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(54) Title: COMPOUNDS AND COMPOSITIONS AS STAT3 DEGRADERS AND USES THEREOF

(57) Abstract: Described herein are compounds of Formula I and their pharmaceutically acceptable salts, solvates, or stereoisomers, as well as their uses (e.g., for degrading certain proteins such as STAT3).



COMPOUNDS AND COMPOSITIONS AS STAT3 DEGRADERS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/598,413, filed November 13, 2023; and U.S. Provisional Application No. 63/484,640, filed February 13, 2023, the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] The signal transducer and activator of transcription (STAT) proteins play important roles in biological processes. For example, the abnormal activation of STAT signaling pathways is implicated in cancer, autoimmune diseases, rheumatoid arthritis, asthma, diabetes, and other human diseases. *See, e.g., Miklosy et al., Nat Rev Drug Discov 12:611-629 (2013).*

[0003] The STAT protein family is composed of seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Structurally, they share five domains: an amino-terminal domain, a coiled-coil domain, a DNA-binding domain, an SH2 domain, and a carboxy-terminal transactivation domain. The transactivation domain contains one or two amino acid residues that are crucial for the activity of the STAT protein. In particular, phosphorylation of a particular tyrosine residue promotes dimerization, whereas phosphorylation of a particular serine residue enhances transcriptional activation.

[0004] STAT proteins promote fundamental cellular processes, including cell growth and differentiation, development, apoptosis, immune responses, and inflammation. In particular, STAT3 function may be abnormal in the context of cancer, and this abnormality represents an underlying mechanism of STAT3 for promoting malignant transformation and progression. Constitutively active STAT3 is detected in numerous malignancies, including breast, melanoma, prostate, head and neck squamous cell carcinoma (HNSCC), multiple myeloma, pancreatic, ovarian, and brain tumors. Aberrant STAT3 signaling promotes tumorigenesis and tumor progression partly through dysregulating the expression of critical genes that control cell growth and survival, angiogenesis, migration, invasion, or metastasis. These genes include those that encode p21^{WAF1/CIP2}, cyclin D1, MYC, BCL-X, BCL-2, vascular endothelial growth factor (VEGF), matrix metalloproteinase 1 (MMP1), MMP7 and MMP9, and survivin. STAT3 may also play a role in the suppression of tumor immune surveillance. Consequently, the

genetic and pharmacological modulation of persistently active STAT3 was shown to control the tumor phenotype and to lead to tumor regression *in vivo*.

[0005] There exists a need in the art for STAT3 inhibitors and STAT3 degraders having physical and pharmacological properties that allow them to be used in therapeutic applications for treating disease.

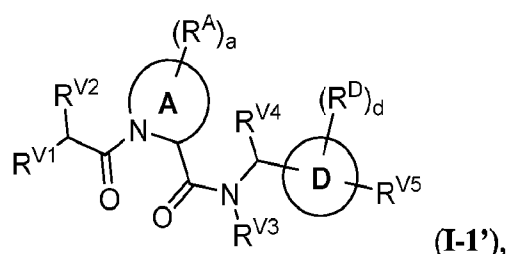
SUMMARY

[0006] In certain aspects, the present disclosure provides compounds of Formula I:

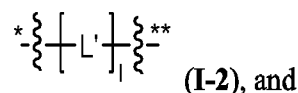
T-L-V (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof, wherein:

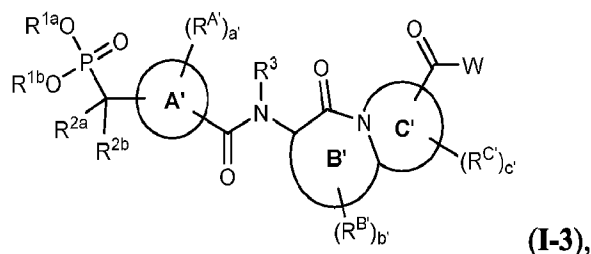
V is of Formula **I-1'**



L is of Formula **I-2**



T is of Formula **I-3**



wherein each of the variables in Formulae I, I-1, I-2, and I-3, is described, embodied, and exemplified herein.

[0007] In certain aspects, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein, and a pharmaceutically acceptable excipient.

[0008] In certain aspects, the present disclosure provides methods of degrading a protein (*e.g.*, STAT3) in a subject or biological sample comprising administering a compound disclosed herein to the subject or contacting the biological sample with the compound disclosed herein.

[0009] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading a protein (*e.g.*, STAT3) in a subject or biological sample.

[0010] In certain aspects, the present disclosure provides compounds disclosed herein for use in degrading a protein (*e.g.*, STAT3) in a subject or biological sample.

[0011] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof, comprising administering to the subject a compound disclosed herein (*e.g.*, in a therapeutically effective amount).

[0012] In certain aspects, the present disclosure provides methods of treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof, comprising administering to the subject a compound disclosed herein (*e.g.*, in a therapeutically effective amount).

[0013] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0014] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0015] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0016] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

DETAILED DESCRIPTION

[0017] The present disclosure relates to compounds and compositions that are useful as degraders for certain proteins (*e.g.*, STAT3). The present disclosure also relates to methods of degrading certain proteins (*e.g.*, STAT3) comprising contacting the STAT3 protein with a compound disclosed herein. The invention also relates to methods of treating a STAT3-mediated disease or condition in a subject in need thereof by administering (*e.g.*, in a therapeutically effective amount) a compound disclosed herein. The invention further relates to methods of treating a STAT3-mediated disease or condition in a subject in need thereof,

comprising administering (e.g., in a therapeutically effective amount) a pharmaceutical composition comprising an amount of a compound disclosed herein.

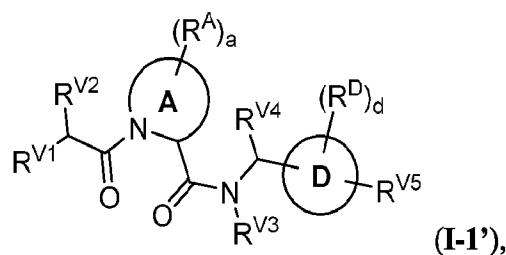
Compounds of the Present Disclosure

[0018] In certain aspects, the present disclosure provides compounds of Formula I:

T-L-V (I),

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

V is of Formula I-1'



wherein:

Ring A is 5- to 7-membered heterocycle;

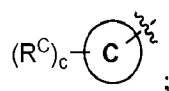
each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

a is an integer selected from 0 to 10, as valency permits;

Ring D' is C₆ aryl or 5- to 6-membered heteroaryl;

each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

d is an integer selected from 0 to 4;

$$R^{V1} \text{ is } -NR^{V1'}-\text{, } -O-\text{, or}$$


$R^{V1'}$ is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

Ring C is C_6 aryl or 5- to 6-membered heteroaryl;

each R^C is independently $-\xi^{**}$, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

** denotes attachment to L;

c is an integer selected from 0 to 5, as valency permits;

R^{V2} is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

R^{V2} is C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is attached to L and optionally substituted with one or more R^u ;

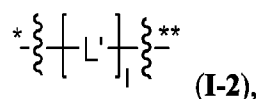
R^{V3} is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

R^{V4} is $-(C_{1-3} \text{ alkylene})-^{**}$; wherein the alkylene is optionally substituted with one or more R^u and ** denotes attachment to L; or

R^{V4} is hydrogen, C_{1-6} alkyl, C_{1-8} heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u ; and

R^{V5} is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

L is of Formula I-2



wherein:

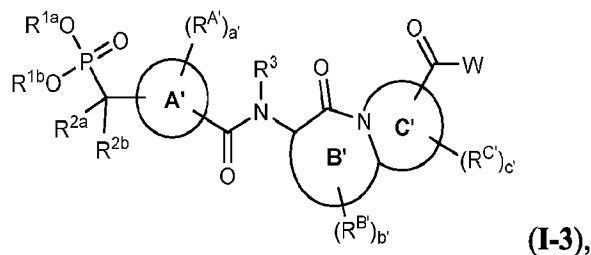
* denotes attachment to T and ** denotes attachment to V;

each L' is independently C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, C_{6-10} arylene, 5- to 10-membered heteroarylene, $-C(=O)-$, $-C(=O)N(R^{L'})-$, $-C(=O)O-$, $-N(R^{L'})-$, $-O-$, $-S-$, or $-S(=O)_2-$, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u ;

each occurrence of $R^{L'}$ is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

l is an integer selected from 0 to 6,

T is of Formula **I-3**



wherein:

R^{1a} and R^{1b} are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

R^{2a} and R^{2b} are independently hydrogen or halogen;

R^{2a} and R^{2b} together form an oxo; or

R^{2a} and R^{2b} , together with the carbon atom to which they are attached, form C_{3-6} carbocycle or 3- to 6-membered heterocycle, wherein the carbocycle or heterocycle is optionally substituted with one or more R^u ;

Ring A' is C_{6-10} aryl or 5- to 10-membered heteroaryl;

each $R^{A'}$ is independently halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or -

$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

a' is an integer selected from 0 to 6, as valency permits;

R^3 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

Ring B' is 3- to 12-membered heterocycle;

each $R^{B'}$ is independently $-\xi^*$, oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-12} heteroalkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

* denotes attachment to L ;

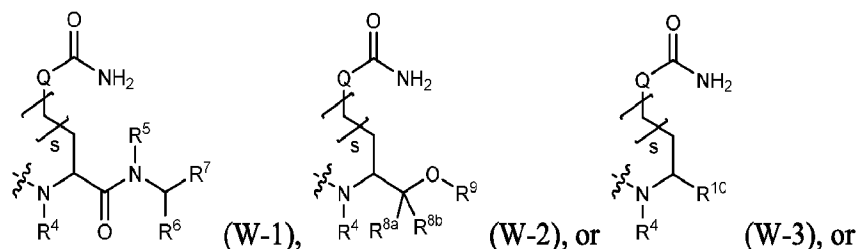
b' is an integer selected from 0 to 6, as valency permits;

Ring C' is 3- to 8-membered heterocycle;

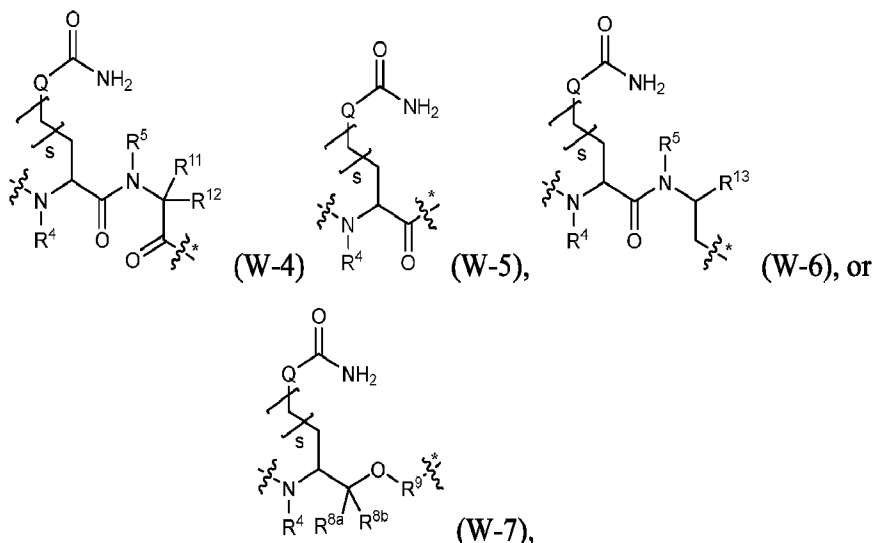
each $R^{C'}$ is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

c' is an integer selected from 0 to 6, as valency permits;

W is



W is



wherein:

* denotes attachment to L;

Q is absent; or

Q is $-C(R^Q)_2-$, $-O-$, and $-N(R^{Q'})-$;

each R^Q is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

two R^Q , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

$R^{Q'}$ is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

s is an integer selected from 0 to 4;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl,

alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R⁶ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a};

R⁷ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{7a}; or

R⁷ is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^{7b};

each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

or

R⁶ and R⁷, together with the carbon atom to which they are attached, form C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

R⁹ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{9a};

each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -

$\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{R}^a$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{10} is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylamino, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{11} is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

R^{12} is hydrogen, C_{1-6} alkyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-(\text{C}_{1-6} \text{ alkylene})-(\text{C}_{3-12} \text{ carbocyclyl})$, $-(\text{C}_{1-6} \text{ alkylene})-(3- \text{ to } 12\text{-membered heterocyclyl})$, $-(\text{C}_{1-6} \text{ alkylene})-(\text{C}_{6-10} \text{ aryl})$, or $-(\text{C}_{1-6} \text{ alkylene})-(5- \text{ to } 10\text{-membered heteroaryl})$, wherein the alkyl, alkylene, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^{12a} ;

each R^{12a} is independently oxo, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-\text{SR}^b$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{S}(=\text{O})_2\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})_2\text{OR}^b$, $-\text{NR}^c\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{R}^a$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{11} and R^{12} , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ; or

R^{11} and R^5 , together with the intervening atoms, form 4- to 8-membered heterocyclyl optionally substituted with one or more R^u ; and

R^{13} is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ,

wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl;

each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0019] In certain embodiment, the compound is not

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-2-(((S)-1-(4-ethynylphenyl)ethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-2-((4-ethynylbenzyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((5-((R)-1-((2S,4R)-2-(((S)-1-(4-ethynylphenyl)ethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-fluorophenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((5-((R)-1-((2S,4R)-2-((4-ethynylbenzyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-fluorophenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((5-((R)-1-((2S,4R)-2-(((S)-1-(4-ethynylphenyl)ethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((5-((S)-1-((2S,4R)-2-(((S)-1-(4-ethynylphenyl)ethyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((5-((R)-1-((2S,4R)-2-((4-ethynylbenzyl)carbamoyl)-4-hydroxypyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-fluoro-3-(3-((5-((R)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-fluoro-3-(3-((5-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-

methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-fluoro-3-(3-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-fluoro-3-(3-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((R)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(3-(3-((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)-2-methylphenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid,

diethyl (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-6-carbonyl)phosphonate,

diethyl (2-(((5S,8R,10aS)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-6-carbonyl)phosphonate, or

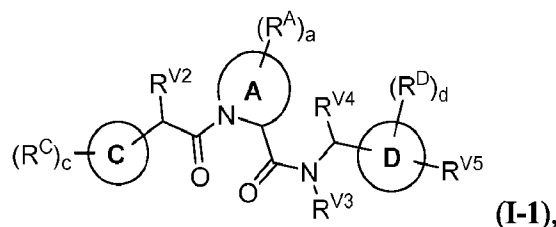
diethyl (2-(((4S,7R)-2-acetyl-7-(((S)-5-amino-1-(2-chloro-3-(3-((5-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)isoxazol-3-yl)oxy)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-5-oxo-2,3,4,5,7,8-hexahydro-1H-[1,5]diazocino[3,2,1-hi]indol-4-yl)carbamoyl)-1H-indole-6-carbonyl)phosphonate.

[0020] In certain embodiments, the present disclosure provides compounds of Formula I:

T-L-V (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof, wherein:

V is of Formula **I-1**



wherein:

Ring A is 5- to 7-membered heterocycle;

each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl,

alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

a is an integer selected from 0 to 10, as valency permits;

Ring C is C₆ aryl or 5- to 6-membered heteroaryl;

each R^C is independently $\overset{**}{\text{---}}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

** denotes attachment to L;

c is an integer selected from 0 to 5, as valency permits;

Ring D' is C₆ aryl or 5- to 6-membered heteroaryl;

each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

d is an integer selected from 0 to 4;

R^{V2} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

R^{V2} is C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is attached to L and optionally substituted with one or more R^u; or

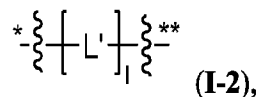
one R^C and R^{V2}, together with the intervening atoms, form C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

R^{V3} is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

R^{V4} is hydrogen, C₁₋₆ alkyl, C₁₋₈ heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u; and

R^{V5} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

L is of Formula I-2



wherein:

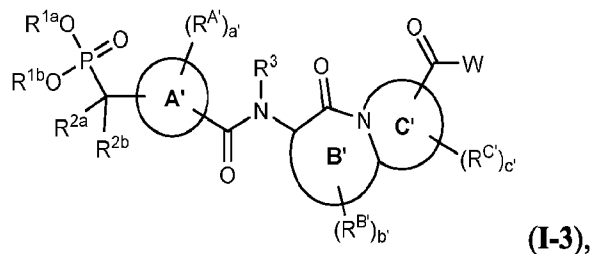
* denotes attachment to T and ** denotes attachment to V;

each L' is independently C₁₋₆ alkylene, C₁₋₆ heteroalkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₃₋₁₂ carbocyclylene, 3- to 12-membered heterocyclylene, C₆₋₁₀ arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^{L'})-, -C(=O)O-, -N(R^{L'})-, -O-, -S-, or -S(=O)₂-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u;

each occurrence of R^{L'} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

l is an integer selected from 0 to 6,

T is of Formula I-3



wherein:

R^{1a} and R^{1b} are independently hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

R^{2a} and R^{2b} are independently hydrogen or halogen;

R^{2a} and R^{2b} together an oxo; or

R^{2a} and R^{2b}, together with the carbon atom to which they are attached, form a C₃₋₆ carbocycle or 3- to 6-membered heterocycle, wherein the carbocycle or heterocycle is optionally substituted with one or more R^u;

Ring A' is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R^A is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

a' is an integer selected from 0 to 6, as valency permits;

R³ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

Ring B' is 3- to 12-membered heterocycle;

each R^{B'} is independently $-\overset{*}{\underset{\text{L}}{\text{S}}}$, oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

* denotes attachment to L;

b' is an integer selected from 0 to 6, as valency permits;

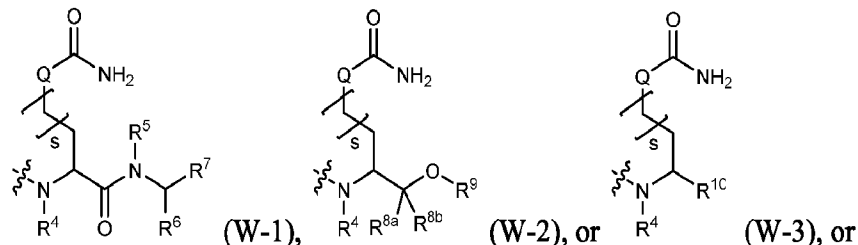
Ring C' is 3- to 8-membered heterocycle;

each R^{C'} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -

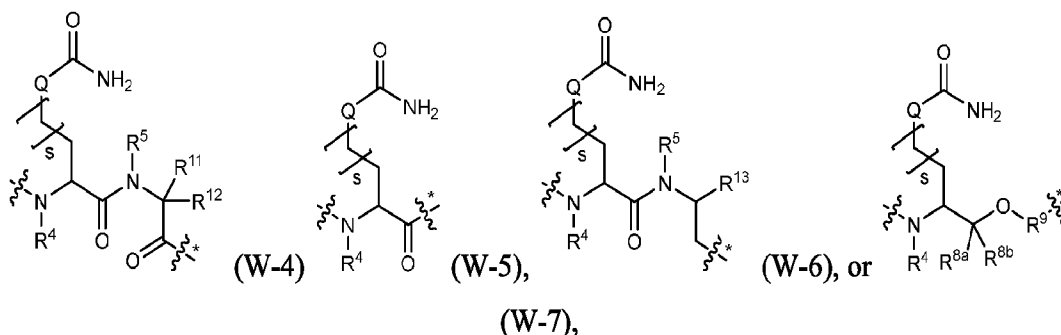
$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

c' is an integer selected from 0 to 6, as valency permits;

W is



W is



wherein:

* denotes attachment to L;

Q is absent; or

Q is $-C(R^Q)_2-$, $-O-$, and $-N(R^{Q'})-$;

each R^Q is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

two R^Q , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

$R^{Q'}$ is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

s is an integer selected from 0 to 4;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, -

$S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^6 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a} ;

R^7 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{7a} ; or

R^7 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^{7b} ; each R^{6a} and each R^{7a} are independently halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

each R^{7b} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

or

R^6 and R^7 , together with the carbon atom to which they are attached, form C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{8a} and R^{8b} are independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylamino, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

R^9 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{9a} ;

each R^{9a} is independently halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, -

$S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{10} is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylamino, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkoxy, alkylamino, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{11} is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

R^{12} is hydrogen, C_{1-6} alkyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-(C_{1-6} \text{ alkylene})-(C_{3-12} \text{ carbocyclyl})$, $-(C_{1-6} \text{ alkylene})-(3- \text{ to } 12\text{-membered heterocyclyl})$, $-(C_{1-6} \text{ alkylene})-(C_{6-10} \text{ aryl})$, or $-(C_{1-6} \text{ alkylene})-(5- \text{ to } 10\text{-membered heteroaryl})$, wherein the alkyl, alkylene, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^{12a} ;

each R^{12a} is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{11} and R^{12} , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ; or

R^{11} and R^5 , together with the intervening atoms, form 4- to 8-membered heterocyclyl optionally substituted with one or more R^u ; and

R^{13} is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ,

wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl; or two R^u, together with the one or more intervening atoms, form C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

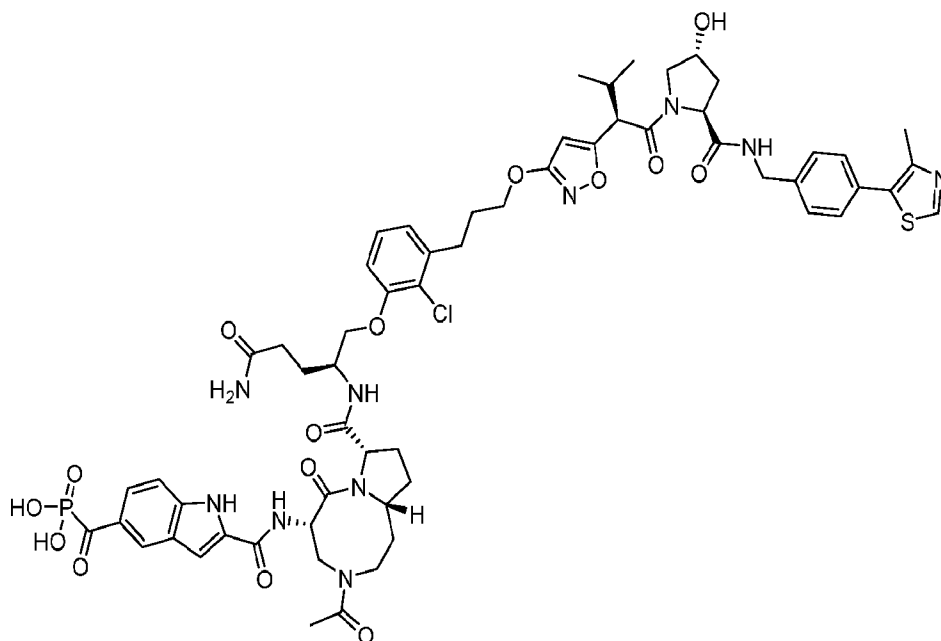
or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

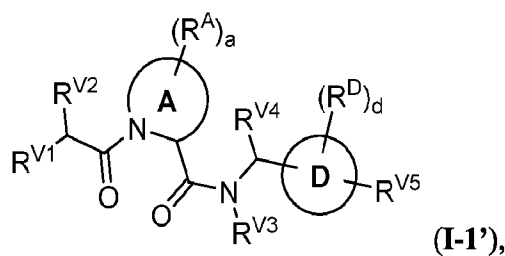
wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0021] In certain embodiments, the compound is not



[0022] In certain embodiments, V is of Formula I-1'



wherein:

Ring A is 5- to 7-membered heterocycle;

each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

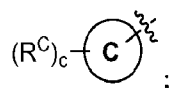
a is an integer selected from 0 to 10, as valency permits;

Ring D' is C₆ aryl or 5- to 6-membered heteroaryl;

each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

d is an integer selected from 0 to 4;

R^{V1} is $-\text{NR}^{V1'}-\overset{\xi}{\underset{\xi}{\text{---}}}$, $-\text{O}-\overset{\xi}{\underset{\xi}{\text{---}}}$, or



$R^{V1'}$ is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

Ring C is C_6 aryl or 5- to 6-membered heteroaryl;

each R^C is independently $-\overset{\xi}{\underset{\xi}{\text{---}}}$, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

** denotes attachment to L;

c is an integer selected from 0 to 5, as valency permits;

R^{V2} is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

R^{V2} is C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is attached to L and optionally substituted with one or more R^u ;

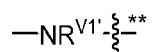
R^{V3} is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

R^{V4} is $-(\text{C}_{1-3} \text{ alkylene})-\text{**}$; wherein the alkylene is optionally substituted with one or more R^u and ** denotes attachment to L; or

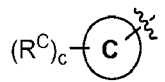
R^{V4} is hydrogen, C_{1-6} alkyl, C_{1-8} heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u ; and

R^{V5} is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

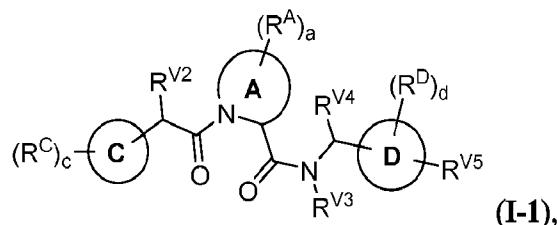
[0023] In certain embodiments, R^{V1} is



[0024] In certain embodiments, R^{V1} is



[0025] In certain embodiments, V is of Formula I-1



wherein:

Ring A is 5- to 7-membered heterocycle;

each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

a is an integer selected from 0 to 10, as valency permits;

Ring C is C₆ aryl or 5- to 6-membered heteroaryl;

each R^C is independently $\text{---}\overset{**}{\underset{z}{\text{C}}}\text{---}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

** denotes attachment to L;

c is an integer selected from 0 to 5, as valency permits;

Ring D' is C₆ aryl or 5- to 6-membered heteroaryl;

each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

d is an integer selected from 0 to 4;

R^{V2} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u ;

R^{V2} is C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is attached to L and optionally substituted with one or more R^u ; or

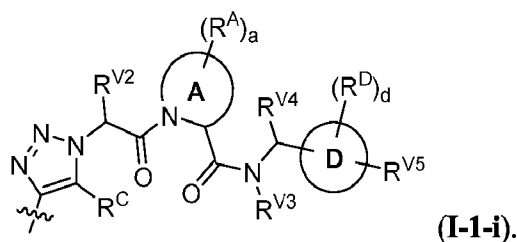
one R^C and R^{V2} , together with the intervening atoms, form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

R^{V3} is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

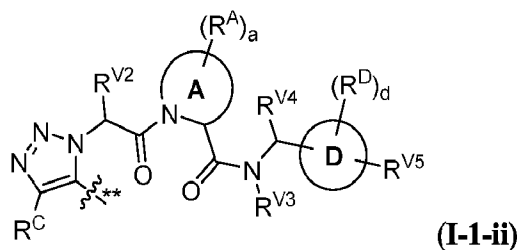
R^{V4} is hydrogen, C_{1-6} alkyl, C_{1-8} heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u ; and

R^{V5} is hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

[0026] In certain embodiments, **V** is of Formula **I-1-i**



[0027] In certain embodiments, **V** is of Formula **I-1-ii**



[0028] In certain embodiments, Ring A is 5- to 7-membered heterocycle. In certain embodiments, Ring A is 5-membered heterocycle. In certain embodiments, Ring A is 6-membered heterocycle. In certain embodiments, Ring A is 7-membered heterocycle.

[0029] In certain embodiments, each R^A is independently oxo, halogen (*e.g.*, $-F$, $-Cl$, $-Br$, or $-I$), $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino,

methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0030] In certain embodiments, each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0031] In certain embodiments, each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0032] In certain embodiments, each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered

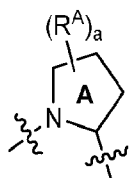
heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

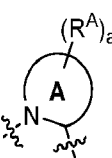
[0033] In certain embodiments, at least one R^A is -OH.

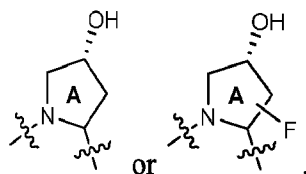
[0034] In certain embodiments, a is 0. In certain embodiments, a is 1. In certain embodiments, a is 2. In certain embodiments, a is 3. In certain embodiments, a is 4, as valency permits. In certain embodiments, a is 5, as valency permits. In certain embodiments, a is 6, as valency permits. In certain embodiments, a is 7, as valency permits. In certain embodiments, a is 8, as valency permits. In certain embodiments, a is 9, as valency permits. In certain embodiments, a is 10, as valency permits.

[0035] In certain embodiments, a is 1 or 2, and at least one of R^A is -OH.

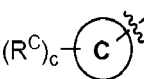
[0036] In certain embodiments,  is

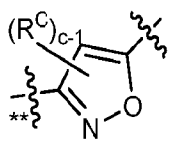


[0001] In certain embodiments,  is



[0037] In certain embodiments, Ring C is C_6 aryl (*i.e.*, phenyl) or 5- to 6-membered heteroaryl (*e.g.*, heteroaryl comprising one 5- or 6-membered ring and 1-4 heteroatoms selected from N, O, and S). In certain embodiments, Ring C is C_6 aryl (*i.e.*, phenyl). In certain embodiments, Ring C is 5-membered heteroaryl. In certain embodiments, Ring C is 6-membered heteroaryl.

[0038] In certain embodiments,  is not



[0039] In certain embodiments, Ring C is not isoxazoly.

[0040] In certain embodiments, Ring C is 5-membered heteroaryl comprising one nitrogen atom. In certain embodiments, Ring C is 5-membered heteroaryl comprising two nitrogen atoms. In certain embodiments, Ring C is 5-membered heteroaryl comprising three nitrogen atoms. In certain embodiments, Ring C is 5-membered heteroaryl comprising four nitrogen atoms.

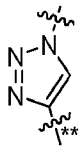
[0041] In certain embodiments, Ring C is 5-membered heteroaryl comprising at least one nitrogen atom. In certain embodiments, Ring C is 5-membered heteroaryl comprising at least two nitrogen atoms. In certain embodiments, Ring C is 5-membered heteroaryl comprising at least three nitrogen atoms. In certain embodiments, Ring C is 5-membered heteroaryl comprising at least four nitrogen atoms.

[0042] In certain embodiments, Ring C is 6-membered heteroaryl comprising one nitrogen atom. In certain embodiments, Ring C is 6-membered heteroaryl comprising two nitrogen atoms. In certain embodiments, Ring C is 6-membered heteroaryl comprising three nitrogen atoms. In certain embodiments, Ring C is 6-membered heteroaryl comprising four nitrogen atoms.

[0043] In certain embodiments, Ring C is 6-membered heteroaryl comprising at least one nitrogen atom. In certain embodiments, Ring C is 6-membered heteroaryl comprising at least two nitrogen atoms. In certain embodiments, Ring C is 6-membered heteroaryl comprising at least three nitrogen atoms. In certain embodiments, Ring C is 6-membered heteroaryl comprising at least four nitrogen atoms.

[0044] In certain embodiments, all heteroatoms in Ring C must be nitrogen.

