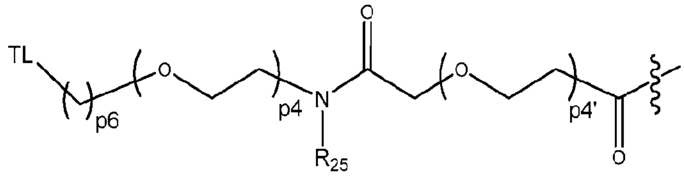

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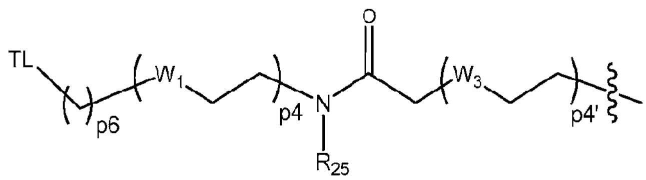

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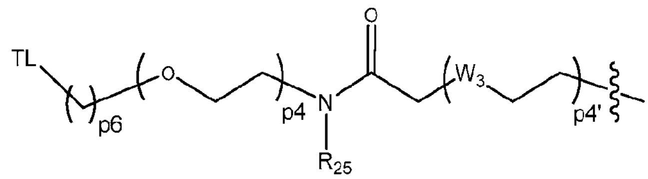

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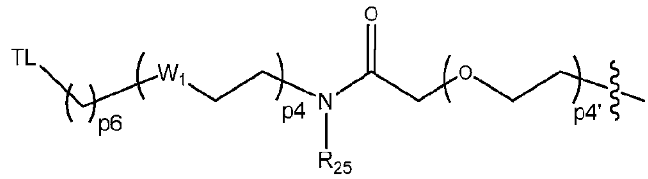

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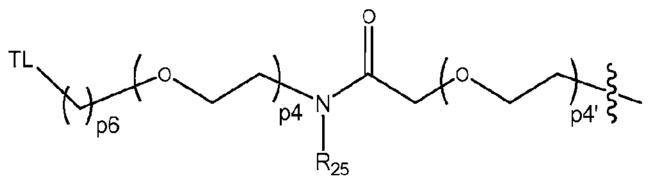

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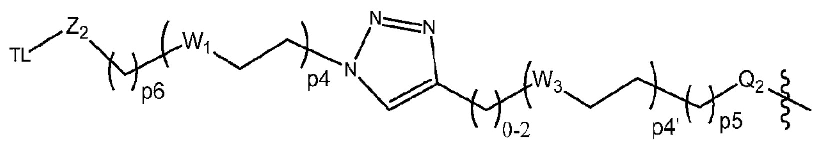

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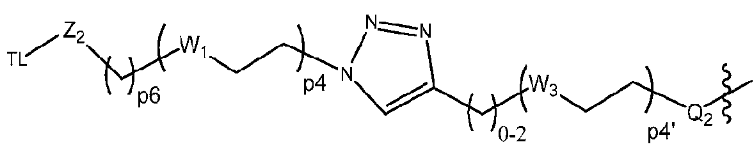

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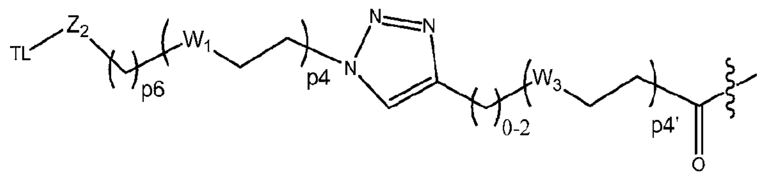

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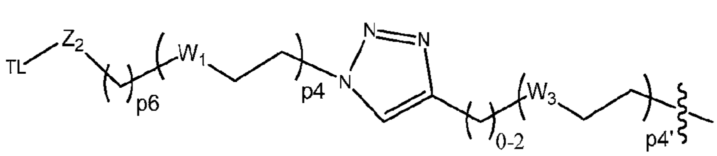

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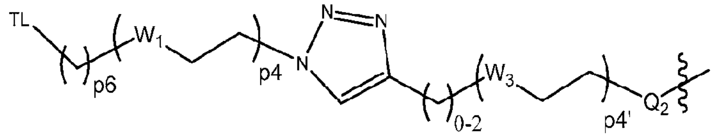

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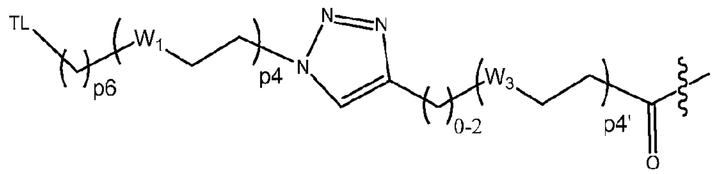

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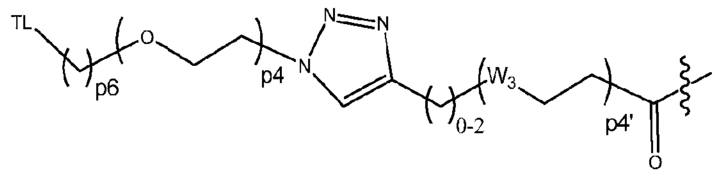

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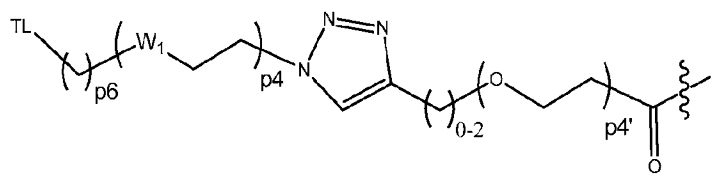

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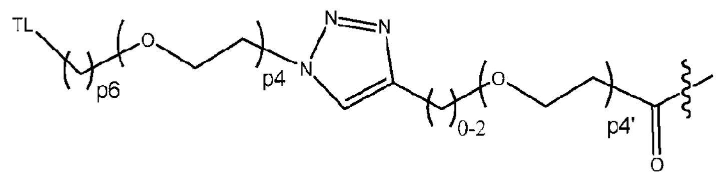

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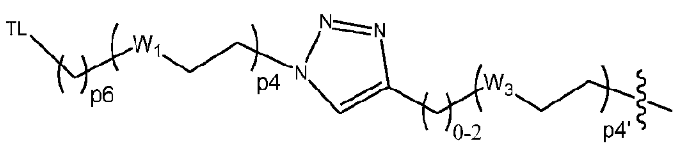

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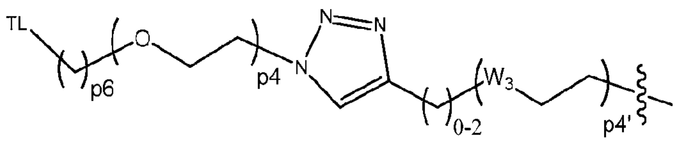

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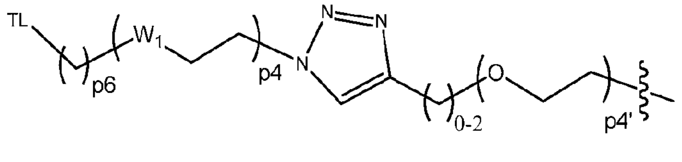
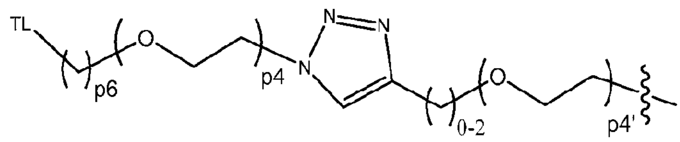


(L2w), and



(L2x)

wherein Z_2, W_1, W_3, Q_2, TL, R_{25}, p4, p4', and p6 are each as described above.

Any one of the Degrons described herein can be covalently bound to any one of the Linkers described herein. Any one of the Targeting Ligands described herein can be covalently bound to any one of the Linkers described herein.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2a – L2x. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2a-L2c. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2d-L2g. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2h-L2k. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2l-L2m. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2n -L2p. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2q-L2t. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1, and the Linker is selected from L2u-L2x.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2a – L2x. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2a-L2c. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2d-L2g. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2h-L2k. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2l-L2m. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2n -L2p. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2q-L2t. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l, and the Linker is selected from L2u-L2x.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2a – L2x. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2a-L2c. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2d-L2g. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2h-L2k. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2l-L2m. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2n -L2p. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2q-L2t. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2, and the Linker is selected from L2u-L2x.

In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2a – L2x. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2a-L2c. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2d-L2g. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2h-L2k. In one embodiment, the present application relates to the Degron-Linker

(DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2l-L2m. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2n -L2p. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2q-L2t. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2a or D2b, and the Linker is selected from L2u-L2x.

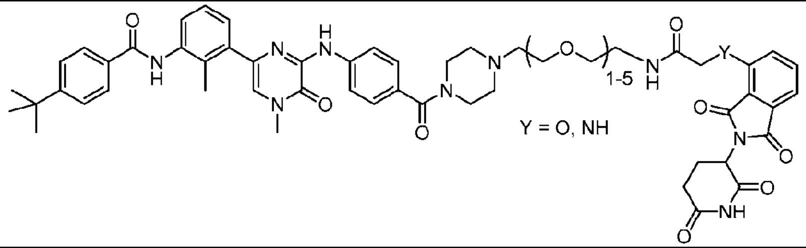
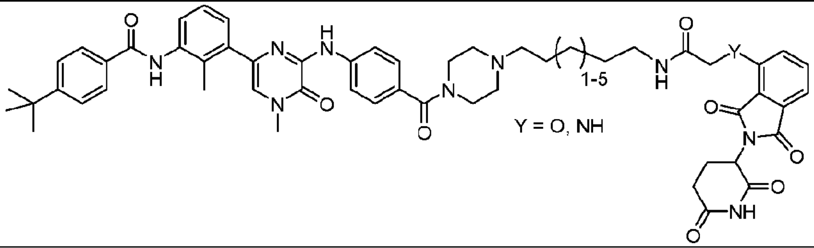
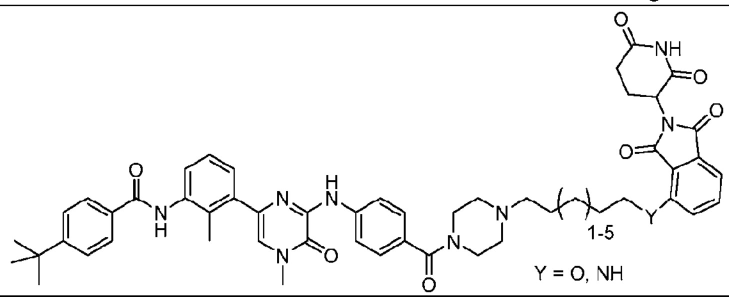
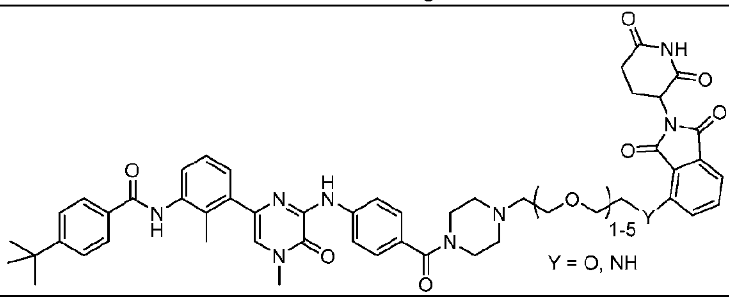
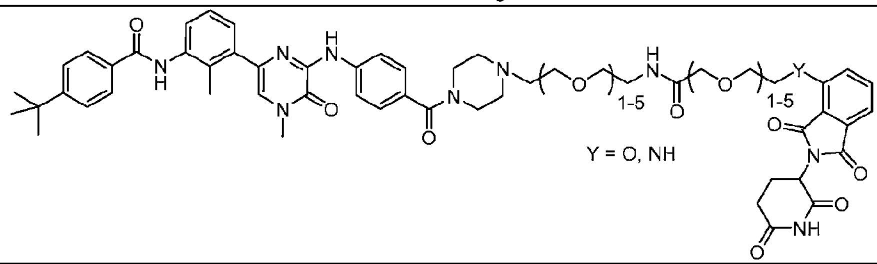
In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2a – L2x. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2a-L2c. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2d-L2g. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2h-L2k. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2l-L2m. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2n -L2p. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2q-L2t. In one embodiment, the present application relates to the Degron-Linker (DL), wherein the Degron is of Formula D2c or D2d, and the Linker is selected from L2u-L2x.

In one embodiment, the Linker is designed and optimized based on SAR (structure-activity relationship) and X-ray crystallography of the Targeting Ligand with regard to the location of attachment for the Linker.

In one embodiment, the optimal Linker length and composition vary by the Targeting Ligand and can be estimated based upon X-ray structure of the Targeting Ligand bound to its target. Linker length and composition can be also modified to modulate metabolic stability and pharmacokinetic (PK) and pharmacodynamics (PD) parameters.

Some embodiments of present application relate to the bifunctional compounds having one of the following structures in Table A:

Table A

Structure






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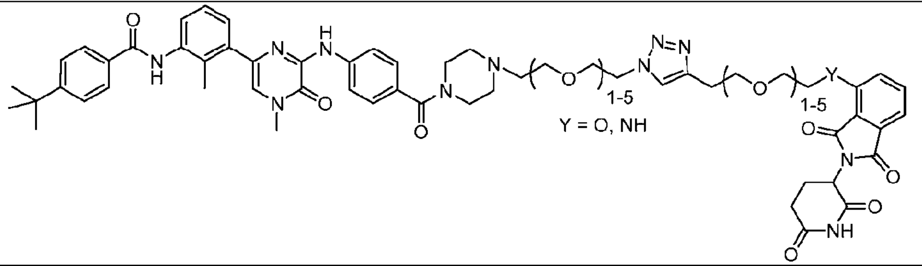
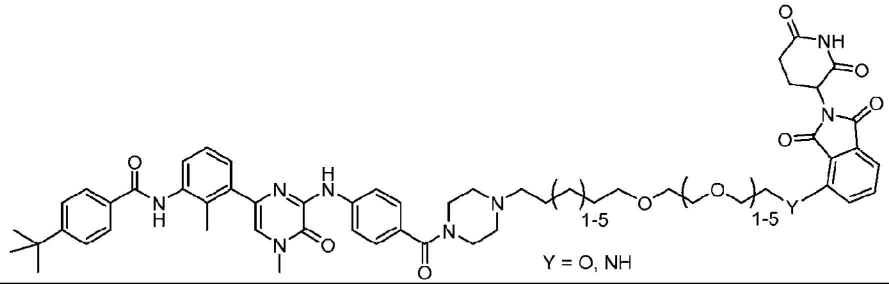
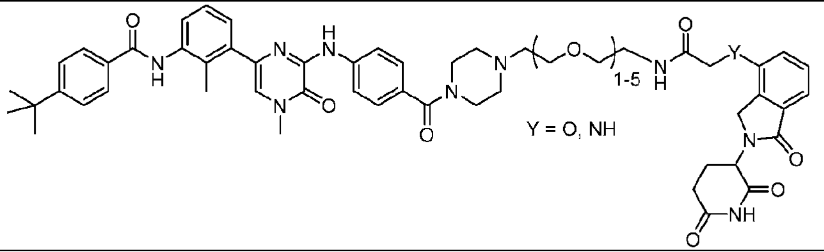
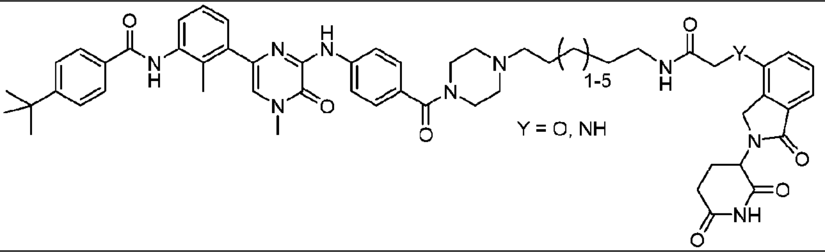
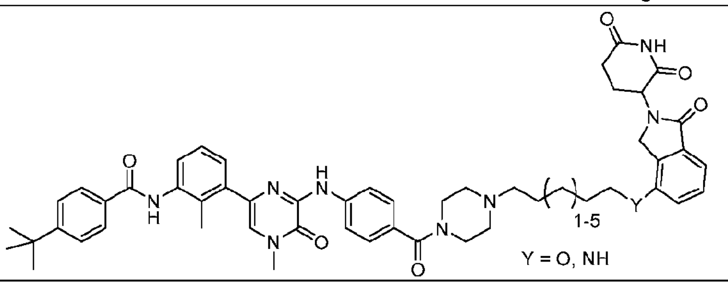

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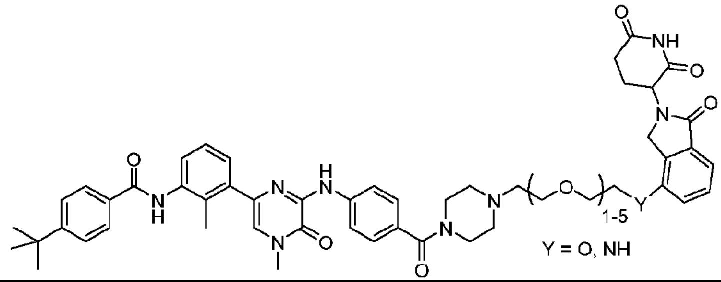
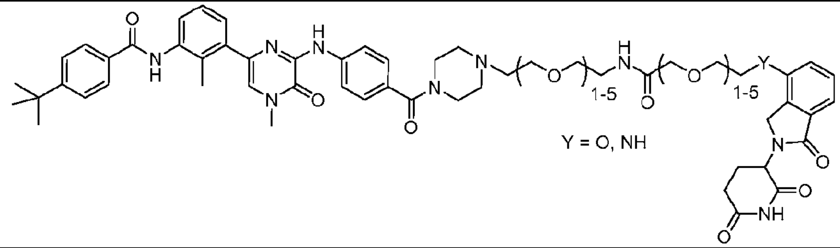
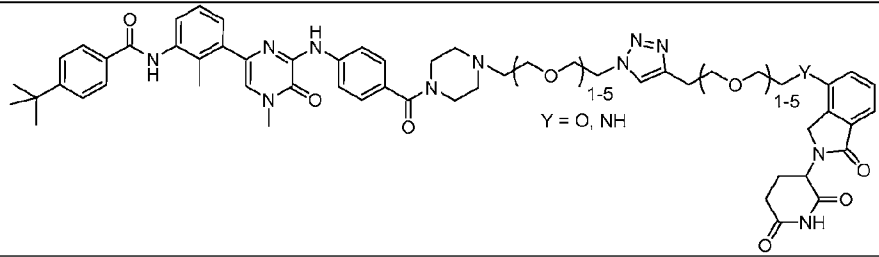
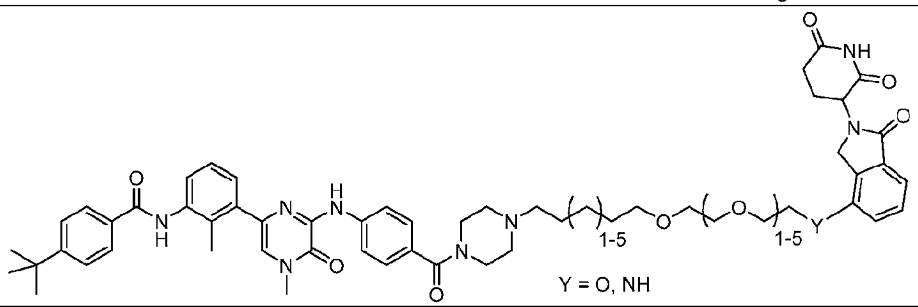
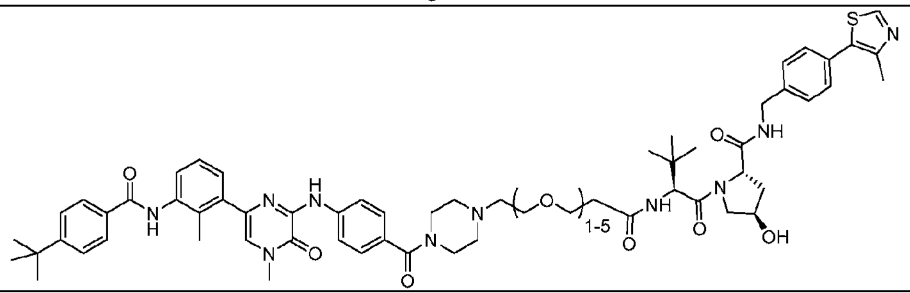