[0045] In certain embodiments, Ring C is isoxazoly. In certain embodiments, Ring C is triazolyl. In certain embodiments, Ring C is 1,2,3-triazolyl. In certain embodiments, Ring C is



[0046] In certain embodiments, each R^C is independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-

butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0047] In certain embodiments, each R^C is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0048] In certain embodiments, each R^C is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0049] In certain embodiments, each R^C is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl,

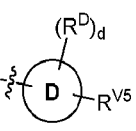
wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

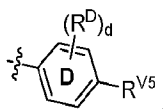
[0050] In certain embodiments, c is 0. In certain embodiments, c is 1. In certain embodiments, c is 2. In certain embodiments, c is 3. In certain embodiments, c is 4, as valency permits. In certain embodiments, c is 5, as valency permits.

[0051] In certain embodiments, c is 0.

[0052] In certain embodiments, Ring D is C₆ aryl (*i.e.*, phenyl) or 5- to 6-membered heteroaryl (*e.g.*, heteroaryl comprising one 5- or 6-membered ring and 1-4 heteroatoms selected from N, O, and S). In certain embodiments, Ring D is C₆ aryl (*i.e.*, phenyl). In certain embodiments, Ring D is 5-membered heteroaryl. In certain embodiments, Ring D is 6-membered heteroaryl.

[0053] In certain embodiments, Ring D is phenyl.

[0054] In certain embodiments,  is



[0055] In certain embodiments, each R^D is independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl

(C₃), 1-butynyl (C₄), 2-butynyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0056] In certain embodiments, each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0057] In certain embodiments, each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0058] In certain embodiments, each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0059] In certain embodiments, d is 0. In certain embodiments, d is 1. In certain embodiments, d is 2. In certain embodiments, d is 3. In certain embodiments, d is 4.

[0060] In certain embodiments, R^{V2} is hydrogen or C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)) optionally substituted with one or more R^u. In certain embodiments, R^{V2} is hydrogen. In certain embodiments, R^{V2} is C₁₋₆ alkyl optionally substituted with one or more R^u.

[0061] In certain embodiments, R^{V2} is 2-propyl or *t*-butyl.

[0062] In certain embodiments, R^{V2} is C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆),

cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)) or 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the carbocyclyl or heterocyclyl is attached to L and optionally substituted with one or more R^u.

[0063] In certain embodiments, one R^C and R^{V2}, together with the intervening atoms, form 12 carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)) or 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0064] In certain embodiments, R^{V3} is hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), or cyclohexadienyl (C₆)), 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S), -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0065] In certain embodiments, R^{V3} is hydrogen or C₁₋₆ alkyl. In certain embodiments, R^{V3} is hydrogen. In certain embodiments, R^{V3} is C₁₋₆ alkyl.

[0066] In certain embodiments, R^{V4} is hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₈ heteroalkyl (*e.g.*, C₁₋₈ heteroalkylene comprising 1-7 heteroatoms selected from N, O, and S), wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u. In certain embodiments, R^{V4} is hydrogen. In certain embodiments, R^{V4} is C₁₋₆ alkyl optionally substituted with one or more R^u. In certain embodiments, R^{V4} is methyl. In certain

embodiments, R^{V4} is C_{1-6} heteroalkyl optionally substituted with one or more R^u . In certain embodiments, R^{V4} is $MeO(CH_2O)CH_2-$.

[0067] In certain embodiments, R^{V5} is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C_{1-6} alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{2-6} alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C_{2-6} alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C_{3-12} carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C_{6-10} aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

[0068] In certain embodiments, R^{V5} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino,

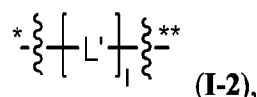
alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0069] In certain embodiments, R^{V5} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0070] In certain embodiments, R^{V5} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0071] In certain embodiments, R^{V5} is halogen or 5- to 6-membered heteroaryl (*e.g.*, heteroaryl comprising one 5- or 6-membered ring and 1-3 heteroatoms selected from N, O, and S) optionally substituted with one or more R^u. In certain embodiments, R^{V5} is 5-membered heteroaryl optionally substituted with one or more R^u. In certain embodiments, R^{V5} is thiazolyl optionally substituted with one or more R^u. In certain embodiments, R^{V5} is 6-membered heteroaryl optionally substituted with one or more R^u.

[0072] In certain embodiments, L is of Formula I-2



wherein:

* denotes attachment to T and ** denotes attachment to V;

each L' is independently C₁₋₆ alkylene, C₁₋₆ heteroalkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₃₋₁₂ carbocyclylene, 3- to 12-membered heterocyclylene, C₆₋₁₀ arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^{L'})-, -C(=O)O-, -N(R^{L'})-, -O-, -S-, or -S(=O)₂-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u;

each occurrence of R^{L'} is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

l is an integer selected from 0 to 6.

[0073] In certain embodiments, each L' is independently C₁₋₆ alkylene (*e.g.*, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), and hexylene (-CH₂CH₂CH₂CH₂CH₂CH₂-)), C₁₋₆ heteroalkylene (*e.g.*, C₁₋₆ heteroalkylene comprising 1-7 heteroatoms selected from N, O, and S), C₂₋₆ alkenylene (*e.g.*, ethenylene (C₂), 1-propenylene (C₃), 2-propenylene (C₃), 1-butenylene (C₄), 2-butenylene (C₄), butadienylene (C₄), pentenylene (C₅), pentadienylene (C₅), or hexenylene (C₆)), C₂₋₆ alkynylene (*e.g.*, ethynylene (C₂), 1-propynylene (C₃), 2-propynylene (C₃), 1-butynylene (C₄), 2-butynylene (C₄), pentynylene (C₅), or hexynylene (C₆)), C₃₋₁₂ carbocyclylene (*e.g.*, cyclopropylene (C₃), cyclopropenylene (C₃), cyclobutylene (C₄), cyclobutenylene (C₄), cyclopentylene (C₅), cyclopentenylene (C₅), cyclohexylene (C₆), cyclohexenylene (C₆), cyclohexadienylene (C₆), cycloheptylene (C₇), cycloheptenylene (C₇), cycloheptadienylene (C₇), cycloheptatrienylene (C₇), cyclooctylene (C₈), cyclooctenylene (C₈), bicyclo[2.2.1]heptanylene (C₇), bicyclo[2.2.2]octanylene (C₈), cyclononylene (C₉), cyclononenylene (C₉), cyclodecylene (C₁₀), cyclodecenylene (C₁₀), octahydro-1*H*-indenylene (C₉), decahydronaphthalenylene (C₁₀), or spiro[4.5]decanylene (C₁₀)), 3- to 12-membered heterocyclylene (*e.g.*, heterocyclylene comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ arylene (*e.g.*, phenylene or naphthylene), 5- to 10-membered heteroarylene (*e.g.*, heteroarylene comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -C(=O)-, -C(=O)N(R^{L2})-, -C(=O)O-, -N(R^{L2})-, -O-, -S-, or -S(=O)₂-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u.

[0074] In certain embodiments, each L' is independently C₁₋₆ alkylene, C₁₋₆ heteroalkylene (*e.g.*, C₁₋₆ heteroalkylene comprising 1-7 heteroatoms selected from N, O, and S), C₃₋₁₂ carbocyclylene, 3- to 12-membered heterocyclylene, -C(=O)-, -C(=O)N(R^L)-, -C(=O)O-, -N(R^L)-, -O-, -S-, or -S(=O)₂-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u.

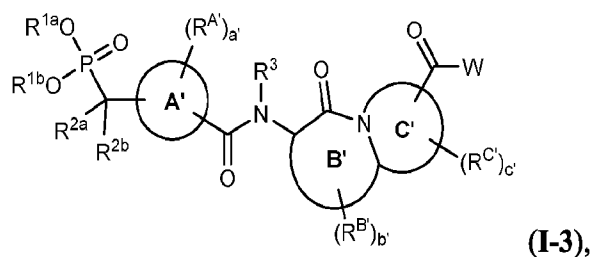
[0075] In certain embodiments, each occurrence of R^L is independently hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butynyl (C₄), 2-butynyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl

(C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0076] In certain embodiments, each occurrence of R^{L'} is independently hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0077] In certain embodiments, *l* is 0. In certain embodiments, *l* is 1. In certain embodiments, *l* is 2. In certain embodiments, *l* is 3. In certain embodiments, *l* is 4. In certain embodiments, *l* is 5. In certain embodiments, *l* is 6.

[0078] In certain embodiments, **T** is of Formula **I-3**



wherein:

R^{1a} and R^{1b} are independently hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

R^{2a} and R^{2b} are independently hydrogen or halogen;

R^{2a} and R^{2b} together an oxo; or

R^{2a} and R^{2b}, together with the carbon atom to which they are attached, form C₃₋₆ carbocycle or 3- to 6-membered heterocycle, wherein the carbocycle or heterocycle is optionally substituted with one or more R^u;

Ring A' is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl;

each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl,

C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

a' is an integer selected from 0 to 6, as valency permits;

R³ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

Ring B' is 3- to 12-membered heterocycle;

each R^{B'} is independently $-\overset{*}{\underset{\text{L}}{\text{Z}}}$, oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

* denotes attachment to L;

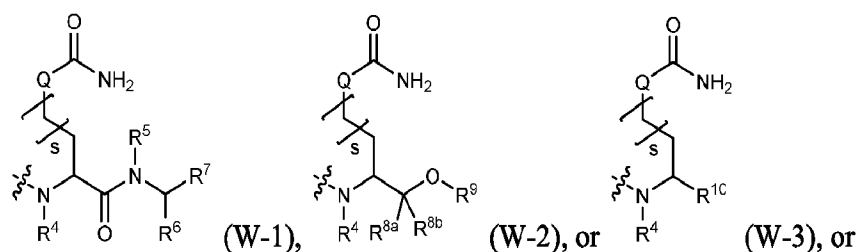
b' is an integer selected from 0 to 6, as valency permits;

Ring C' is 3- to 8-membered heterocycle;

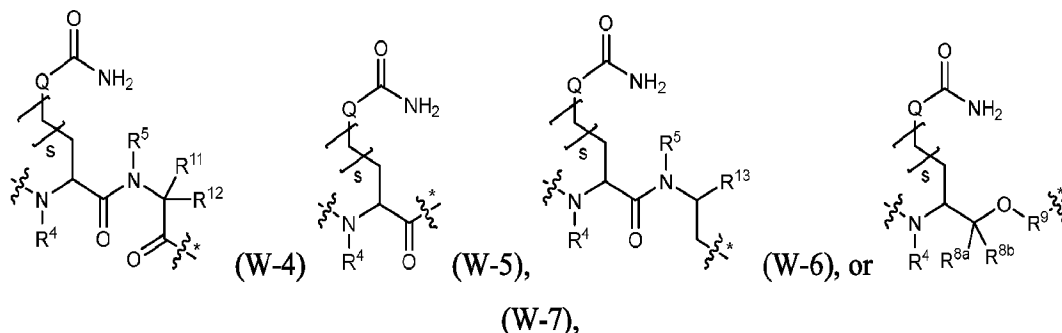
each R^{C'} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

c' is an integer selected from 0 to 6, as valency permits;

W is



W is



wherein:

* denotes attachment to L;

Q is absent; or

Q is $-C(R^Q)_2-$, $-O-$, and $-N(R^{Q'})-$;

each R^Q is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

two R^Q , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

$R^{Q'}$ is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

s is an integer selected from 0 to 4;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R⁶ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a};

R⁷ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{7a}; or

R⁷ is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^{7b};

each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

or

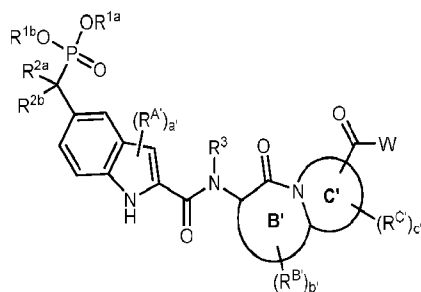
R⁶ and R⁷, together with the carbon atom to which they are attached, form C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

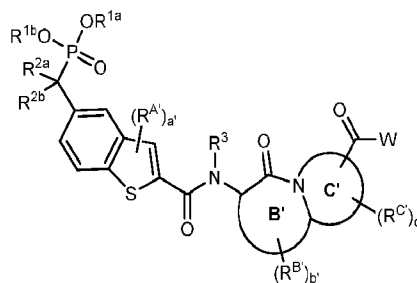
R⁹ is C₆₋₁₀ aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{9a};

each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -

- $C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{10} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkenyl, alkynyl, alkoxy, alkylamino, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{11} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u ;
- R^{12} is hydrogen, C₁₋₆ alkyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁₋₆ alkylene)-(C₃₋₁₂ carbocyclyl), -(C₁₋₆ alkylene)-(3- to 12-membered heterocyclyl), -(C₁₋₆ alkylene)-(C₆₋₁₀ aryl), or -(C₁₋₆ alkylene)-(5- to 10-membered heteroaryl), wherein the alkyl, alkylene, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^{12a} ;
- each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{11} and R^{12} , together with the carbon atom to which they are attached, form C₃₋₆ carbocyclyl or 3- to 6-membered heterocyclyl, wherein carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ; or
- R^{11} and R^5 , together with the intervening atoms, form 4- to 8-membered heterocyclyl optionally substituted with one or more R^u ; and
- R^{13} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .
- [0079] In certain embodiments, T is of Formula I-3-i-a or I-3-i-b

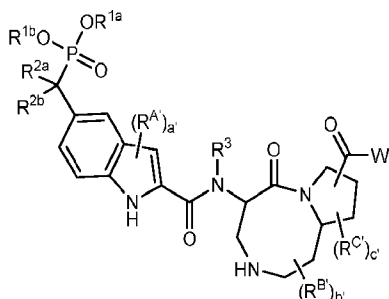


(I-3-i-a) or

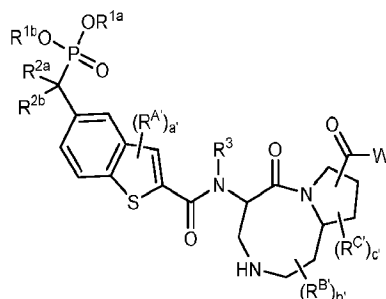


(I-3-i-b).

[0080] In certain embodiments, **T** is of Formula **I-3-ii-a** or **I-3-ii-b**



(I-3-ii-a) or



(I-3-ii-b).

[0081] In certain embodiments, R^{1a} and R^{1b} are independently hydrogen or C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)) optionally substituted with one or more R^u .

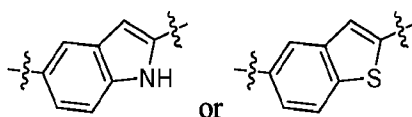
[0082] In certain embodiments, R^{2a} and R^{2b} are independently hydrogen or halogen (*e.g.*, -F, -Cl, -Br, or -I). In certain embodiments, R^{2a} and R^{2b} are independently halogen. In certain embodiments, at least one of R^{2a} and R^{2b} is halogen. In certain embodiments, R^{2a} and R^{2b} are both -F. In certain embodiments, R^{2a} and R^{2b} are both -Cl.

[0083] In certain embodiments, R^{2a} and R^{2b} together form an oxo.

[0084] In certain embodiments, R^{2a} and R^{2b} , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0085] In certain embodiments, Ring A' is C_{6-10} aryl (*e.g.*, phenyl or naphthyl) or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S).

[0086] In certain embodiments, Ring A' is



[0087] In certain embodiments, each $R^{A'}$ is independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0088] In certain embodiments, each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0089] In certain embodiments, each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0090] In certain embodiments, each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0091] In certain embodiments, each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0092] In certain embodiments, a' is 0. In certain embodiments, a' is 1. In certain embodiments, a' is 2. In certain embodiments, a' is 3, as valency permits. In certain embodiments, a' is 4, as valency permits. In certain embodiments, a' is 5, as valency permits. In certain embodiments, a' is 6, as valency permits.

[0093] In certain embodiments, R³ is hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butynyl (C₄), 2-butynyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings

and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

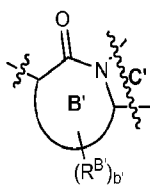
[0094] In certain embodiments, R³ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, 5- to 6-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0095] In certain embodiments, R³ is hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

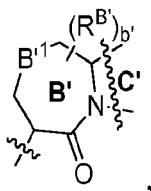
[0096] In certain embodiments, R³ is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0097] In certain embodiments, R³ is hydrogen.

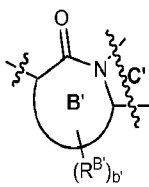
[0098] In certain embodiments, Ring B' is 3- to 12-membered heterocycle (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S).

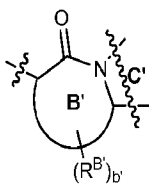


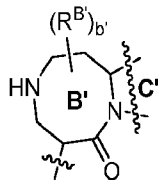
[0099] In certain embodiments, is



wherein B'¹ is -NHCH₂-, -CH₂NH-, or -CH₂CH₂-.



[0100] In certain embodiments,  is



[0101] In certain embodiments, each $R^{B'}$ is independently $-\overset{*}{\underset{z}{\text{C}}}-$, oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₁₂ heteroalkyl (C₁₋₁₂ alkyl comprising 1-10 heteroatoms selected from N, O, and S), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl

(e.g., heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (e.g., phenyl or naphthyl), 5- to 10-membered heteroaryl (e.g., heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0102] In certain embodiments, each R^{B'} is independently $-\frac{\xi^*}{\xi}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0103] In certain embodiments, each R^{B'} is independently $-\frac{\xi^*}{\xi}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0104] In certain embodiments, each R^{B'} is independently $-\frac{\xi^*}{\xi}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0105] In certain embodiments, each R^{B'} is independently $-\frac{\xi^*}{\xi}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0106] In certain embodiments, b' is 0. In certain embodiments, b' is 1. In certain embodiments, b' is 2. In certain embodiments, b' is 3, as valency permits. In certain embodiments, b' is 4, as valency permits. In certain embodiments, b' is 5, as valency permits. In certain embodiments, b' is 6, as valency permits.

[0107] In certain embodiments, each R^{B'} is independently $\text{---}\overset{\text{---}}{\underset{\text{---}}{\text{Z}}}\text{---}$, -C(=O)R^a, or -C(=O)OR^b.

[0108] In certain embodiments, at least one R^{B'} is $\text{---}\overset{\text{---}}{\underset{\text{---}}{\text{Z}}}\text{---}$. In certain embodiments, at least one R^{B'} is -C(=O)R^a. In certain embodiments, at least one R^{B'} is -C(=O)OR^b.

[0109] In certain embodiments, Ring C' is 3- to 8-membered heterocycle (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-3 heteroatoms selected from N, O, and S).

[0110] In certain embodiments, each R^{C'} is independently $\text{---}\overset{\text{---}}{\underset{\text{---}}{\text{Z}}}\text{---}$, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*,

heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

[0111] In certain embodiments, each R^C is independently $-\xi^{**}$, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

[0112] In certain embodiments, each R^C is independently $-\xi^{**}$, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, C_6 aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

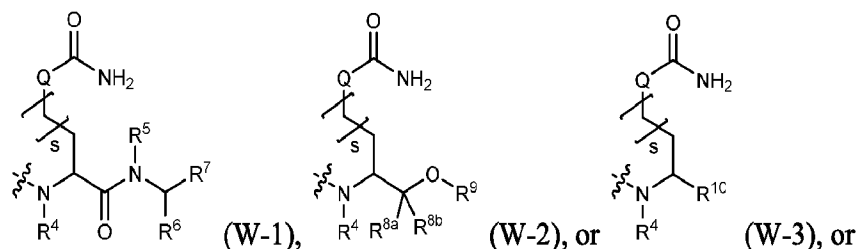
[0113] In certain embodiments, each R^C is independently $-\xi^{**}$, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0114] In certain embodiments, each R^C is independently $-\xi^{**}$, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

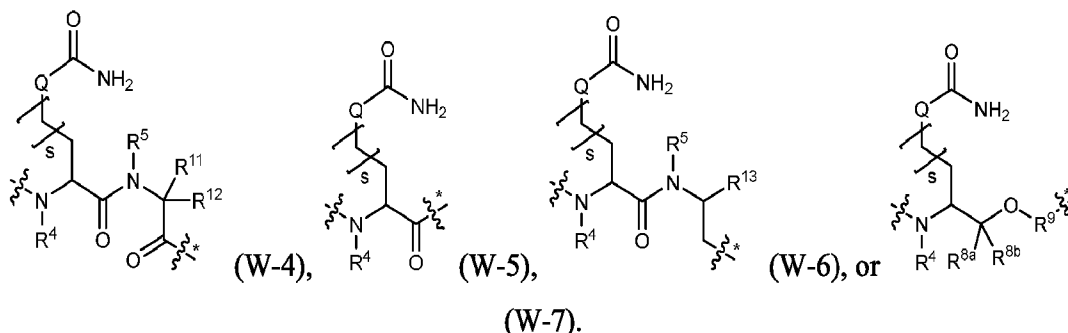
[0115] In certain embodiments, c' is 0. In certain embodiments, c' is 1. In certain embodiments, c' is 2. In certain embodiments, c' is 3, as valency permits. In certain embodiments, c' is 4, as valency permits. In certain embodiments, c' is 5, as valency permits. In certain embodiments, c' is 6, as valency permits.

[0116] In certain embodiments,

W is



W is



[0117] In certain embodiments, Q is absent. In certain embodiments, Q is $-C(R^Q)_2-$, $-O-$, and $-N(R^Q)-$.

[0118] In certain embodiments, each R^Q is independently hydrogen, halogen (*e.g.*, $-F$, $-Cl$, $-Br$, or $-I$), $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl (*e.g.*, methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{1-6} alkoxy (*e.g.*, methoxy (C_1), ethoxy (C_2), propoxy (C_3), *i*-propoxy (C_3), *n*-butoxy (C_4), *i*-butoxy (C_4), *s*-butoxy (C_4), *t*-butoxy (C_4), pentoxy (C_5), or hexoxy (C_6)), C_{1-6} alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C_{3-6} carbocyclyl (*e.g.*, cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), or cyclohexadienyl (C_6)), or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms

selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0119] In certain embodiments, two R^Q, together with the carbon atom to which they are connected, form C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), or cyclohexadienyl (C₆)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S), wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0120] In certain embodiments, R^{Q'} is hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), or cyclohexadienyl (C₆)), 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S), -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0121] In certain embodiments, *s* is 0. In certain embodiments, *s* is 1. In certain embodiments, *s* is 2. In certain embodiments, *s* is 3. In certain embodiments, *s* is 4.

[0122] In certain embodiments, R⁴ and R⁵ are independently hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein

the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0123] In certain embodiments, R⁴ and R⁵ are independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, 5- to 6-membered heteroaryl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0124] In certain embodiments, R⁴ and R⁵ are independently hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0125] In certain embodiments, R⁴ and R⁵ are both hydrogen.

[0126] In certain embodiments, R⁶ and R⁷ are independently C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a} or R^{7b}, respectively.

[0127] In certain embodiments, R⁶ is unsubstituted. In certain embodiments, R⁶ is substituted with one R^{6a}. In certain embodiments, R⁶ is substituted with two R^{6a}. In certain embodiments, R⁶ is substituted with three R^{6a}. In certain embodiments, R⁶ is substituted with four R^{6a}. In certain embodiments, R⁶ is substituted with five R^{6a}.

[0128] In certain embodiments, R⁷ is unsubstituted. In certain embodiments, R⁷ is substituted with one R^{7a}. In certain embodiments, R⁷ is substituted with two R^{7a}. In certain embodiments, R⁷ is substituted with three R^{7a}. In certain embodiments, R⁷ is substituted with four R^{7a}. In certain embodiments, R⁷ is substituted with five R^{7a}.

[0129] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-

butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (e.g., ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (e.g., ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (e.g., cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (e.g., heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (e.g., phenyl or naphthyl), 5- to 10-membered heteroaryl (e.g., heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0130] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0131] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0132] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0133] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0134] In certain embodiments, each R^{6a} and each R^{7a} are independently halogen, C₁₋₆ alkyl, C₁₋₆ alkylamino, or -S(=O)₂R^a, wherein the alkyl or alkylamino is optionally substituted with one or more R^u .

[0135] In certain embodiments, at least one R^{6a} is halogen. In certain embodiments, at least one R^{6a} is C₁₋₆ alkyl, wherein the alkyl is optionally substituted with one or more R^u . In certain embodiments, at least one R^{6a} is C₁₋₆ alkylamino, wherein the alkylamino is optionally substituted with one or more R^u . In certain embodiments, at least one R^{6a} is -S(=O)₂R^a.

[0136] In certain embodiments, at least one R^{7a} is halogen. In certain embodiments, at least one R^{7a} is C₁₋₆ alkyl, wherein the alkyl is optionally substituted with one or more R^u . In certain embodiments, at least one R^{7a} is C₁₋₆ alkylamino, wherein the alkylamino is optionally substituted with one or more R^u . In certain embodiments, at least one R^{7a} is -S(=O)₂R^a.

[0137] In certain embodiments, R^7 is hydrogen or C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)) optionally substituted with one or more R^{7b} .

[0138] In certain embodiments, each R^{7b} is independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino,

propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0139] In certain embodiments, each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0140] In certain embodiments, each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0141] In certain embodiments, each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0142] In certain embodiments, R⁶ and R⁷, together with the carbon atom to which they are attached, form C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇),

cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0143] In certain embodiments, R^{8a} and R^{8b} are independently hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*,

heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0144] In certain embodiments, R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0145] In certain embodiments, R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0146] In certain embodiments, R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0147] In certain embodiments, R^{8a} and R^{8b} are both hydrogen.

[0148] In certain embodiments, R⁹ is C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl) or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the aryl or heteroaryl is optionally substituted with one or more R^{7b}.

[0149] In certain embodiments, R⁹ is unsubstituted. In certain embodiments, R⁹ is substituted with one R^{9a}. In certain embodiments, R⁹ is substituted with two R^{9a}. In certain embodiments, R⁹ is substituted with three R^{9a}. In certain embodiments, R⁹ is substituted with four R^{9a}. In certain embodiments, R⁹ is substituted with five R^{9a}.

[0150] In certain embodiments, each R^{9a} is independently halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino,

methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (e.g., ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (e.g., ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (e.g., cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (e.g., heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (e.g., phenyl or naphthyl), 5- to 10-membered heteroaryl (e.g., heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0151] In certain embodiments, each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0152] In certain embodiments, each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0153] In certain embodiments, each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0154] In certain embodiments, each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0155] In certain embodiments, each R^{9a} is independently halogen or -S(=O)₂R^a. In certain embodiments, at least one R^{9a} is independently halogen. In certain embodiments, at least one R^{9a} is independently -S(=O)₂R^a.

[0156] In certain embodiments, R¹⁰ is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl

(C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0157] In certain embodiments, R¹⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0158] In certain embodiments, R¹⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0159] In certain embodiments, R¹⁰ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0160] In certain embodiments, R¹¹ is hydrogen or C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)) optionally substituted with one or more R^u. In certain embodiments, R¹¹ is hydrogen.

[0161] In certain embodiments, R¹² is hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5

heteroatoms selected from N, O, and S), -(C₁₋₆ alkylene)-(C₃₋₁₂ carbocyclyl), -(C₁₋₆ alkylene)-(3- to 12-membered heterocyclyl), -(C₁₋₆ alkylene)-(C₆₋₁₀ aryl), or -(C₁₋₆ alkylene)-(5- to 10-membered heteroaryl), wherein the alkyl, alkylene, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^{12a}.

[0162] In certain embodiments, R¹² is -(C₁₋₆ alkylene)-(C₆₋₁₀ aryl) or -(C₁₋₆ alkylene)-(5- to 10-membered heteroaryl), wherein the alkylene is optionally substituted with one or more R^{12a}, and aryl or heteroaryl is optionally substituted with one or more R^{12a}.

[0163] In certain embodiments, R¹² is unsubstituted. In certain embodiments, R¹² is substituted with one R^{12a}. In certain embodiments, R¹² is substituted with two R^{12a}. In certain embodiments, R¹² is substituted with three R^{12a}. In certain embodiments, R¹² is substituted with four R^{12a}. In certain embodiments, R¹² is substituted with five R^{12a}.

[0164] In certain embodiments, each R^{12a} is independently oxo, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉),

decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0165] In certain embodiments, each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0166] In certain embodiments, each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0167] In certain embodiments, each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0168] In certain embodiments, each R^{12a} is independently halogen, C₁₋₆ alkyl, C₁₋₆ alkylamino, or -S(=O)₂R^a, wherein the alkyl or alkylamino is optionally substituted with one or more R^u. In certain embodiments, at least one R^{12a} is halogen. In certain embodiments, at least one R^{12a} is C₁₋₆ alkyl, wherein the alkyl is optionally substituted with one or more R^u. In certain embodiments, at least one R^{12a} is C₁₋₆ alkylamino, wherein the alkylamino is optionally substituted with one or more R^u. In certain embodiments, at least one R^{12a} is -S(=O)₂R^a.

[0169] In certain embodiments, R¹¹ and R¹², together with the carbon atom to which they are attached, form C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), or cyclopropenyl (C₃)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S), wherein carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

[0170] In certain embodiments, R¹¹ and R⁵ taken together form 4- to 8-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 4- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S) optionally substituted with one or more R^u.

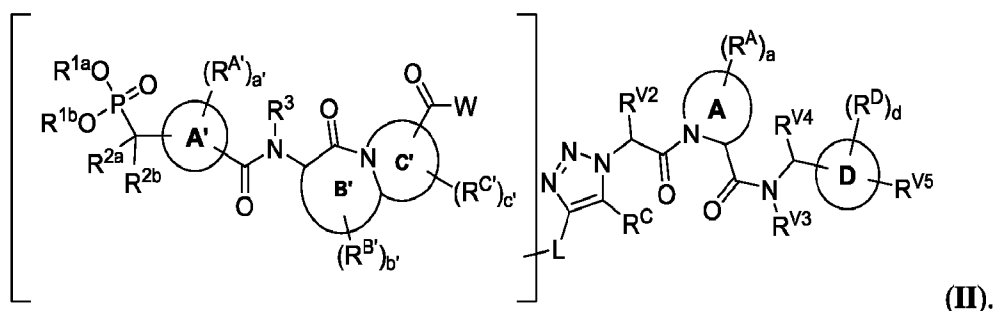
[0171] In certain embodiments, R¹³ is hydrogen, halogen (*e.g.*, -F, -Cl, -Br, or -I), -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0172] In certain embodiments, R¹³ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

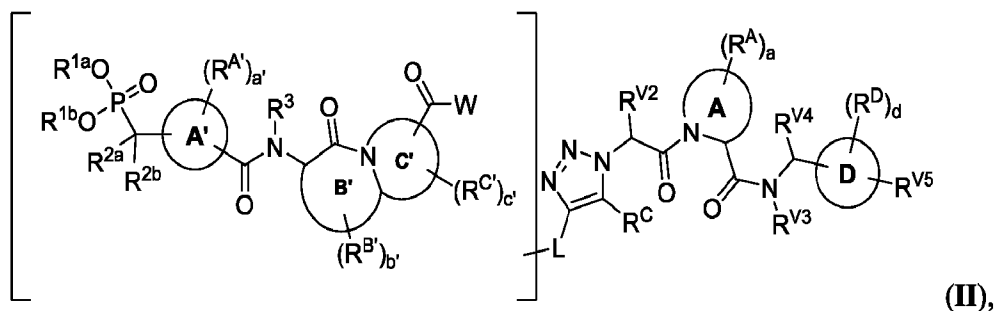
[0173] In certain embodiments, R^{13} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0174] In certain embodiments, R^{13} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0175] In certain embodiments, the compound is a compound of Formula II

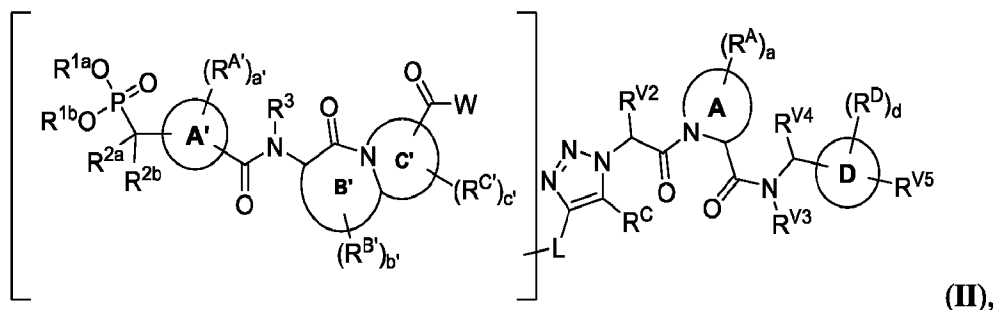


[0176] In certain embodiments, the compound is a compound of Formula II



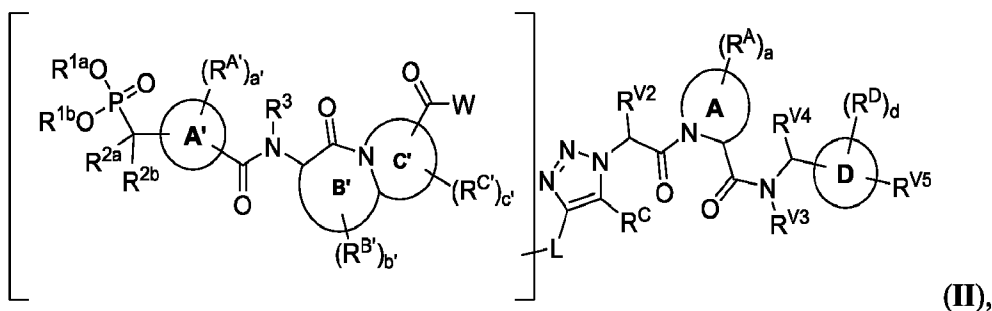
wherein one $R^{B'}$ is $-\frac{\xi^*}{\xi}$.

[0177] In certain embodiments, the compound is a compound of Formula II



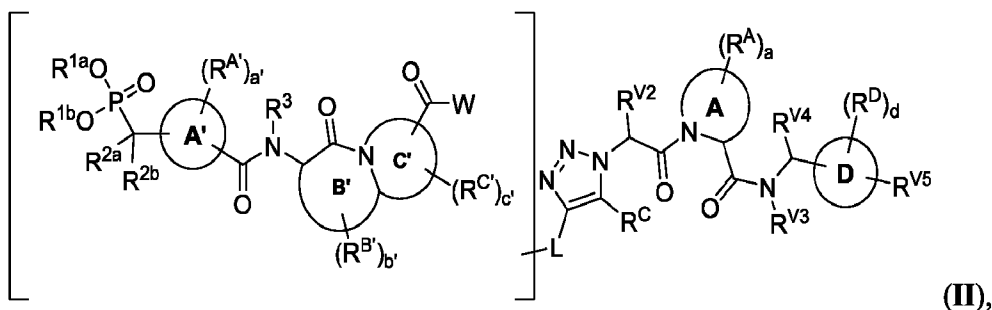
wherein W is W-4.

[0178] In certain embodiments, the compound is a compound of Formula II



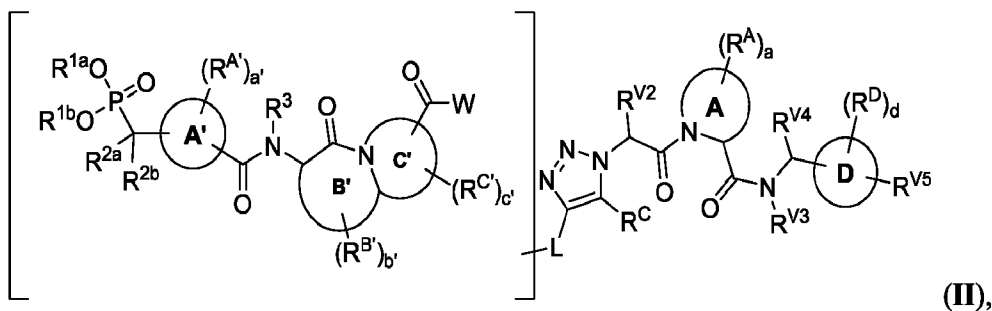
wherein W is W-5.

[0179] In certain embodiments, the compound is a compound of Formula II



wherein W is W-6.

[0180] In certain embodiments, the compound is a compound of Formula II



wherein W is W-7.

[0181] In certain embodiments, each R^a is independently C_{1-6} alkyl (e.g., methyl (C_1), ethyl (C_2), *n*-propyl (C_3), *i*-propyl (C_3), *n*-butyl (C_4), *i*-butyl (C_4), *s*-butyl (C_4), *t*-butyl (C_4), pentyl (C_5), or hexyl (C_6)), C_{2-6} alkenyl (e.g., ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), pentenyl (C_5), pentadienyl (C_5), or hexenyl (C_6)), C_{2-6} alkynyl (e.g., ethynyl (C_2), 1-propynyl (C_3), 2-propynyl (C_3), 1-butylnyl (C_4), 2-butylnyl (C_4), pentynyl (C_5), or hexynyl (C_6)), C_{3-12} carbocyclyl (e.g., cyclopropyl (C_3), cyclopropenyl (C_3), cyclobutyl (C_4), cyclobutenyl (C_4), cyclopentyl (C_5), cyclopentenyl (C_5), cyclohexyl (C_6), cyclohexenyl (C_6), cyclohexadienyl (C_6), cycloheptyl (C_7), cycloheptenyl (C_7), cycloheptadienyl (C_7), cycloheptatrienyl (C_7), cyclooctyl (C_8), cyclooctenyl (C_8), bicyclo[2.2.1]heptanyl (C_7), bicyclo[2.2.2]octanyl (C_8), cyclononyl (C_9), cyclononenyl (C_9), cyclodecyl (C_{10}), cyclodecenyl (C_{10}), octahydro-1*H*-indenyl (C_9), decahydronaphthalenyl

(C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0182] In certain embodiments, each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl.

[0183] In certain embodiments, each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0184] In certain embodiments, each R^a is independently C₁₋₆ alkyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0185] In certain embodiments, each R^b is independently hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0186] In certain embodiments, each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl.

[0187] In certain embodiments, each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0188] In certain embodiments, each R^b is independently hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, or C₂₋₆ alkynyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0189] In certain embodiments, each R^c and each R^d is independently hydrogen, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), or 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

[0190] In certain embodiments, each R^c and each R^d is independently hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0191] In certain embodiments, R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), wherein the heterocyclyl is optionally substituted with one or more R^u.

[0192] In certain embodiments, R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z.

[0193] In certain embodiments, R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0194] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl (*e.g.*, methyl (C₁), ethyl (C₂), *n*-propyl (C₃), *i*-propyl (C₃), *n*-butyl (C₄), *i*-butyl (C₄), *s*-butyl (C₄), *t*-butyl (C₄), pentyl (C₅), or hexyl (C₆)), C₁₋₆ alkoxy (*e.g.*, methoxy (C₁), ethoxy (C₂), propoxy (C₃), *i*-propoxy (C₃), *n*-butoxy (C₄), *i*-butoxy (C₄), *s*-butoxy (C₄), *t*-butoxy (C₄), pentoxy (C₅), or hexoxy (C₆)), C₁₋₆ alkylamino (*e.g.*, dimethylamino, diethylamino, di-*n*-propylamino, di-*i*-propylamino, di-*n*-butylamino, di-*i*-butylamino, di-*s*-butylamino, di-*t*-butylamino, dipentylamino, dihexylamino, methylethylamino, methyl-*n*-propylamino, methyl-*i*-propylamino, methyl-*n*-butylamino, methyl-*i*-butylamino, methyl-*s*-butylamino, methyl-*t*-butylamino, methylpentylamino, methylhexylamino, ethyl-*n*-propylamino, ethyl-*i*-propylamino, ethyl-*n*-butylamino, ethyl-*s*-butylamino, ethyl-*i*-butylamino, ethyl-*t*-butylamino, ethylpentylamino, ethylhexylamino, propyl-*n*-butylamino, propyl-*i*-butylamino, propyl-*s*-butylamino, propyl-*t*-butylamino, propylpentylamino, propylhexylamino, *n*-butylpentylamino, *i*-butylpentylamino, *s*-butylpentylamino, *t*-butylpentylamino, *n*-butylhexylamino, *i*-butylhexylamino, *s*-butylhexylamino, *t*-butylhexylamino, or pentylhexylamino), C₂₋₆ alkenyl (*e.g.*, ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), pentenyl (C₅), pentadienyl (C₅), or hexenyl (C₆)), C₂₋₆ alkynyl (*e.g.*, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butylnyl (C₄), 2-butylnyl (C₄), pentynyl (C₅), or hexynyl (C₆)), C₃₋₁₂ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), or spiro[4.5]decanyl (C₁₀)), 3- to 12-membered heterocyclyl (*e.g.*, heterocyclyl comprising one or two 3- to 8-membered rings and 1-5 heteroatoms selected from N, O, and S), C₆₋₁₀ aryl (*e.g.*, phenyl or naphthyl), 5- to 10-membered heteroaryl (*e.g.*, heteroaryl comprising one or two 5- or 6-membered rings and 1-5 heteroatoms selected from N, O, and S), -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0195] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0196] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, C₆ aryl, or 5- to 6-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0197] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl or heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0198] In certain embodiments, each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl or heterocyclyl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0199] In certain embodiments, two R^u, together with the carbon atom(s) to which they are attached, form C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), or cyclohexadienyl (C₆)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0200] In certain embodiments, two geminal R^u, together with the carbon atom to which they are attached, form C₃₋₆ carbocyclyl (*e.g.*, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆),

or cyclohexadienyl (C₆)) or 3- to 6-membered heterocyclyl (*e.g.*, heterocyclyl comprising one 3- to 6-membered ring and 1-3 heteroatoms selected from N, O, and S).

[0201] Embodiments of the variables in any of the Formulae described herein, *e.g.*, Formulae I-1, I-1-i, I-1-ii, I-2, I-3-i, I-3-ii, I-3-iii, I-3-iv, and I-3-v, as applicable, are described below. Any of the variables can be any moiety as described in the embodiments below. In addition, the combination of any moieties described for any of the variables, as applicable, with any moieties described for any of the remaining variables, is also contemplated.

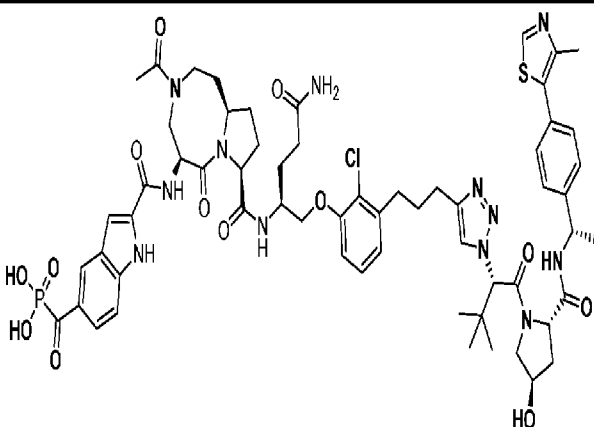
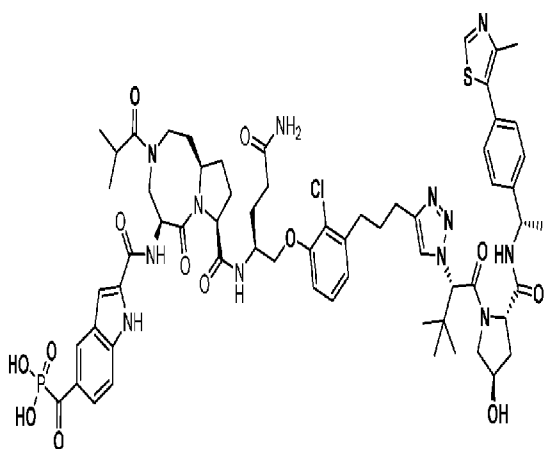
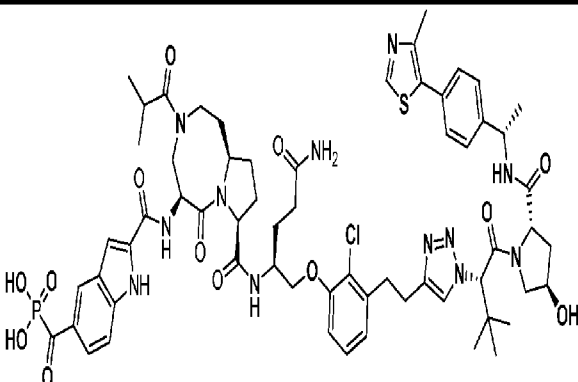
[0202] Without wishing to be limited by this statement, while various options for variables are described herein, it is understood that the present disclosure intends to encompass operable embodiments having combinations of the options. The disclosure may be interpreted as excluding the non-operable embodiments caused by certain combinations of the options.

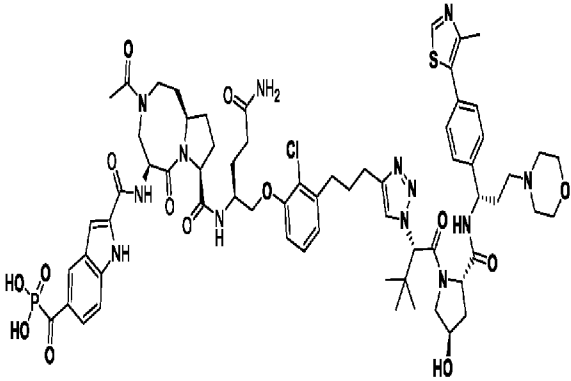
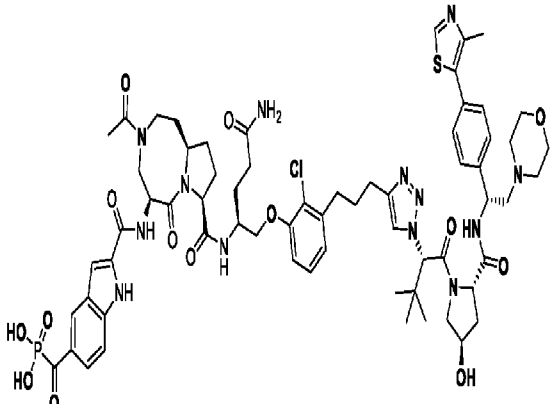
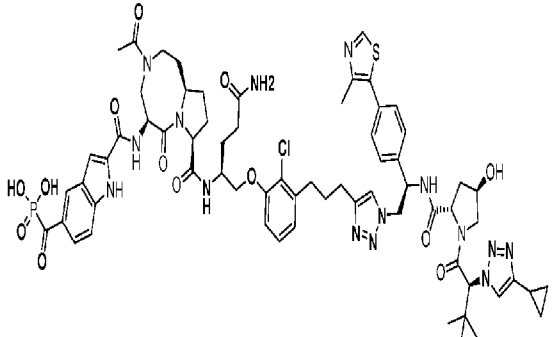
[0203] When a range of values is listed, each discrete value and sub-range within the range are also contemplated. For example, “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

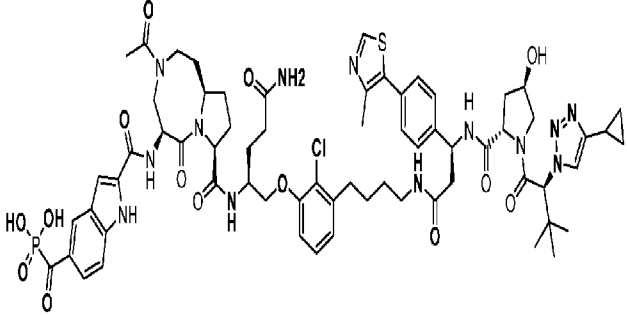
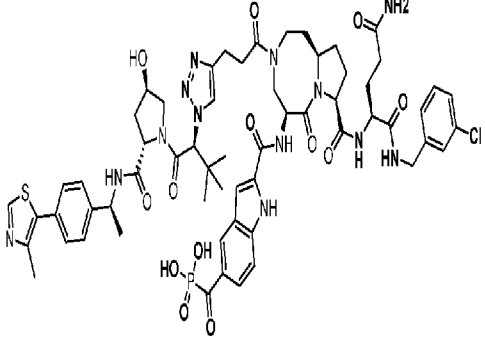
[0204] In certain embodiments, the compound is selected from the compounds in **Table 1** and pharmaceutically acceptable salts thereof.

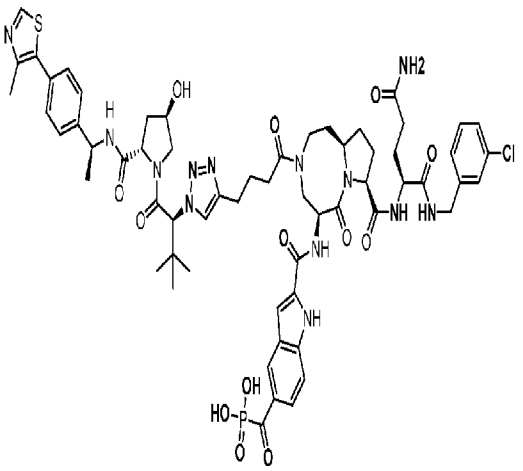
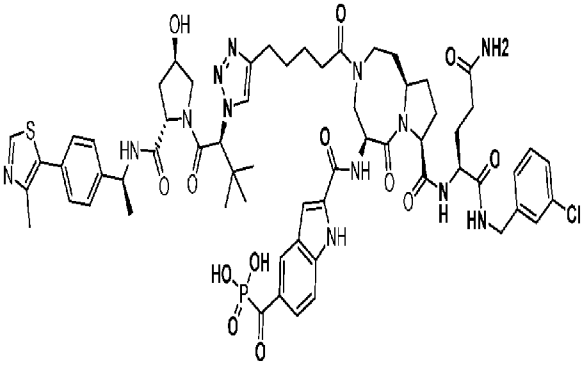
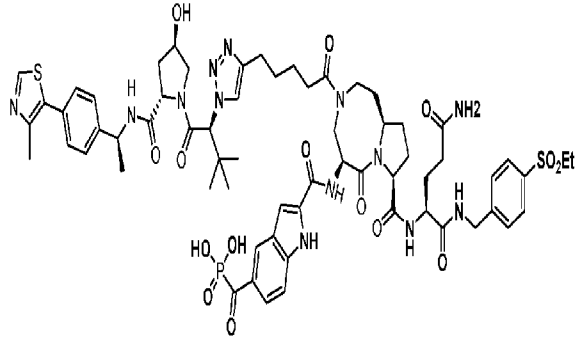
[0205] In certain embodiments, the compound is selected from the compounds in **Table 1**.

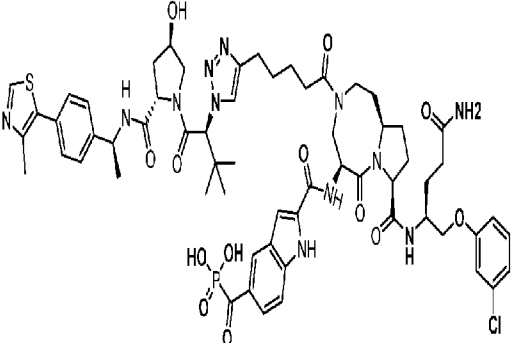
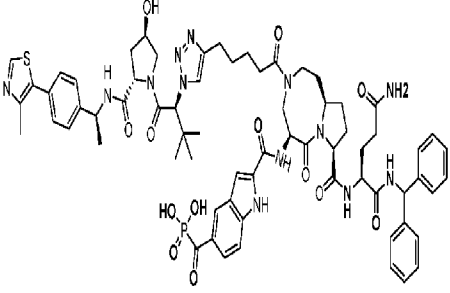
Table 1.

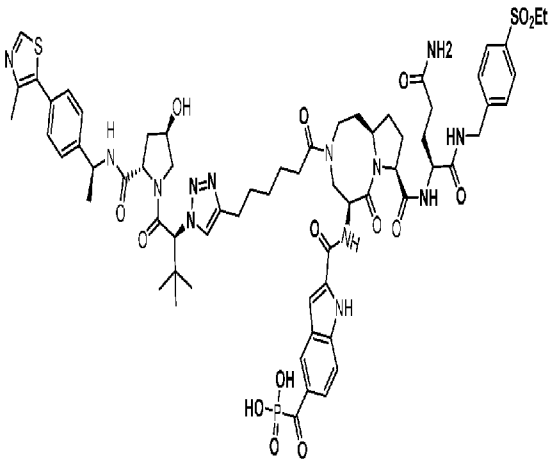
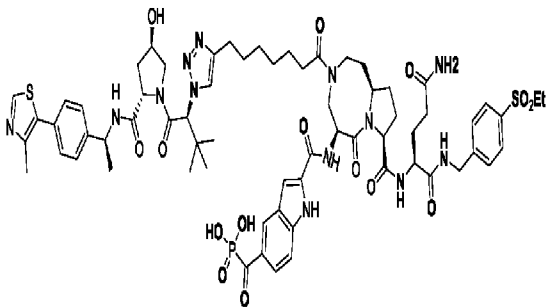
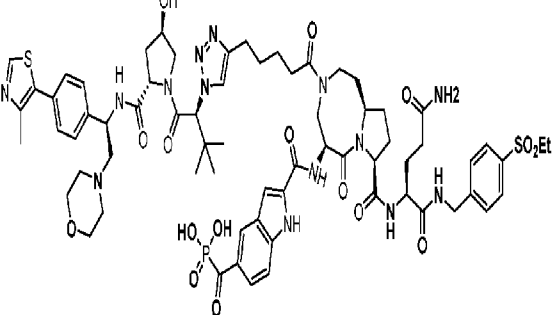
Compound No.	Structure	Chemical Name
1		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-(2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
2		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-(2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-3-isobutyl-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
3		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(2-(1-((S)-1-(2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)ethyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-3-isobutyl-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

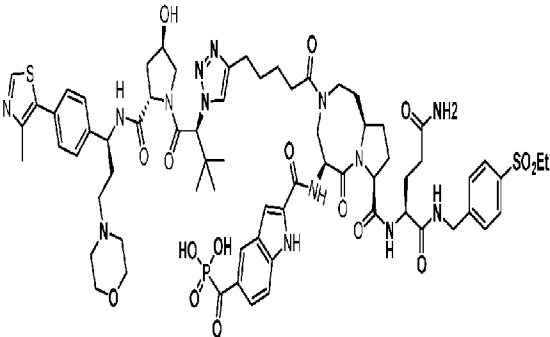
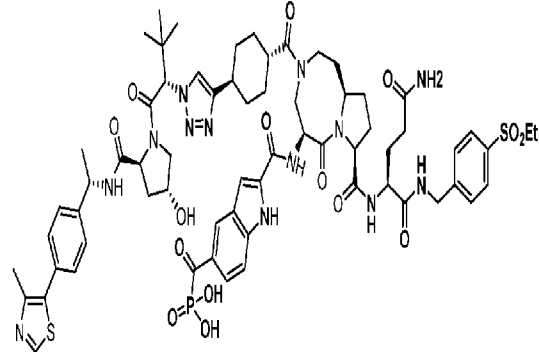
Compound No.	Structure	Chemical Name
		yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
4		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-morpholinopropyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
5		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)-2-morpholinoethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
6		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((R)-2-((2S,4R)-1-((S)-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)-2-(4-(4-methylthiazol-5-yl)phenyl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-

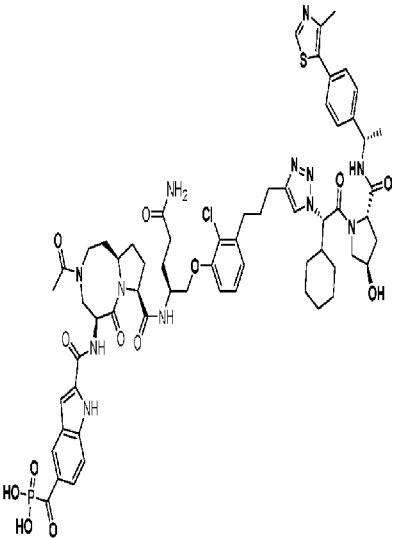
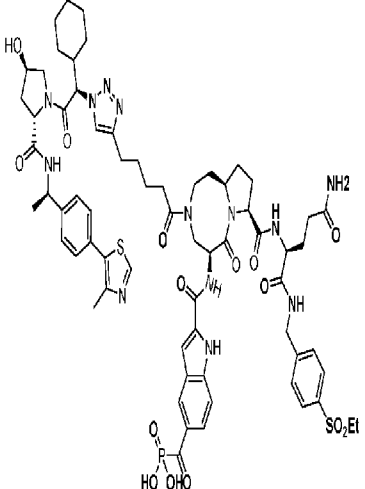
Compound No.	Structure	Chemical Name
		yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
7		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-((S)-3-((2S,4R)-1-((S)-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanamido)butyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
8		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((3-chlorobenzyl)amino)-1,5-dioxopent-2-yl)carbamoyl)-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

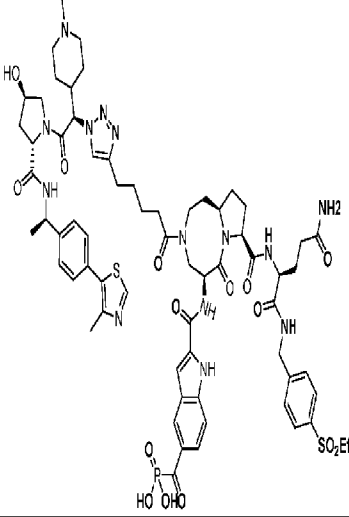
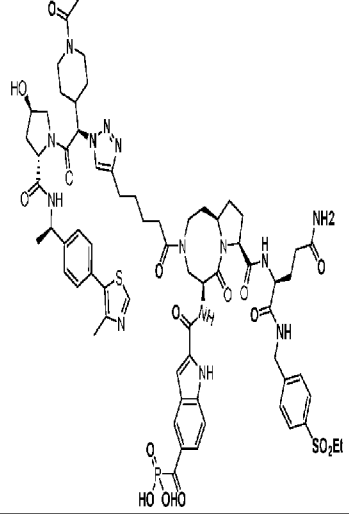
Compound No.	Structure	Chemical Name
9		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((3-chlorobenzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(4-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)butanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
10		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((3-chlorobenzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
11		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-

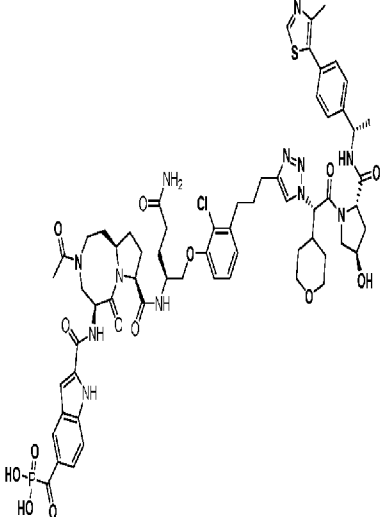
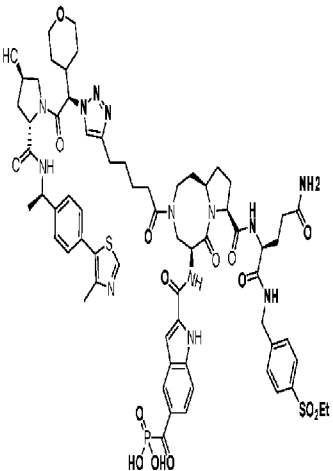
Compound No.	Structure	Chemical Name
		yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
12		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(3-chlorophenoxy)-5-oxopentan-2-yl)carbamoyl)-3-(5-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
13		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
14		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
15		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(7-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)heptanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
16		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)-2-morpholinoethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-

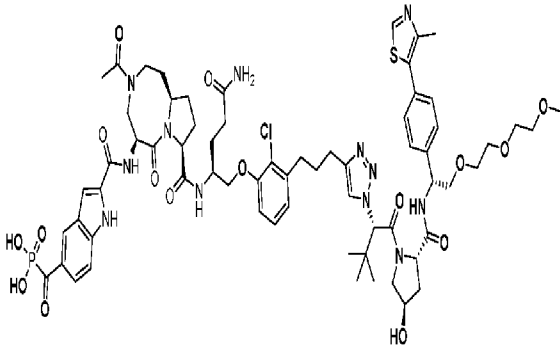
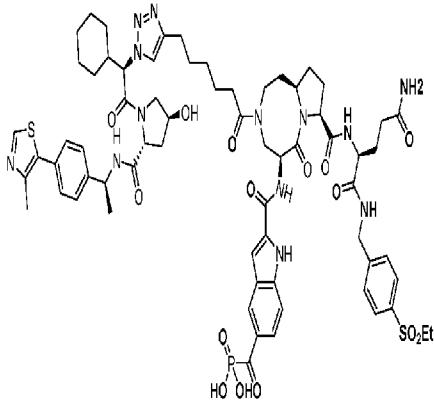
Compound No.	Structure	Chemical Name
		triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
17		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-morpholinopropyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
18		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-((1S,4S)-4-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)cyclohexane-1-carbonyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

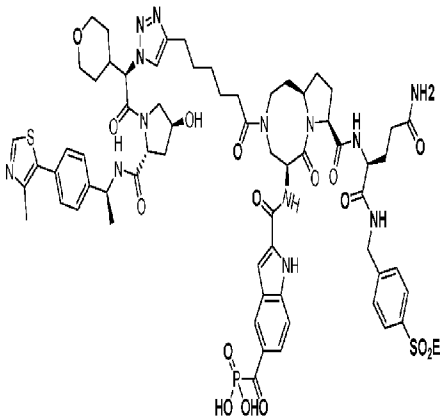
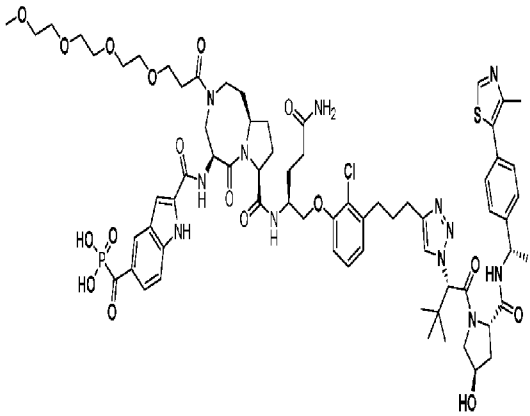
Compound No.	Structure	Chemical Name
19		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-cyclohexyl-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
20		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-1-cyclohexyl-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