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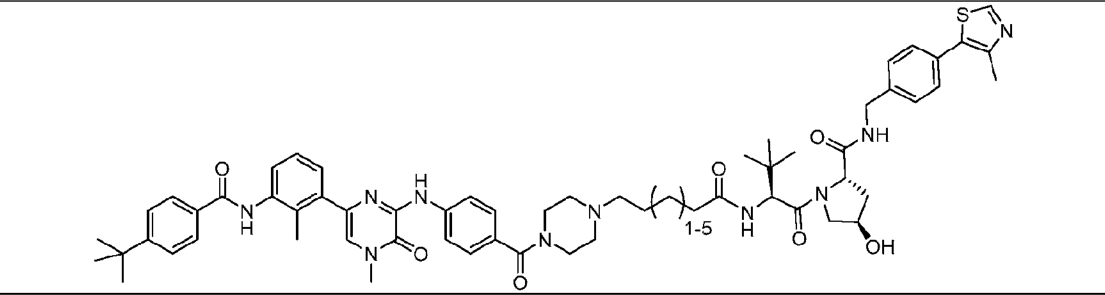
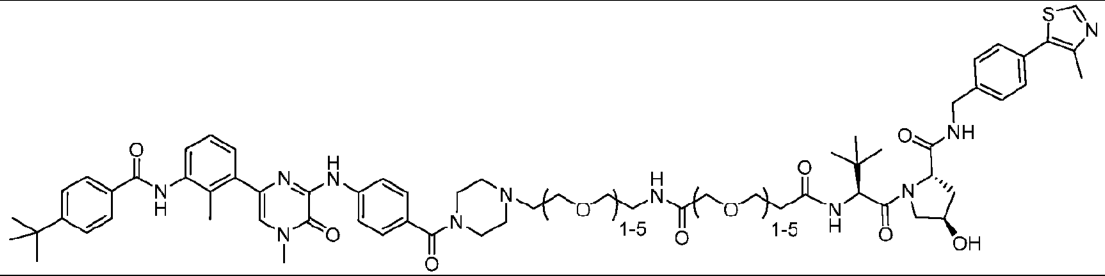
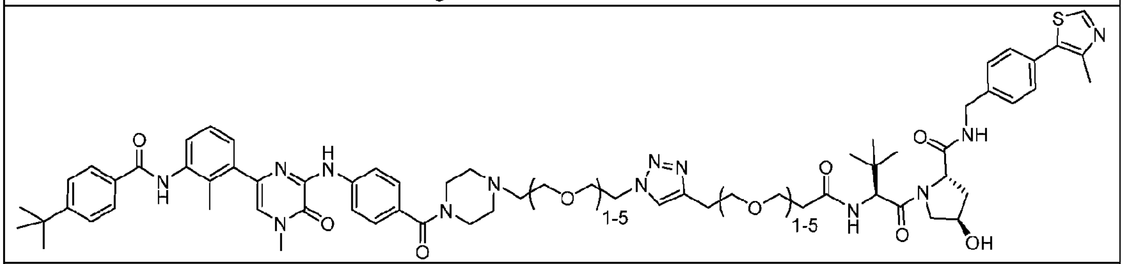
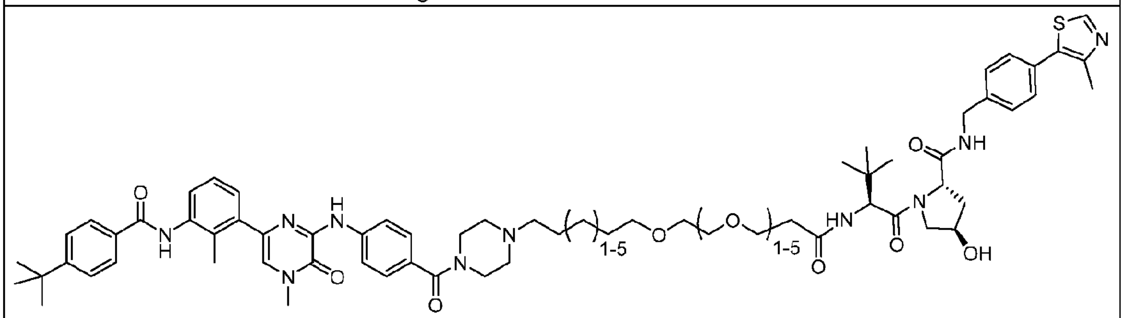
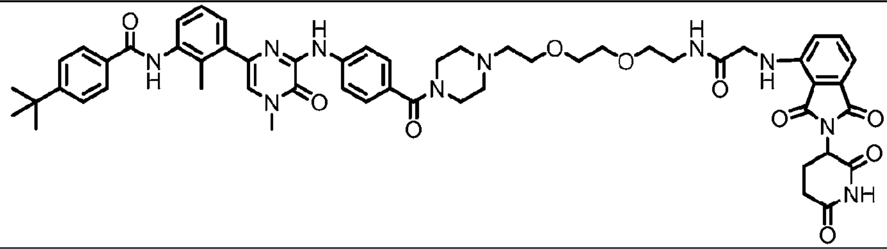
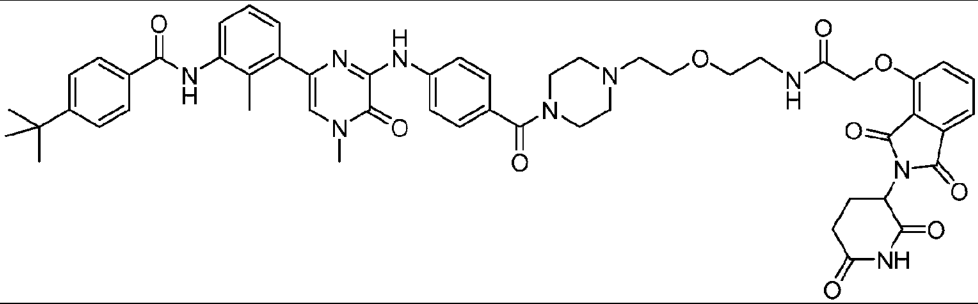
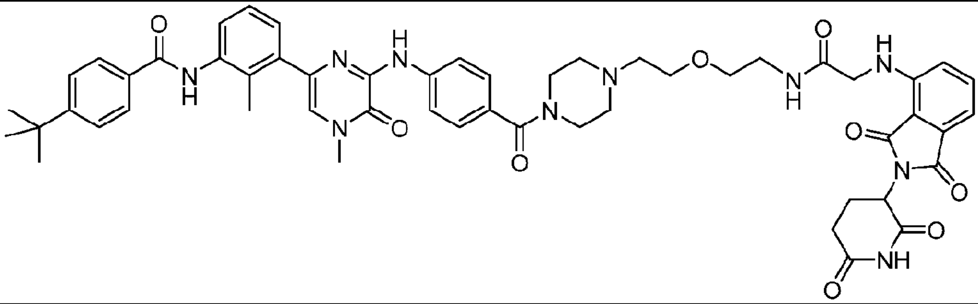
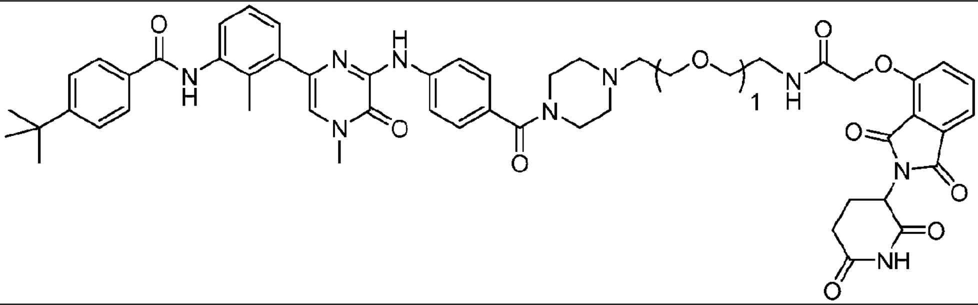
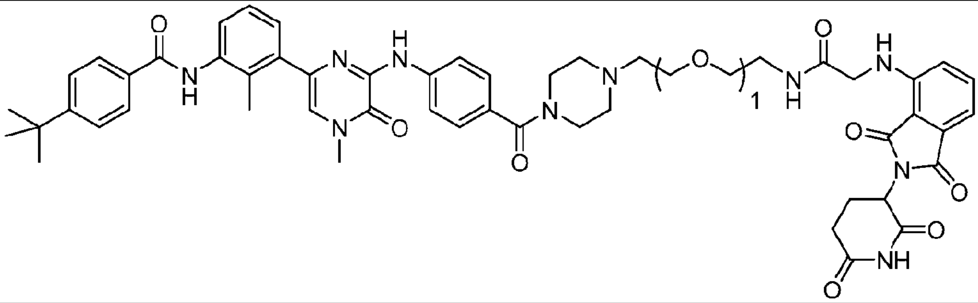
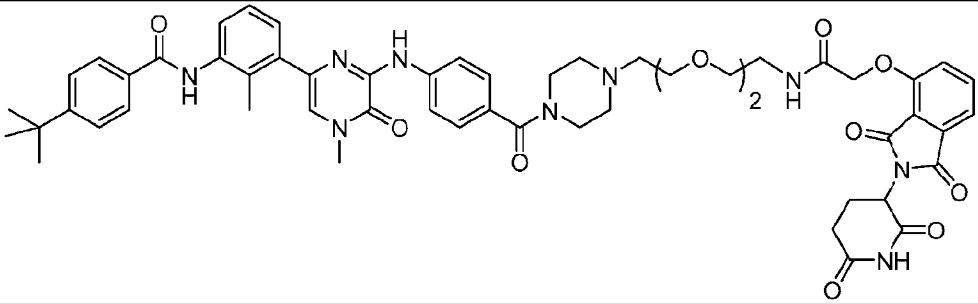
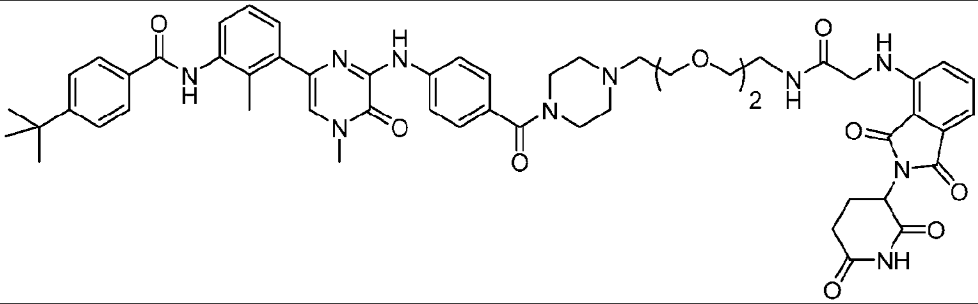
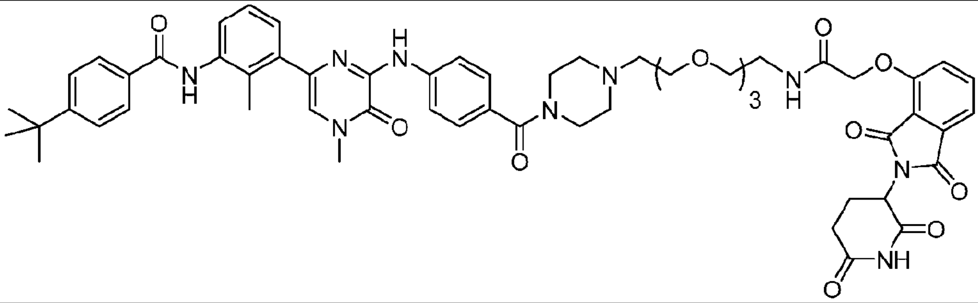
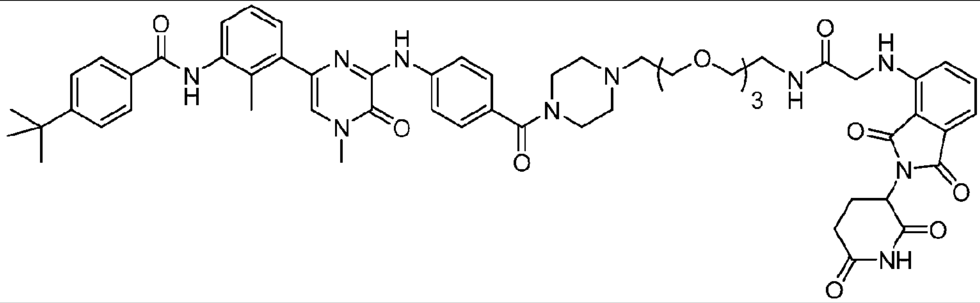
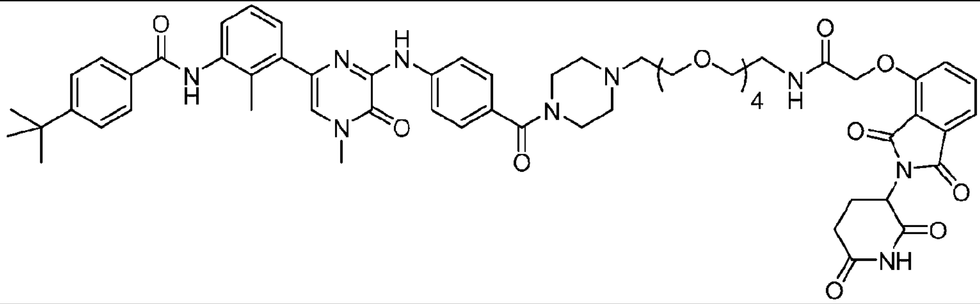
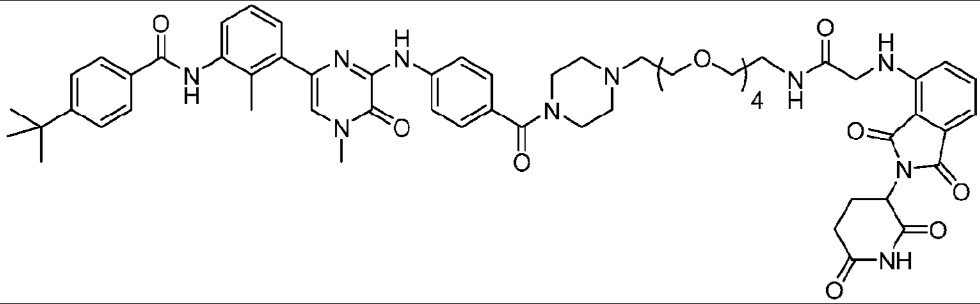
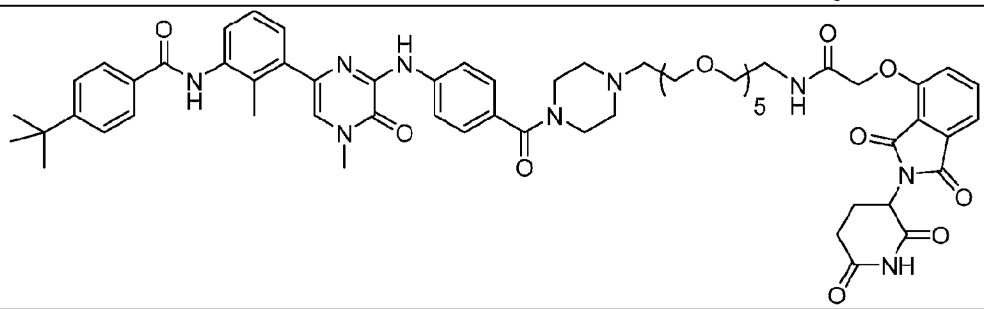





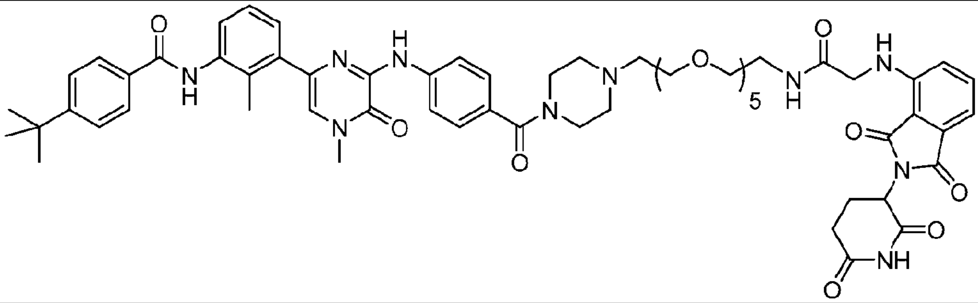
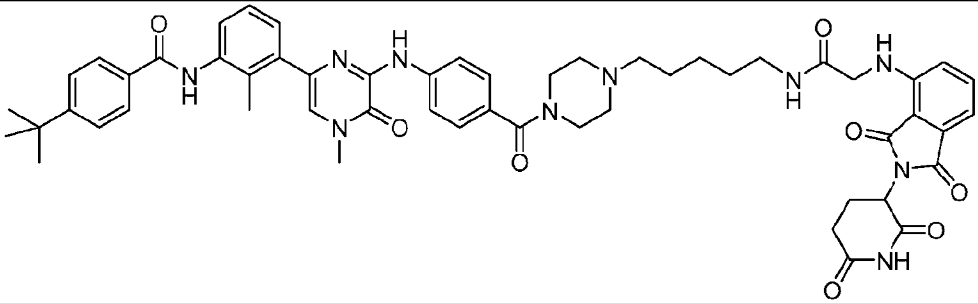
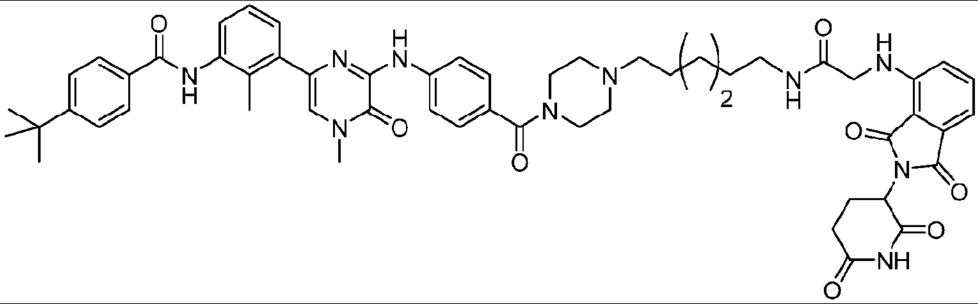
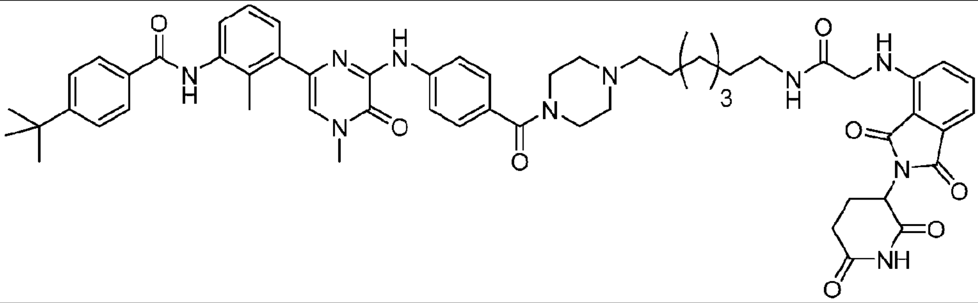
Some embodiments of present application relate to the bifunctional compounds having one of the following structures in Table C:

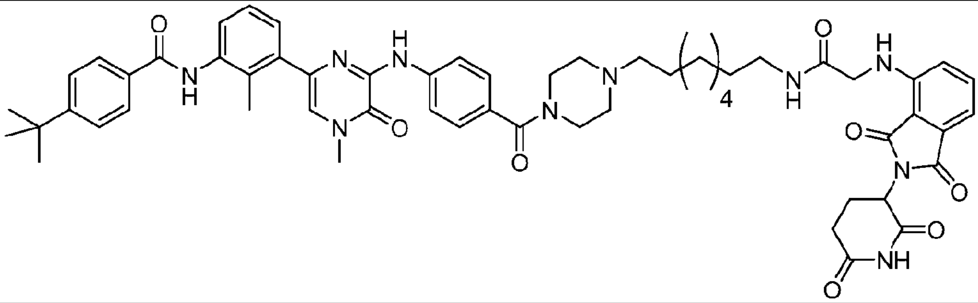
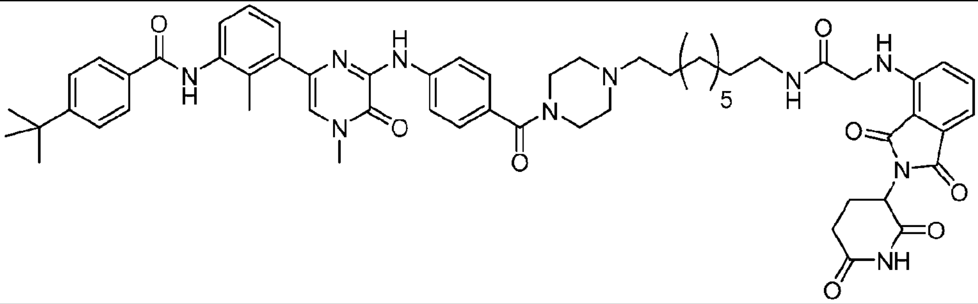
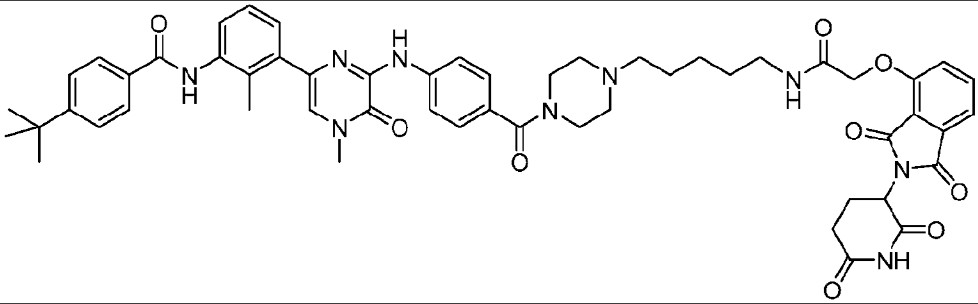
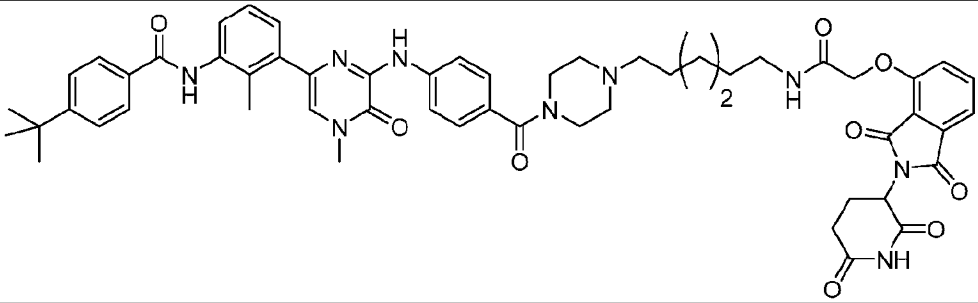
Table C

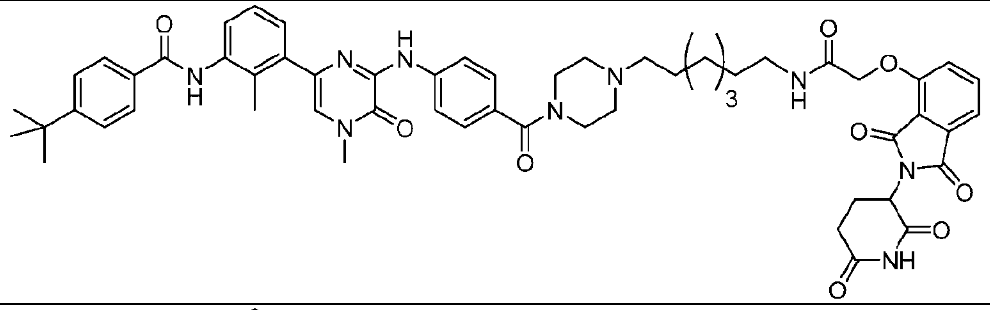
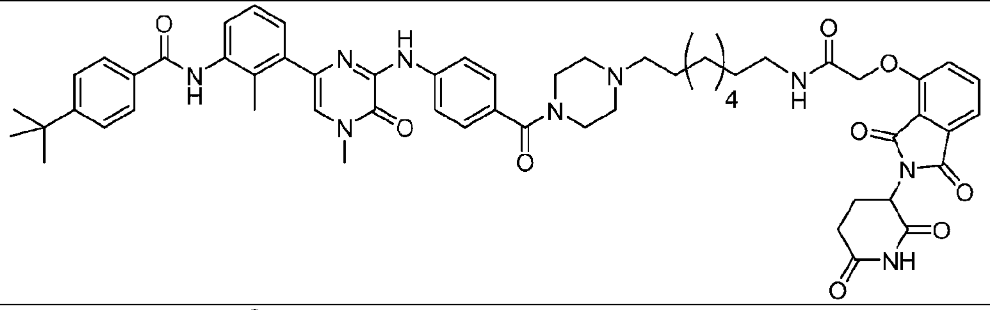
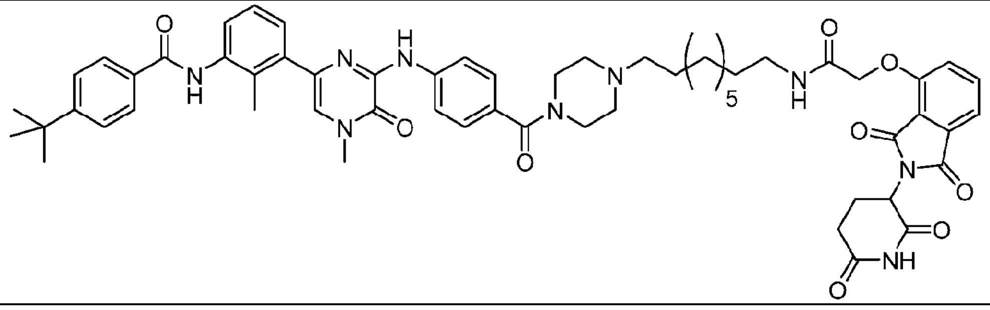
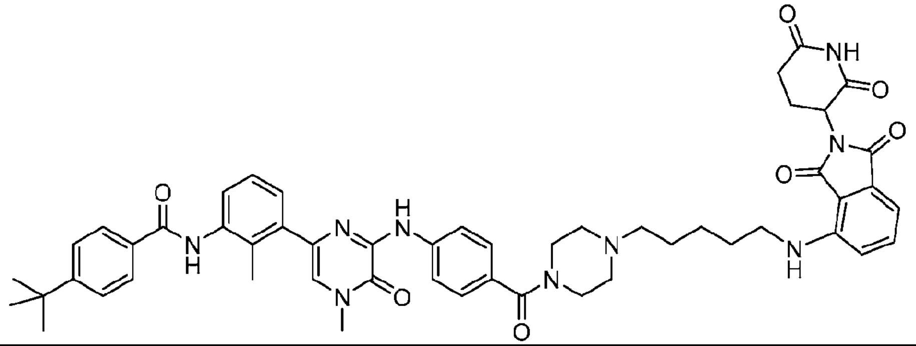
Cmpd No.	Structure
I-5	
I-6	
I-7	
I-8	

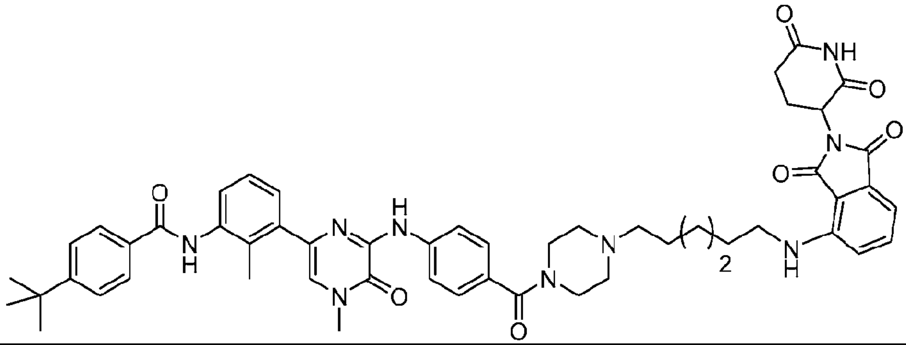
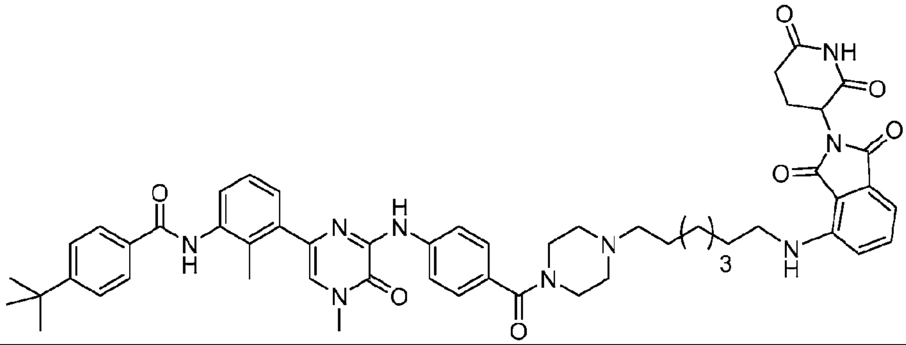
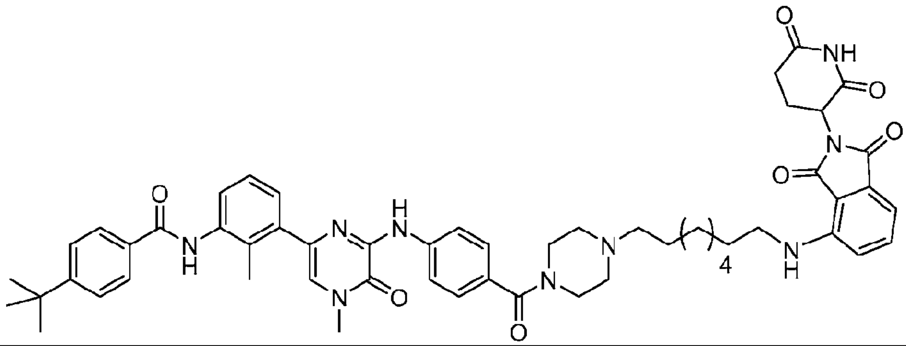
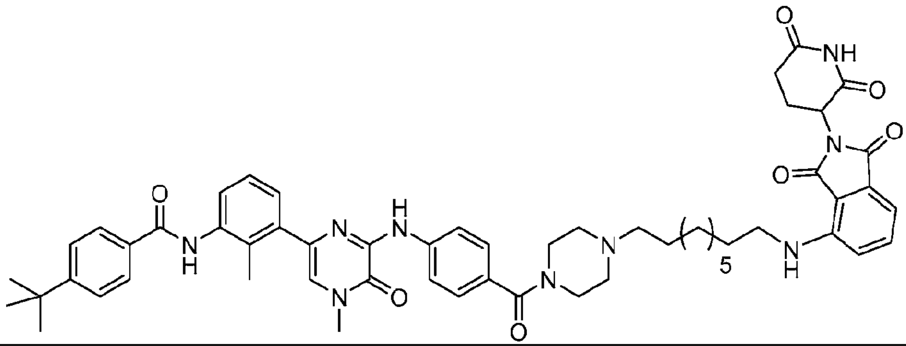
Cmpd No.	Structure
I-9	
I-10	
I-11	
I-12	

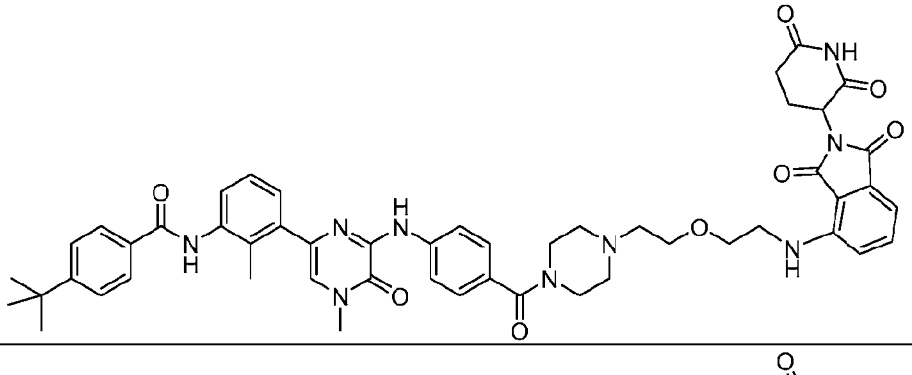
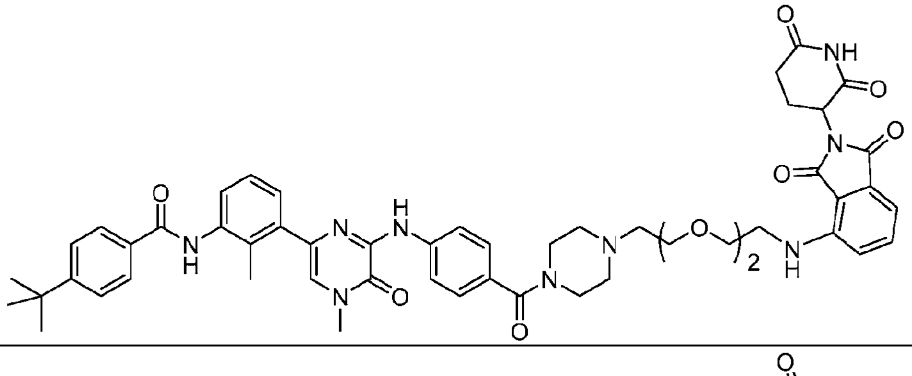
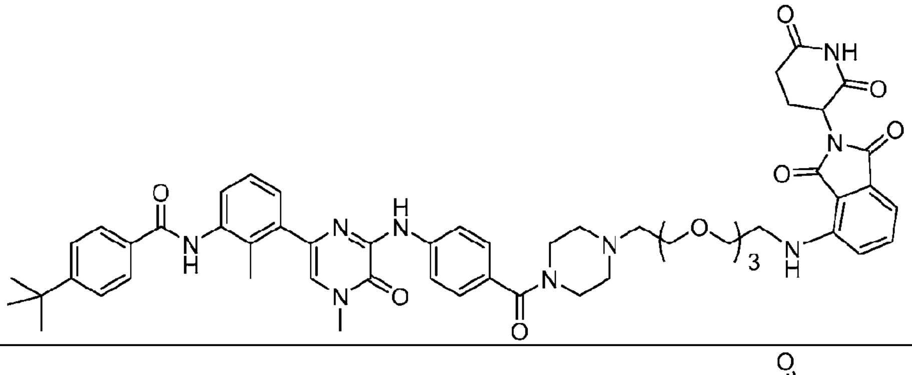
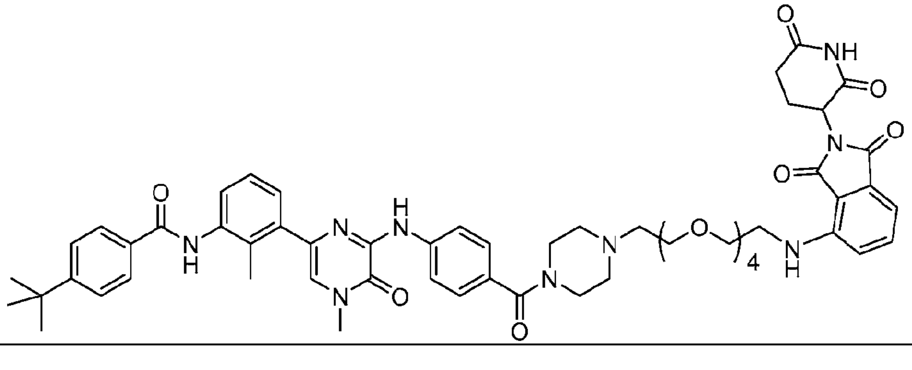
Cmpd No.	Structure
I-13	
I-14	
I-15	
I-16	

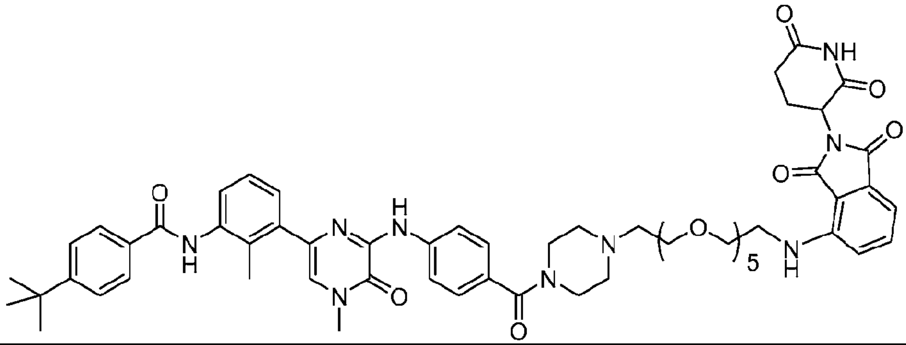
Cmpd No.	Structure
I-17	
I-18	
I-19	
I-20	

Cmpd No.	Structure
I-21	
I-22	
I-23	
I-24	

Cmpd No.	Structure
I-25	
I-26	
I-27	
I-28	

Cmpd No.	Structure
I-29	
I-30	
I-31	
I-32	

Cmpd No.	Structure
I-33	
I-34	
I-35	
I-36	

Cmpd No.	Structure
I-37	

Some of the foregoing compounds can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, stereoisomers and/or diastereomers. Accordingly, compounds of the application may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers. In one embodiment, the compounds of the application are enantiopure compounds. In another embodiment, mixtures of stereoisomers or diastereomers are provided.

Furthermore, certain compounds, as described herein, may have one or more double bonds that can exist as either the Z or E isomer, unless otherwise indicated. The application additionally encompasses the compounds as individual Z/E isomers substantially free of other E/Z isomers and alternatively, as mixtures of various isomers.

In one embodiment, the present application relates to compounds that target proteins, such as BTK for degradation, which have numerous advantages over inhibitors of protein function (*e.g.*, protein activity) and can a) overcome resistance in certain cases; b) prolong the kinetics of drug effect by destroying the protein, thus requiring resynthesis of the protein even after the compound has been metabolized; c) target all functions of a protein at once rather than a specific catalytic activity or binding event; d) expand the number of drug targets by including all proteins that a ligand can be developed for, rather than proteins whose activity (*e.g.*, protein activity) can be affected by a small molecule inhibitor, antagonist or agonist; and e) have increased potency compared to inhibitors due to the possibility of the small molecule acting catalytically.

Some embodiments of the present application relate to degradation or loss of 30% to 100% of the target protein. Some embodiments relate to the loss of 50-100% of the target protein. Other embodiments relate to the loss of 75-95% of the targeted protein.

A bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is capable of modulating (*e.g.*, decreasing) the amount of a targeted protein (*e.g.*, BTK). A bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is also capable of degrading a targeted protein (*e.g.*, BTK) through the UPP pathway. Accordingly, a bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is capable of treating or preventing a disease or disorder in which BTK plays a role. A bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is also capable of treating or preventing a disease or disorder in which BTK plays a role or in which BTK is deregulated (*e.g.*, overexpressed).

Modulation of BTK through UPP-mediated degradation by a bifunctional compound of the application, such as those described herein, provides a novel approach to the treatment, prevention, or amelioration of diseases or disorders in which BTK plays a role including, but not limited to, cancer and metastasis, inflammation, arthritis, systemic lupus erthematosus, skin-related disorders, pulmonary disorders, cardiovascular disease, ischemia, neurodegenerative disorders, liver disease, gastrointestinal disorders, viral and bacterial infections, central nervous system disorders, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy. Further, modulation of BTK through UPP-mediated degradation by a bifunctional compound of the application, such as those described herein, also provides a new paradigm for treating, preventing, or ameliorating diseases or disorders in which BTK is deregulated.

In one embodiment, a bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is more efficacious in treating a disease or condition (*e.g.*, cancer) than, or is capable of treating a disease or condition resistant to, the Targeting

Ligand, when the Targeting Ligand is administered alone (*i.e.*, not bonded to a Linker and a Degron). In one embodiment, a bifunctional compound of the present application (*e.g.*, a bifunctional compound of any of the formulae described herein, or selected from any bifunctional compounds described herein) is capable of modulating (*e.g.*, decreasing) the amount of BTK, and thus is useful in treating a disease or condition (*e.g.*, cancer) in which BTK plays a role.

In one embodiment, the bifunctional compound of the present application that is more efficacious in treating a disease or condition than, or is capable of treating a disease or condition resistant to, the Targeting Ligand, when the Targeting Ligand is administered alone (*i.e.*, not bonded to a Linker and a Degron), is more potent in inhibiting the growth of cells (*e.g.*, cancer cells) or decreasing the viability of cells (*e.g.*, cancer cells), than the Targeting Ligand, when the Targeting Ligand is administered alone (*i.e.*, not bonded to a Linker and a Degron). In one embodiment, the bifunctional compound inhibits the growth of cells (*e.g.*, cancer cells) or decreases the viability of cells (*e.g.*, cancer cells) at an IC_{50} that is lower than the IC_{50} of the Targeting Ligand (when the Targeting Ligand is administered alone (*i.e.*, not bonded to a Linker and a Degron)) for inhibiting the growth or decreasing the viability of the cells. In one embodiment, the IC_{50} of the bifunctional compound is at most 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 8%, 5%, 4%, 3%, 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 50%, 40%, 30%, 20%, 10%, 8%, 5%, 4%, 3%, 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 30%, 20%, 10%, 8%, 5%, 4%, 3%, 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 10%, 8%, 5%, 4%, 3%, 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 5%, 4%, 3%, 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 2%, 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the IC_{50} of the bifunctional compound is at most 1%, 0.8%, 0.5%, 0.4%, 0.3%, 0.2%, or 0.1% of the IC_{50} of the Targeting Ligand. In one embodiment, the bifunctional compound inhibits the growth of cells (*e.g.*, cancer cells) or decreases the viability of cells (*e.g.*, cancer cells) at an E_{max}

that is lower than the E_{max} of the Targeting Ligand (when the Targeting Ligand is administered alone (*i.e.*, not bonded to a Linker and a Degron)) for inhibiting the growth or decreasing the viability of the cells. In one embodiment, the E_{max} of the bifunctional compound is at most 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 8%, 5%, 4%, 3%, 2%, or 1% of the E_{max} of the Targeting Ligand. In one embodiment, the E_{max} of the bifunctional compound is at most 50%, 40%, 30%, 20%, 10%, 8%, 5%, 4%, 3%, 2%, or 1% of the E_{max} of the Targeting Ligand. In one embodiment, the E_{max} of the bifunctional compound is at most 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10% of the E_{max} of the Targeting Ligand.

In some embodiments, the inhibition of BTK activity is measured by IC_{50}.

In some embodiments, the inhibition of BTK activity is measured by EC_{50}.

Potency of the inhibitor can be determined by EC_{50} value. A compound with a lower EC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher EC_{50} value. In some embodiments, the substantially similar conditions comprise determining a BTK-dependent cell proliferation, *in vitro* or *in vivo* (*e.g.*, in cells expressing BTK).

Potency of the inhibitor can also be determined by IC_{50} value. A compound with a lower IC_{50} value, as determined under substantially similar conditions, is a more potent inhibitor relative to a compound with a higher IC_{50} value. In some embodiments, the substantially similar conditions comprise determining a BTK-dependent cell proliferation, *in vitro* or *in vivo* (*e.g.*, in cells expressing BTK).

In one embodiment, the bifunctional compounds of the present application are useful as anticancer agents, and thus may be useful in the treatment of cancer, by effecting tumor cell death or inhibiting the growth of tumor cells. In certain exemplary embodiments, the disclosed anticancer agents are useful in the treatment of cancers and other proliferative disorders, including, but not limited to breast cancer, cervical cancer, colon and rectal cancer, leukemia, lung cancer (*e.g.*, non-small cell lung cancer), melanoma, multiple myeloma, non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, prostate cancer, gastric cancer, leukemias (*e.g.*, myeloid, lymphocytic, myelocytic and lymphoblastic leukemias), malignant melanomas, and T-cell lymphoma.

A "selective BTK inhibitor," can be identified, for example, by comparing the ability of a compound to inhibit BTK kinase activity to its ability to inhibit other kinases. For example, a substance may be assayed for its ability to inhibit BTK kinase activity, as well as another kinase. In some embodiments, the selectivity can be identified by measuring the EC_{50} or IC_{50} of the compounds.

Definitions

Listed below are definitions of various terms used in this application. These definitions apply to the terms as they are used throughout this specification and claims, unless otherwise limited in specific instances, either individually or as part of a larger group.

The term "alkyl," as used herein, refers to saturated, straight or branched-chain hydrocarbon radicals containing, in certain embodiments, between one and six carbon atoms. For example C_1-C_3 alkyl includes methyl, ethyl, n-propyl, and isopropyl. Examples of C_1-C_6 alkyl radicals include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, tert-butyl, neopentyl, and n-hexyl radicals.

The term "alkoxy" refers to an -O-alkyl radical. For example C_1-C_3 alkoxy includes methoxy, ethoxy, n-propoxy, and isopropoxy. Examples of C_1-C_6 alkyl radicals include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, tert-butoxy, neopentoxy, and n-hexoxy radicals.

The terms "hal," "halo," and "halogen," as used herein, refer to an atom selected from fluorine, chlorine, bromine and iodine.

The term "aryl," as used herein, refers to a mono- or poly-cyclic carbocyclic ring system having one or more aromatic rings, fused or non-fused, including, but not limited to, phenyl, naphthyl, tetrahydronaphthyl, indanyl, indenyl and the like.

The term "aralkyl," as used herein, refers to an alkyl residue attached to an aryl ring. Examples include, but are not limited to, benzyl, phenethyl and the like.

The term "cycloalkyl," as used herein, denotes a monovalent group derived from a monocyclic or polycyclic saturated or partially unsaturated carbocyclic ring compound. Examples of C_3-C_8 cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentyl and cyclooctyl; and examples of C_3-C_{12}-cycloalkyl include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, bicyclo [2.2.1] heptyl, and bicyclo [2.2.2] octyl. Also contemplated is a monovalent group derived from a monocyclic or polycyclic carbocyclic ring compound having at least one carbon-carbon double bond by the removal of a single hydrogen atom. Examples of such groups include, but are not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, and the like.

The term "heteroaryl," as used herein, refers to a mono- or poly-cyclic (*e.g.*, bi-, or tri-cyclic or more) fused or non-fused, radical or ring system having at least one aromatic ring, having from five to ten ring atoms of which one ring atoms is selected from S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from S, O, and N; and the remaining ring atoms are carbon. Heteroaryl includes, but is not limited to, pyridinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzooxazolyl, quinoxalinyl, and the like.

The term "heteroaralkyl," as used herein, refers to an alkyl residue attached to a heteroaryl ring. Examples include, but are not limited to, pyridinylmethyl, pyrimidinylethyl and the like.

The term "heterocyclyl," or "heterocycloalkyl," as used herein, refers to a non-aromatic 3-, 4-, 5-, 6- or 7-membered ring or a bi- or tri-cyclic group fused of non-fused system, where (i) each ring contains between one and three heteroatoms independently selected from oxygen, sulfur and nitrogen, (ii) each 5-membered ring has 0 to 1 double bonds and each 6-membered ring has 0 to 2 double bonds, (iii) the nitrogen and sulfur heteroatoms may optionally be oxidized, and (iv) the nitrogen heteroatom may optionally be quaternized. Representative heterocycloalkyl groups include, but are not limited to, [1,3]dioxolane, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl.

The term "alkylamino" refers to a group having the structure -NH(C_1-C_{12} alkyl), *e.g.*, -NH(C_1-C_6 alkyl), where C_1-C_{12} alkyl is as previously defined.

The term "dialkylamino" refers to a group having the structure -N(C_1-C_{12} alkyl)$_2$, *e.g.*, -NH(C_1-C_6 alkyl), where C_1-C_{12} alkyl is as previously defined.

The term "acyl" includes residues derived from acids, including but not limited to carboxylic acids, carbamic acids, carbonic acids, sulfonic acids, and phosphorous acids. Examples include aliphatic carbonyls, aromatic carbonyls, aliphatic sulfonyls, aromatic sulfinyls, aliphatic sulfinyls, aromatic phosphates and aliphatic phosphates. Examples of aliphatic carbonyls include, but are not limited to, acetyl, propionyl, 2-fluoroacetyl, butyryl, 2-hydroxy acetyl, and the like.

In accordance with the application, any of the aryls, substituted aryls, heteroaryls and substituted heteroaryls described herein, can be any aromatic group. Aromatic groups can be substituted or unsubstituted.

As described herein, compounds of the application may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the application. It will be appreciated that the phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted." In general, the term "substituted", whether preceded by the term "optionally" or not, refers to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The terms "optionally substituted", "optionally substituted alkyl," "optionally substituted "optionally substituted alkenyl," "optionally substituted alkynyl", "optionally substituted cycloalkyl," "optionally substituted cycloalkenyl," "optionally substituted aryl", "optionally substituted heteroaryl," "optionally substituted aralkyl", "optionally substituted heteroaralkyl," "optionally substituted heterocycloalkyl," and any other optionally substituted group as used herein, refer to groups that are substituted or unsubstituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with substituents including, but not limited to:

-F, -CI, -Br, -I, -OH, protected hydroxy, $-NO_2$, -CN, $-NH_2$, protected amino, -NH-C_1-C_{12}-alkyl, -NH-C_2-C_{12}-alkenyl, -NH-C_2-C_{12}-alkenyl, -NH -C_3-C_{12}-cycloalkyl, -NH-aryl, -NH -heteroaryl, -NH -heterocycloalkyl, -dialkylamino, -diarylamino, -diheteroarylamino, -O-C_1-C_{12}-alkyl, -O-C_2-C_{12}-alkenyl, -O-C_2-C_{12}-alkenyl, -O-C3-C_{12}-cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocycloalkyl, -C(O)-C_1-C_{12}-alkyl, -C(O)-C_2-C_{12}-alkenyl, -C(O)-C_2-C_{12}-alkenyl, -C(O)-C_3-C_{12}-cycloalkyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, $-CONH_2$, -CONH-C_1-C_{12}-alkyl, -CONH-C_2-C_{12}-alkenyl, -CONH-C_2-C_{12}-alkenyl, -CONH-C_3-C_{12}-cycloalkyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocycloalkyl,-OCO_2-C_1-C_{12}-alkyl, -OCO_2-C_2-C_{12}-alkenyl, -OCO_2-C_2-C_{12}-alkenyl, -OCO_2-C_3-C_{12}-cycloalkyl, -OCO_2-aryl, -OCO_2-heteroaryl, -OCO_2-heterocycloalkyl, $-OCONH_2$, -OCONH-C_1-C_{12}-alkyl, -OCONH- C_2-C_{12}-alkenyl, -OCONH- C_2-C_{12}-alkenyl,

-OCONH-C_3-C_{12}-cycloalkyl, -OCONH-aryl, -OCONH-heteroaryl, -OCONH-heterocycloalkyl, -NHC(O)-C_1-C_{12}-alkyl, -NHC(O)-C_2-C_{12}-alkenyl, -NHC(O)-C_2-C_{12}-alkenyl, -NHC(O)-C_3-C_{12}-cycloalkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocycloalkyl, -$NHCO_2$-C_1-C_{12}-alkyl, -$NHCO_2$-C_2-C_{12}-alkenyl, -$NHCO_2$-C_2-C_{12}-alkenyl, -$NHCO_2$-C_3-C_{12}-cycloalkyl, -$NHCO_2$-aryl, -$NHCO_2$-heteroaryl, -$NHCO_2$- heterocycloalkyl, NHC(O)NH_2, -NHC(O)NH-C_1-C_{12}-alkyl, -NHC(O)NH-C_2-C_{12}-alkenyl, -NHC(O)NH-C_2-C_{12}-alkenyl, -NHC(O)NH-C_3-C_{12}-cycloalkyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, NHC(O)NH-heterocycloalkyl, -NHC(S)NH_2, -NHC(S)NH-C_1-C_{12}-alkyl, -NHC(S)NH-C_2-C_{12}-alkenyl, -NHC(S)NH-C_2-C_{12}-alkenyl, -NHC(S)NH-C_3-C_{12}-cycloalkyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocycloalkyl, -NHC(NH)NH_2, -NHC(NH)NH- C_1-C_{12}-alkyl, -NHC(NH)NH-C_2-C_{12}-alkenyl, -NHC(NH)NH-C_2-C_{12}-alkenyl, -NHC(NH)NH-C_3-C_{12}-cycloalkyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NHheterocycloalkyl, -NHC(NH)-C_1-C_{12}-alkyl, -NHC(NH)-C_2-C_{12}-alkenyl, -NHC(NH)-C_2-C_{12}-alkenyl, -NHC(NH)-C_3-C_{12}-cycloalkyl, -NHC(NH)-aryl, -NHC(NH)-heteroaryl, -NHC(NH)-heterocycloalkyl, -C(NH)NH-C_1-C_{12}-alkyl, -C(NH)NH-C_2-C_{12}-alkenyl, -C(NH)NH-C_2-C_{12}-alkenyl, C(NH)NH-C_3-C_{12}-cycloalkyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NHheterocycloalkyl, -S(O)-C_1-C_{12}-alkyl,- S(O)-C_2-C_{12}-alkenyl,- S(O)-C_2-C_{12}-alkenyl, -S(O)-C_3-C_{12}-cycloalkyl,- S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocycloalkyl -SO_2NH_2, -SO_2NH-C_1-C_{12}-alkyl, -SO_2NH-C_2-C_{12}-alkenyl, -SO_2NH-C_2-C_{12}-alkenyl, -SO_2NH-C_3-C_{12}-cycloalkyl, -SO_2NH-aryl, -SO_2NH-heteroaryl, -SO_2NH-heterocycloalkyl, -$NHSO_2$-C_1-C_{12}-alkyl, -$NHSO_2$-C_2-C_{12}-alkenyl,- $NHSO_2$-C_2-C_{12}-alkenyl, -$NHSO_2$-C_3-C_{12}-cycloalkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -$NHSO_2$-heterocycloalkyl, -CH_2NH_2, -$CH_2SO_2CH_3$, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -C_3-C_{12}-cycloalkyl, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S-C_1-C_{12}-alkyl, -S-C_2-C_{12}-alkenyl, -S-C_2-C_{12}-alkenyl, -S-C_3-C_{12}-cycloalkyl, -S-aryl, -S-heteroaryl, -S-heterocycloalkyl, or methylthiomethyl.

It is understood that the aryls, heteroaryls, alkyls, and the like can be substituted.

The term "cancer" includes, but is not limited to, the following cancers: epidermoid Oral: buccal cavity, lip, tongue, mouth, pharynx; Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma, and teratoma; Lung: bronchogenic carcinoma (squamous cell or epidermoid, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, larynx, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel or small intestines (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel or large intestines (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma), colon, colon-rectum, colorectal, rectum; Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor (nephroblastoma), lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma, biliary passages; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma (pinealoma), glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma (serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma), granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma), breast; Hematologic: blood (myeloid leukemia (acute and chronic), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma) hairy cell; lymphoid disorders; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, keratoacanthoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis, Thyroid gland: papillary thyroid carcinoma, follicular thyroid carcinoma; medullary thyroid carcinoma, undifferentiated thyroid cancer, multiple endocrine neoplasia type 2A, multiple endocrine neoplasia type 2B, familial medullary thyroid cancer, pheochromocytoma, paraganglioma; and Adrenal glands: neuroblastoma. Thus, the term "cancerous cell" as provided herein, includes a cell afflicted by any one of the above-identified conditions.

The term “BTK" herein refers to Bruton's tyrosine kinase.

The term "subject" as used herein refers to a mammal. A subject therefore refers to, for example, dogs, cats, horses, cows, pigs, guinea pigs, and the like. Preferably the subject is a human. When the subject is a human, the subject may be referred to herein as a patient.

"Treat", "treating" and "treatment" refer to a method of alleviating or abating a disease and/or its attendant symptoms.

As used herein, “preventing” or “prevent” describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

The term “targeted protein(s)” is used interchangeably with “target protein(s)”, unless the context clearly dictates otherwise. In one embodiment, a “targeted protein” is BTK.

The terms “disease(s)”, “disorder(s)”, and “condition(s)” are used interchangeably, unless the context clearly dictates otherwise.

The term "therapeutically effective amount" of a bifunctional compound or pharmaceutical composition of the application, as used herein, means a sufficient amount of the bifunctional compound or pharmaceutical composition so as to decrease the symptoms of a disorder in a subject. As is well understood in the medical arts a therapeutically effective amount of a bifunctional compound or pharmaceutical composition of this application will be at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present application will be decided by the attending physician within the scope of sound medical judgment. The specific inhibitory dose for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts of the compounds formed by the process of the present application which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, *et al.* describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977). The salts can be prepared in situ during the final isolation and purification of the compounds of the application, or separately by reacting the free base or acid function with a suitable acid or base.

Examples of pharmaceutically acceptable salts include, but are not limited to, nontoxic acid addition salts: salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid, or with organic acids such as acetic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid. Other pharmaceutically acceptable salts include, but are not limited to, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, alkyl having from 1 to 6 carbon atoms, sulfonate and aryl sulfonate.

As used herein, the term "pharmaceutically acceptable ester" refers to esters of the bifunctional compounds formed by the process of the present application which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include, but are not limited to, formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein, refers to those prodrugs of the bifunctional compounds formed by the process of the present application which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals with undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the present application. "Prodrug", as used herein, means a compound which is convertible *in vivo* by metabolic means (*e.g.*, by hydrolysis) to afford any compound delineated by the formulae of the instant application. Various forms of prodrugs are known in the art, for example, as discussed in Bundgaard, (ed.), Design of Prodrugs, Elsevier (1985); Widder, et al. (ed.), Methods in Enzymology, vol. 4, Academic Press (1985); Krogsgaard-Larsen, et al., (ed). "Design and Application of Prodrugs, Textbook of Drug Design and Development, Chapter 5, 113-191 (1991); Bundgaard, et al., Journal of Drug Deliver Reviews, 8:1-38(1992); Bundgaard, J. of Pharmaceutical Sciences, 77:285 et seq. (1988); Higuchi and Stella (eds.) Prodrugs as Novel Drug Delivery Systems, American Chemical Society (1975); and Bernard Testa & Joachim Mayer, "Hydrolysis In Drug And Prodrug Metabolism: Chemistry, Biochemistry And Enzymology," John Wiley and Sons, Ltd. (2002).

This application also encompasses pharmaceutical compositions containing, and methods of treating disorders through administering, pharmaceutically acceptable prodrugs of bifunctional compounds of the application. For example, compounds of the application having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (*e.g.*, two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of the application. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxy carbonyls, as outlined in *Advanced Drug Delivery Reviews*, 1996, 19, 1 15. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in *J. Med. Chem.* 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

The application also provides for a pharmaceutical composition comprising a therapeutically effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In another aspect, the application provides a kit comprising a bifunctional compound capable of inhibiting BTK activity selected from one or more compounds disclosed herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, optionally in combination with a second agent and instructions for use in treating cancer.

In another aspect, the application provides a method of synthesizing a bifunctional compound disclosed herein.

The synthesis of the bifunctional compounds of the application can be found herein and in the Examples below.

Other embodiments are a method of making a bifunctional compound of any of the formulae herein using any one, or combination of, reactions delineated herein. The method can include the use of one or more intermediates or chemical reagents delineated herein.

Another aspect is an isotopically labeled bifunctional compound of any of the formulae delineated herein. Such compounds have one or more isotope atoms which may or may not be radioactive (*e.g.*, ^{3}H, ^{2}H, ^{14}C, ^{13}C, ^{18}F, ^{35}S, ^{32}P, ^{125}I, and ^{131}I) introduced into the bifunctional compound. Such compounds are useful for drug metabolism studies and diagnostics, as well as therapeutic applications.

A bifunctional compound of the application can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a bifunctional compound of the application can be prepared by reacting the free acid form of the bifunctional compound with a pharmaceutically acceptable inorganic or organic base.

Alternatively, the salt forms of the bifunctional compounds of the application can be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the bifunctional compounds of the application can be prepared from the corresponding base addition salt or acid addition salt from, respectively. For example, a bifunctional compound of the application in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (*e.g.*, ammonium hydroxide solution, sodium hydroxide, and the like). A bifunctional compound of the application in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (*e.g.*, hydrochloric acid, *etc.*).

Prodrugs of the bifunctional compounds of the application can be prepared by methods known to those of ordinary skill in the art (*e.g.*, for further details see Saulnier et al., (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized bifunctional compound of the application with a suitable carbamylating agent (*e.g.*, 1,1-acyloxyalkylcarbanochloridate, para-nitrophenyl carbonate, or the like).

Protected derivatives of the bifunctional compounds of the application can be made by means known to those of ordinary skill in the art. A detailed description of techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry", 3rd edition, John Wiley and Sons, Inc., 1999.