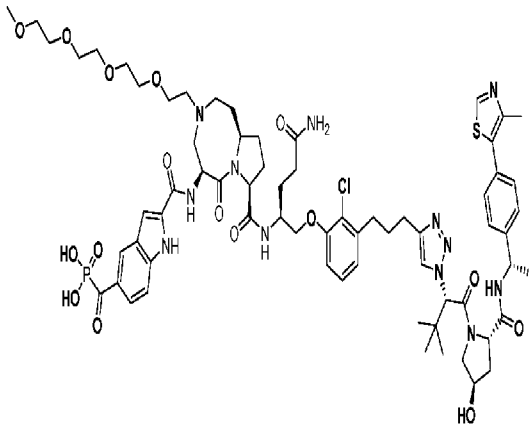
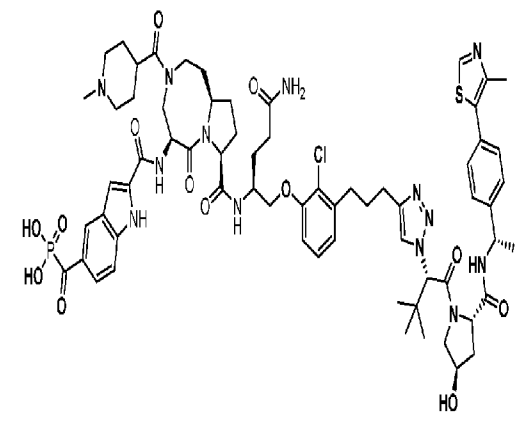
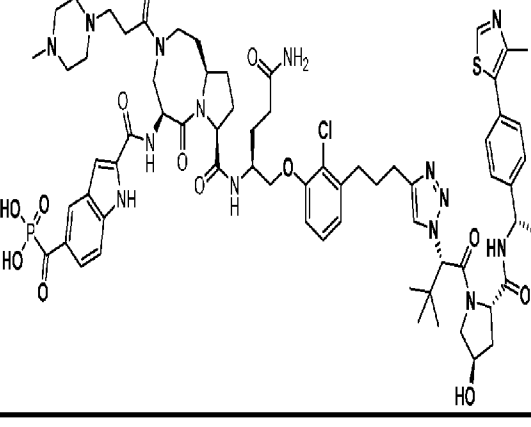
Compound No.	Structure	Chemical Name
21		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-1-(1-methylpiperidin-4-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
22		(2-(((5S,8S,10aR)-3-(5-(1-((R)-1-(1-acetyl)pyrrolidin-4-yl)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
23		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
24		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

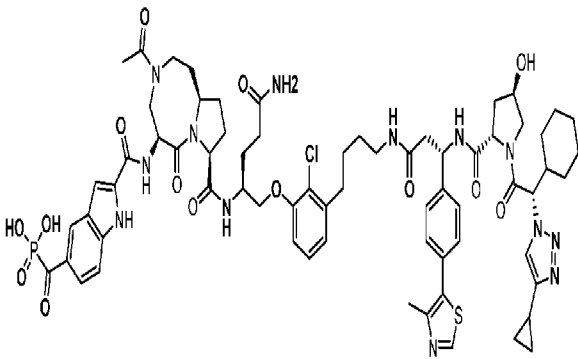
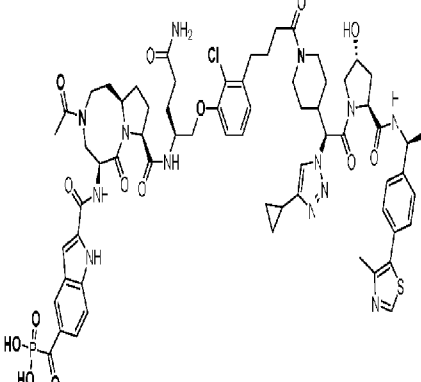
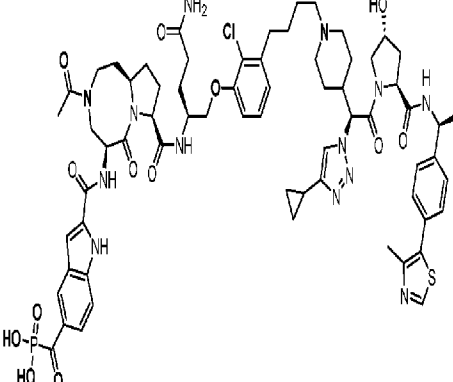
Compound No.	Structure	Chemical Name
25		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
26		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-(2-(2-methoxyethoxy)ethoxy)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

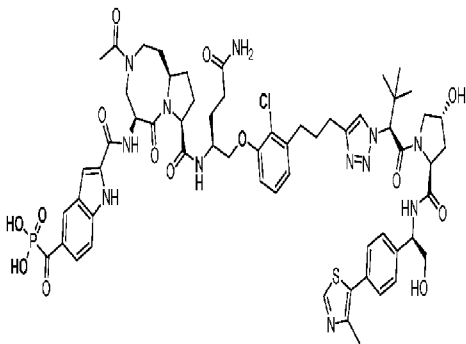
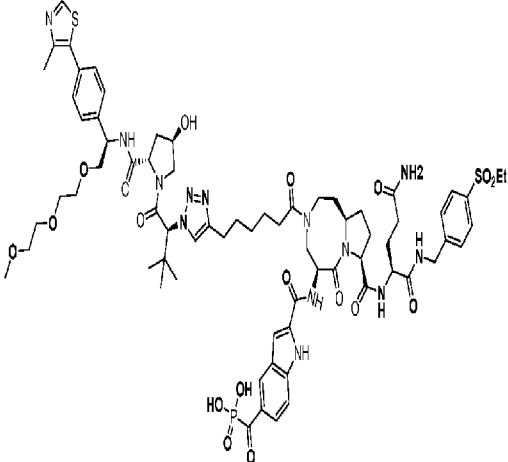
Compound No.	Structure	Chemical Name
27		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-(2-(2-methoxyethoxy)ethoxy)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
28		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((R)-1-cyclohexyl-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

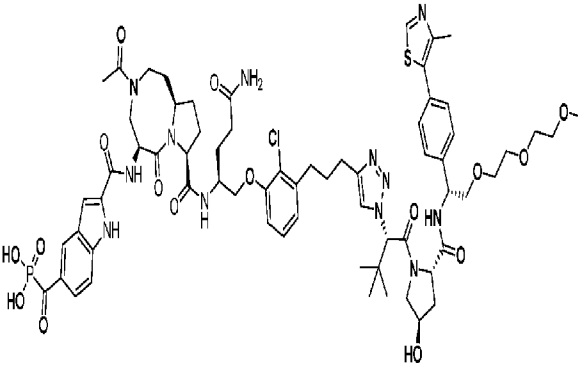
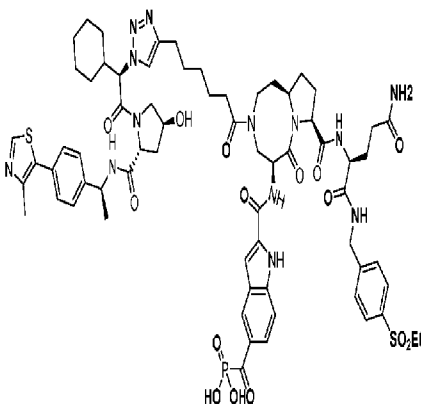
Compound No.	Structure	Chemical Name
29		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((R)-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
30		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxo-3-(2,5,8,11-tetraoxatetradecan-14-oyl)decahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

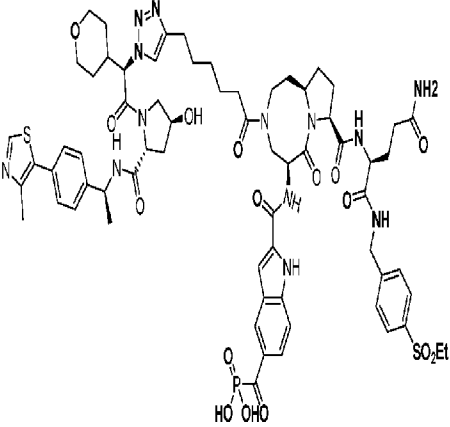
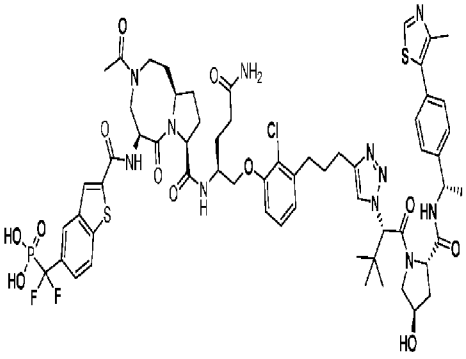
Compound No.	Structure	Chemical Name
31		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxo-3-(2,5,8,11-tetraoxatridecan-13-yl)decahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
32		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-3-(1-methylpiperidine-4-carbonyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
33		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-3-(3-(4-methylpiperazin-1-yl)propanoyl)-6-oxodecahydropyrrolo[1,2-

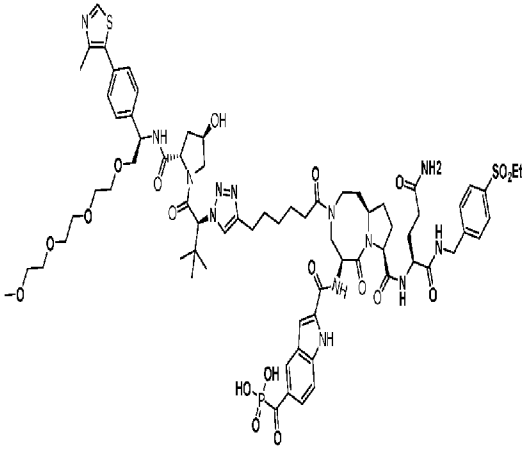
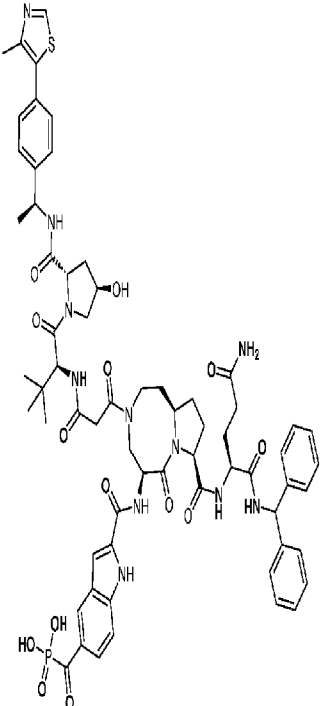
Compound No.	Structure	Chemical Name
		a[[1,5]diazocin-5-yl)carbamoyl]-1H-indole-5-carbonyl)phosphonic acid
34		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(4-(ethylsulfonyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-3-(5-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
35		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((R)-13-(4-(4-methylthiazol-5-yl)phenyl)-2,5,8,11-tetraoxatridecan-13-yl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

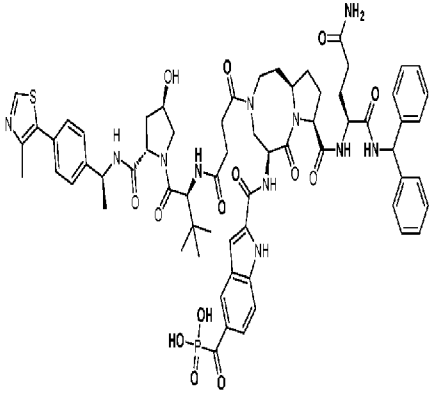
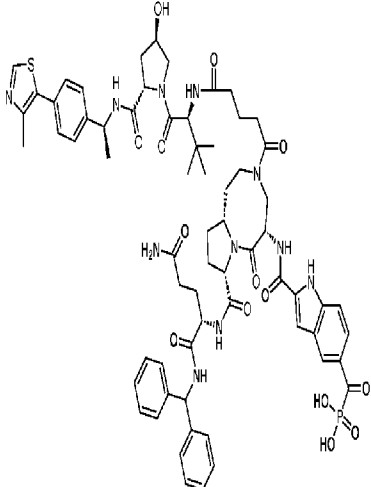
Compound No.	Structure	Chemical Name
36		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-((S)-3-((2S,4R)-1-((S)-2-cyclohexyl-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetyl)-4-hydroxypyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanamido)butyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
37		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-(4-((S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)piperidin-1-yl)-4-oxobutyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
38		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-(4-((S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)piperidin-1-yl)butyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-

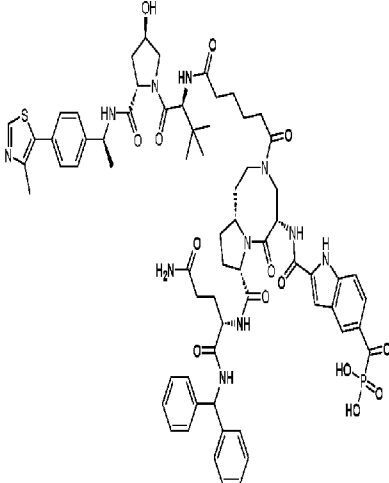
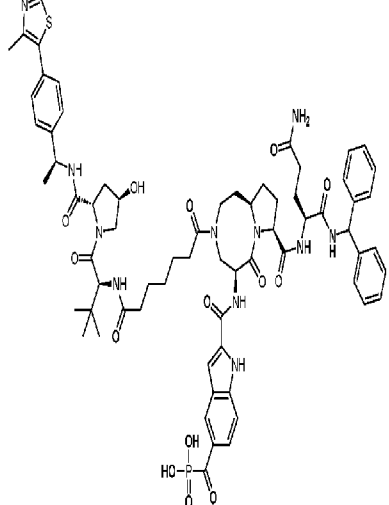
Compound No.	Structure	Chemical Name
		yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
39		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
40		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopent-2-yl)carbamoyl)-3-(6-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-(2-(2-methoxyethoxy)ethoxy)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

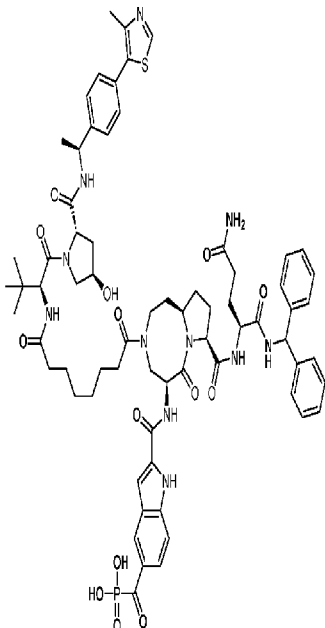
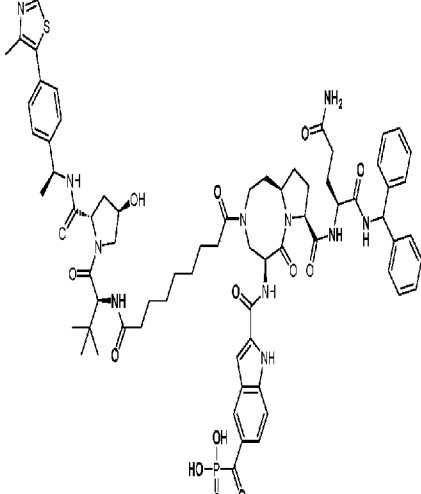
Compound No.	Structure	Chemical Name
41		(2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-(2-(2-methoxyethoxy)ethoxy)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
42		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopent-2-yl)carbamoyl)-3-(6-(1-((R)-1-cyclohexyl-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

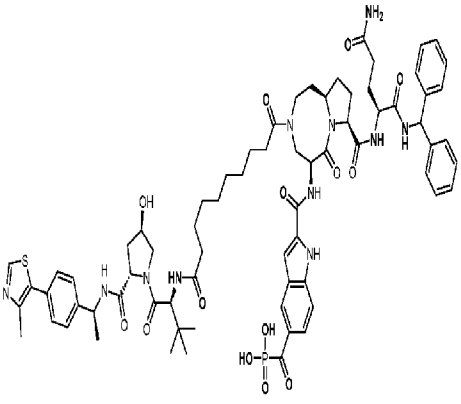
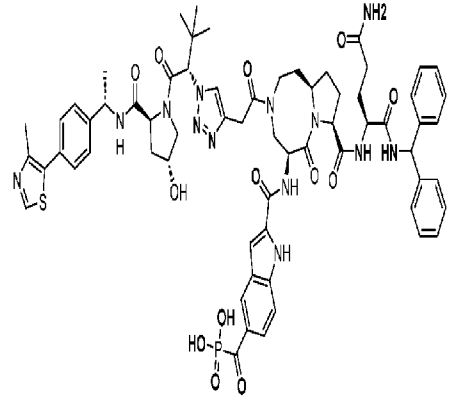
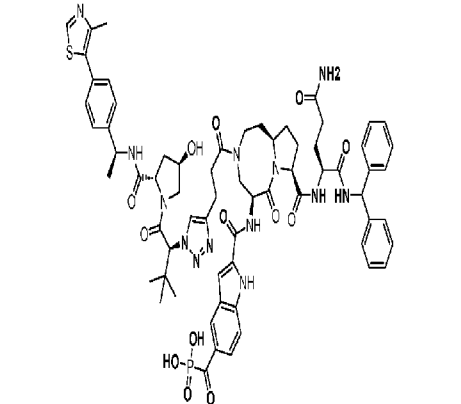
Compound No.	Structure	Chemical Name
43		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((R)-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
44		((2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)benzo[b]thiophen-5-yl)difluoromethyl)phosphonic acid

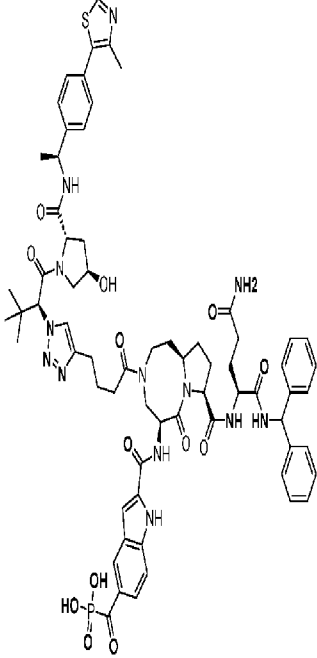
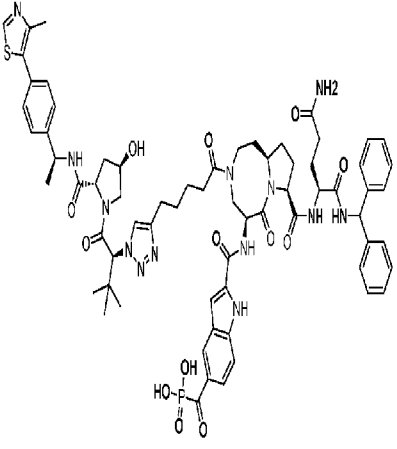
Compound No.	Structure	Chemical Name
45		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((R)-13-(4-(4-methylthiazol-5-yl)phenyl)-2,5,8,11-tetraoxatridecan-13-yl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
46		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(3-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

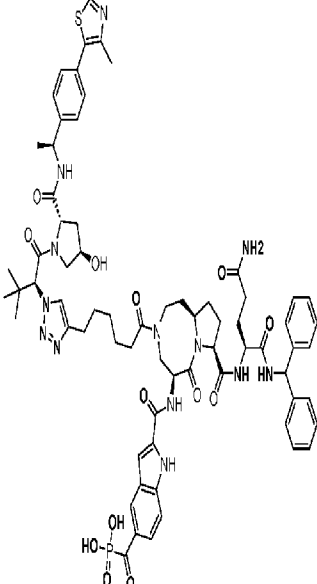
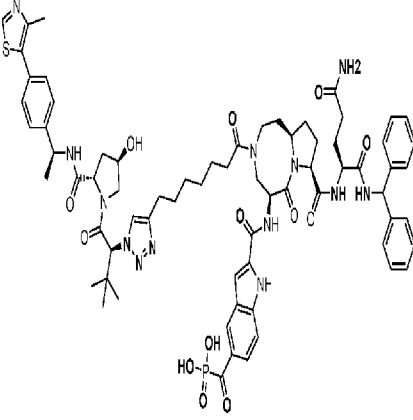
Compound No.	Structure	Chemical Name
47		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(4-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
48		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-5-oxopentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

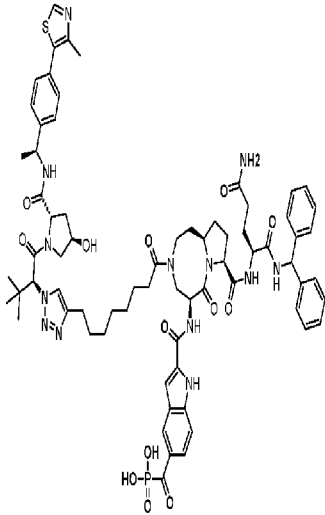
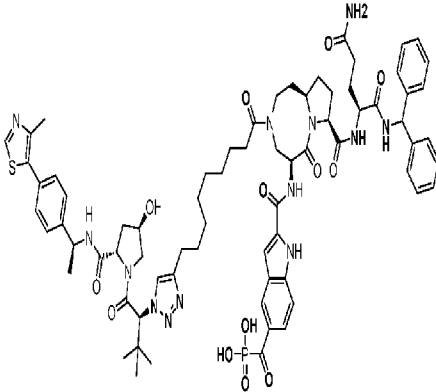
Compound No.	Structure	Chemical Name
49		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
50		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(7-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-7-oxoheptanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
51		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(8-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-8-oxooctanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
52		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(9-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-9-oxononanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
53		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(10-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
54		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(2-(1-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)acetyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
55		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(3-(1-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
56		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(4-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)butanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
57		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
58		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
59		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(7-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)heptanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

Compound No.	Structure	Chemical Name
60		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(8-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)octanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid
61		(2-(((5S,8S,10aR)-8-(((S)-5-amino-1-(benzhydrylamino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(9-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)nonanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

[0206] The compounds of the present disclosure possess advantageous characteristics, as compared to known compounds, such as known STAT3 degraders. For example, the compounds of the present disclosure display more potent degradation activity against certain proteins, *e.g.*, STAT3, more favorable pharmacokinetic properties (*e.g.*, as measured by $C_{\max}$, $T_{\max}$, and/or AUC), and/or less interaction with other cellular targets (*e.g.*, hepatic cellular transporter such as OATP1B1) and accordingly improved safety (*e.g.*, drug-drug interaction). These beneficial properties of the compounds of the present disclosure can be measured according to methods commonly available in the art, such as methods exemplified herein.

[0207] Due to the existence of double bonds, the compounds of the present disclosure may be in *cis* or *trans*, or Z or E, configuration. It is understood that although one configuration may be depicted in the structure of the compounds or formulae of the present disclosure, the present disclosure also encompasses the other configuration. For example, the compounds or formulae of the present disclosure may be depicted in *cis* or *trans*, or Z or E, configuration.

[0208] In one embodiment, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a pharmaceutically acceptable salt. In another embodiment, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a solvate. In another embodiment, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a hydrate.

Pharmaceutically acceptable salts

[0209] In certain embodiments, the compounds disclosed herein exist as their pharmaceutically acceptable salts. In certain embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In certain embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0210] In certain embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In certain embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0211] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate,

bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate, metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undeconate, and xylenesulfonate.

[0212] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0213] In certain embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[0214] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In certain embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[0215] “Solvate” refers to forms of the compound that are associated with a solvent or water (also referred to as “hydrate”), usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the disclosure may be prepared *e.g.*, in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0216] Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates”. For example, a complex with water is known as a “hydrate”. Solvates are within the scope of the disclosure.

[0217] It will also be appreciated by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary from solvate to solvate. Thus, all crystalline forms or the pharmaceutically acceptable solvates thereof are contemplated and are within the scope of the present disclosure.

[0218] In certain embodiments, the compounds described herein exist as solvates. The present disclosure provides for methods of treating diseases by administering such solvates. The present disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0219] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the

solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Isomers (stereoisomers, geometric isomer, tautomer, etc.)

[0220] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.”

[0221] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers.” When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R - and S - sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- or (-)- isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a “racemic mixture”.

[0222] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an “S” form of the compound is substantially free from the “R” form of the compound and is, thus, in enantiomeric excess of the “R” form. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0223] As used herein and unless otherwise indicated, the term “enantiomerically pure (R)-compound” refers to at least about 95% by weight (R)-compound and at most about 5% by weight (S)-compound, at least about 99% by weight (R)-compound and at most about 1% by weight (S)-compound, or at least about 99.9 % by weight (R)-compound and at most about 0.1% by weight (S)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0224] As used herein and unless otherwise indicated, the term “enantiomerically pure (S)-compound” refers to at least about 95% by weight (S)-compound and at most about 5% by

weight (R)-compound, at least about 99% by weight (S)-compound and at most about 1% by weight (R)-compound or at least about 99.9% by weight (S)-compound and at most about 0.1% by weight (R)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0225] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure (R)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (R)-compound. In certain embodiments, the enantiomerically pure (R)-compound in such compositions can, for example, comprise, at least about 95% by weight (R)-compound and at most about 5% by weight (S)-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure (S)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (S)-compound. In certain embodiments, the enantiomerically pure (S)-compound in such compositions can, for example, comprise, at least about 95% by weight (S)-compound and at most about 5% by weight (R)-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[0226] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0227] In certain embodiments, the compounds described herein exist as geometric isomers. In certain embodiments, the compounds described herein possess one or more double bonds. The compounds disclosed herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (E), and *zusammen* (Z) isomers as well as the corresponding mixtures thereof. All geometric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure.

[0228] In certain embodiments, the compounds disclosed herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds disclosed herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. All diastereomeric, enantiomeric, and epimeric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure.

[0229] In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or interconversion are useful for the applications described herein. In certain embodiments, the

compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In certain embodiments, dissociable complexes are preferred. In certain embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In certain embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Tautomers

[0230] In certain embodiments, compounds described herein exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

[0231] Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and an adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro-forms of phenylnitromethane, that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest. All tautomeric forms of the compounds disclosed herein are contemplated and are within the scope of the disclosure. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Pharmaceutical Compositions

[0232] In certain embodiments, the compound described herein is administered as a pure chemical. In certain embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0233] Accordingly, the present disclosure provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0234] In certain embodiments, the compound provided herein is substantially pure, in that it contains less than about 5%, less than about 1%, or less than about 0.1% of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0235] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0236] In certain embodiments, the pharmaceutical composition is formulated for oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, intrapulmonary, intradermal, intrathecal and epidural and intranasal administration. Parenteral administration includes intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In certain embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, or ophthalmic administration. In certain embodiments, the pharmaceutical composition is formulated for oral administration. In certain embodiments, the pharmaceutical composition is formulated for intravenous injection. In certain embodiments, the pharmaceutical composition is formulated as a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye drop, or an ear drop. In certain embodiments, the pharmaceutical composition is formulated as a tablet.

Preparation and Characterization of the Compounds

[0237] The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, the compounds of

the present disclosure 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. The compounds of the present disclosure (*i.e.*, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein)) can be synthesized by following the general synthetic scheme below as well as the steps outlined in the examples, schemes, procedures, and/or synthesis described herein (*e.g.*, Examples).

General Synthetic Scheme

[0238] Those skilled in the art will recognize if a stereocenter exists in the compounds of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compound 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).

[0239] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka) (Pittsburgh, PA).

[0240] Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[0241] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which

are available in most public and university libraries, as well as through on-line. Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (e.g., those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

Biological Assays

[0242] The biological activities of the compounds of the present disclosure can be assessed with methods and assays known in the art.

[0243] For example, cell viability may be determined by CellTiter-Glo 2.0 Cell Viability Assay. In a typical procedure, cells seeded at certain amounts of cells (e.g., 1000 cells) per well are incubated with serially diluted compounds for certain period (e.g., 4 days) under certain conditions (e.g., at 37° C with 5% CO₂). At the end of treatment, CellTiter-Glo 2.0 is added to the wells and luminescence is acquired on TECAN SPARK plate reader. Untreated cells are used as control. Data points are fit with an equation (e.g., a four-parameter equation) to generate a concentration-response curve. IC₅₀ values are calculated using a nonlinear regression analysis of the mean ± SD from triplicate.

[0244] STAT3 degradation may be determined by HiBiT assay. STAT3-HiBiT KI HeLa cell line, which is a clone created by using CRISPR-Cas9 to fuse HiBiT to the 3' end of STAT3 in HeLa cells, may be used for this assay. In a typical procedure, cells seeded at certain amounts of cells (e.g., 20000 cells) per well are incubated with serially diluted compounds for certain period of time (e.g., 24 hours) under certain conditions (e.g., at 37° C with 5% CO₂). At the end of treatment, Nano-Glo HiBiT Lytic Detection reagents is added to the wells and luminescence is acquired on TECAN SPARK plate reader. Untreated cells are used as control. Data points are fit with a four-parameter equation to generate a concentration-response curve. IC₅₀ values are calculated using a nonlinear regression analysis of the mean ± SD from triplicate.

Methods of Use

[0245] In certain aspects, the present disclosure provides methods of degrading a protein in a subject or biological sample comprising administering the compound disclosed herein to the subject or contacting the biological sample with the compound disclosed herein.

[0246] In certain aspects, the present disclosure provides uses of the compound disclosed herein in the manufacture of a medicament for degrading a protein in a subject or biological sample.

[0247] In certain aspects, the present disclosure provides compounds disclosed herein for use in degrading a protein in a subject or biological sample.

[0248] In certain embodiments, the protein is STAT3.

[0249] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof, comprising administering to the subject a compound disclosed herein (*e.g.*, in a therapeutically effective amount).

[0250] In certain aspects, the present disclosure provides methods of treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof, comprising administering to the subject a compound disclosed herein (*e.g.*, in a therapeutically effective amount).

[0251] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0252] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0253] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0254] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder (*e.g.*, a STAT3-mediated disease or disorder) in a subject in need thereof.

[0255] In certain embodiments, cancer, an autoimmune disease, an inflammatory disorder, a neurodegenerative disease, a viral disease, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

[0256] In certain embodiments, the subject is a mammal.

[0257] In certain embodiments, the subject is a human.

Definitions

[0258] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

Chemical Definitions

[0259] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, Organic Chemistry, University Science Books, Sausalito, 1999; Smith and March, March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0260] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPFC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. *See*, for example, Jacques et al., Enantiomers, Racemates and Resolutions (Wiley Interscience, New York, 1981); Wilen et al., Tetrahedron 33:2725 (1977); Eliel, Stereochemistry of Carbon Compounds (McGraw-Hill, NY, 1962); and Wilen, Tables of Resolving Agents and Optical Resolutions p. 268 (E.F. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0261] The disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0262] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, "C₁₋₆ alkyl" is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0263] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present disclosure. When

describing the disclosure, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein. The articles “a” and “an” may be used herein to refer to one or more than one (*i.e.*, at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

[0264] “Alkyl” as used herein, refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C₁₋₂₀ alkyl”). In certain embodiments, an alkyl group has 1 to 12 carbon atoms (“C₁₋₁₂ alkyl”). In certain embodiments, an alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In certain embodiments, an alkyl group has 1 to 9 carbon atoms (“C₁₋₉ alkyl”). In certain embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In certain embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In certain embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”, which is also referred to herein as “lower alkyl”). In certain embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In certain embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In certain embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In certain embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In certain embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), *n*-propyl (C₃), isopropyl (C₃), *n*-butyl (C₄), *tert*-butyl (C₄), *sec*-butyl (C₄), isobutyl (C₄), *n*-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and *n*-hexyl (C₆). Additional examples of alkyl groups include *n*-heptyl (C₇), *n*-octyl (C₈) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C₁₋₁₀ alkyl (*e.g.*, -CH₃). In certain embodiments, the alkyl group is substituted C₁₋₁₀ alkyl. Common alkyl abbreviations include Me (-CH₃), Et (-CH₂CH₃), *i*-Pr (-CH(CH₃)₂), *n*-Pr (-CH₂CH₂CH₃), *n*-Bu (-CH₂CH₂CH₂CH₃), or *i*-Bu (-CH₂CH(CH₃)₂).

[0265] “Alkylene” as used herein, refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkylene groups include, but are not limited to, methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{CH}_2-$), propylene ($-\text{CH}_2\text{CH}_2\text{CH}_2-$), butylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), pentylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), hexylene ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$), and the like. Exemplary substituted divalent alkylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene ($-\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2-$), substituted ethylene ($-\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2-$), substituted propylene ($-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)_2\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{CH}_3)_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2-$), and the like.

[0266] “Alkenyl” as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds (e.g., 1, 2, 3, or 4 carbon-carbon double bonds), and optionally one or more carbon-carbon triple bonds (e.g., 1, 2, 3, or 4 carbon-carbon triple bonds) (“ C_{2-20} alkenyl”). In certain embodiments, alkenyl does not contain any triple bonds. In certain embodiments, an alkenyl group has 2 to 10 carbon atoms (“ C_{2-10} alkenyl”). In certain embodiments, an alkenyl group has 2 to 9 carbon atoms (“ C_{2-9} alkenyl”). In certain embodiments, an alkenyl group has 2 to 8 carbon atoms (“ C_{2-8} alkenyl”). In certain embodiments, an alkenyl group has 2 to 7 carbon atoms (“ C_{2-7} alkenyl”). In certain embodiments, an alkenyl group has 2 to 6 carbon atoms (“ C_{2-6} alkenyl”). In certain embodiments, an alkenyl group has 2 to 5 carbon atoms (“ C_{2-5} alkenyl”). In certain embodiments, an alkenyl group has 2 to 4 carbon atoms (“ C_{2-4} alkenyl”). In certain embodiments, an alkenyl group has 2 to 3 carbon atoms (“ C_{2-3} alkenyl”). In certain embodiments, an alkenyl group has 2 carbon atoms (“ C_2 alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C_{2-4} alkenyl groups include ethenyl (C_2), 1-propenyl (C_3), 2-propenyl (C_3), 1-butenyl (C_4), 2-butenyl (C_4), butadienyl (C_4), and the like. Examples of C_{2-6} alkenyl groups include the aforementioned C_{2-4} alkenyl groups as well as pentenyl (C_5), pentadienyl (C_5), hexenyl (C_6), and the like. Additional examples of alkenyl include heptenyl (C_7), octenyl (C_8), octatrienyl (C_8), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents e.g., for instance from 1 to

5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

[0267] “Alkenylene” as used herein, refers to an alkenyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkenylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkenylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkenylene groups include, but are not limited to, ethenylene (-CH=CH-) and propenylene (e.g., -CH=CHCH₂-, -CH₂-CH=CH-). Exemplary substituted divalent alkenylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted ethylene (-C(CH₃)=CH-, -CH=C(CH₃-), substituted propylene (e.g., -C(CH₃)=CHCH₂-, -CH=C(CH₃)CH₂-, -CH=CHCH(CH₃)-, -CH=CHC(CH₃)₂-, -CH(CH₃)-CH=CH-, -C(CH₃)₂-CH=CH-, -CH₂-C(CH₃)=CH-, -CH₂-CH=C(CH₃-), and the like.

[0268] “Alkynyl” as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds (e.g., 1, 2, 3, or 4 carbon-carbon triple bonds), and optionally one or more carbon-carbon double bonds (e.g., 1, 2, 3, or 4 carbon-carbon double bonds) (“C₂₋₂₀ alkynyl”). In certain embodiments, alkynyl does not contain any double bonds. In certain embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In certain embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In certain embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In certain embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In certain embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In certain embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In certain embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In certain embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In certain embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one

or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

[0269] “Alkynylene” as used herein, refers to a linear alkynyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkynylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkynylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary divalent alkynylene groups include, but are not limited to, substituted or unsubstituted ethynylene, substituted or unsubstituted propynylene, and the like.

[0270] The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (e.g., 1, 2, 3, or 4) heteroatoms (e.g., oxygen, sulfur, nitrogen, boron, silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, i.e., between the point of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms (“C₁₋₁₀ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms (“C₁₋₉ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms (“C₁₋₈ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms (“C₁₋₇ heteroalkyl”). In certain embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms (“C₁₋₆ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms (“C₁₋₅ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and/or 2 heteroatoms (“C₁₋₄ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom (“C₁₋₃ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom (“C₁₋₂ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“C₁ heteroalkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms (“C₂₋₆ heteroalkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more

substituents. In certain embodiments, the heteroalkyl group is an unsubstituted C₁₋₁₀ heteroalkyl. In certain embodiments, the heteroalkyl group is a substituted C₁₋₁₀ heteroalkyl.

[0271] The term “heteroalkenyl,” as used herein, refers to an alkenyl group, as defined herein, which further comprises one or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.*, between the point of attachment. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₁₀ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₉ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₈ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₇ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms (“C₂₋₆ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“C₂₋₅ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“C₂₋₄ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom (“C₂₋₃ heteroalkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“C₂₋₆ heteroalkenyl”). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an “unsubstituted heteroalkenyl”) or substituted (a “substituted heteroalkenyl”) with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted C₂₋₁₀ heteroalkenyl. In certain embodiments, the heteroalkenyl group is a substituted C₂₋₁₀ heteroalkenyl.

[0272] The term “heteroalkynyl,” as used herein, refers to an alkynyl group, as defined herein, which further comprises one or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms are inserted between a carbon atom and the parent molecule, *i.e.*, between the point of attachment. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₁₀ heteroalkynyl”). In certain

embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₉ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₈ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“C₂₋₇ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms (“C₂₋₆ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“C₂₋₅ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“C₂₋₄ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom (“C₂₋₃ heteroalkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“C₂₋₆ heteroalkynyl”). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an “unsubstituted heteroalkynyl”) or substituted (a “substituted heteroalkynyl”) with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted C₂₋₁₀ heteroalkynyl. In certain embodiments, the heteroalkynyl group is a substituted C₂₋₁₀ heteroalkynyl.

[0273] Analogous to “alkylene,” “alkenylene,” and “alkynylene” as defined above, “heteroalkylene,” “heteroalkenylene,” and “heteroalkynylene,” as used herein, refer to a divalent radical of heteroalkyl, heteroalkenyl, and heteroalkynyl group respectively. When a range or number of carbons is provided for a particular “heteroalkylene,” “heteroalkenylene,” or “heteroalkynylene,” group, it is understood that the range or number refers to the range or number of carbons in the linear divalent chain. “Heteroalkylene,” “heteroalkenylene,” and “heteroalkynylene” groups may be substituted or unsubstituted with one or more substituents as described herein.

[0274] “Aryl” refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) 4n+2 aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; e.g., anthracyl). Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-

indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particular aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is substituted C₆₋₁₄ aryl.

[0275] “Heteroaryl” refers to a radical of a 5- to 14-membered monocyclic or polycyclic $4n+2$ aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-8 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5- to 14-membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings.

[0276] “Heteroaryl” also includes ring systems wherein the heteroaryl group, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the heteroaryl or the one or more aryl groups, and in such instances, the number of ring members designates the total number of ring members in the fused (aryl/heteroaryl) ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heteroaryl or the one or more aryl groups. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0277] In certain embodiments, a heteroaryl is a 5- to 10-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 10-membered heteroaryl”). In certain embodiments, a heteroaryl is a 5- to 9-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 9-membered heteroaryl”). In certain embodiments, a heteroaryl is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 8-membered heteroaryl”). In certain embodiments, a

heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 6-membered heteroaryl”). In certain embodiments, the 5- to 6-membered heteroaryl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5- to 14-membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5- to 14-membered heteroaryl.

[0278] 5-membered heteroaryl containing one heteroatom includes, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0279] “Carbocyclyl” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 12 ring carbon atoms (“C₃₋₁₂ carbocyclyl”) and zero heteroatoms in the nonaromatic ring system. In certain embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In certain embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In certain embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms

("C₃₋₆ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 12 ring carbon atoms ("C₅₋₁₂ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C₅₋₁₀ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms ("C₅₋₈ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 or 6 ring carbon atoms ("C₅₋₆ carbocyclyl"). Exemplary C₃₋₆ carbocyclyl include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like.

[0280] In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 12 ring carbon atoms ("C₃₋₁₂ carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms ("C₃₋₁₀ carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 8 ring carbon atoms ("C₃₋₈ carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 3 to 6 ring carbon atoms ("C₃₋₆ carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having from 5 to 12 ring carbon atoms ("C₅₋₁₂ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms ("C₅₋₁₀ carbocyclyl"). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms ("C₅₋₈ carbocyclyl"). In certain embodiments, "carbocyclyl" is a monocyclic, saturated carbocyclyl group having 5 or 6 ring carbon atoms ("C₅₋₆ carbocyclyl"). Examples of C₅₋₆ carbocyclyl include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ carbocyclyl include the aforementioned C₅₋₆ carbocyclyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ carbocyclyl include the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a carbocyclyl group is independently unsubstituted (an "unsubstituted carbocyclyl") or substituted (a "substituted carbocyclyl") with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₂ carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C₃₋₁₂ carbocyclyl.

[0281] In certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or polycyclic (“polycyclic carbocyclyl”) that contains a fused, bridged or spiro ring system and can be saturated or can be partially unsaturated. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, i.e., unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₂ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₂ carbocyclyl.

[0282] “Fused carbocyclyl” or “fused carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of carbons in the fused carbocyclyl ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0283] “Spiro carbocyclyl” or “spiro carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the carbocyclyl rings in which the spiro structure is embedded. In such instances, the number of carbons designates the total number of carbons of the carbocyclyl rings in which the spiro structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the spiro structure is embedded.

[0284] “Bridged carbocyclyl” or “bridged carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, form bridged structure with, i.e., share more than one atoms (as such, share more than one bonds) with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the carbocyclyl rings in which the bridged structure is embedded. In such instances, the number of carbons designates the total number of carbons of the bridged rings. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the bridged structure is embedded.

[0285] “Heterocyclyl” refers to a radical of a 3- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3- to 12-membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation,

azirdinyl, oxiranyl, thiorenlyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0286] In certain embodiments, a heterocyclyl group is a 5- to 12-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5- to 12-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 10-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon ("5- to 10-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 8-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 8-membered heterocyclyl"). In certain embodiments, a heterocyclyl group is a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur ("5- to 6-membered heterocyclyl"). In certain embodiments, the 5- to 6-membered

heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0287] In certain embodiments, a heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (“polycyclic heterocyclyl”) that contains a fused, bridged or spiro ring system, and can be saturated or can be partially unsaturated. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl group, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, and in such instances, the number of ring members designates the total number of ring members in the entire ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heterocyclyl or the one or more carbocyclyl groups. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, i.e., unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3- to 12-membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3- to 12-membered heterocyclyl.

[0288] “Fused heterocyclyl” or “fused heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of ring members in the fused ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0289] “Spiro heterocyclyl” or “spiro heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded.

[0290] “Bridged heterocyclyl” or “bridged heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, form bridged structure with, i.e., share more than one

atoms (as such, share more than one bonds) with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the bridged structure is embedded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the bridged structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the bridged rings.

[0291] “Hetero” when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, sulfur, boron, phosphorus, or silicon heteroatom, as valency permits. Hetero may be applied to any of the hydrocarbyl groups described above having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0292] “Alkoxy” as used herein, refers to the group -OR, wherein R is alkyl as defined herein. C₁₋₆ alkoxy refers to the group -OR, wherein each R is C₁₋₆ alkyl, as defined herein. Exemplary C₁₋₆ alkyl is set forth above.

[0293] “Alkylamino” as used herein, refers to the group -NHR or -NR₂, wherein each R is independently alkyl, as defined herein. C₁₋₆ alkylamino refers to the group -NHR or -NR₂, wherein each R is independently C₁₋₆ alkyl, as defined herein. Exemplary C₁₋₆ alkyl is set forth above.

[0294] “Oxo” refers to =O. When a group other than aryl and heteroaryl or an atom is substituted with an oxo, it is meant to indicate that two geminal radicals on that group or atom form a double bond with an oxygen radical. When a heteroaryl is substituted with an oxo, it is meant to indicate that a resonance structure/tautomer involving a heteroatom provides a carbon atom that is able to form two geminal radicals, which form a double bond with an oxygen radical.

[0295] “Halo” or “halogen” refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[0296] “Protecting group” as used herein is art-recognized and refers to a chemical moiety introduced into a molecule by chemical modification of a functional group (e.g., hydroxyl, amino, thio, and carboxylic acid) to obtain chemoselectivity in a subsequent chemical reaction, during which the unmodified functional group may not survive or may interfere with the chemical reaction. Common functional groups that need to be protected include but not limited to hydroxyl, amino, thiol, and carboxylic acid. Accordingly, the protecting groups are termed hydroxyl-protecting groups, amino-protecting groups, thiol-protecting groups, and carboxylic acid-protecting groups, respectively.

[0297] Common types of hydroxyl-protecting groups include but not limited to ethers (*e.g.*, methoxymethyl (MOM), β -Methoxyethoxymethyl (MEM), tetrahydropyranyl (THP), *p*-methoxyphenyl (PMP), *t*-butyl, triphenylmethyl (Trityl), allyl, and benzyl ether (Bn)), silyl ethers (*e.g.*, *t*-butyldiphenylsilyl (TBDPS), trimethylsilyl (TMS), triisopropylsilyl (TIPS), tri-*iso*-propylsilyloxymethyl (TOM), and *t*-butyldimethylsilyl (TBDMS)), and esters (*e.g.*, pivalic acid ester (Piv) and benzoic acid ester (benzoate; Bz)).

[0298] Common types of amino-protecting groups include but not limited to carbamates (*e.g.*, *t*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), *p*-methoxybenzyl carbonyl (Moz or MeOZ), 2,2,2-trichloroethoxycarbonyl (Troc), and benzyl carbamate (Cbz)), esters (*e.g.*, acetyl (Ac); benzoyl (Bz), trifluoroacetyl, and phthalimide), amines (*e.g.*, benzyl (Bn), *p*-methoxybenzyl (PMB), *p*-methoxyphenyl (PMP), and triphenylmethyl (trityl)), and sulfonamides (*e.g.*, tosyl (Ts), *N*-alkyl nitrobenzenesulfonamides (Nosyl), and 2-nitrophenylsulfenyl (Nps)).

[0299] Common types of thiol-protecting groups include but not limited to sulfide (*e.g.*, *p*-methylbenzyl (Meb), *t*-butyl, acetamidomethyl (Acm), and triphenylmethyl (Trityl)).

[0300] Common types of carboxylic acid-protecting groups include but not limited to esters (*e.g.*, methyl ester, triphenylmethyl (Trityl), *t*-butyl ester, benzyl ester (Bn), *S*-*t*-butyl ester, silyl esters, and orthoesters) and oxazoline.

[0301] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

Other Definitions

[0302] "Pharmaceutically acceptable" means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0303] "Pharmaceutically acceptable salt" refers to a salt of a compound of the disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid,

benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo [2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid , 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid , gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion , an alkaline earth ion , or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of nontoxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0304] A “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or an adult subject (*e.g.*, young adult, middle aged adult or senior adult) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal.

[0305] An “effective amount” means the amount of a compound that, when administered to a subject for treating or preventing a disease, is sufficient to affect such treatment or prevention. The “effective amount” can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated. A “therapeutically effective amount” refers to the effective amount for therapeutic treatment. A “prophylactically effective amount” refers to the effective amount for prophylactic treatment.

[0306] “Preventing”, “prevention” or “prophylactic treatment” refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a subject not yet exposed to a disease-causing agent, or in a subject who is predisposed to the disease in advance of disease onset).

[0307] The term “prophylaxis” is related to “prevention,” and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to

immobilization, and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0308] “Treating” or “treatment” or “therapeutic treatment” of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.*, arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment, “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In a further embodiment, “treating” or “treatment” relates to slowing the progression of the disease.

[0309] The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability or within statistical experimental error, and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, 3%, 4%, or 5% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, or 3% of the stated number or numerical range.

[0310] The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, “consist of” or “consist essentially of” the described features.

[0311] The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, *i.e.*, elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, *i.e.*, “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” may refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only

(optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0312] As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[0313] As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) may refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[0314] While the present teachings have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

[0315] While various inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for

performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

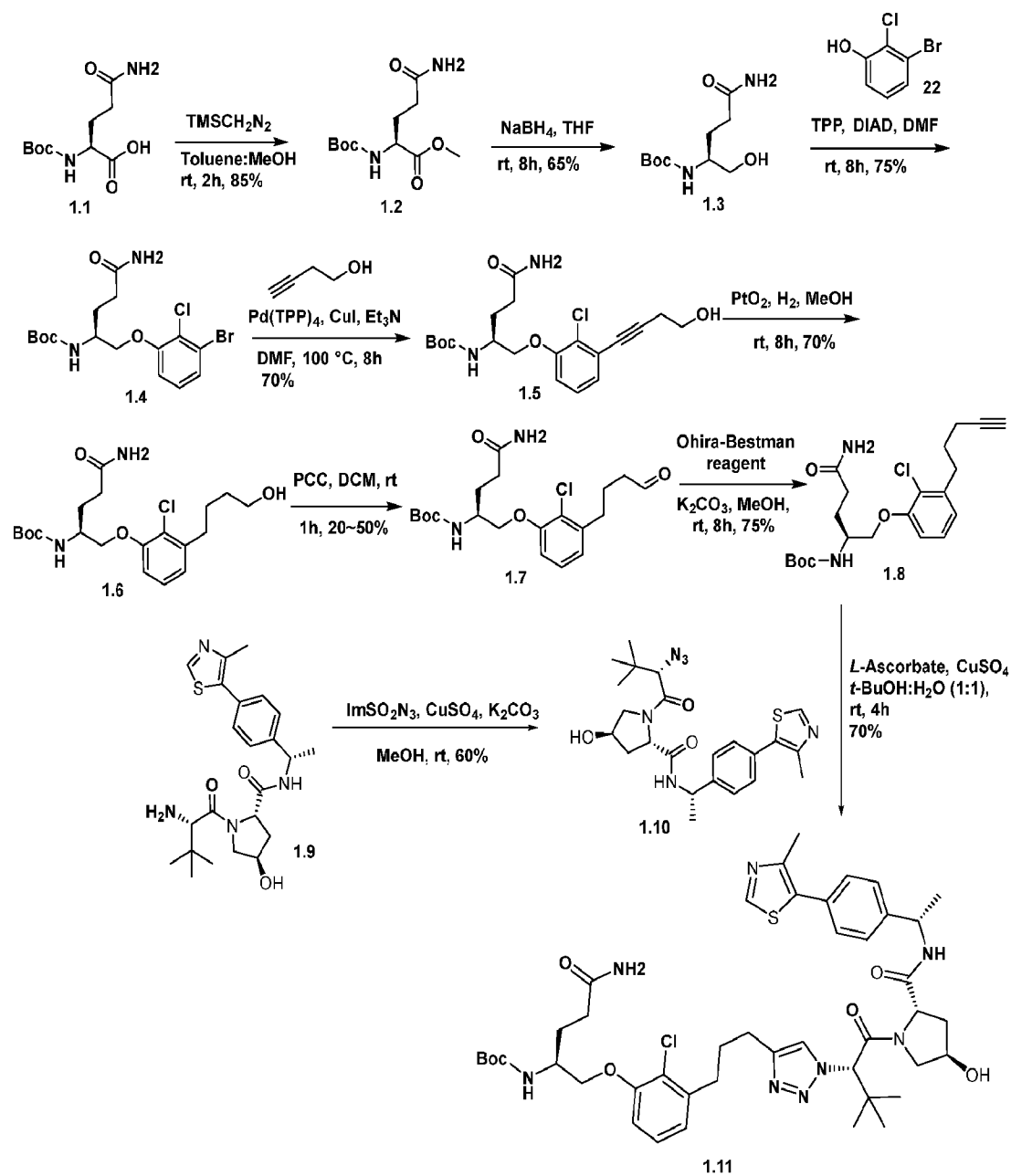
[0316] The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made by one of ordinary skill in the art without departing from the spirit and scope of the appended claims. All embodiments that come within the spirit and scope of the following claims and equivalents thereto are claimed.

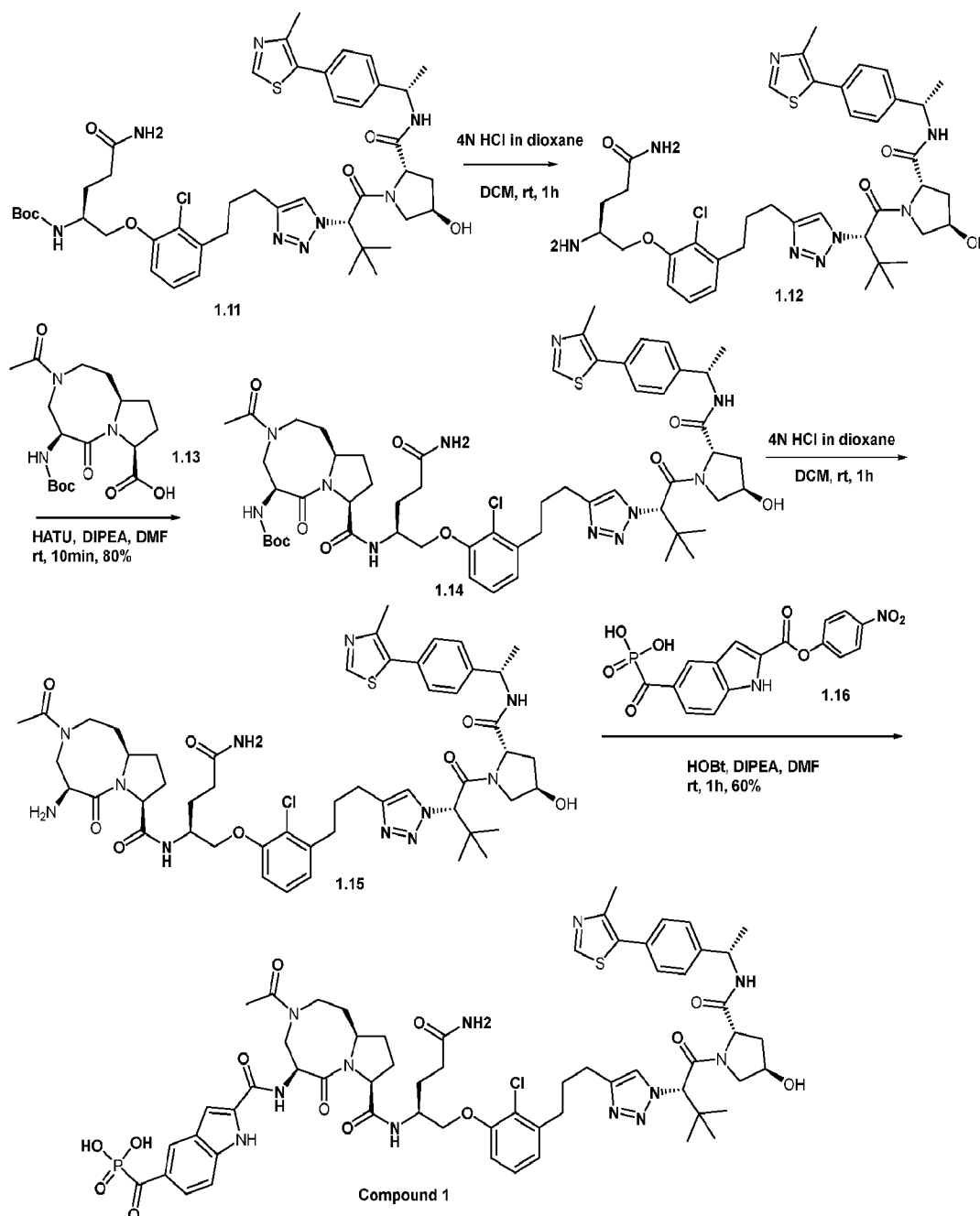
EXAMPLES

[0317] In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

I. Synthesis and Characterization

Compound 1. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



**Compound 1.2:**

[0318] To a stirred solution of compound 1.1 (1eq) in toluene and methanol (10:1) at room temperature, TMS-diazomethane (1.1 eq) was added dropwise. The mixture was then stirred for another 2 hours at room temperature. After completion of the reaction, solvent was evaporated under reduced pressure and the crude product was purified using flash column chromatography. UPLC–MS calculated $[M + H]^+$: 261.1, found: 287.3.

Compound 1.3:

[0319] To a stirred solution of compound 1.2 (1 eq) in methanol at 0 °C, NaBH_4 (1.5 eq) was added portion wise. The reaction mixture was then allowed to warm at room temperature and

stirred for overnight. After completion of the reaction, it was quenched with saturated solution of ammonium chloride. Organic solvent was removed under reduced pressure and the crude was extracted with ethyl acetate (thrice). Organic solvent was dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was purified using column chromatography. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 233.1, found: 233.2.

Compound 1.4:

[0320] To a stirred solution of compound 1.3 (1 eq), compound 22 (1.2 eq), and TPP (1.5 eq) in DMF at 0 °C, DIAD (1.5 eq) is added. The reaction was the allowed to warm at room temperature and stirred overnight. After completion of the reaction, the mixture was extracted with ethyl acetate and water. The product was the purified using flash column chromatography. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 421.0, found: 421.1.

Compound 1.5:

[0321] A mixture of compound 1.4 (1 eq), homopropargyl alcohol (2 eq), and triethyl amine (5 eq) in DMF was degassed for 10 mins and parged with nitrogen. $\text{Pd}(\text{PPh}_3)_4$ (0.05 eq) and CuI (0.03 eq) were added to the reaction mixture sequentially and the mixture was heated at 100 °C for overnight. The mixture was extracted with ethyl acetate and water to remove DMF and the product was purified using flash column chromatography. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 411.1, found: 411.5.

Compound 1.6:

[0322] To a degassed solution of compound 1.5 (1 eq) in methanol, PtO_2 (0.1 eq) was added under nitrogen atmosphere and the mixture was purged with hydrogen gas using hydrogen balloon. The mixture was stirred for another 8h under hydrogen atmosphere. After completion, solvent was evaporated under reduced pressure and product was purified using column chromatography. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 415.1, found: 415.2.

Compound 1.7:

[0323] To a stirred solution of compound 1.6 (1 eq) in DCM at rt, PCC (1.5 eq) was added under nitrogen atmosphere and the mixture was stirred at rt for another 1h. Solvent was evaporated under reduced pressure and the product was purified using column chromatography. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 413.1, found: 413.4.

Compound 1.8:

[0324] To a stirred solution of compound 1.7 (1 eq), Ohira-Bestmann (1.5 eq) in methanol at room temperature K_2CO_3 was added, and the mixture was stirred for overnight. After completion of the reaction, organic solvent was evaporated under reduced pressure and the

crude was purified using column chromatography (MeOH:DCM, 10%). UPLC–MS calculated $[M + H]^+$: 409.1, found: 409.0.

Compound 1.11:

[0325] To a stirred solution of compound 1.8 (1 eq), compound 12 (1 eq), and L-ascorbate in tert-butanol: water (1:1) at room temperature, CuSO₄ was added, and the mixture was stirred for another 4 hr. After completion of the reaction, compound was purified using reverse phase chromatography (Acetonitrile:H₂O). UPLC–MS calculated $[M + H]^+$: 879.3, found: 879.4.

Compound 1.12:

[0326] Compound 1.11 was dissolved in DCM and 4 (N) HCl in dioxane was added to it at room temperature. The mixture was stirred for another 1 hr. After completion of the reaction solvent was evaporated and the crude product was used for the next step. UPLC–MS calculated $[M + H]^+$: 779.4, found: 779.5.

Compound 1.14:

[0327] To a stirred solution of compound 1.12 (1 eq), compound 1.13 (1 eq), and HATU (1 eq) in DMF at room temperature, DIPEA (1.5 eq) was added and the mixture was stirred for 10 min. The product was then purified using preparative HPLC (ACN:H₂O). UPLC–MS calculated $[M + H]^+$: 1130.5, found: 1130.5.