Compounds of the present application can be conveniently prepared or formed during the process of the application, as solvates (*e.g.*, hydrates). Hydrates of bifunctional compounds of the present application can be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Acids and bases useful in the methods herein are known in the art. Acid catalysts are any acidic chemical, which can be inorganic (*e.g.*, hydrochloric, sulfuric, nitric acids, aluminum trichloride) or organic (*e.g.*, camphorsulfonic acid, p-toluenesulfonic acid, acetic acid, ytterbium triflate) in nature. Acids are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions. Bases are any basic chemical, which can be inorganic (*e.g.*, sodium bicarbonate, potassium hydroxide) or organic (*e.g.*, triethylamine, pyridine) in nature. Bases are useful in either catalytic or stoichiometric amounts to facilitate chemical reactions.

Combinations of substituents and variables envisioned by this application are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (*e.g.*, therapeutic or prophylactic administration to a subject).

When any variable (*e.g.*, R_{14}) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with one or more R_{14} moieties, then R_{14} at each occurrence is selected independently from the definition of R_{14}. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds within a designated atom's normal valency.

In addition, some of the compounds of this application have one or more double bonds, or one or more asymmetric centers. Such compounds can occur as racemates, racemic mixtures, single enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- *or E-* or Z- double isomeric forms, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-, or as (D)- or (L)- for amino acids. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. The configuration of any carbon-carbon double bond appearing herein is selected for convenience only and is not intended to designate a particular configuration unless the text so states; thus a carbon-carbon double bond depicted arbitrarily herein as *trans* may be *cis, trans,* or a mixture of the two in any proportion. All such isomeric forms of such compounds are expressly included in the present application.

Optical isomers may be prepared from their respective optically active precursors by the procedures described herein, or by resolving the racemic mixtures. The resolution can be carried out in the presence of a resolving agent, by chromatography or by repeated crystallization or by some combination of these techniques which are known to those skilled in the art. Further details regarding resolutions can be found in Jacques, *et al., Enantiomers, Racemates, and Resolutions* (John Wiley & Sons, 1981).

"Isomerism" means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereoisomers", and stereoisomers that are non-superimposable mirror images of each other are termed "enantiomers" or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a "racemic mixture".

A carbon atom bonded to four non-identical substituents is termed a "chiral center".

"Chiral isomer" means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture". When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al., Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al., Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al., Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

"Geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds. These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

Furthermore, the structures and other compounds discussed in this application include all atropic isomers thereof. "Atropic isomers" are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques; it has been possible to separate mixtures of two atropic isomers in select cases.

"Tautomer" is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as a mixture of a tautomeric set in solution. In solid form, usually one tautomer predominates. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertable by tautomerizations is called tautomerism.

Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose. Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), amine-enamine and enamine-enamine. The compounds of this application may also be represented in multiple tautomeric forms, in such instances, the application expressly includes all tautomeric forms of the compounds described herein (*e.g.*, alkylation of a ring system may result in alkylation at multiple sites, the application expressly includes all such reaction products).

In the present application, the structural formula of the bifunctional compound represents a certain isomer for convenience in some cases, but the present application includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like. In the present specification, the structural formula of the compound represents a certain isomer for convenience in some cases, but the present application includes all isomers, such as geometrical isomers, optical isomers based on an asymmetrical carbon, stereoisomers, tautomers, and the like.

Additionally, the compounds of the present application, for example, the salts of the bifunctional compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Non-limiting examples of hydrates include monohydrates, dihydrates, *etc.* Non-limiting examples of solvates include ethanol solvates, acetone solvates, *etc.*

"Solvate" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H_2O.

The synthesized bifunctional compounds can be separated from a reaction mixture and further purified by a method such as column chromatography, high pressure liquid chromatography, or recrystallization. As can be appreciated by the skilled artisan, further methods of synthesizing the bifunctional compounds of the formulae herein will be evident to those of ordinary skill in the art. Additionally, the various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. In addition, the solvents, temperatures, reaction durations, *etc.* delineated herein are for purposes of illustration only and one of ordinary skill in the art will recognize that variation of the reaction conditions can produce the desired bridged macrocyclic products of the present application. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the compounds described herein are known in the art and include, for example, those such as described in R. Larock, Comprehensive Organic Transformations, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, Protective Groups in Organic Synthesis, 2d. Ed., John Wiley and Sons (1991); L. Fieser and M. Fieser, Fieser and Fieser's Reagents for Organic

Synthesis, John Wiley and Sons (1994); and L. Paquette, ed., Encyclopedia of Reagents for Organic Synthesis, John Wiley and Sons (1995), and subsequent editions thereof.

The compounds of this application may be modified by appending various functionalities via any synthetic means delineated herein to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (*e.g.*, blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion.

The compounds of the application are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

Method of Synthesizing the Compounds

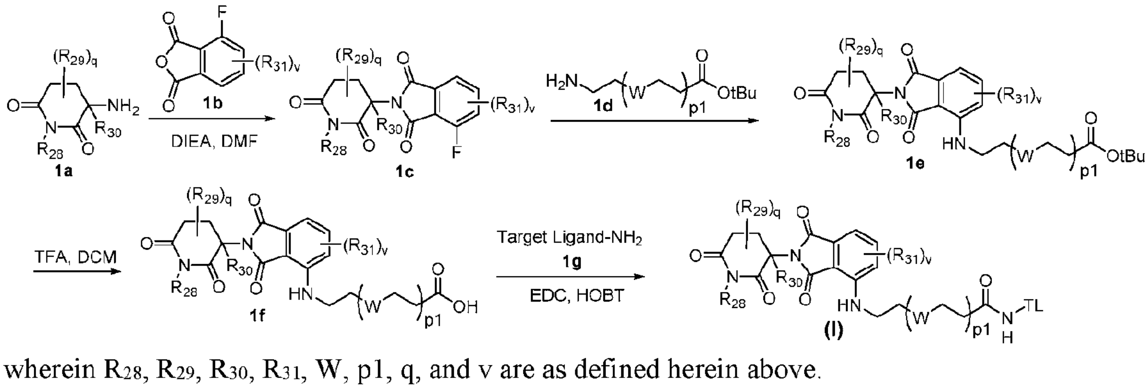
Compounds of the present application can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; and Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999, incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art. The following descriptions of synthetic methods are designed to illustrate, but not to limit, general procedures for the preparation of compounds of the present application. The processes generally provide the desired final compound at or near the end of the overall process, although it may be desirable in certain instances to further convert the compound to a pharmaceutically acceptable salt, ester or prodrug thereof. Suitable synthetic routes are depicted in the schemes below.

Those skilled in the art will recognize if a stereocenter exists in the compounds disclosed herein. Accordingly, the present application includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

The compounds of the present application can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present application can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below.

Compounds of the present application can be synthesized by following the steps outlined in General Scheme 1 and 2 which comprise different sequences of assembling intermediates. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

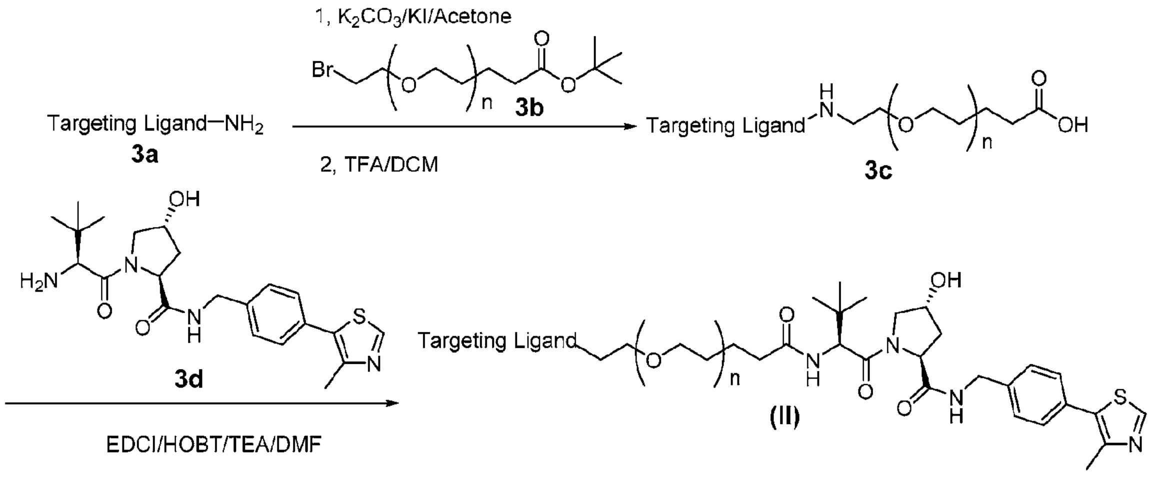
General Scheme 1: Synthesis of Thalidomide-based Degronimids



wherein R_{28}, R_{29}, R_{30}, R_{31}, W, p1, q, and v are as defined herein above.

The general way of preparing representative compounds of the present application (*i.e.*, Compound of formula (**I**) shown above) using intermediates **1a**, **1b**, **1c**, **1d**, **1e**, **1f**, and **1g** is outlined in **General Scheme 1**. Reaction of **1a** with **1b** in the presence of a base, *i.e.*, diisopropylethylamine (DIPEA), and in a solvent, *i.e.*, dimethylformamide (DMF), provides intermediate **1c**. Reaction of **1d** with fluoride **1c** provides intermediate **1e**. Deprotection of the **1e** in the presence of TFA in a solvent, *i.e.*, dichloromethane (DCM) or methanol (MeOH), provides **1f**. Coupling of **1f** and Target Ligand (TL) **1g** under standard coupling conditions using a coupling reagent, *i.e.*, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and hydroxybenzotriazole, in a solvent, *i.e.*, DCM or DMF, provides bifunctional compound of formula (I).

General Scheme 2: Synthesis of VHL-based Degronimids



The general way of preparing representative compounds of the present application (*i.e.*, Compound of formula **(II)** shown above) using intermediates **3a**, **3b**, **3c**, and **3d** is outlined in **General Scheme 2**. Reaction of **3a** with **3b** in the presence of potassium iodide (KI), a base, *i.e.*, potassium carbonate (K_2CO_3), and in a solvent, *i.e.*, acetone), followed by Boc deprotection in the presence of strong acid (*i.e.*, hydrochloric acid (HCl) or trifluoroacetic acid (TFA)) in a solvent, *i.e.*, dichloromethane (DCM) or methanol (MeOH) provides intermediate **3c**. Coupling of amine **3d** and Target Ligand **3c** under standard coupling conditions using a coupling reagent, *i.e.*, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI) and hydroxybenzotriazole (HOBt), and a base (*i.e.*, triethylamine (TEA)) in a solvent, *i.e.*, DCM or DMF, provides bifunctional compound of formula **(II)** in shown in General Scheme 2.

Biological Assays

Cell Viability assay

Wild-type or cereblon null cells are treated with various concentrations of a bifunctional compound of the application and allowed to grow. Cells are then assayed to determine cell viability by measuring the amount of ATP present, which is an indicator of cell metabolic activity. Results are graphed as relative luminescent values.

Methods of the Application

In another aspect, the application provides a method of modulating a kinase, comprising contacting the kinase with a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, or with a pharmaceutical composition disclosed herein. In some embodiments, the kinase is BTK.

In another aspect, the application provides a method of inhibiting a kinase, comprising contacting the kinase with a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, or with a pharmaceutical composition disclosed herein. In some embodiments, the kinase is BTK.

In still another aspect, the application provides a method of inhibiting BTK, the method comprising administering to a subject in need thereof an effective amount of a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

In still another aspect, the application provides a method of inhibiting BTK, the method comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier.

Another aspect of the application provides a method of treating or preventing a disease, the method comprising administering to a subject in need thereof an effective amount of a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. In some embodiments, the disease is mediated by a kinase. In further embodiments, the kinase is BTK.

Another aspect of the application provides a method of treating or preventing a disease, the method comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier. In some embodiments, the disease is mediated by a kinase. In further embodiments, the kinase is BTK.

In some embodiments, the disease is mediated by BTK (*e.g.*, BTK plays a role in the initiation or development of the disease).

In certain embodiments, the disease or disorder is cancer or a proliferation disease.

In further embodiments, the disease or disorder is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, pancreas cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, hepatocellular carcinoma, papillary renal carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, or solid tumors.

In further embodiments, the disease or disorder is sarcoma. In further embodiments, the disease or disorder is sarcoma of the bones, muscles, tendons, cartilage, nerves, fat, or blood vessels. In further embodiments, the disease or disorder is soft tissue sarcoma, bone sarcoma, or osteosarcoma. In further embodiments, the disease or disorder is angiosarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, Karposi's sarcoma, osteosarcoma, gastrointestinal stromal tumor, Synovial sarcoma, Pleomorphic sarcoma, chondrosarcoma, Ewing's sarcoma, reticulum cell sarcoma, meningiosarcoma, botryoid sarcoma, rhabdomyosarcoma, or embryonal rhabdomyosarcoma.

In further embodiments, the disease or disorder is multiple myeloma.

In other embodiments, the disease or disorder is inflammation, arthritis, rheumatoid arthritis, spondyiarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erthematosus (SLE), skin-related conditions, psoriasis, eczema, bums, dermatitis, neuroinflammation, allergy, pain, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis, cardiomyopathy, stroke including ischemic and hemorrhagic stroke, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, and ischemia resulting from cardiac/coronary bypass, neurodegenerative disorders, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, autoimmune disease, graft vs. host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, cancer, leukemia, lymphoma, colorectal cancer, brain cancer, bone cancer, epithelial call-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal cancer, lip cancer, mouth cancer, esophageal cancer, small bowel cancer, stomach cancer, colon cancer, liver cancer, bladder cancer, pancreas cancer, ovarian cancer, cervical cancer, lung cancer, breast cancer, skin cancer, squamous cell and/or basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial cells throughout the body, chronic myelogenous leukemia (CML), acute myeloid leukemia (AML) and acute promyelocytic leukemia (APL), angiogenesis including neoplasia, metastasis, central nervous system disorders, central nervous system disorders having an inflammatory or apoptotic component, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, spinal cord injury, and peripheral neuropathy, or B-Cell Lymphoma.

In further embodiments, the disease or disorder is inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erthematosus (SLE), skin-related conditions, psoriasis, eczema, dermatitis, pain, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoisosis, asthma, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), congestive heart failure, cardiac reperfusion injury, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, leukemia or lymphoma.

Another aspect of the application provides a method of treating a kinase mediated disorder, the method comprising administering to a subject in need thereof an effective amount of a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. In some embodiments, the bifunctional compound is an inhibitor of BTK. In other embodiments, the subject is administered an additional therapeutic agent. In other embodiments, the bifunctional compound and the additional therapeutic agent are administered simultaneously or sequentially.

Another aspect of the application provides a method of treating a kinase mediated disorder, the method comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier. In some embodiments, the bifunctional compound is an inhibitor of BTK. In other embodiments, the subject is administered an additional therapeutic agent. In other embodiments, the pharmaceutical composition comprising a bifunctional compound and the additional therapeutic agent are administered simultaneously or sequentially.

In other embodiments, the disease or disorder is cancer. In further embodiments, the cancer is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, pancreas cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, hepatocellular carcinoma, papillary renal carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, or solid tumors.

Another aspect of the present application relates to a method of treating or preventing a proliferative disease. The method comprises administering to a subject in need thereof an effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

Another aspect of the present application relates to a method of treating or preventing a proliferative disease. The method comprises administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprises activated BTK, comprising administering to a subject in need thereof an effective amount of a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

In another aspect, the application provides a method of treating or preventing cancer, wherein the cancer cell comprises activated BTK, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier.

In certain embodiments, the BTK activation is selected from mutation of BTK, amplification of BTK, expression of BTK, and ligand mediated activation of BTK.

Another aspect of the application provides a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of BTK inhibition for the treatment of cancer, comprising administering to the subject an effective amount of a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof.

Another aspect of the application provides a method of treating or preventing cancer in a subject, wherein the subject is identified as being in need of BTK inhibition for the treatment of cancer, comprising administering to the subject an effective amount of a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier.

In certain embodiments, the application provides a method of treating any of the disorders described herein, wherein the subject is a human. In certain embodiments, the application provides a method of preventing any of the disorders described herein, wherein the subject is a human.

In another aspect, the application provides a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, for use in the manufacture of a medicament for treating or preventing a disease in which BTK plays a role.

In still another aspect, the application provides a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof for use in treating or preventing a disease in which BTK plays a role.

In another aspect, the application provides a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof f and a pharmaceutically acceptable carrier, for use in the manufacture of a medicament for treating or preventing a disease in which BTK plays a role.

In still another aspect, the application provides a pharmaceutical composition comprising a bifunctional compound disclosed herein, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof and a pharmaceutically acceptable carrier, for use in treating or preventing a disease in which BTK plays a role.

As inhibitors of BTK, the bifunctional compounds and compositions of this application are particularly useful for treating or lessening the severity of a disease, condition, or disorder where a protein kinase is implicated in the disease, condition, or disorder. In one aspect, the present application provides a method for treating or lessening the severity of a disease, condition, or disorder where a protein kinase is implicated in the disease state. In another aspect, the present application provides a method for treating or lessening the severity of a protein kinase mediated disease, condition, or disorder where inhibition of enzymatic activity is implicated in the treatment of the disease. In another aspect, this application provides a method for treating or lessening the severity of a disease, condition, or disorder with bifunctional compounds that inhibit enzymatic activity by binding to the protein kinase. Another aspect provides a method for treating or lessening the severity of a protein kinase mediated disease, condition, or disorder by inhibiting enzymatic activity of the protein kinase with a protein kinase inhibitor.

In some embodiments, said method is used to treat or prevent a condition selected from autoimmune diseases, inflammatory diseases, proliferative and hyperproliferative diseases, immunologically-mediated diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cardiovascular diseases, hormone related diseases, allergies, asthma, and Alzheimer's disease. In other embodiments, said condition is selected from a proliferative disorder and a neurodegenerative disorder.

One aspect of this application provides bifunctional compounds that are useful for the treatment of diseases, disorders, and conditions characterized by excessive or abnormal cell proliferation. Such diseases include, but are not limited to, a proliferative or hyperproliferative disease, and a neurodegenerative disease. Examples of proliferative and hyperproliferative diseases include, without limitation, cancer. The term "cancer" includes, but is not limited to, the following cancers: breast; ovary; cervix; prostate; testis, genitourinary tract; esophagus; larynx, glioblastoma; neuroblastoma; stomach; skin, keratoacanthoma; lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma; bone; colon; colorectal; adenoma; pancreas, adenocarcinoma; thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma; seminoma; melanoma; sarcoma; bladder carcinoma; liver carcinoma and biliary passages; kidney carcinoma; myeloid disorders; lymphoid disorders, Hodgkin's, hairy cells; buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx; small intestine; colonrectum, large intestine, rectum, brain and central nervous system; chronic myeloid leukemia (CML), and leukemia. The term "cancer" includes, but is not limited to, the following cancers: myeloma, lymphoma, or a cancer selected from gastric, renal, or and the following cancers: head and neck, oropharangeal, non-small cell lung cancer (NSCLC), endometrial, hepatocarcinoma, Non-Hodgkins lymphoma, and pulmonary.

The term "cancer" refers to any cancer caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, lymphomas and the like. For example, cancers include, but are not limited to, mesothelioma, leukemias and lymphomas such as cutaneous T-cell lymphomas (CTCL), noncutaneous peripheral T-cell lymphomas, lymphomas associated with human T-cell lymphotrophic virus (HTLV) such as adult T-cell leukemia/lymphoma (ATLL), B-cell lymphoma, acute nonlymphocytic leukemias, chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, lymphomas, and multiple myeloma, non-Hodgkin lymphoma, acute lymphatic leukemia (ALL), chronic lymphatic leukemia (CLL), Hodgkin's lymphoma, Burkitt lymphoma, adult T-cell leukemia lymphoma, acute-myeloid leukemia (AML), chronic myeloid leukemia (CML), or hepatocellular carcinoma. Further examples include myelodisplastic syndrome, childhood solid tumors such as brain tumors, neuroblastoma, retinoblastoma, Wilms' tumor, bone tumors, and soft-tissue sarcomas, common solid tumors of adults such as head and neck cancers (*e.g.*, oral, laryngeal, nasopharyngeal and esophageal), genitourinary cancers (*e.g.*, prostate, bladder, renal, uterine, ovarian, testicular), lung cancer (*e.g.*, small-cell and non-small cell), breast cancer, pancreatic cancer, melanoma and other skin cancers, stomach cancer, brain tumors, tumors related to Gorlin's syndrome (*e.g.*, medulloblastoma, meningioma, *etc.*), and liver cancer. Additional exemplary forms of cancer which may be treated by the subject bifunctional compounds include, but are not limited to, cancer of skeletal or smooth muscle, stomach cancer, cancer of the small intestine, rectum carcinoma, cancer of the salivary gland, endometrial cancer, adrenal cancer, anal cancer, rectal cancer, parathyroid cancer, and pituitary cancer.

Additional cancers that the bifunctional compounds described herein may be useful in preventing, treating and studying are, for example, colon carcinoma, familiary adenomatous polyposis carcinoma and hereditary non-polyposis colorectal cancer, or melanoma. Further, cancers include, but are not limited to, labial carcinoma, larynx carcinoma, hypopharynx carcinoma, tongue carcinoma, salivary gland carcinoma, gastric carcinoma, adenocarcinoma, thyroid cancer (medullary and papillary thyroid carcinoma), renal carcinoma, kidney parenchyma carcinoma, cervix carcinoma, uterine corpus carcinoma, endometrium carcinoma, chorion carcinoma, testis carcinoma, urinary carcinoma, melanoma, brain tumors such as glioblastoma, astrocytoma, meningioma, medulloblastoma and peripheral neuroectodermal tumors, gall bladder carcinoma, bronchial carcinoma, multiple myeloma, basalioma, teratoma, retinoblastoma, choroidea melanoma, seminoma, rhabdomyosarcoma, craniopharyngeoma, osteosarcoma, chondrosarcoma, myosarcoma, liposarcoma, fibrosarcoma, Ewing sarcoma, and plasmocytoma. In one aspect of the application, the present application provides for the use of one or more bifunctional compounds of the application in the manufacture of a medicament for the treatment of cancer, including without limitation the various types of cancer disclosed herein.

In some embodiments, the bifunctional compounds of this application are useful for treating cancer, such as colorectal, thyroid, breast, and lung cancer; and myeloproliferative disorders, such as polycythemia vera, thrombocythemia, myeloid metaplasia with myelofibrosis, chronic myelogenous leukemia, chronic myelomonocytic leukemia, hypereosinophilic syndrome, juvenile myelomonocytic leukemia, and systemic mast cell disease. In some embodiments, the bifunctional compounds of this application are useful for treating hematopoietic disorders, in particular, acute-myelogenous leukemia (AML), chronic-myelogenous leukemia (CML), acute-promyelocytic leukemia, and acute lymphocytic leukemia (ALL).

This application further embraces the treatment or prevention of cell proliferative disorders such as hyperplasias, dysplasias and pre-cancerous lesions. Dysplasia is the earliest form of pre-cancerous lesion recognizable in a biopsy by a pathologist. The subject bifunctional compounds may be administered for the purpose of preventing said hyperplasias, dysplasias or pre-cancerous lesions from continuing to expand or from becoming cancerous. Examples of pre-cancerous lesions may occur in skin, esophageal tissue, breast and cervical intra-epithelial tissue.

Another aspect of this application provides a method for the treatment or lessening the severity of a disease selected from a proliferative or hyperproliterative disease, or a neurodegenerative disease, comprising administering an effective amount of a bifunctional compound, or a pharmaceutically acceptable composition comprising a bifunctional compound, to a subject in need thereof.

As inhibitors of BTK kinase, the compounds and compositions of this application are also useful in biological samples. One aspect of the application relates to inhibiting protein kinase activity in a biological sample, which method comprises contacting said biological sample with a bifunctional compound of the application or a composition comprising said bifunctional compound. The term "biological sample", as used herein, means an *in vitro* or an ex vivo sample, including, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof. Inhibition of protein kinase activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ- transplantation, and biological specimen storage.

Another aspect of this application relates to the study of BTK kinase in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such protein kinases; and the comparative evaluation of new protein kinase inhibitors. Examples of such uses include, but are not limited to, biological assays such as enzyme assays and cell-based assays.

The activity of the compounds and compositions of the present application as BTK inhibitors may be assayed *in vitro*, *in vivo*, or in a cell line. *In vitro* assays include assays that determine inhibition of either the enzyme activity or ATPase activity of the activated kinase. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to the protein kinase and may be measured either by radio labelling the inhibitor prior to binding, isolating the inhibitor/BTK complex and determining the amount of radio label bound, or by running a competition experiment where new inhibitors are incubated with the kinase bound to known radioligands. Detailed conditions for assaying a compound utilized in this application as an inhibitor of various kinases are set forth in the Examples below.

In accordance with the foregoing, the present application further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a bifunctional compound of the application, or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired.

Pharmaceutical Compositions

In another aspect, the application provides a pharmaceutical composition comprising a therapeutically effective amount of a bifunctional compound of the present application or an enantiomer, diastereomer, or stereoisomer thereof, or pharmaceutically acceptable salt, hydrate, solvate, or prodrug thereof, and a pharmaceutically acceptable carrier.

Bifunctional compounds of the application can be administered as pharmaceutical compositions by any conventional route, in particular enterally, *e.g.*, orally, *e.g.*, in the form of tablets or capsules, or parenterally, *e.g.*, in the form of injectable solutions or suspensions, or topically, *e.g.*, in the form of lotions, gels, ointments or creams, or in a nasal or suppository form. Pharmaceutical compositions comprising a compound of the present application in free form or in a pharmaceutically acceptable salt form in association with at least one pharmaceutically acceptable carrier or diluent can be manufactured in a conventional manner by mixing, granulating or coating methods. For example, oral compositions can be tablets or gelatin capsules comprising the active ingredient together with a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and or polyvinylpyrrolidone; if desired d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) absorbents, colorants, flavors and sweeteners. Injectable compositions can be aqueous isotonic solutions or suspensions, and suppositories can be prepared from fatty emulsions or suspensions. The compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, they may also contain other therapeutically valuable substances. Suitable formulations for transdermal applications include an effective amount of a compound of the present application with a carrier. A carrier can include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. Matrix transdermal formulations may also be used. Suitable formulations for topical application, *e.g.*, to the skin and eyes, are preferably aqueous solutions, ointments, creams or gels well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

The pharmaceutical compositions of the present application comprise a therapeutically effective amount of a compound of the present application formulated together with one or more pharmaceutically acceptable carriers. As used herein, the term "pharmaceutically acceptable carrier" means a non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylenepolyoxy propylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes, oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate, agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water, isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

The pharmaceutical compositions of this application can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, or as an oral or nasal spray.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

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

In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

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

Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents.

Dosage forms for topical or transdermal administration of a compound of this application include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, eye ointments, powders and solutions are also contemplated as being within the scope of this application.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this application, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to the compounds of this application, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants such as chlorofluorohydrocarbons.

Transdermal patches have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Compounds and compositions of the application can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, *e.g.*, an anti-proliferative, anti-cancer, immunomodulatory or anti-inflammatory agent. Where the compounds of the application are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth. Compounds and compositions of the application can be administered in therapeutically effective amounts in a combinational therapy with one or more therapeutic agents (pharmaceutical combinations) or modalities, *e.g.*, anti-proliferative, anti-cancer, immunomodulatory or anti-inflammatory agent, and/or non-drug therapies, *etc.* For example, synergistic effects can occur with anti-proliferative, anti-cancer, immunomodulatory or anti-inflammatory substances. Where the compounds of the application are administered in conjunction with other therapies, dosages of the co-administered compounds will of course vary depending on the type of co-drug employed, on the specific drug employed, on the condition being treated and so forth.

Combination therapy includes the administration of the subject compounds in further combination with one or more other biologically active ingredients (such as, but not limited to, a second BTK inhibitor, a second and different antineoplastic agent, a kinase inhibitor and non-drug therapies (such as, but not limited to, surgery or radiation treatment). For instance, the compounds of the application can be used in combination with other pharmaceutically active compounds, preferably compounds that are able to enhance the effect of the compounds of the application. The compounds of the application can be administered simultaneously (as a single preparation or separate preparation) or sequentially to the other drug therapy or treatment modality. In general, a combination therapy envisions administration of two or more drugs during a single cycle or course of therapy.

In another aspect of the application, the compounds may be administered in combination with one or more separate pharmaceutical agents, *e.g.*, a chemotherapeutic agent, an immunotherapeutic agent, or an adjunctive therapeutic agent.

EXAMPLES

Analytical Methods, Materials, and Instrumentation

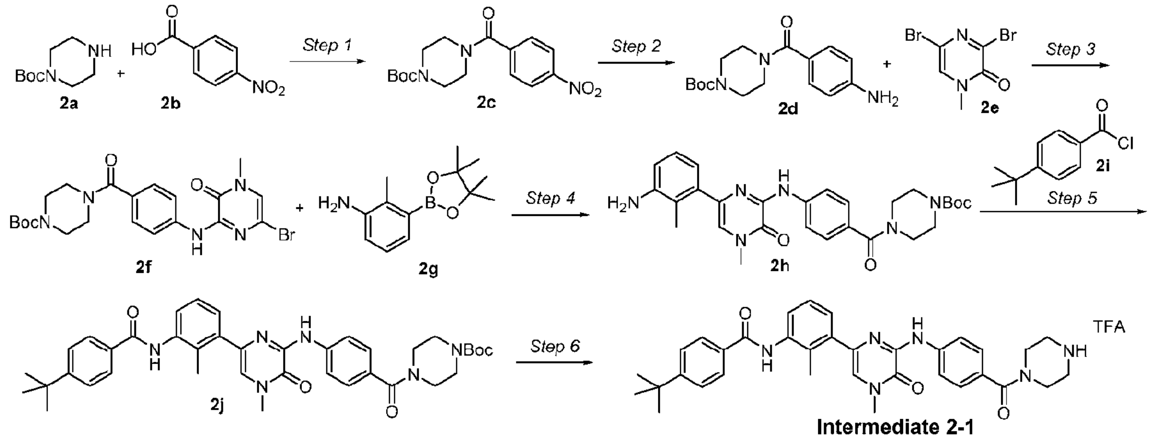
All reactions are monitored on a Waters Acquity UPLC/MS system (Waters PDA eλ Detector, QDa Detector, Sample manager – FL, Binary Solvent Manager) using Acquity UPLC® BEH C18 column (2.1 x 50 mm, 1.7 µm particle size): solvent gradient = 90% A at 0 min, 1% A at 1.8 min; solvent A = 0.1% formic acid in Water; solvent B = 0.1% formic acid in Acetonitrile; flow rate : 0.6 mL/min. Reaction products are purified by flash column chromatography using CombiFlash®Rf with Teledyne Isco Redi*Sep*®Rf High Performance Gold or Silicycle Silia*Sep*™ High Performance columns (4 g, 12 g, 24 g, 40 g, or 80 g), Waters HPLC system using SunFire™ Prep C18 column (19 x 100 mm, 5 μm particle size): solvent gradient = 80% A at 0 min, 5% A at 25 min; solvent A = 0.035% TFA in Water; solvent B = 0.035% TFA in MeOH; flow rate : 25 mL/min (Method A), and Waters Acquity UPLC/MS system (Waters PDA eλ Detector, QDa Detector, Sample manager – FL, Binary Solvent Manager) using Acquity UPLC® BEH C18 column (2.1 x 50 mm, 1.7 μm particle size): solvent gradient = 80% A at 0 min, 5% A at 2 min; solvent A = 0.1% formic acid in Water; solvent B = 0.1% formic acid in Acetonitrile; flow rate : 0.6 mL/min (method B). The purity of all compounds is over 95% and is analyzed with Waters LC/MS system. ^{1}H NMR is obtained using a 500 MHz Bruker Avance III. Chemical shifts are reported relative to dimethyl sulfoxide (δ = 2.50) for ^{1}H NMR. Data are reported as (*br* = broad, *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *m* = multiplet).

Abbreviations used in the following examples and elsewhere herein are:

br	broad
DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ESI	electrospray ionization
EtOAc	ethyl acetate
HCl	hydrochloric acid
h	hour(s)
HPLC	high-performance liquid chromatography
LCMS	liquid chromatography–mass spectrometry
m	multiplet
MeOH	methanol
MHz	megahertz
min	minutes
MS	mass spectrometry
NMR	nuclear magnetic resonance
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)dipalladium(0)
ppm	parts per million

TFA trifluoroacetic acid

Example 1: Synthesis of 4-(*tert*-butyl)-N-(2-methyl-3-(4-methyl-5-oxo-6-((4-(piperazine-1-carbonyl)phenyl)amino)-4,5-dihydropyrazin-2-yl)phenyl)benzamide trifluoroacetic acid salt (Intermediate 2-1)



Step 1. ***tert*-butyl 4-(4-nitrobenzoyl)piperazine-1-carboxylate (2c)**

To a solution of *tert*-butyl piperazine-1-carboxylate (**2a**, 3.1 g, 16.6 mmol, 1 equiv.), 4-nitrobenzoic acid (**2b**, 2.8 g, 16.6. mmol, 1 equiv.), N,N-diisopropylethylamine (5.8 mL, 33.2 mmol, 2 equiv.), and hydroxybenzotriazole (2.2 g, 16.6 mmol, 1 equiv.) in anhydrous DCM (40 mL) was added N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (3.8 g, 20.0 mmol, 1.2 equiv.) at 0 °C. The resulting solution was warmed to room temperature and then stirred for 24 h. Water was added and the mixture was extracted three times with DCM. The combined organic layers were dried with Na_2SO_4, filtered, and concentrated. The resulting crude product was then purified via silica gel column chromatography to obtain the product **2c** as a yellow solid (4.6 g, 13.7 mmol, 82% yield).

Step 2. ***Tert*-butyl 4-(4-aminobenzoyl)piperazine-1-carboxylate (2d)**

To a degassed solution of *tert*-butyl 4-(4-nitrobenzoyl)piperazine-1-carboxylate (**2c**, 4.1 g, 12.3 mmol, 1 equiv.) in anhydrous MeOH (40 mL) was added Pd/C (10% wt., dry; 600 mg). The reaction was sealed, fitted with a H_2 balloon and then stirred for 3 h at room temperature. The reaction mixture was filtered through Celite and then concentrated to obtain the product **2d** as a white foam (3.7 g, 12 mmol, 98% yield).

Step 3. ***tert*-butyl 4-(4-((6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazine-1-carboxylate (2f)**

A solution of tert-butyl 4-(4-aminobenzoyl)piperazine-1-carboxylate (**2d**, 1.7 g, 5.7 mmol, 1 equiv.), 3,5-dibromo-1-methylpyrazin-2(1H)-one (**2e**, 1.8 g, 6.8 mmol, 1.2 equiv.) and N,N-diisopropylethylamine (1.48 mL, 8.5 mmol, 1.5 equiv.) in N,N-dimethylacetamide (5 mL) was stirred in a sealed vial at 105 °C for 30 h. The reaction was cooled to room temperature and EtOAc (20 mL) was then added. The solid precipitate was filtered and dried on high vacuum overnight to provide tert-butyl 4-(4-((6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazine-1-carboxylate **2f**. The product was carried onto the next step without further purification.

Step 4. ***Tert*-butyl 4-(4-((6-(3-amino-2-methylphenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazine-1-carboxylate (2h)**

Tert-butyl 4-(4-((6-bromo-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazine-1-carboxylate (**2f**, 1 g, 2.0 mmol, 1 equiv.) was dissolved in anhydrous 1,4-dioxane (6 mL) and Na_2CO_3 (323 mg, 3.0 mmol, 1.5 equiv.) and H_2O (1.2 mL) was added. The mixture was degassed by bubbling N_2 gas through the reaction solution for 10 min. $Pd(PPh_3)_4$ (328 mg, 0.28 mmol, 0.14 equiv.) was then added and the vial was sealed and then stirred at 105 °C for 16 h. The resulting mixture was cooled to r.t. and filtered through Celite. The filtrate was concentrated, the resulting residue was redissolved in EtOAc, and the organic layer was washed with saturated $NaHCO_3$(aq). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified *via* silica gel column chromatography to provide the product **2h** as a white solid (244 mg, 0.47 mmol, 27% yield).

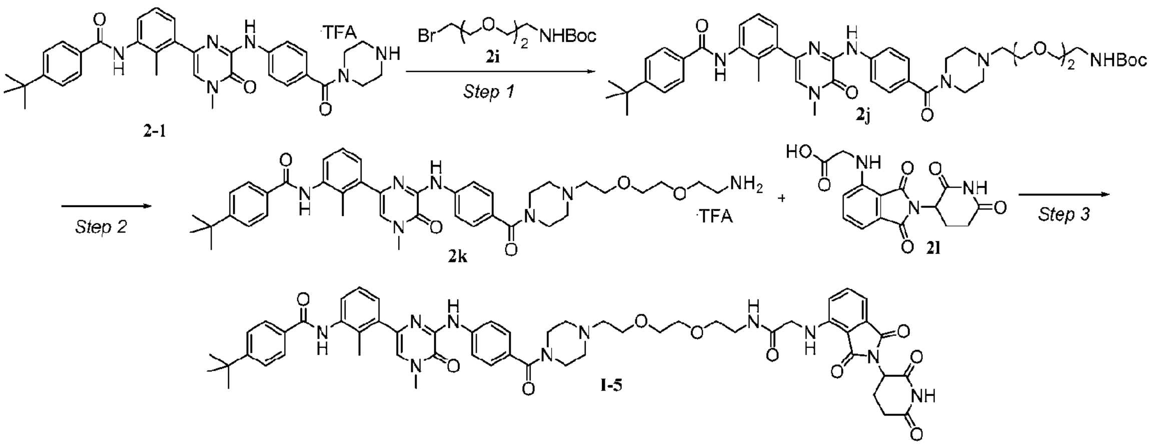
Step 5. **4-(*tert*-butyl)-N-(2-methyl-3-(4-methyl-5-oxo-6-((4-(piperazine-1-carbonyl)phenyl)amino)-4,5-dihydropyrazin-2-yl)phenyl)benzamide trifluoroacetic acid salt (2j).**

To a solution of *tert*-butyl 4-(4-((6-(3-amino-2-methylphenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazine-1-carboxylate (**2h**, 238 mg, 0.46 mmol, 1 equiv.) in anhydrous DCM (4 mL) was added anhydrous pyridine (56 µL, 0.68 mmol, 1.5 equiv.) and 4-*tert*-butyl benzoyl chloride (107 µL, 0.55 mmol, 1.2 equiv.). After stirring at room temperature for 1 h, the reaction mixture was concentrated to provide **2j** as crude solid, which was carried onto next step directly without further purification.

Step 6. **4-(*tert*-butyl)-N-(2-methyl-3-(4-methyl-5-oxo-6-((4-(piperazine-1-carbonyl)phenyl)amino)-4,5-dihydropyrazin-2-yl)phenyl)benzamide trifluoroacetic acid salt (2-1).**

4-(*tert*-butyl)-N-(2-methyl-3-(4-methyl-5-oxo-6-((4-(piperazine-1-carbonyl)phenyl) amino)-4,5-dihydropyrazin-2-yl)phenyl)benzamide trifluoroacetic acid salt (**2j**) was dissolved in anhydrous DCM (3 mL) and trifluoroacetic acid (3 mL) was added. After stirring for 2 h, the reaction mixture was concentrated. The resulting crude product was dissolved in DMSO and purified using a HPLC chromatography on a reverse phase C18 column to afford intermediate **2-1** as a white solid (154 mg, 0.22 mmol, 48% yield over two steps). ^{1}H NMR (500 MHz, DMSO) δ 9.90 (s, 1H), 9.50 (s, 1H), 8.85 (s, 2H), 8.11 (d, J = 8.7 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.42 – 7.34 (m, 3H), 7.33 – 7.27 (m, 3H), 3.67 (bs, 4H), 3.57 (s, 3H), 3.17 (bs, 4H), 2.28 (s, 3H), 1.33 (s, 9H).

Example 2: Synthesis of 4-(*tert*-butyl)-N-(3-(6-((4-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)ethoxy)ethoxy)ethyl)piperazine-1-carbonyl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)benzamide (I-5).



Step 1. ***tert*-butyl (2-(2-(4-(4-((6-(3-(4-(tert-butyl)benzamido)-2-methylphenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazin-1-yl)ethoxy)ethyl)carbamate (2j).**

4-(tert-butyl)-N-(2-methyl-3-(4-methyl-5-oxo-6-((4-(piperazine-1-carbonyl)phenyl)amino)-4,5-dihydropyrazin-2-yl)phenyl)benzamide trifluoroacetic acid salt (**2-1**, 112 mg, 0.163 mmol, 1 equiv.), tert-butyl (2-(2-(2-bromoethoxy)ethoxy)ethyl)carbamate (**2i**, 111 mg, 0.356 mmol, 2 equiv.), and K_2CO_3 (113 mg, 0.815 mmol, 5 equiv.) were dissolved in anhydrous DMF (2 mL) and then stirred at 80 °C in a sealed vial for 8 h. The reaction mixture was cooled to room temperature and water (3 mL) was added. The resulting mixture was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with H_2O (2 x 3 mL) and brine (1 x 3 mL), dried with Na_2SO_4, filtered, and concentrated to afford **2j** as an oil which was carried onto the next step without further purification.