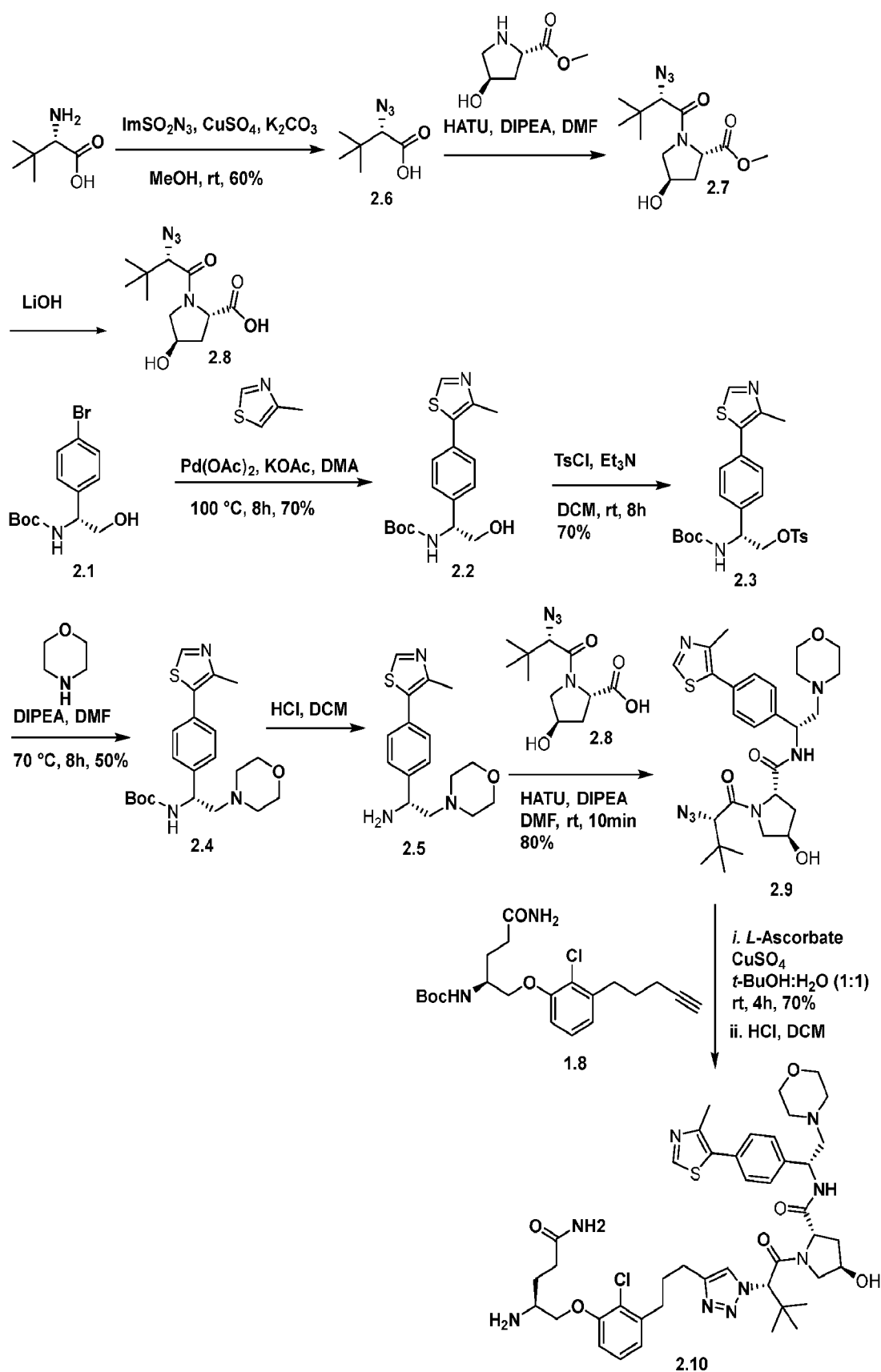
Compound 1.15:

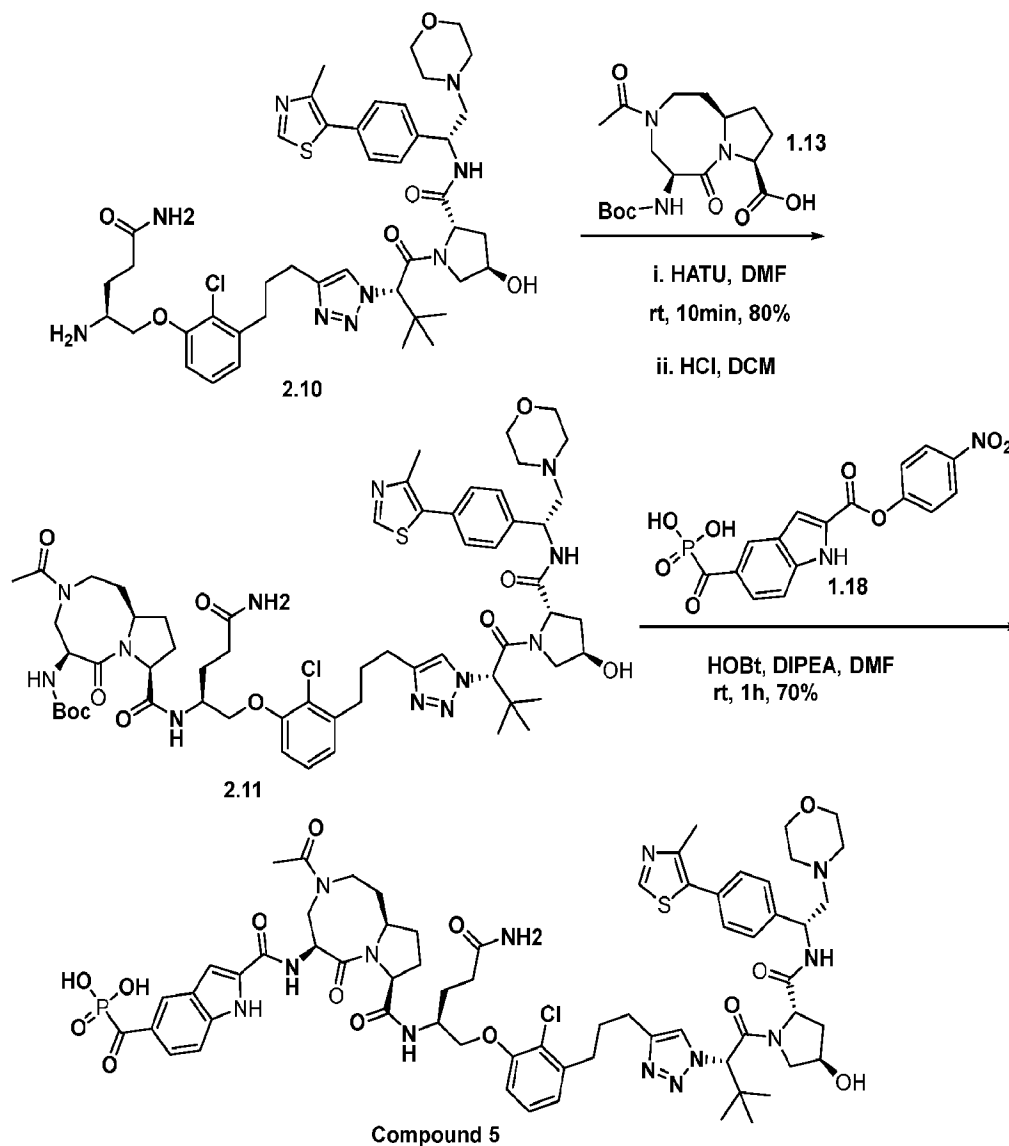
[0328] The compound 1.14 was dissolved in DCM and 4 (N) HCl in dioxane was added to it and stirred for an hour. After the completion of the reaction, organic solvent was evaporated under reduced pressure and the product was used for the next step. UPLC–MS calculated $[M + H]^+$: 1030.4, found: 1030.5.

Compound 1:

[0329] To a stirred solution of compound 1.15 (1 eq), compound 1.16 (1.1 eq), and HOBt (1 eq) in DMF at rt, DIPEA (1.5 eq) was added, and the mixture was stirred at rt for an hour. After completion of the reaction product was purified using preparative HPLC. UPLC–MS calculated $[M + 2H]^{2+}/2$: 641.2, found: 641.7

Compound 5. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)-2-morpholinoethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid





General procedure to make VHL ligand 2.9:

Compound 2.2:

[0330] To a stirred degassed solution of compound 2.1 (1 eq), 4-methylthiazole (2 eq), and KOAc (3 eq) in DMA at room temperature, Pd(OAc)₂ (0.05 eq) was added. The mixture was then heated to 100 °C using heating oil bath and stirred for overnight. After complete conversion of starting material (monitored by UPLC mass spectrography), the reaction was cooled to room temperature and diluted with water. The mixture was extracted with ethyl acetate and organic layer was washed with NaHCO₃ and brine and dried over Na₂SO₄. Solvent was evaporated and the product was purified using flash column chromatography. UPLC-MS calculated [M + H]⁺: 335.1, found: 335.2.

Compound 2.3:

[0331] To a stirred solution of compound 2.2 (1 eq) in DCM, triethyl amine (1.5 eq) and TsCl (1.2 eq), DMAP (0.1 eq) were added sequentially and the mixture was stirred for 8 h. After completion of the reaction, the mixture was extracted with DCM and water. Organic layer was washed with brine and dried over Na₂SO₄. The product was then purified using flash column chromatography. UPLC–MS calculated $[M + H]^+$: 489.1, found: 489.1.

Compound 2.4:

[0332] A mixture of compound 2.3 (1 eq), morpholine (5 eq), DIPEA (1.5 eq) in DMF was heated to 90 °C for 8 h. After complete conversion of starting material 2.3, the reaction mixture was cooled to room temperature and diluted with water and extracted with ethyl acetate. The product was purified using flash column chromatography. UPLC–MS calculated $[M + H]^+$: 404.1, found: 404.3.

Compound 2.5:

[0333] Compound 2.4 was dissolved in DCM and HCl in dioxane was added to it. The mixture was stirred in room temperature for 1 h. After completion of the reaction, solvent was evaporated under reduced pressure and the crude product was used for the next step. UPLC–MS calculated $[M + H]^+$: 304.1, found: 304.3.

Compound 2.6:

[0334] To a stirred solution of (*s*)-2-Amino-3,3-dimethylbutanoic acid (1 eq), 1H-Imidazole-1-sulfonyl azide (1 eq), and CuSO₄ (0.1 eq) in methanol at 0 °C, K₂CO₃ (2 eq) was added portion wise. The mixture was warmed at room temperature and stirred for overnight. After the reaction was stirred for 16 h, it was diluted with water and acidified with 2 (N) HCl up to pH 5. Organic solvent was evaporated under reduced pressure and the mixture was extracted with ethyl acetate. Organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was used for the next step.

Compound 2.7:

[0335] To a stirred solution of crude product 2.6 (1 eq), H-Hyp-OMe HCl (1 eq), and HATU (1 eq) in DMF, DIPEA (1.5 eq) was added at room temperature and the mixture was stirred for 30min. The reaction mixture was diluted with water and extracted with ethyl acetate. The product was purified using reverse phase column chromatography (ACN:H₂O). UPLC–MS calculated $[M + H]^+$: 285.1, found: 285.1.

Compound 2.8:

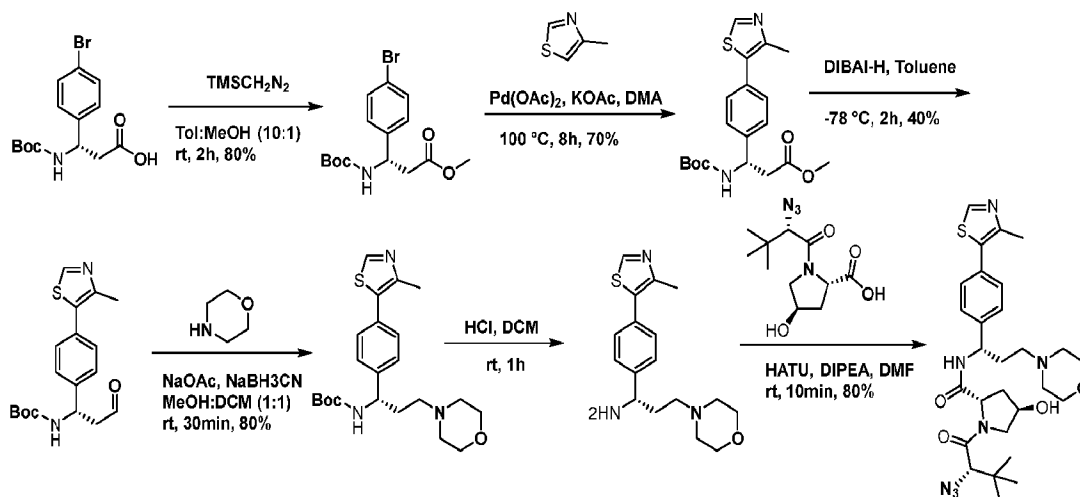
[0336] To a stirred solution of compound 2.7 (1 eq) in methanol: water (1:1), LiOH (2 eq) was added at room temperature and the mixture was stirred for another 2h. After completion of the reaction (monitored by UPLC mass), the mixture was acidified with 2 (N) HCl up to pH 5.

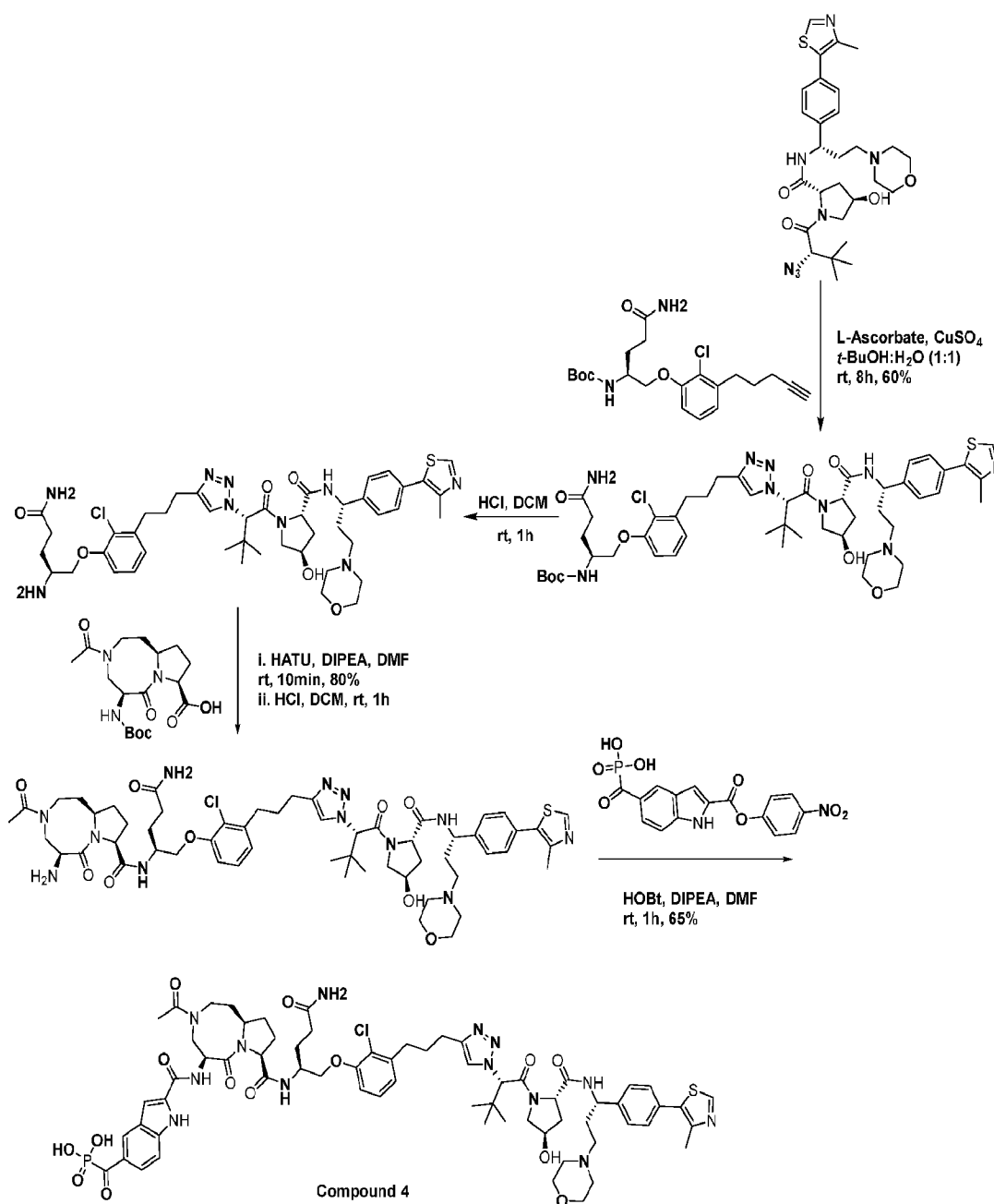
Organic solvent was evaporated under reduced pressure and the mixture was extracted with ethyl acetate for several times. Organic layer was evaporated under reduced pressure and the product was purified using reverse phase column chromatography. UPLC–MS calculated $[M + H]^+$: 271.1, found: 271.1.

Compound 2.9:

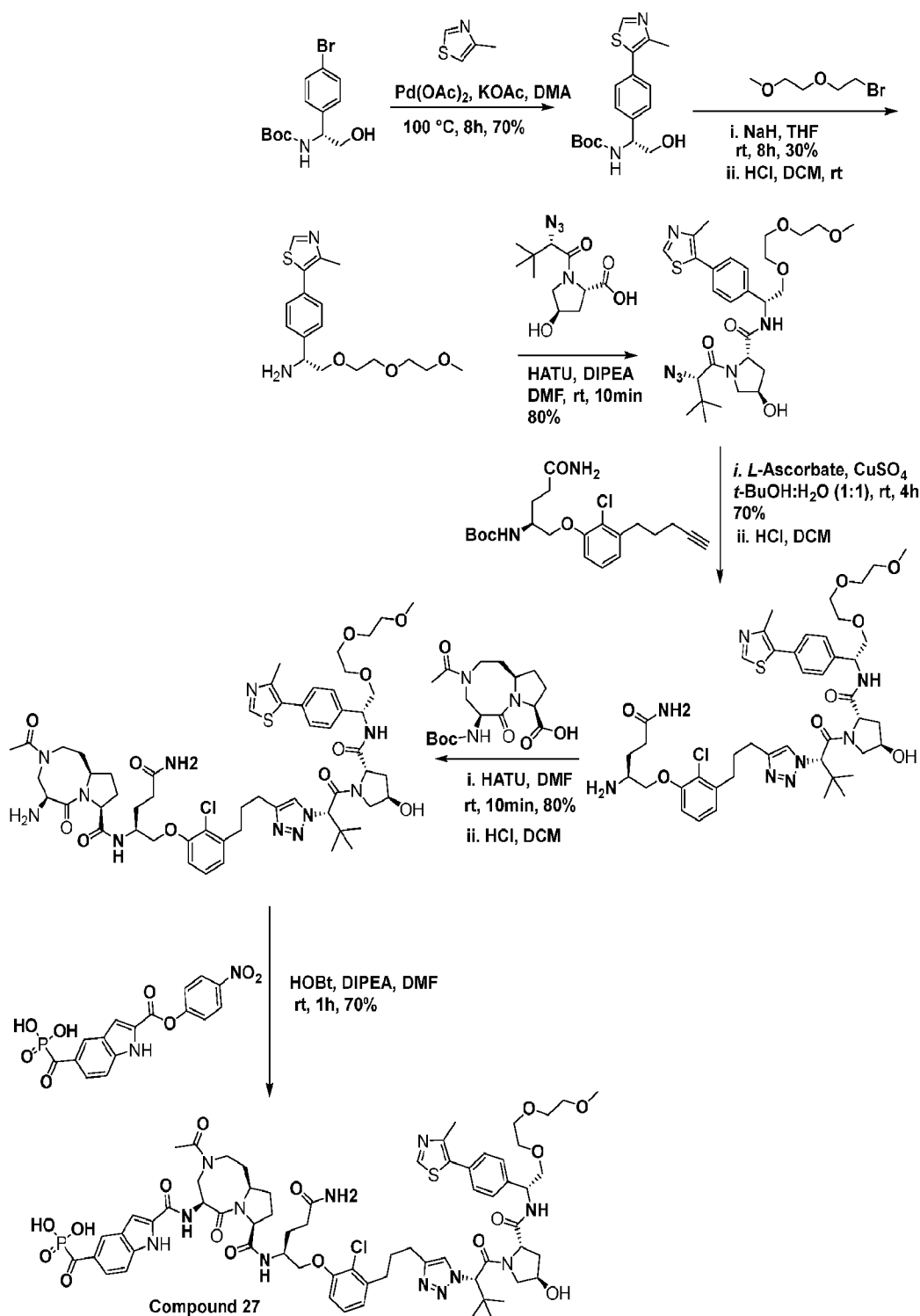
[0337] To a stirred solution of compound 2.8 (1 eq), 2.6 (1 eq), and HATU (1 eq) IN DMF, DIPEA was added at rt. The reaction was stirred for another 30 min at the same temperature. The product was purified using reverse phase column chromatography. UPLC–MS calculated $[M + H]^+$: 556.2, found: 556.3.

Compound 4. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)-3-morpholinopropyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid





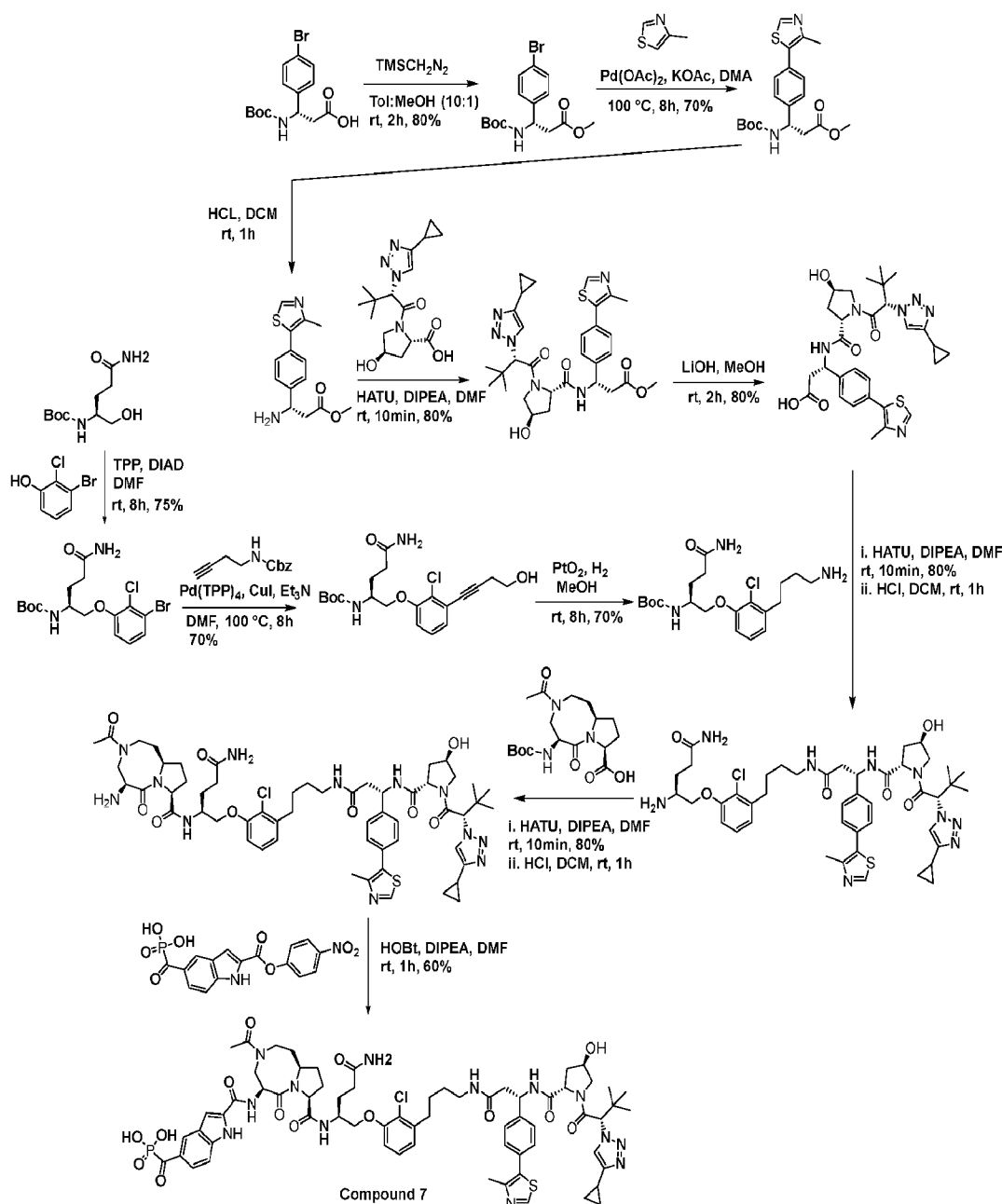
Compound 27. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-(((S)-1-((2S,4R)-4-hydroxy-2-(((R)-2-(2-(2-methoxyethoxy)ethoxy)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



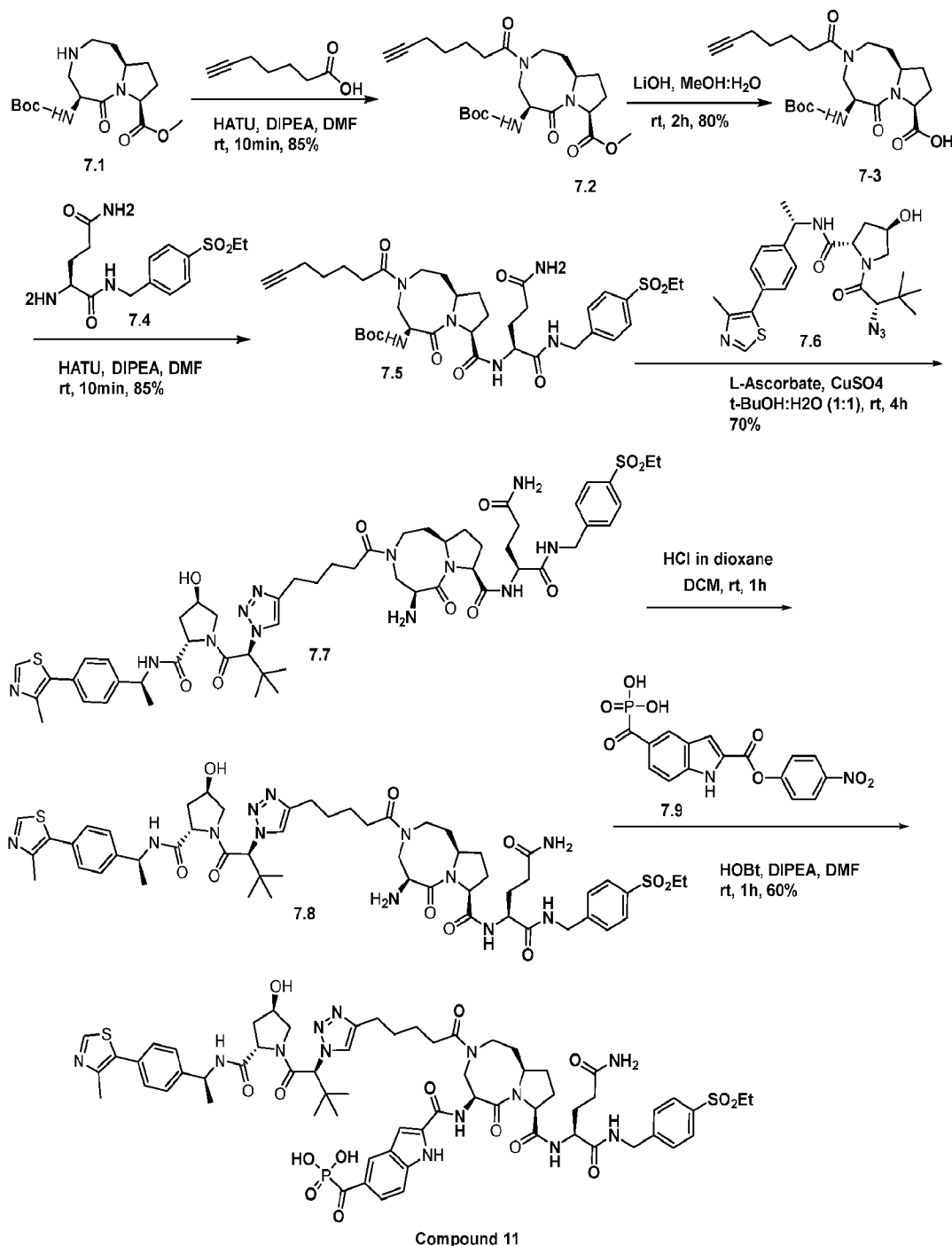
Compound 6. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((R)-2-((2S,4R)-1-((S)-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamido)-2-(4-(4-methylthiazol-5-yl)phenyl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



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Compound 11. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid

**Compound 7.2:**

[0338] A stirred solution of compound 7.1 (1 eq), 7-octynoic acid, (1 eq), and HATU (1 eq) in DMF, DIPEA was added. The mixture was stirred at rt for another 10 min. After completion of the reaction the product was purified using reverse phase column chromatography. UPLC-MS calculated $[M + H]^+$: 450.2, found: 450.3.

Compound 7.3:

[0339] To a stirred solution of 7.2 (1 eq) in methanol:water (1:1) at room temperature, LiOH (2 eq) was added and the mixture was stirred at the same temperature for another two hours.

After completion of the reaction, the mixture was acidified with 2 (N) HCl up to pH 5. Organic solvent was evaporated, and the crude was extracted with ethyl acetate. Crude product was purified using flash column chromatography. UPLC–MS calculated $[M + H]^+$: 436.2, found: 436.3.

Compound 7.5:

[0340] To a stirred solution of compound 7.3 (1 eq), compound 7.4 (1eq), and HATU (1 eq) in DMF, DIPEA was added, and the mixture was stirred at room temperature for another 10 min. After completion of the reaction product was purified using reverse phase column chromatography. UPLC–MS calculated $[M + H]^+$: 745.3, found: 745.4.

Compound 7.7:

[0341] To a stirred solution of compound 7.5 (1 eq), compound 7.6 (1 eq), and L-Ascorbate (2 eq) in t-butanol: water (1:1), CuSO₄, 5H₂O (1.5 eq) was added at room temperature. The mixture was stirred at rt for another 4 h to complete. The crude was filtered off and the product was purified using reverse phase column chromatography (ACN:H₂O). UPLC–MS calculated $[M + 2H]^+/2$: 608.2, found: 608.52.

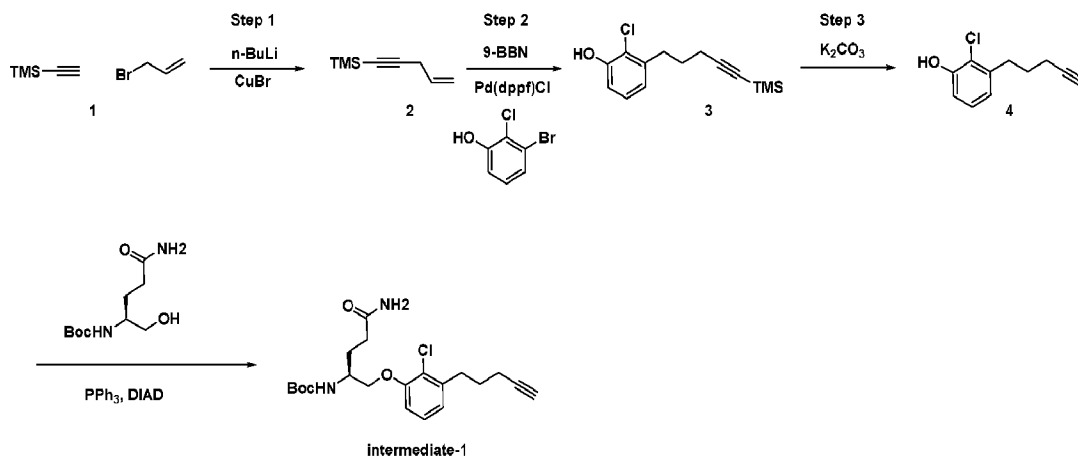
Compound 7.8:

[0342] The compound 7.7 was dissolved in DCM and 4 (N) HCl in dioxane was added to it and stirred for an hour. After the completion of the reaction, organic solvent was evaporated under reduced pressure and the product was used for the next step. UPLC–MS calculated $[M + H]^+$: 1115.5, found: 1115.7

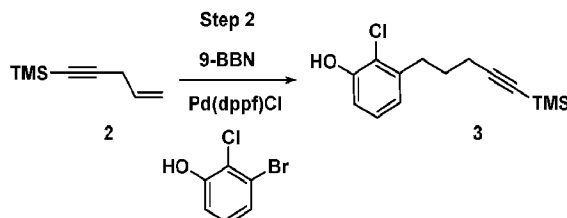
Compound 11:

[0343] To a stirred solution of compound 7.8 (1 eq), compound 7.9 (1.1 eq), and HOBt (1 eq) in DMF at rt, DIPEA (1.5 eq) was added, and the mixture was stirred at rt for an hour. After completion of the reaction product was purified using preparative HPLC. UPLC–MS calculated $[M + 2H]^{2+}/2$: 683.7, found: 684.0.

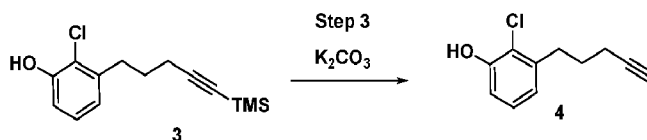
Synthesis of intermediate 1:



[0344] n-BuLi in hexanes (2.5m, 24 mL, 60 mmol) was added to a solution of trimethylsilylacetylene (5.6 mL, 40 mmol) in THF (30 mL) at -78°C. After stirring for 30 min at -78°C, CuBr (287mg, 2.0 mmol) and allyl bromide (5.5 mL, 64 mmol) were added. After stirring for 5 h at 50 °C, the reaction mixture was quenched with saturated aqueous NH₄Cl, extracted with ether, washed with brine, dried over MgSO₄, and concentrated. Column chromatography (silica gel, DCM/ether) afforded **2** (5.4g, 97.6%) as a colorless oil.



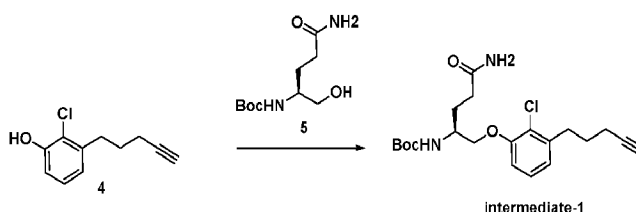
[0345] 9-BBN in THF (0.5m, 80 mL, 40 mmol) was added to neat **2** (5.4 gram, 39 mmol) at 0°C. After stirring overnight at rt. NaOH aq (5M, 32mL, 160mmol) was added and stir for 30min at rt. 3-bromo-2-chlorophenol (8.3g, 40mmol) and Pd(dppf)Cl₂ (1.63g, 2mmol) were added and stir at 60°C for 1 hour, the reaction mixture was quenched with saturated aqueous NaHCO₃, extracted with EA, washed with brine, dried over MgSO₄, and concentrated. Column chromatography (silica gel, hexanes/EA) afforded **3** (7.5g, 72%) as a pale yellow oil.