Step 2. **N-(3-(6-((4-(4-(2-(2-(2-aminoethoxy)ethoxy)ethyl)piperazine-1-carbonyl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4-(tert-butyl)benzamide trifluoroacetic acid salt (2k).**

tert-butyl (2-(2-(4-(4-((6-(3-(4-(tert-butyl)benzamido)-2-methylphenyl)-4-methyl-3-oxo-3,4-dihydropyrazin-2-yl)amino)benzoyl)piperazin-1-yl)ethoxy)ethyl)carbamate (**2j**) was dissolved in anhydrous DCM (2 mL), and trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred for 20 min. The resulting solution was concentrated and purified using HPLC on a reverse phase C18 column to afford **2k** as a white solid (16 mg, 0.02 mmol, 12% yield over two steps). ^{1}H NMR (500 MHz, DMSO) δ 9.91 (s, *J* = 8.0 Hz, 1H), 9.51 (s, *J* = 18.5 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, *2H),* 7.95 (*d, J* = 8.5 Hz, 2H), 7.84 (s, *J* = 18.4 Hz, 3H), 7.58 – 7.51 (m, 2H), 7.43 – 7.33 (m, 3H), 7.33 – 7.23 (m, 3H), 3.82 – 3.68 (m, 2H), 3.65 – 3.52 (m, 10H), 3.40 – 3.23 (m, 7H), 3.19 – 3.04 (m, 2H), 3.04 – 2.87 (m, 2H), 2.29 (s, 3H), 1.33 (s, 9H).

Step 3. **4-(tert-butyl)-N-(3-(6-((4-(4-(2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)ethoxy)ethoxy)ethyl)piperazine-1-carbonyl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)benzamide (I-5).**

To a solution of N-(3-(6-((4-(4-(2-(2-(2-aminoethoxy)ethoxy)ethyl)piperazine-1-carbonyl)phenyl)amino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4-(tert-butyl)benzamide trifluoroacetic acid salt (**2k**, 8 mg, 0.0815 mmol), (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)glycine (**2l**, 40 mg, 0.122 mmol, 1.5 equiv.), and diisopropylethylamine (43 μL, 0.244 mmol, 3 equiv.) in anhydrous DMF (1 mL), was added 1-[Bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (50 mg, 0.130

mmol, 1.6 equiv.) and the resulting mixture was stirred at r.t. for 1 h. The reaction mixture was purified using HPLC on a reverse phase C18 column followed by further purification *via* silica gel column to provide **I-5** as a yellow solid (9.4 mg, 0.0092 mmol, 11% yield). ^{1}H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 9.88 (s, 1H), 9.44 (s, 1H), 8.14 (t, *J* = 5.4 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.56 (dd, *J* = 18.7, 8.0 Hz, 3H), 7.42 – 7.20 (m, 6H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.94 (t, *J* = 5.6 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 5.07 (dd, *J* = 12.7, 5.3 Hz, 1H), 3.92 (d, *J* = 5.5 Hz, 2H), 3.69 – 3.36 (m, 16H), 3.28 – 3.19 (m, 2H), 2.89 (dd, *J* = 21.4, 9.5 Hz, 1H), 2.56 (dd, *J* = 26.9, 13.2 Hz, 3H), 2.41 (s, 4H), 2.28 (s, 3H), 2.09 – 1.96 (m, 1H), 1.32 (s, 9H).

Example 3: Cell Assay and Western blotting

MOLM14 cells were treated with DMSO or with 40 nM, 200 nM, 1 μM of a BTK bifunctional inhibitor compound of the disclosure for 4 or 12 hours, followed by protein lysate harvest and Western blotting analysis of BTK , Aurora A, and α-tubulin levels. Cells treated with Compound I-5 showed BTK degradation (FIG. 1).

Western blotting

Cells are lysed using RIPA buffer supplemented with protease inhibitor cocktail (Roche) and *phosSTOP* phosphatase inhibitor cocktail (Roche) on ice for 15 minutes. The lysates are spun at 20,000xg for 15 minutes on 4°C and protein concentration is determined using BCA assay (Pierce). The following primary antibodies are used in this study: BTK, GADPH, tubulin and Aurora A kinase (all from Cell Signaling Technology). Blots are imaged using fluorescence-labeled secondary antibodies (LI-COR) on the OdysseyCLxImager (LI-COR). Quantification of band intensities is performed using OdysseyCLx software (LI-COR).

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the present application.

All patents, patent applications, and literature references cited herein are hereby expressly incorporated by reference.

CLAIMS

1. A bifunctional compound of Formula X:

(X),

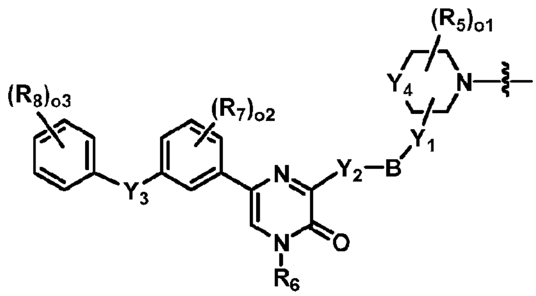
wherein:

the Targeting Ligand is capable of binding to BTK;

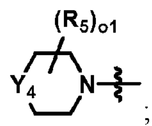
the Linker is a group that covalently binds to the Targeting Ligand and the Degron; and

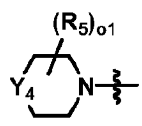
the Degron is capable of binding to a ubiquitin ligase.

2. The bifunctional compound of claim 1, wherein the Targeting Ligand is of Formula TL-I:


(TL-I),

or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, wherein:

B is phenyl or 5- or 6-membered heteroaryl containing 1 or 2 heteroatoms selected from N and S, wherein the phenyl or heteroaryl is optionally substituted with 1 to 3 R_9, wherein when Y_1 is absent, B is bonded to a carbon atom or Y_4 in  ;

Y_1 is absent or C(O), wherein Y_1 is bonded to a carbon atom or Y_4 in  ;

Y_2 is NR_{10a} or O;

Y_3 is $C(O)NR_{10b}$ or $NR_{10b}C(O)$;

Y_4 is NR_5' or, when Y_1 is bonded to Y_4 or when Y_1 is absent and B is bonded to Y_4, Y_4 is N;

R_5' is H, (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, or halogen;

each R_5 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, or oxo;

R_6 is H, (C_1-C_4) alkyl, or (C_1-C_4) haloalkyl;

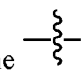
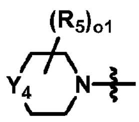
each R_7 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, (C_1-C_4) hydroxyalkyl, halogen, OH, or NH_2;

each R_8 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, halogen, OH, or NH_2;

each R_9 is independently (C_1-C_4) alkyl, (C_1-C_4) haloalkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkoxy, or halogen;

R_{10a} and R_{10b} are each independently H, (C_1-C_4) alkyl, or (C_1-C_4) haloalkyl; and

o1, o2, and o3 are each independently 0, 1, 2, or 3;

wherein the Targeting Ligand is bonded to the Linker via the  next to 

.

3. The bifunctional compound of claim 2, wherein R_6 is (C_1-C_4) alkyl.

4. The bifunctional compound of claim 2 or 3, wherein each R_7 is independently (C_1-C_4) alkyl or (C_1-C_4) hydroxyalkyl.

5. The bifunctional compound of any one of the preceding claims, wherein each R_7 is independently (C_1-C_4) alkyl.

6. The bifunctional compound of any one of the preceding claims, wherein Y_2 is NH.

7. The bifunctional compound of any one of the preceding claims, wherein Y_3 is $C(O)NR_{10b}$.

8. The bifunctional compound of any one of the preceding claims, wherein B is phenyl or pyridinyl.

9. The bifunctional compound of any one of the preceding claims, wherein B is phenyl.

10. The bifunctional compound of any one of the preceding claims, wherein each R_8 is independently (C_1-C_4) alkyl or halogen.

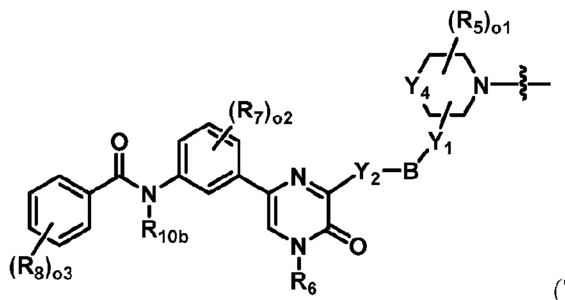
11. The bifunctional compound of any one of the preceding claims, wherein Y_1 is C(O).

12. The bifunctional compound of any one of the preceding claims, wherein o1 is 0.

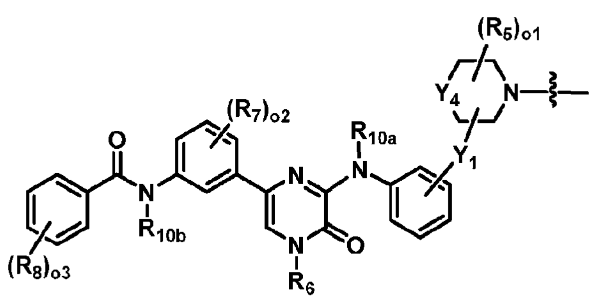
13. The bifunctional compound of any one of the preceding claims, wherein o2 is 1.

14. The bifunctional compound of any one of the preceding claims, wherein o3 is 1.

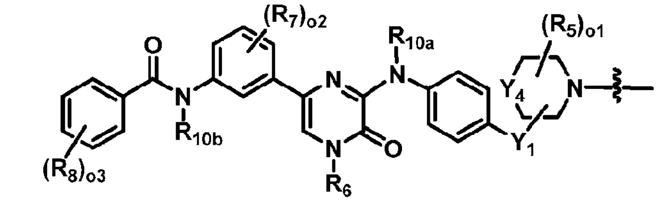
15. The bifunctional compound of claim 2, wherein the Targeting Ligand is of Formula TL-Ia, TL-Ib, TL-Ic, TL-Id, or TL-Ie:



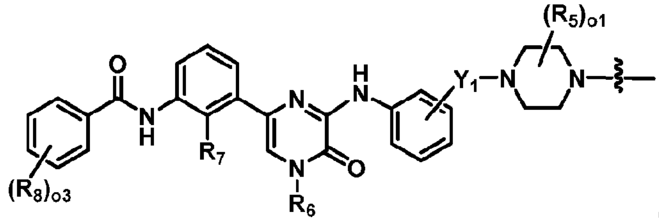
(TL-Ia),



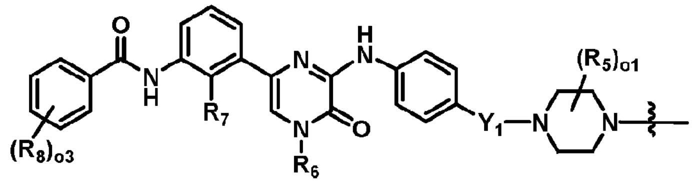
(TL-Ib),



(TL-Ic),

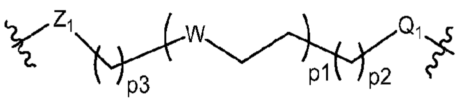


(TL-Id), or



(TL-Ie).

16. The bifunctional compound of any one of claims 1-15, wherein the Linker is of Formula L1:



(L1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein

p1 is an integer selected from 0 to 12;

p2 is an integer selected from 0 to 12;

p3 is an integer selected from 1 to 6;

each W is independently absent, CH_2, O, S, or NR_{24};

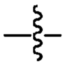
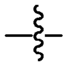
Z_1 is absent, C(O), CH_2, O, $(CH_2)_jNR_{24}$, $O(CH_2)_jC(O)NR_{24}$, $C(O)NR_{24}$, $(CH_2)_jC(O)NR_{24}$, $NR_{24}C(O)$, $(CH_2)_jNR_{24}C(O)$, $(CH_2)_kNR_{24}(CH_2)_jC(O)NR_{24}$, or $NR_{24}(CH_2)_jC(O)NR_{24}$;

each R_{24} is independently H or C_1-C_3 alkyl;

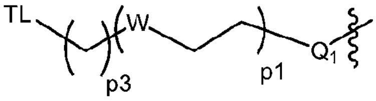
j is 1, 2, or 3;

k is 1, 2, or 3; and

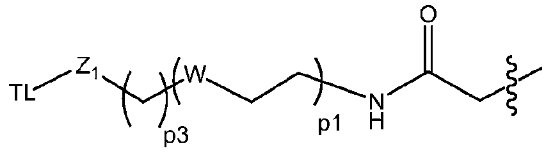
Q_1 is absent, C(O), $NHC(O)CH_2$, $OCH_2C(O)$, or $O(CH_2)_{1-2}$;

wherein the Linker is covalently bonded to a Degron via the  next to Q_1, and covalently bonded to a Targeting Ligand via the  next to Z_1.

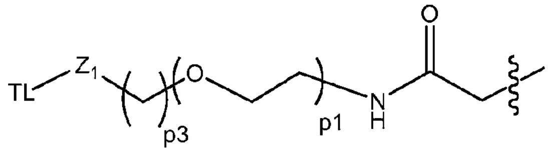
17. The bifunctional compound of claim 16, wherein the Linker is selected from:



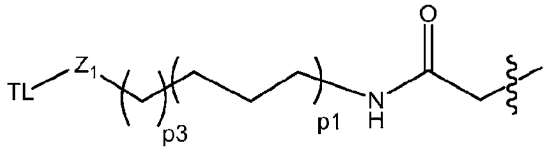
(L1a),



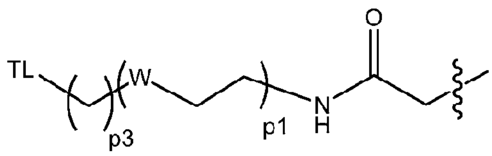
(L1b),



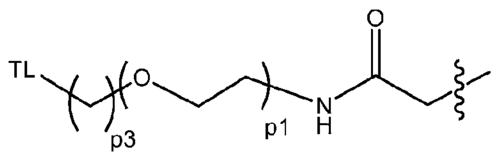
(L1c),



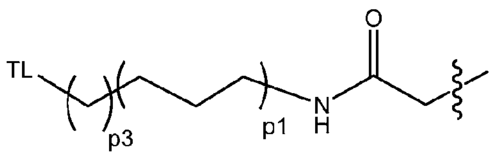
(L1d),



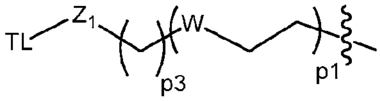
(L1e),

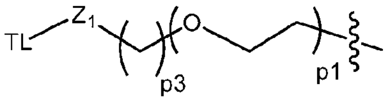


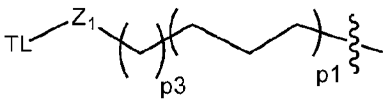
(L1f),

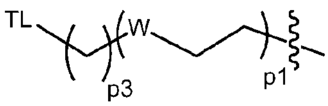


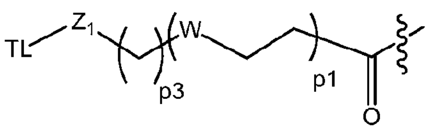
(L1g),

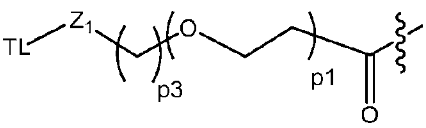
 (L1h),

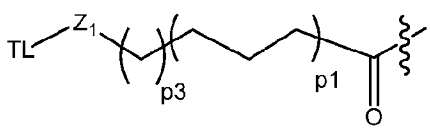
 (L1i),

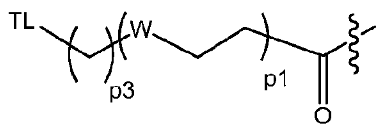
 (L1j),

 (L1k),

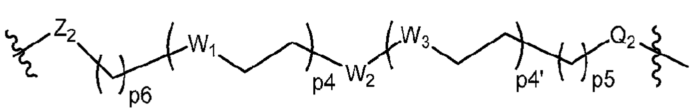
 (L1l),

 (L1m),

 (L1n), and

 (L1o).

18. The bifunctional compound of any one of claims 1-15, wherein the Linker is of Formula L2:

 (L2),

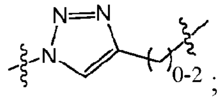
or an enantiomer, diastereomer, or stereoisomer thereof, wherein

p4 and p4' are each independently an integer selected from 0 to 12;

p5 is an integer selected from 0 to 12;

p6 is an integer selected from 1 to 6;

each W_1 is independently absent, CH_2, O, S, or NR_{25};

W_2 is $NR_{25}C(O)(CH_2)_{0\text{-}2}$ or  ;

each W_3 is independently absent, CH_2, O, S, or NR_{25};

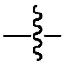
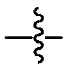
Z_2 is absent, C(O), CH_2, O, $(CH_2)_{j1}NR_{25}$, $O(CH_2)_{j1}C(O)NR_{25}$, $C(O)NR_{25}$, $(CH_2)_{j1}C(O)NR_{25}$, $NR_{25}C(O)$, $(CH_2)_{j1}NR_{25}C(O)$, $(CH_2)_{k1}NR_{25}(CH_2)_{j1}C(O)NR_{25}$,or $NR_{25}(CH_2)_{j1}C(O)NR_{25}$;

each R_{25} is independently H or C_1-C_3 alkyl;

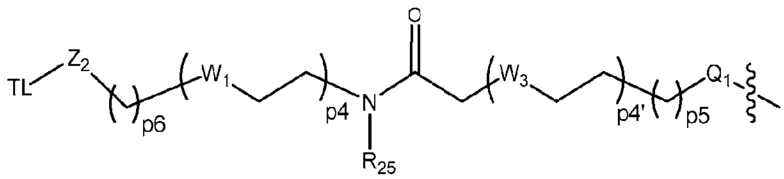
j1 is 1, 2, or 3;

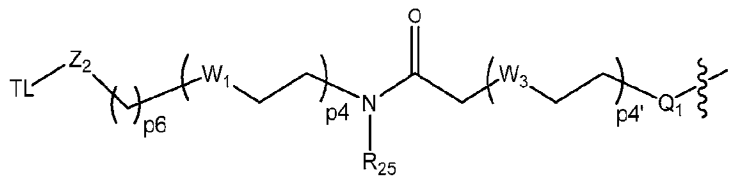
k1 is 1, 2, or 3; and

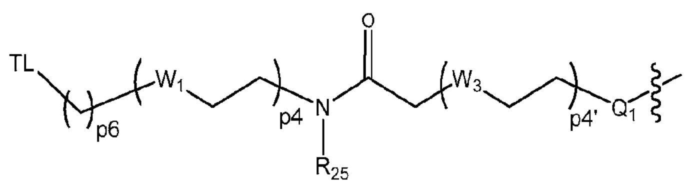
Q_2 is absent, C(O), $NHC(O)CH_2$, or $O(CH_2)_{1\text{-}2}$;

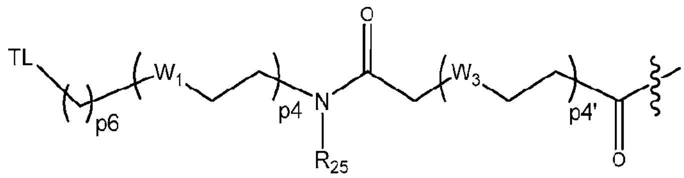
wherein the Linker is covalently bonded to a Degron via the  next to Q_2, and covalently bonded to a Targeting Ligand via the  next to Z_2.