[0346] K₂CO₃ (11.2g, 84 mmol) was added to a solution of **3** (7.5 gram, 28 mmol) in MeOH (140mL) at rt. Detect the reaction by TLC. The reaction mixture was quenched with saturated aqueous NH₄Cl, remove almost MeOH by evaporator rotary. Extracted with EA, washed with

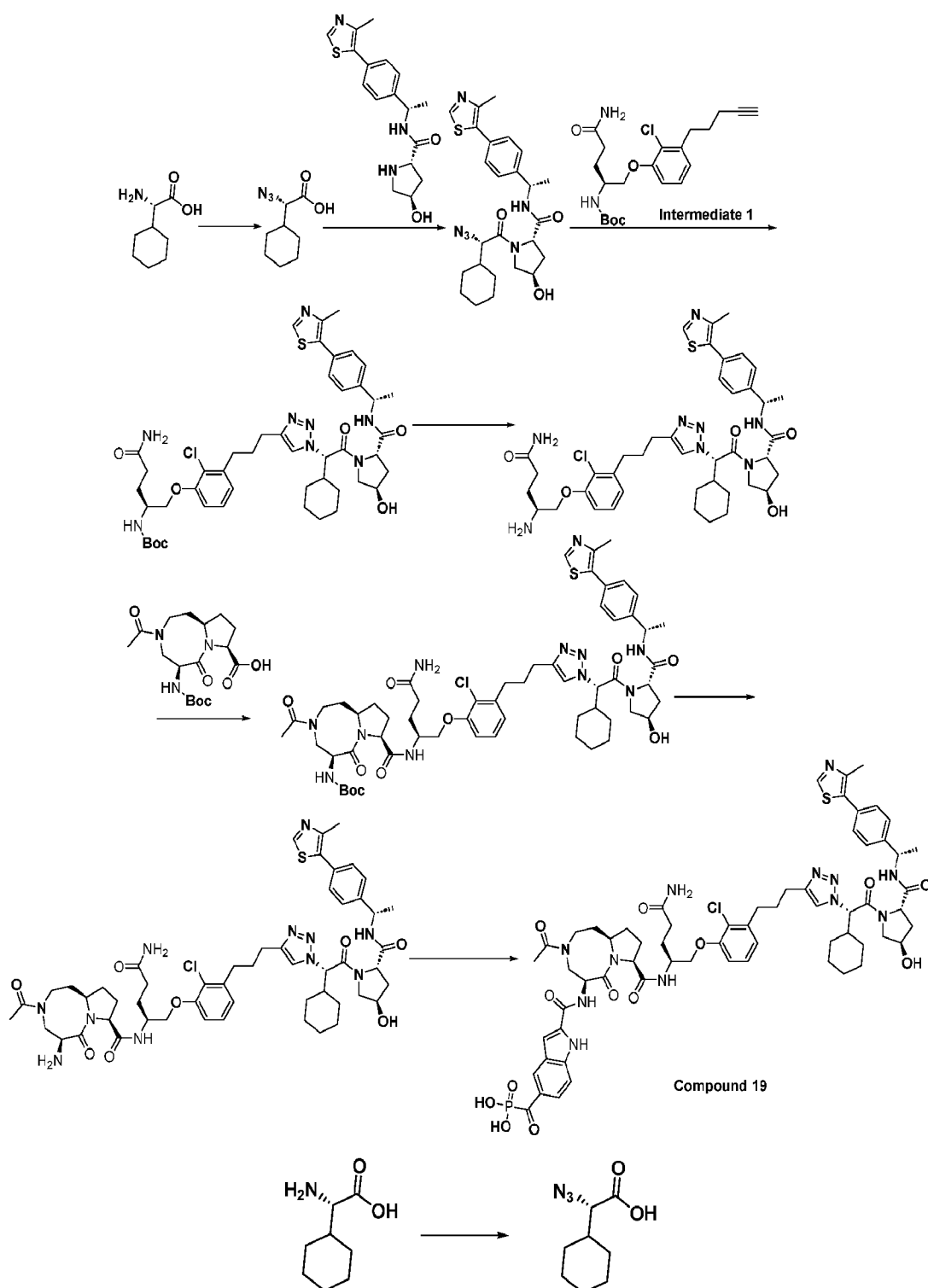
brine, dried over MgSO_4 , and concentrated. Column chromatography (silica gel, hexanes/EA) afforded **4** (4.2 g, 77%) as a pale yellow oil.

[0347] **Compound 7**: DIAD (1.5 mmol) was added dropwise at 0 °C to the mixture of **5** (1 mmol), **6** (1 mmol) and PPh_3P (1.5 mmol) in THF (10 mL), and the mixture was stirred for 3 h at rt. The reaction mixture was concentrated and purified by reverse phase preparative HPLC. The obtained product was dissolved in DCM (20 mL), then trifluoroacetic acid (2 mL) was added slowly. After stirring for 5h at rt, the reaction mixture was evaporated to give the **11** without further purification. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 287.1, found: 287.6.



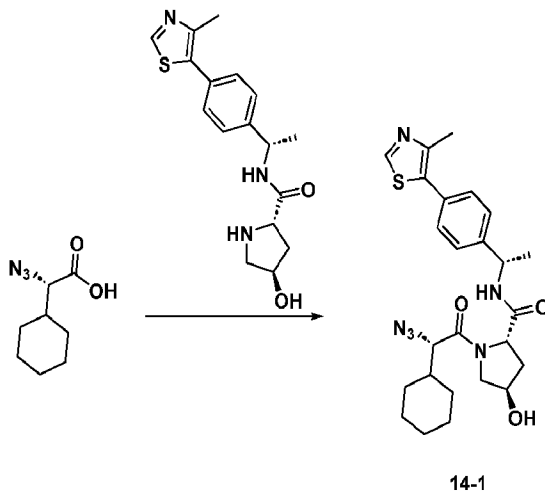
[0348] DIAD (1.5 mmol) was added dropwise at 0 °C to the mixture of **4** (1 mmol), **5** (1 mmol) and PPh_3P (1.5 mmol) in THF (10 mL), and the mixture was stirred for 3 h at rt. The reaction mixture was concentrated and purified by reverse phase preparative HPLC. UPLC–MS calculated $[\text{M} + \text{H}]^+$: 409.2, found: 409.4.

Compound 19. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-1-cyclohexyl-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopent-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid:

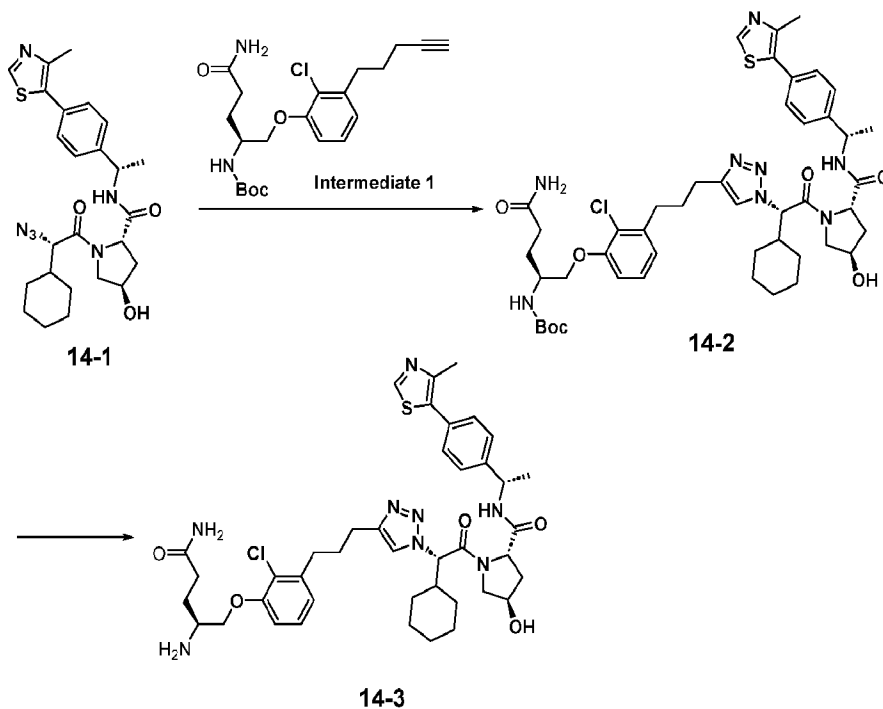


[0349] 1H-imidazole-1-sulfonyl azide (5 mmol) was added to a mixture of (S)-2-amino-2-cyclohexylacetic acid (5.0 mmol), potassium carbonate (12.5 mmol) and cupric sulfate (1 mmol) in methanol (10 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 10 h. After removing the solvent, 10% potassium bisulfate in water (10 mL) was added and extracted with ethyl acetate (100 mL). The organic layer was washed with brine, and dried over sodium sulfate.

The organic layer was concentrated to give crude (S)-2-azido-2-cyclohexylacetic acid which was used without further purification.

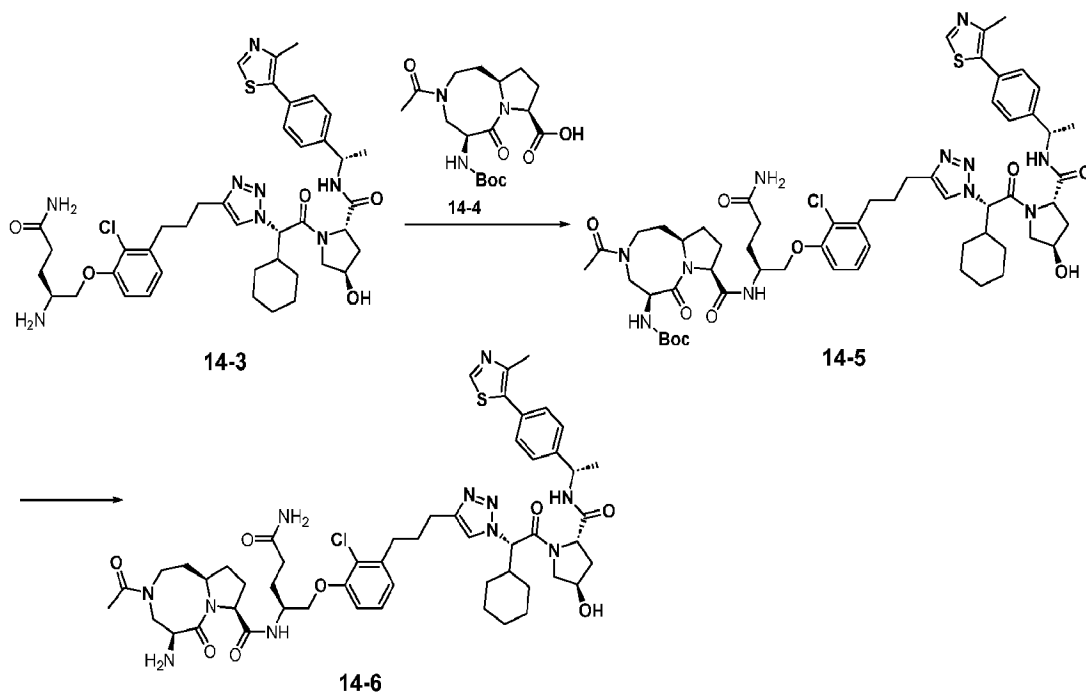


[0350] HATU (4.4 mmol, 1.1 equiv.) was added to a solution of the (S)-2-azido-2-cyclohexylacetic acid (4 mmol, 1 equiv.), (2S,4R)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (4, 1 equiv.) and DIEA (12 mmol, 3 equiv.) in DMF (20 mL) and the resulting mixture was stirred at rt for 1 h. The solution was diluted with EtOAc and washed with H₂O, saturated sodium bicarbonate aqueous solution and brine, and dried over sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel to afford 14-1. UPLC-MS calculated $[M + H]^+$: 497.2, found: 497.6.

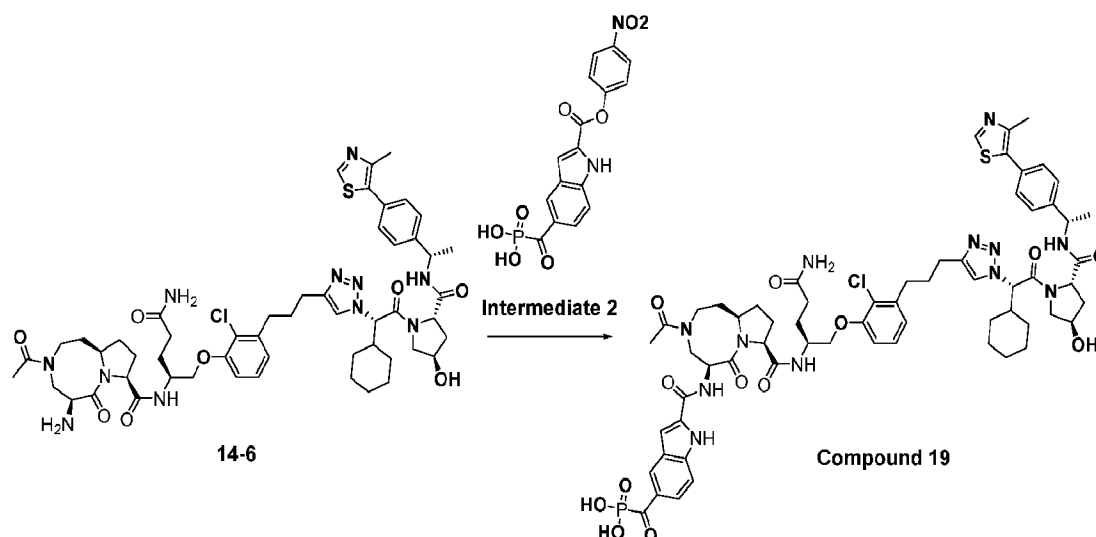


[0351] 14-1 (0.3 mmol), Copper sulfate (0.36 mmol) and Intermediate 1 (0.3 mmol) was added to a solution sodium L-ascorbate (0.9 mmol) in water (4 mL) and tert-Butyl alcohol (8 mL). The reaction was stirred at room temperature for 5 h and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure and the residue was purified by RP-HPLC to yield 14-2. UPLC-MS calculated $[M + H]^+$: 905.4, found: 905.8.

[0352] TFA (1 mL) was added slowly to a solution of the obtained 14-2 in DCM (5 mL) and the resulting reaction solution was stirred at rt for 2 h and then evaporated. The residue was used directly in the next step without further purification as. 14-3: UPLC-MS calculated $[M + H]^+$: 805.4, found: 805.7.

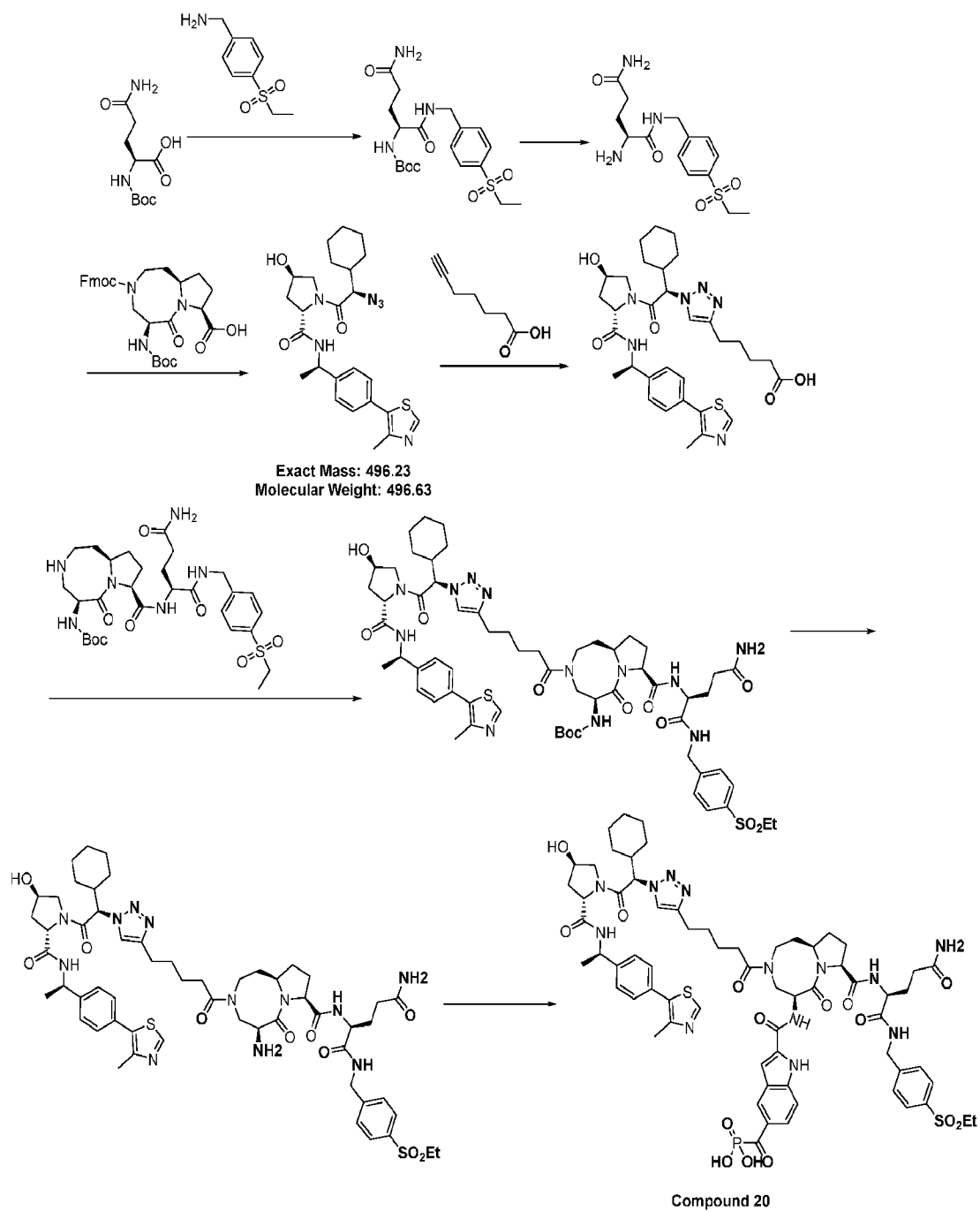


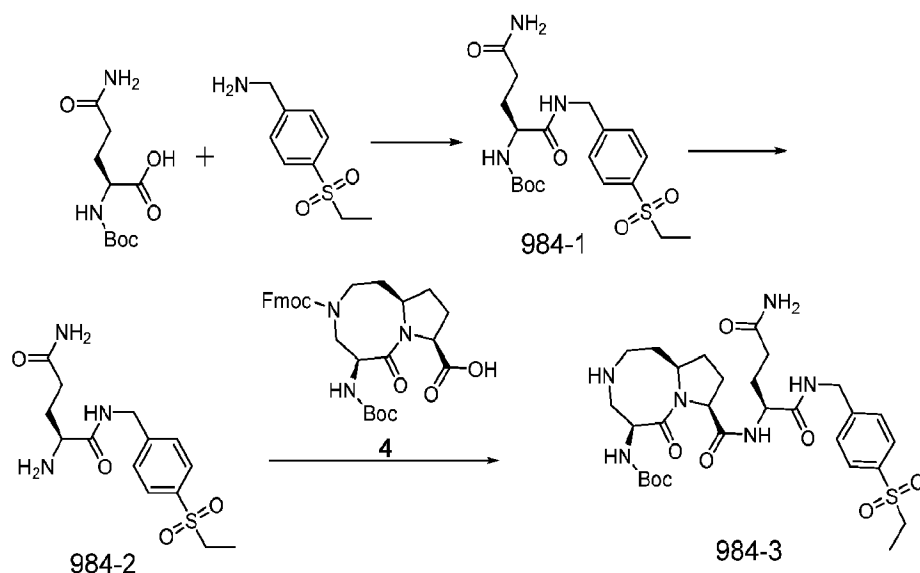
[0353] HATU (0.11 mmol, 1.1 equiv.) was added to a solution of the 14-3 (0.1 mmol, 1 equiv.), 14-4 (0.1 mmol, 1 equiv.) and DIEA (0.3 mmol, 3 equiv.) in DMF (2 mL) and the resulting mixture was stirred at rt for 1 h. This mixture was purified by reverse phase preparative HPLC. The obtained product was dissolved in DCM (5 mL), then trifluoroacetic acid (1 mL) was added slowly. After stirring for 5h at rt, the reaction mixture was evaporated to give the 14-6 without further purification. UPLC-MS calculated $[M + H]^+$: 1056.5, found: 1056.8.



[0354] DIEA (0.15mmol, 3 equiv.) was added to the mixture of Intermediate 2 (0.06 mmol, 1.2 equiv.), compound 14-6 (0.05 mmol, 1 equiv.) and HOBt (0.1 mmol, 2 equiv.) in DMF (3 mL). The resulted mixture was stirred at room temperature for 1 hour. Purification of this reaction mixture by HPLC gave the **Compound 19**. UPLC–MS calculated $[M + 2H]^{2+}$: 654.2, found: 654.8.

Compound 20. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-1-cyclohexyl-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid:

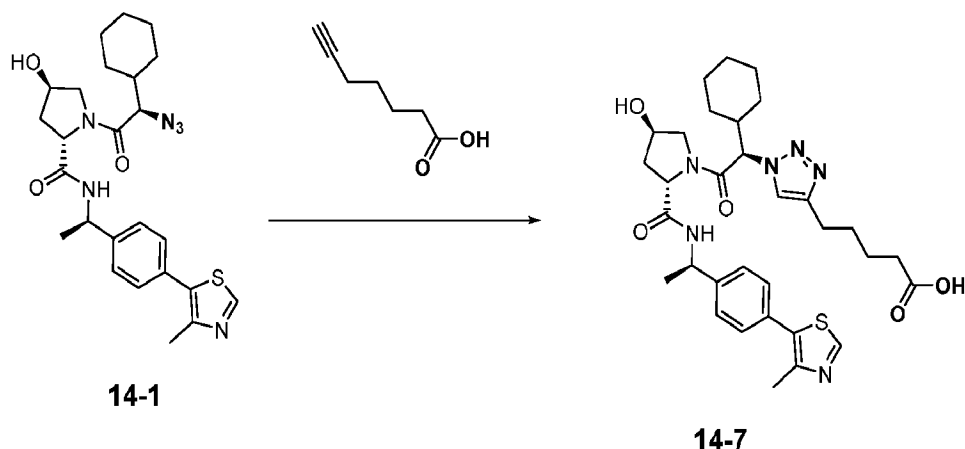




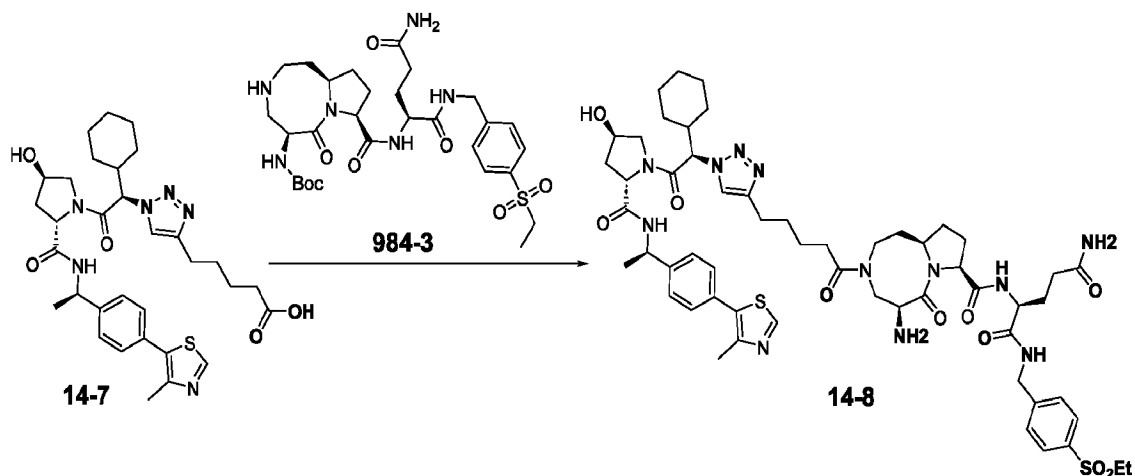
[0355] **984-1**: HATU (8.5 g, 22.3 mmol, 1.1 equiv.) was added to a solution of the Boc-Gln-OH (20.3 mmol, 1 equiv.), (4-(ethylsulfonyl)phenyl)methanamine (20.3 mmol, 1 equiv.) and DIEA (10.6 mL, 60.9 mmol, 3 equiv.) in DMF (60 mL) and the resulting mixture was stirred at rt for 1 h. The solution was diluted with EtOAc and washed with H₂O, saturated sodium bicarbonate aqueous solution and brine, and dried over sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel to afford 984-1. UPLC-MS calculated [M + H]⁺: 428.2, found: 428.7.

[0356] **984-2**: TFA (5 mL) was added slowly to a solution of 984-1 (3 g) in DCM (50 mL) and the resulting reaction solution was stirred at rt for 6 h and then evaporated. The residue was used directly in the next step without further purification. UPLC-MS calculated [M + H]⁺: 328.1, found: 328.5.

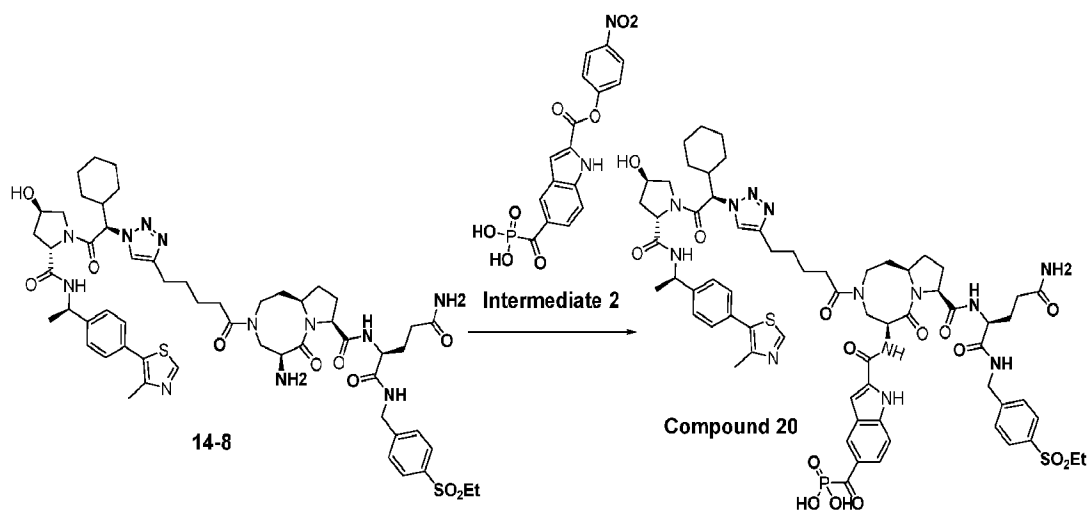
[0357] **984-3**: HATU (0.55 mmol, 1.1 equiv.) was added to a solution of the 984-2 (0.5 mmol, 1 equiv.), **4** (0.5 mmol, 1 equiv.) and DIEA (1.5 mmol, 3 equiv.) in DMF (60 mL) and the resulting mixture was stirred at rt for 1 h. The solution was diluted with EtOAc and washed with H₂O, saturated sodium bicarbonate aqueous solution and brine, and dried over sodium sulfate. After removal of the solvent *in vacuo*, the residue was purified by flash chromatography on silica gel. The obtained product was dissolved in Acetonitrile (10 mL) and Diethylamine (0.5 mL) was added to the solution. The resulting mixture was stirred at rt for 20 min and the solvent was removed under vacuum. The residue was purified by HPLC to yield **984-3**. UPLC-MS calculated [M + H]⁺: 637.3, found: 637.5.



[0358] 14-1 (0.3 mmol), Copper sulfate (0.36 mmol) and hept-6-ynoic acid (0.3 mmol) was added to a solution sodium L-ascorbate (0.9 mmol) in water (4 mL) and tert-Butyl alcohol (8 mL). The reaction was stirred at room temperature for 5 h and extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure and the residue was purified by RP-HPLC to yield 14-7. UPLC-MS calculated $[M + H]^+$: 623.3, found: 623.4.

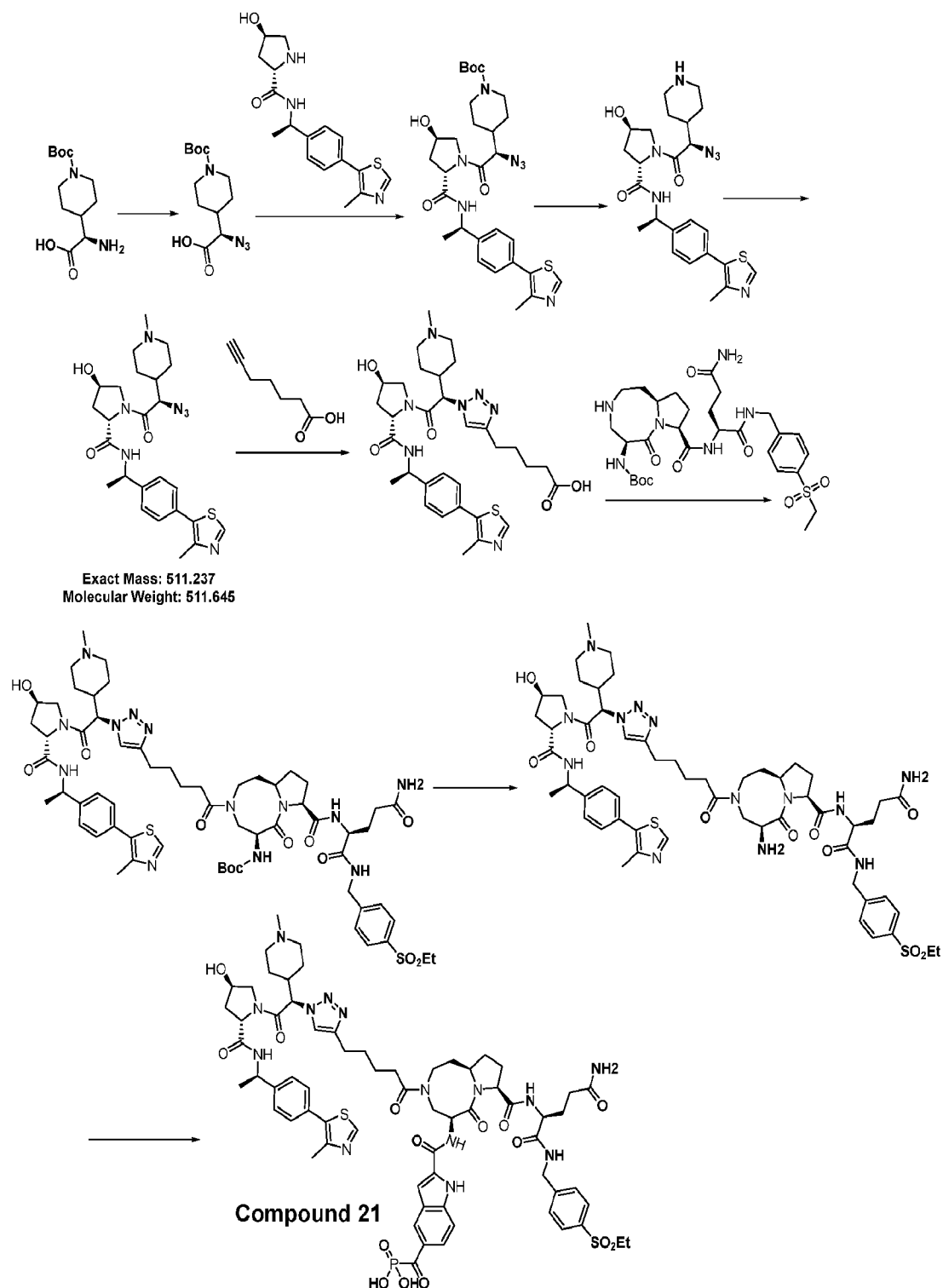


[0359] HATU (0.11 mmol, 1.1 equiv.) was added to a solution of **984-3** (0.1 mmol, 1 equiv.), **14-7** (0.1 mmol, 1 equiv.) and DIEA (0.3 mmol, 3 equiv.) in DMF (2 mL) and the resulting mixture was stirred at rt for 1 h. This mixture was purified by reverse phase preparative HPLC. The obtained product was dissolved in DCM (10 mL), then trifluoroacetic acid (1 mL) was added slowly. After stirring for 5h at rt, the reaction mixture was evaporated to give the **14-8** without further purification. UPLC-MS calculated $[M + H]^+$: 1141.5, found: 1141.4.