19. The bifunctional compound of claim 18, wherein the Linker is selected from:

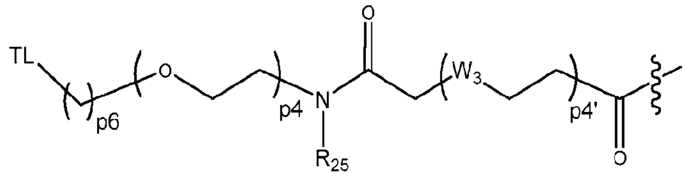

(L2a),


(L2b),

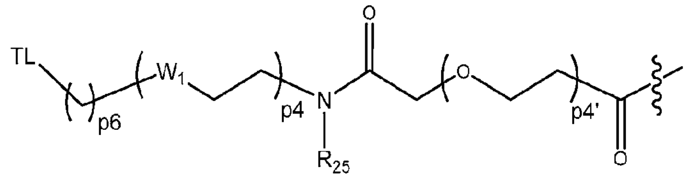

(L2c),



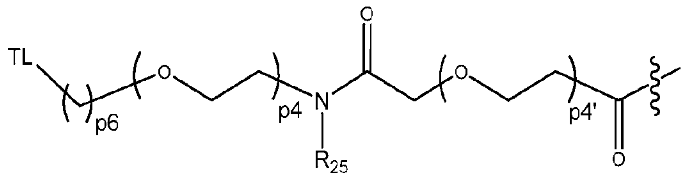
(L2d),



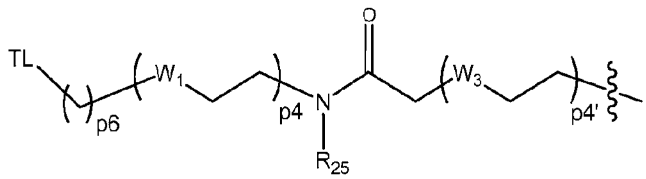
(L2e),



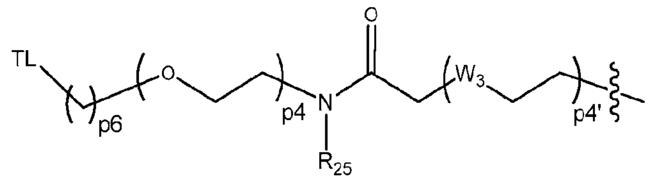
(L2f),



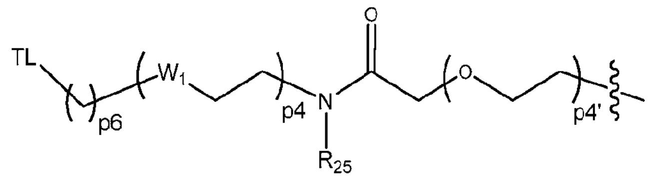
(L2g),



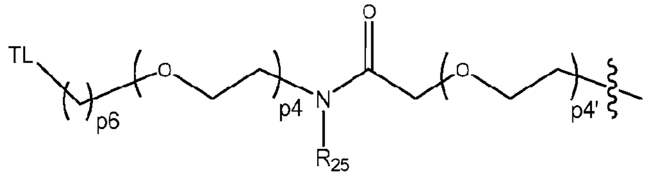
(L2h),



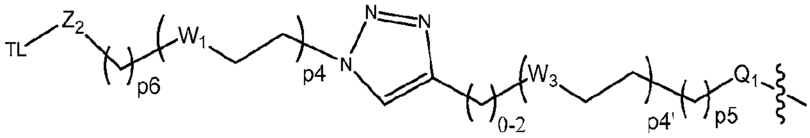
(L2i),



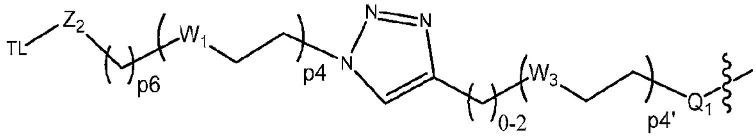
(L2j),



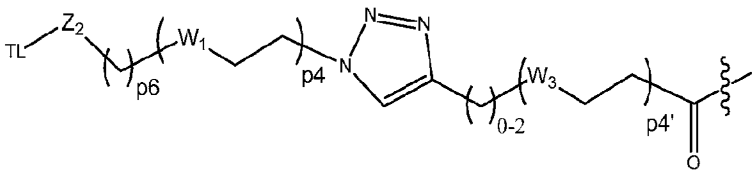
(L2k),



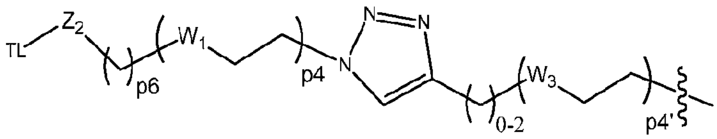
(L2l),



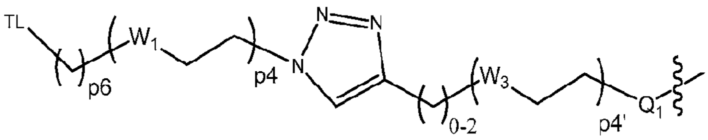
(L2m),



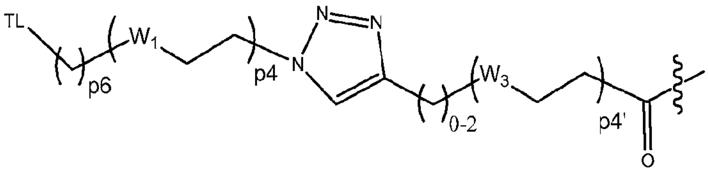
(L2n),



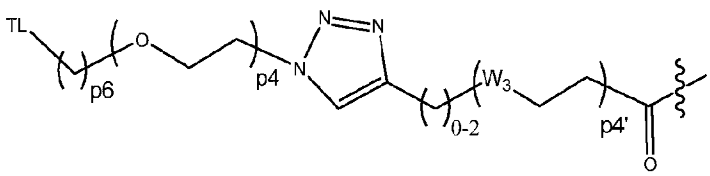
(L2o),



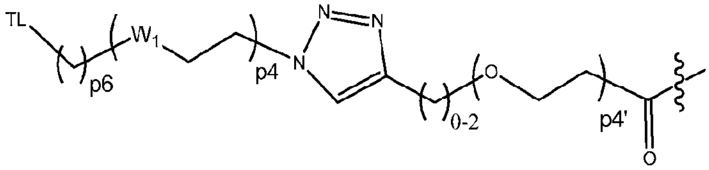
(L2p),

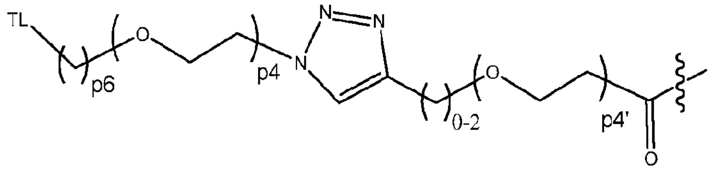


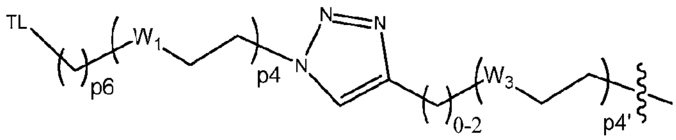
(L2q),

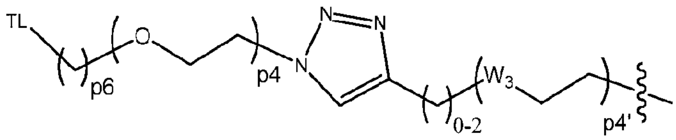


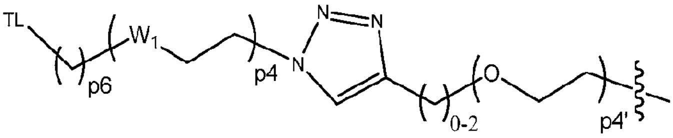
(L2r),

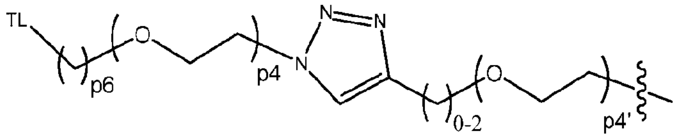

(L2s),


(L2t),

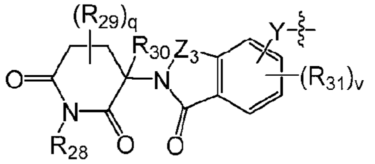

(L2u),


(L2v),


(L2w), and


(L2x).

20. The bifunctional compound of any one of claims 1-19, wherein the Degron is of Formula D1:


(D1),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

Y is a bond, $(CH_2)_{1-6}$, $(CH_2)_{0-6}$-O, $(CH_2)_{0-6}$-C(O)NR_{26}, $(CH_2)_{0-6}$-NR_{26}C(O), $(CH_2)_{0-6}$-NH, or $(CH_2)_{0-6}$-NR_{27};

Z_3 is C(O) or $C(R_{28})_2$;

R_{26} is H or C_1-C_6 alkyl;

R_{27} is C_1-C_6 alkyl or C(O)-C_1-C_6 alkyl;

each R_{28} is independently H or C_1-C_3 alkyl;

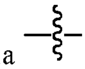
each R_{29} is independently C_1-C_3 alkyl;

R_{30} is H, deuterium, C_1-C_3 alkyl, F, or Cl;

each R_{31} is independently halogen, OH, C_1-C_6 alkyl, or C_1-C_6 alkoxy;

q is 0, 1, or 2; and

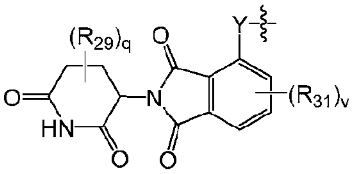
v is 0, 1, 2, or 3,

wherein the Degron is covalently bonded to the Linker via .

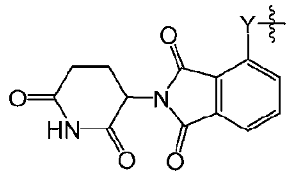
21. The bifunctional compound of claim 20, wherein Z_3 is C(O) or CH_2.

22. The bifunctional compound of claim 20 or 21, wherein Y is a bond, O, or NH.

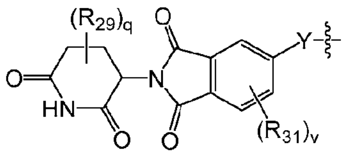
23. The bifunctional compound of any one of claims 20-22, wherein the Degron is of Formula D1a, D1b, D1c, D1d, D1e, D1f, D1g, D1h, D1i, D1j, D1k, or D1l:



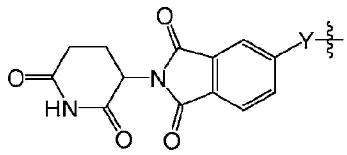
(D1a),



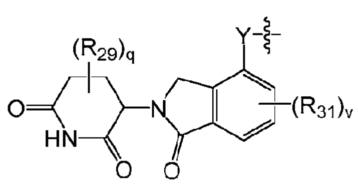
(D1b),



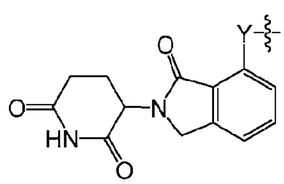
(D1c),



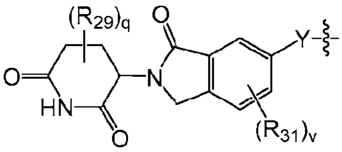
(D1d),

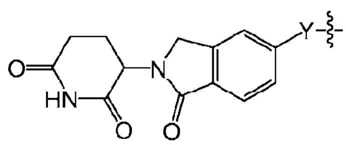


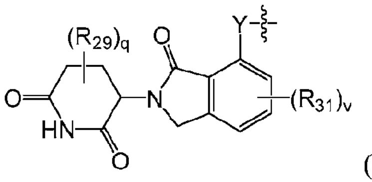
(D1e),

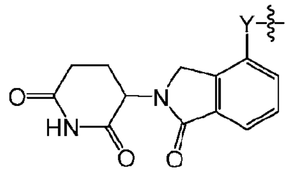


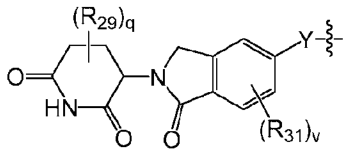
(D1f),

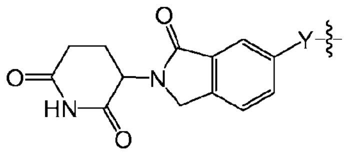

(D1g)


(D1h),

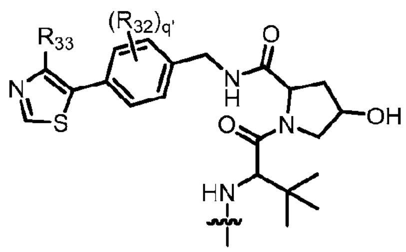

(D1i),


(D1j),


(D1k) or


(D1l).

24. The bifunctional compound of any one of claims 1-19, wherein the Degron is of Formula D2:

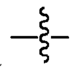

(D2),

or an enantiomer, diastereomer, or stereoisomer thereof, wherein:

each R_{32} is independently C_1-C_3 alkyl;

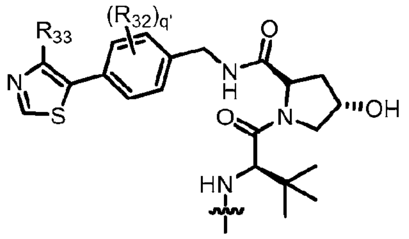
q' is 0, 1, 2, 3 or 4; and

R_{33} is H or C_1-C_3 alkyl,

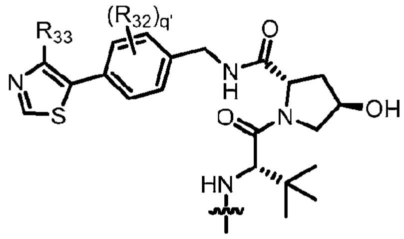
wherein the Degron is covalently bonded to the Linker via .

25. The bifunctional compound of claim 24, wherein R_{33} is methyl.

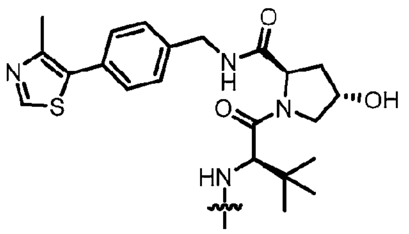
26. The bifunctional compound of claim 24, wherein the Degron is of Formula D2a, D2b, D2c, or D2d:



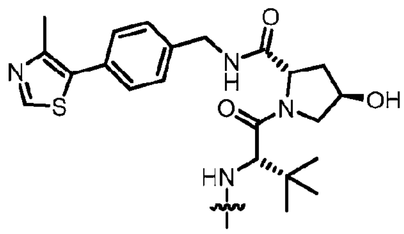
(D2a),



(D2b),



(D2c), or



(D2d).

27. A pharmaceutical composition comprising a therapeutically effective amount of the bifunctional compound of any one of claims 1-26, or an enantiomer, diastereomer, stereoisomer, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. A method of inhibiting or modulating the amount of Bruton's tyrosine kinase (BTK), comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-26.

29. A method of treating or preventing a disease in which BTK plays a role, comprising administering to a subject in need thereof an effective amount of a compound of any one of claims 1-26.

30. The method of claim 29, wherein the disease is cancer or a proliferation disease.

31. The method of claim 30, wherein the cancer is lung cancer, colon cancer, breast cancer, prostate cancer, liver cancer, pancreas cancer, brain cancer, kidney cancer, ovarian cancer, stomach cancer, skin cancer, bone cancer, gastric cancer, breast cancer, pancreatic cancer, glioma, glioblastoma, hepatocellular carcinoma, papillary renal carcinoma, head and neck squamous cell carcinoma, leukemias, lymphomas, myelomas, or solid tumors.

32. Use of a bifunctional compound of any one of claims 1-26 in the manufacture of a medicament for treating or preventing a disease in which BTK plays a role.

33. A bifunctional compound of any one of claims 1-26 for treating or preventing of a disease in which BTK plays a role.

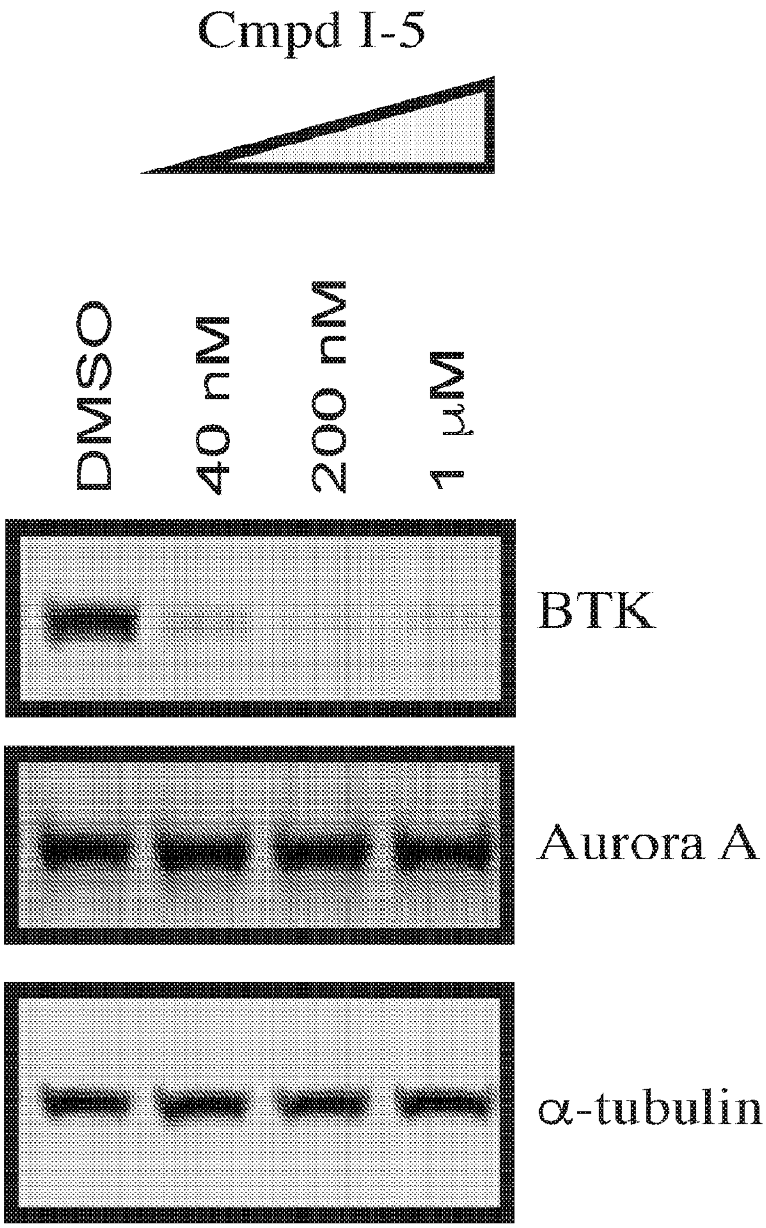


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/063011

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/12(2006.01)i, C07D 401/04(2006.01)i, C07D 417/12(2006.01)i, A61K 31/497(2006.01)i, A61K 31/454(2006.01)i, A61K 31/427(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 403/12; C07D 403/10; C07D 403/14; C12Q 1/48; C07D 213/74; A61P 35/00; C07D 241/20; G01N 33/58; C07D 401/14; C07K 14/72; A61K 47/48; C07D 401/04; C07D 417/12; A61K 31/497; A61K 31/454; A61K 31/427

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) , STN (Registry, Caplus) & Keywords: ubiquitin ligase, targeting ligand, Linker, Degron, Bruton's tyrosine kinase (BTK)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2015-0291562 A1 (ARVINAS, INC.) 15 October 2015 See claims 1-2, 12.	1 2-4,15
Y	WO 2006-099075 A2 (CGI PHARMACEUTICALS, INC.) 21 September 2006 See abstract; and page 146.	2-4,15
A	WO 2016-169989 A1 (GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED) 27 October 2016 See claim 1; and page 2, lines 20-22.	1-4,15
A	WO 2010-000633 A1 (F. HOFFMANN-LA ROCHE AG) 7 January 2010 See page 43.	1-4,15
A	JP 2013-104687 A (CARNA BIOSCIENCES INC.) 30 May 2013 See claim 5.	1-4,15

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

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2018 (16.03.2018)	**16 March 2018 (16.03.2018)**

Name and mailing address of the ISA/KR	Authorized officer
International Application Division Korean Intellectual Property Office 189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea	KAM, YOO LIM
Facsimile No. +82-42-481-8578	Telephone No. +82-42-481-3516

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/063011

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

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

1. ☒ Claims Nos.: 28-31
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 28-31 pertain to methods for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).

2. ☒ Claims Nos.: 17,19,21,25-26,30-31
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 17, 19, 21, 25-26 and 30-31 refer to claims which are not drafted in accordance with the third sentence of Rule 6.4(a).

3. ☒ Claims Nos.: 5-14,16,18,20,22-24,27-29,32-33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this international application, as follows:

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/063011

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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