[0360] DIEA (0.15mmol, 3 equiv.) was added to the mixture of Intermediate 2 (0.06 mmol, 1.2 equiv.), compound 14-8 (0.05 mmol, 1 equiv.) and HOBT (0.1 mmol, 2 equiv.) in DMF (3 mL). The resulted mixture was stirred at room temperature for 1 hour. Purification of this reaction mixture by HPLC gave the **Compound 20**. UPLC–MS calculated $[M + 2H]^{2+}$: 696.8, found: 696.7.

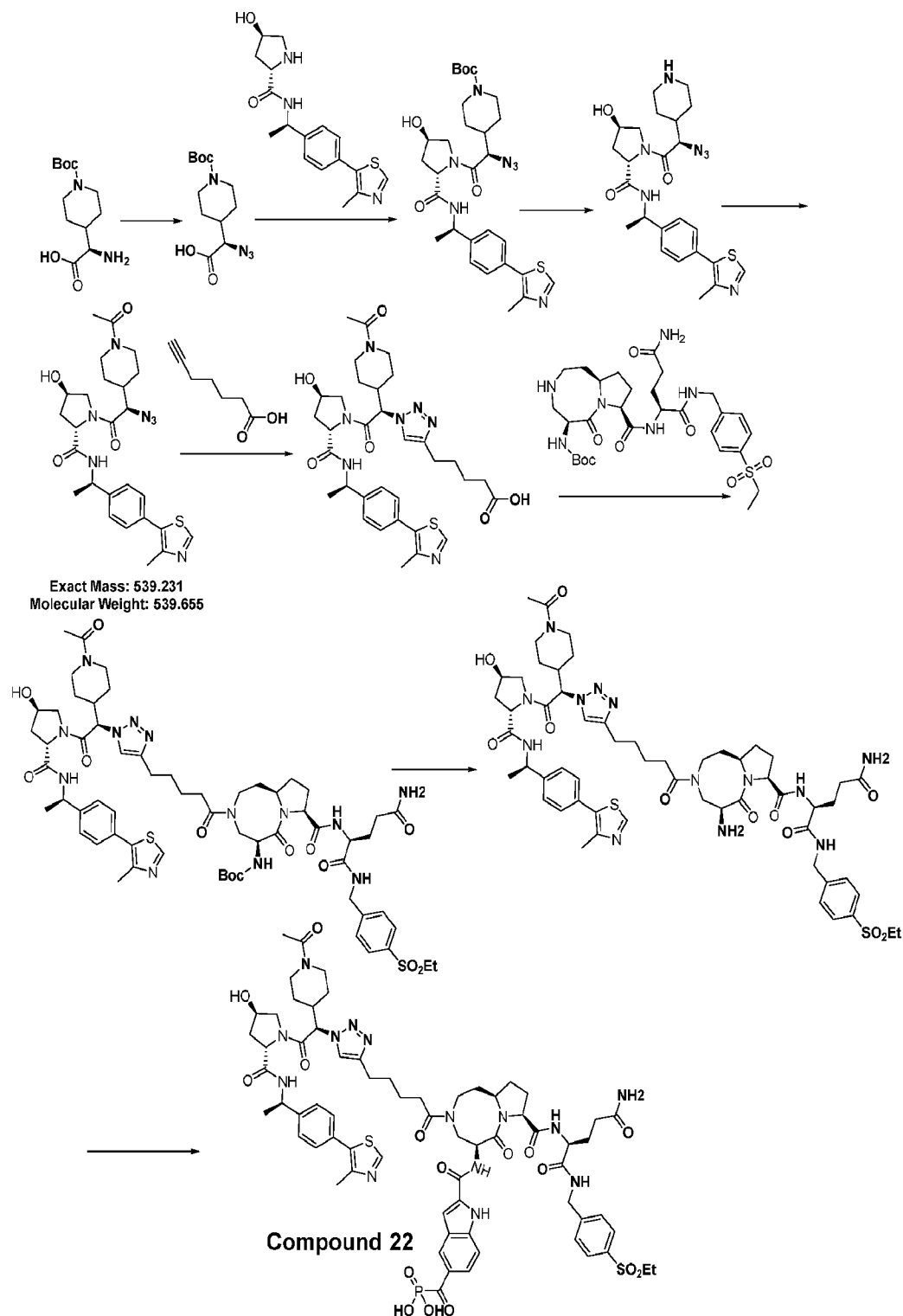
Compound 21. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-1-(1-methylpiperidin-4-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



[0361] **Compound 21** was synthesized by employing the similar procedures as **Compound 20** as shown above.

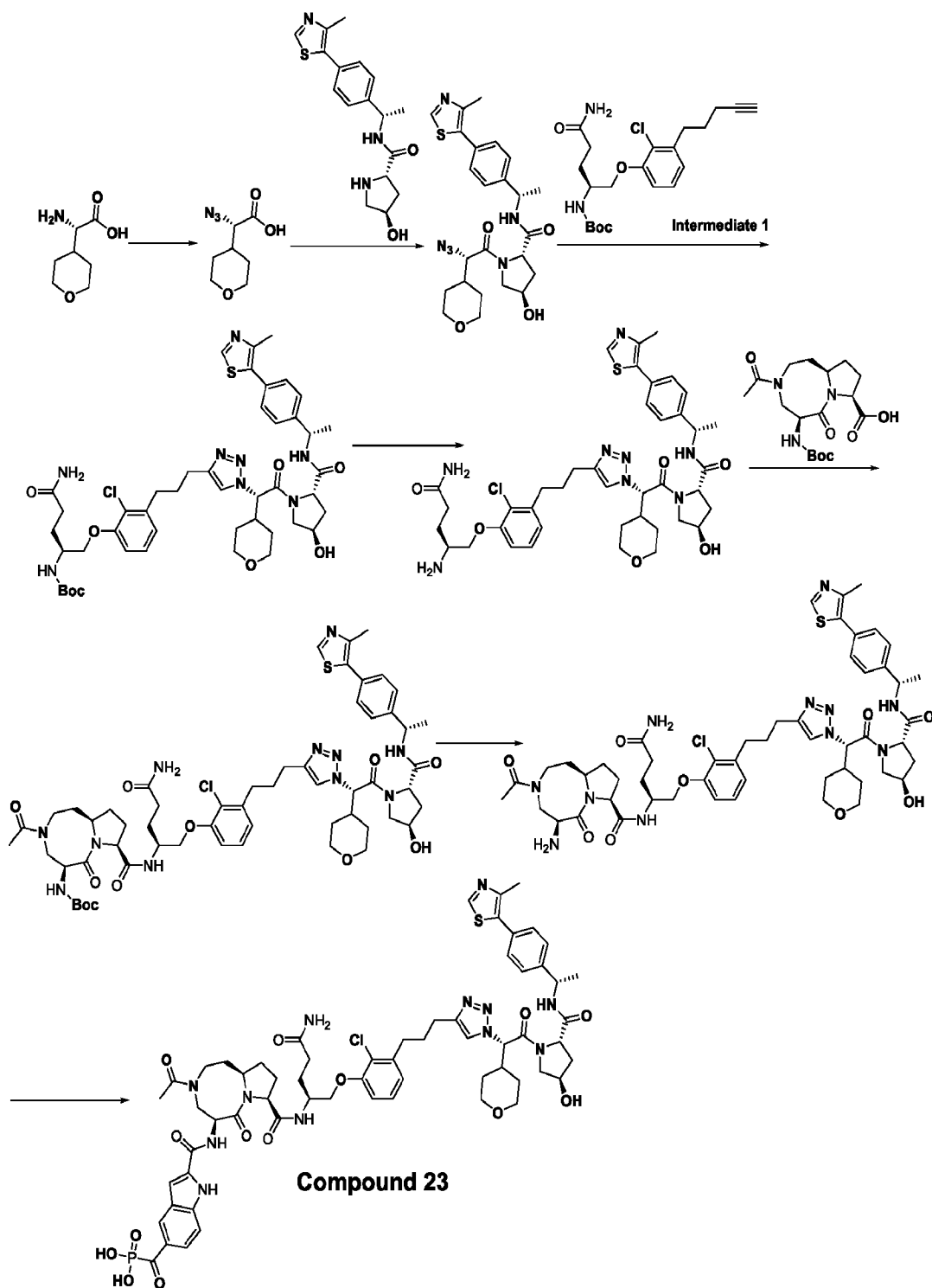
Compound 22. (2-(((5S,8S,10aR)-3-(5-(1-((R)-1-(1-acetylpiperidin-4-yl)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-8-(((S)-5-amino-1-((4-

(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



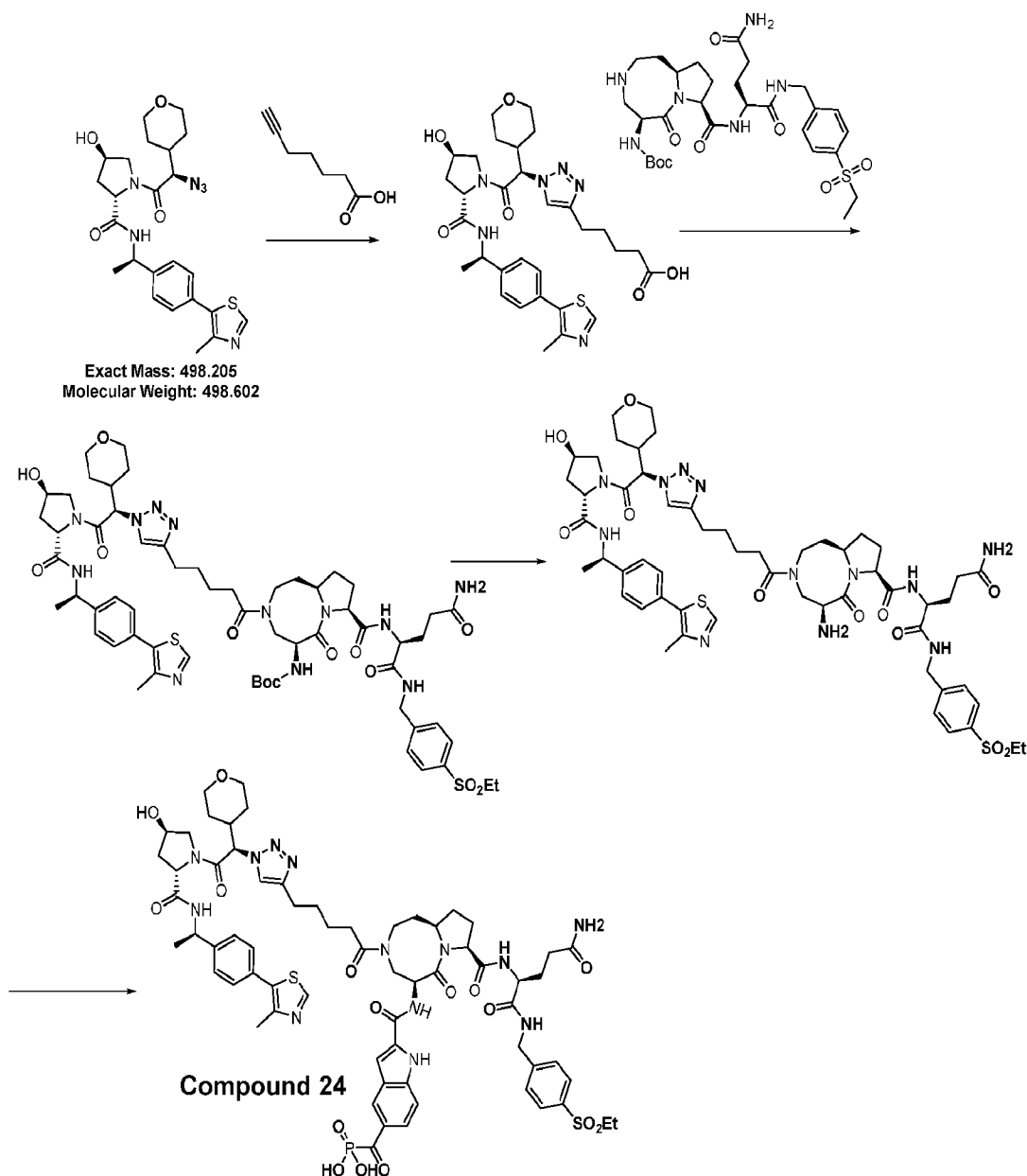
[0362] Compound 22 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 23. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(3-(1-((S)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



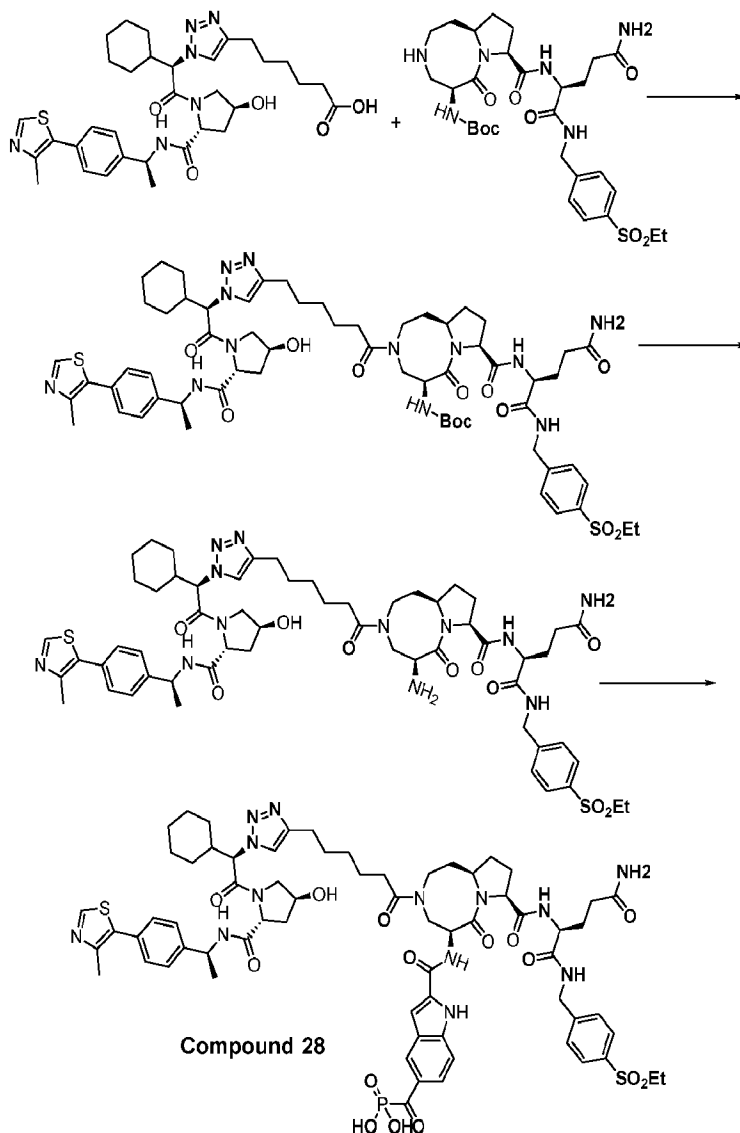
[0363] Compound 23 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 24. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(5-(1-((R)-2-((2S,4R)-4-hydroxy-2-(((R)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)pentanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



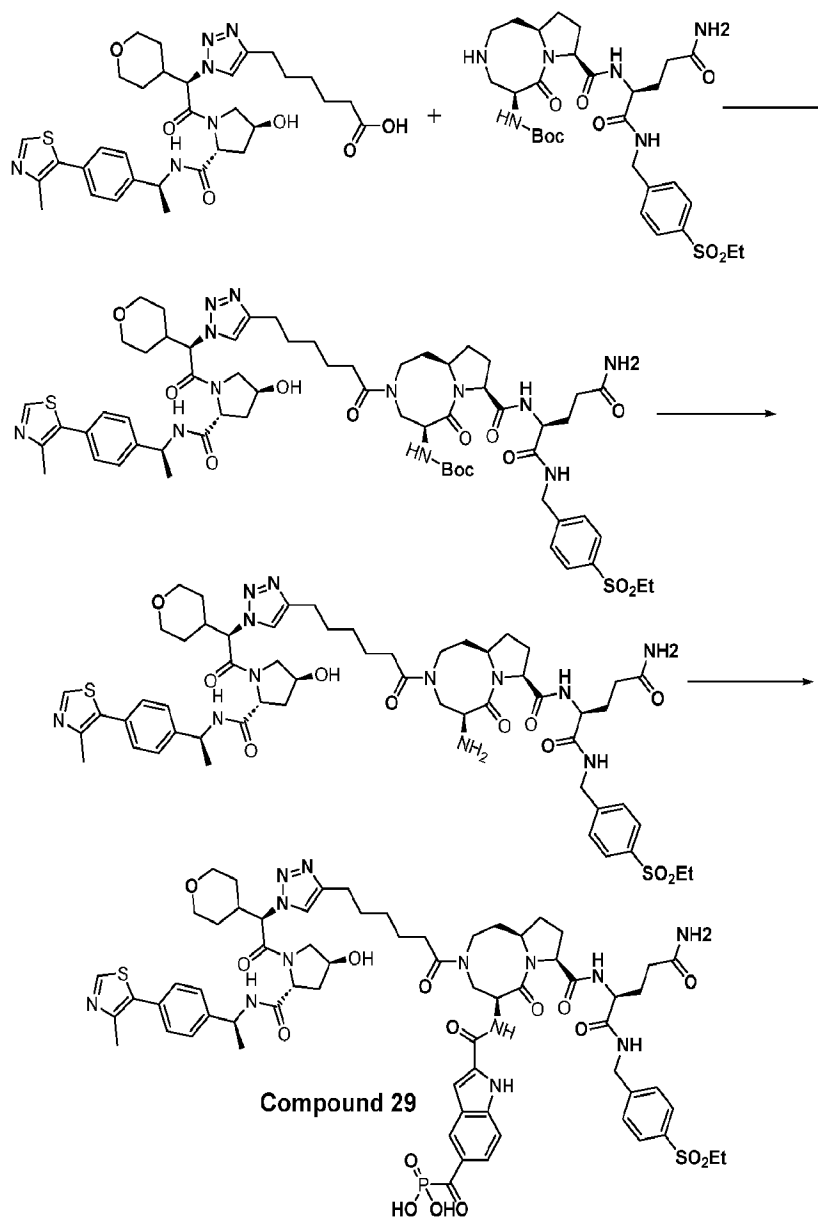
[0364] Compound 24 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 28. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((R)-1-cyclohexyl-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



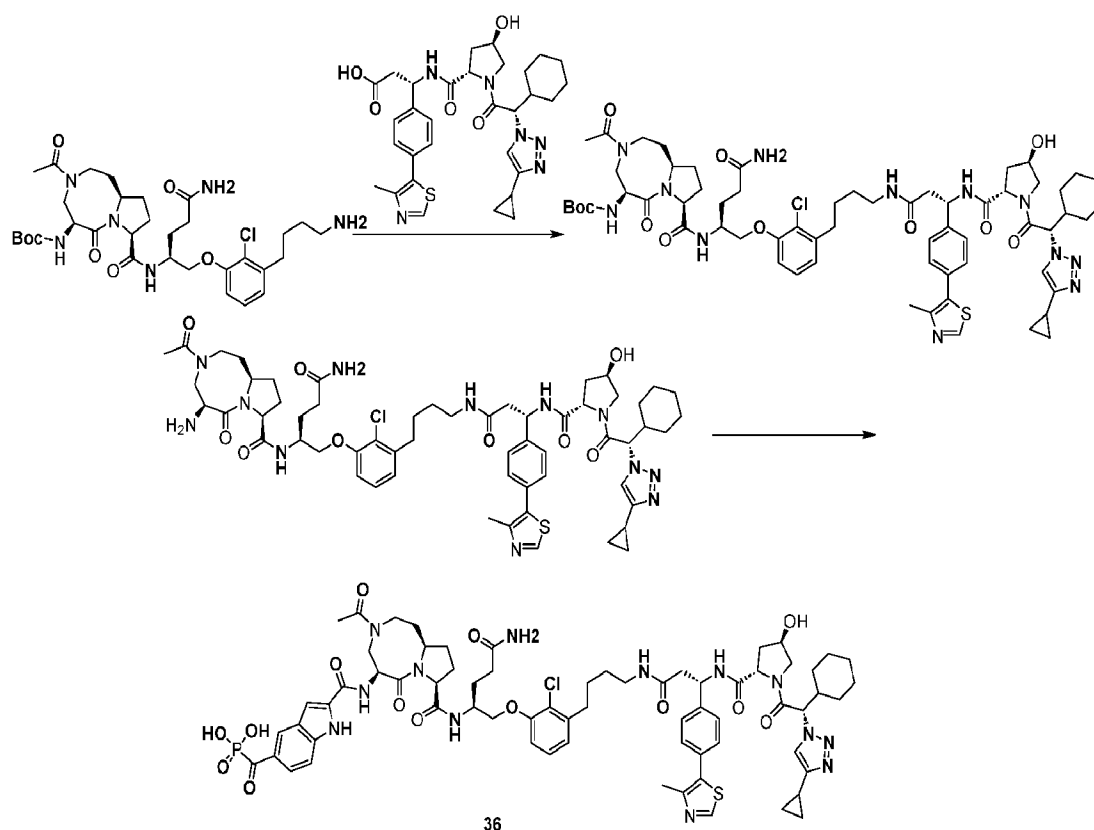
[0365] Compound 28 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 29. (2-(((5S,8S,10aR)-8-(((S)-5-amino-1-((4-(ethylsulfonyl)benzyl)amino)-1,5-dioxopentan-2-yl)carbamoyl)-3-(6-(1-((R)-2-((2R,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl)-1H-1,2,3-triazol-4-yl)hexanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



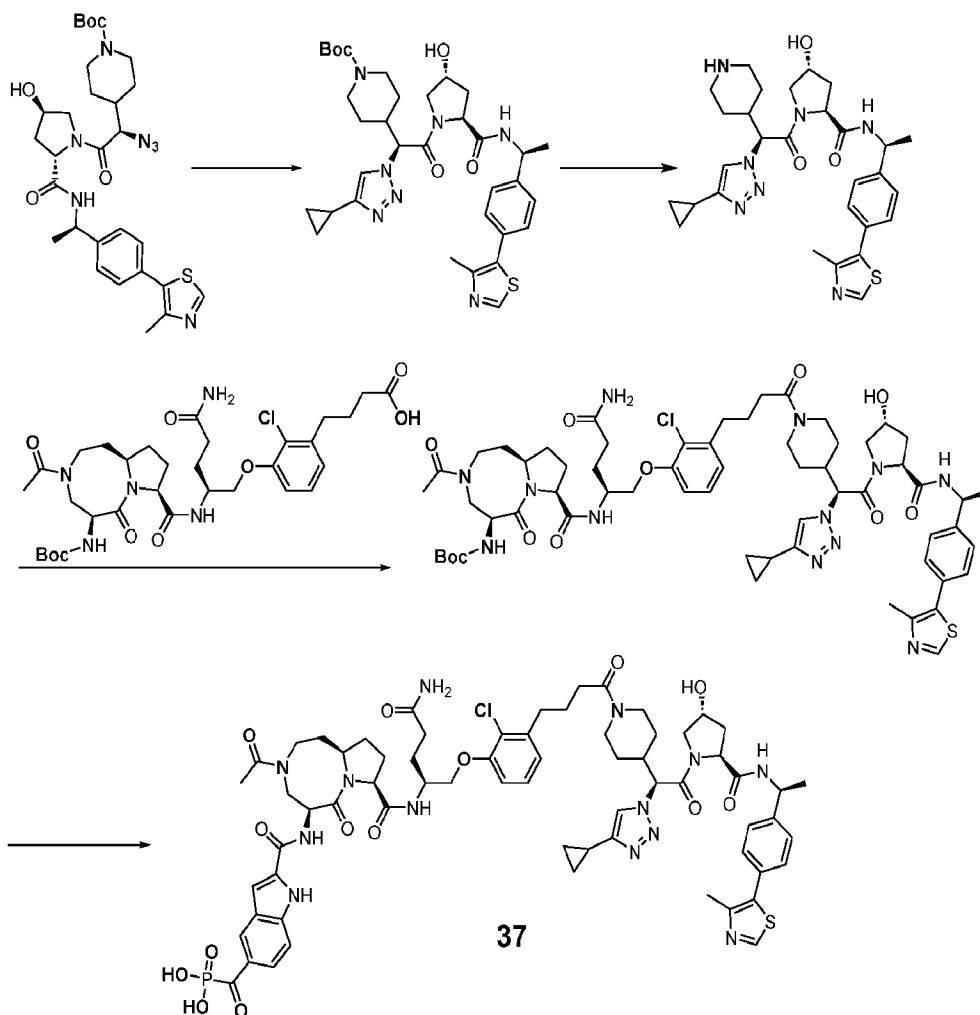
[0366] **Compound 29** was synthesized by employing the similar procedures as **Compound 20** as shown above.

Compound 36. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-(((S)-3-((2S,4R)-1-(((S)-2-cyclohexyl-2-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)acetyl)-4-hydroxypyrrolidine-2-carboxamido)-3-(4-(4-methylthiazol-5-yl)phenyl)propanamido)butyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid.



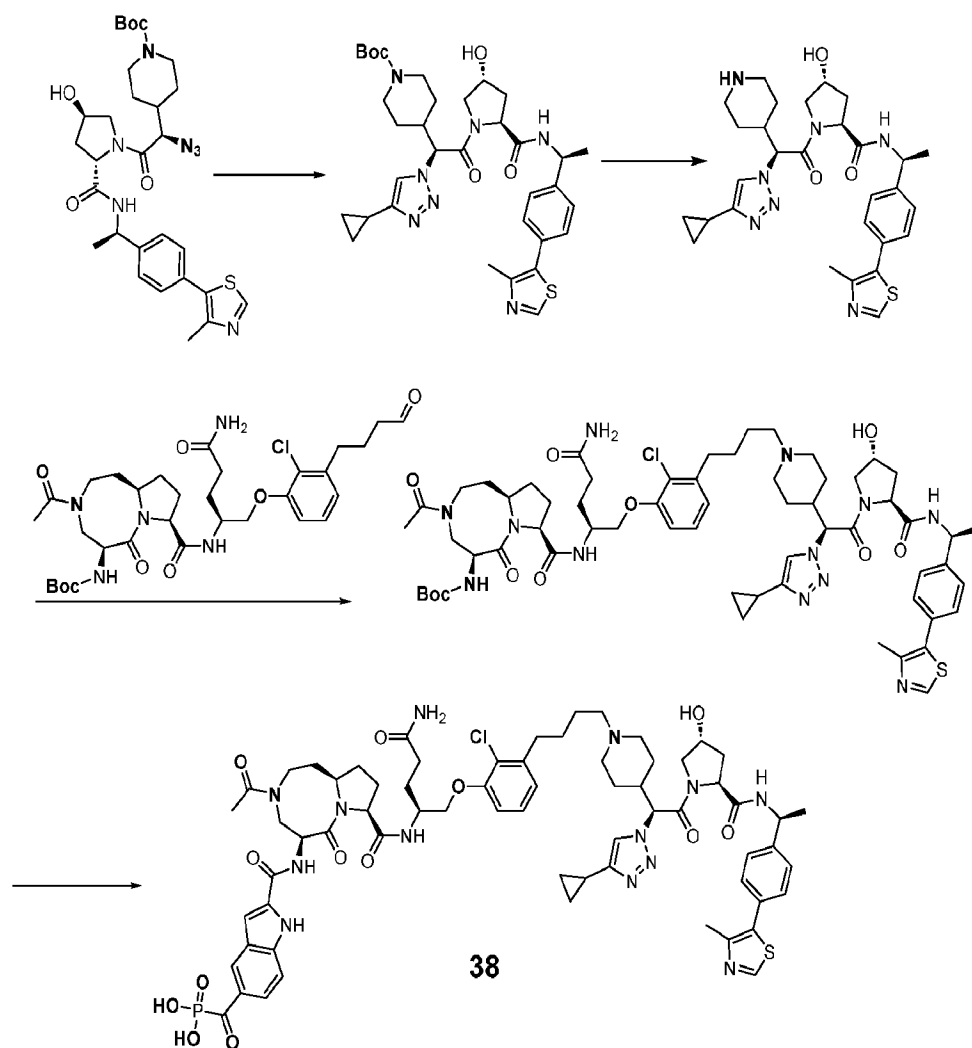
[0367] Compound 36 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 37. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-(4-((S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)piperidin-1-yl)-4-oxobutyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



[0368] Compound 37 was synthesized by employing the similar procedures as Compound 20 as shown above.

Compound 38. (2-(((5S,8S,10aR)-3-acetyl-8-(((S)-5-amino-1-(2-chloro-3-(4-(4-((S)-1-(4-cyclopropyl-1H-1,2,3-triazol-1-yl)-2-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-2-oxoethyl)piperidin-1-yl)butyl)phenoxy)-5-oxopentan-2-yl)carbamoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocin-5-yl)carbamoyl)-1H-indole-5-carbonyl)phosphonic acid



[0369] Compound 38 was synthesized by employing the similar procedures as Compound 20 as shown above.

Table E1. Mass Spec Data

Compound No.	Expected	Observed
	$[M+2H]^{2+}/2$	$[M+2H]^{2+}/2$
1	641.2	641.7
2	655.2	655.7
3	648.2	648.7
4	690.7	691.2
5	683.7	684.4
6	694.7	694.9
7	689.7	689.9
8	640.7	640.9

Compound No.	Expected	Observed
	$[M+2H]^{2+}/2$	$[M+2H]^{2+}/2$
9	647.7	648.1
10	654.7	654.9
11	683.7	684.0
12	641.2	641.4
13	675.7	675.9
14	690.5	690.7
15	697.7	697.8
16	726.2	726.4
17	733.15	733.6
18	696.5	696.7
19	654.2	654.8
20	696.8	696.7
21	704.3	704.2
22	718.3	718.7
23	655.2	655.6
24	697.8	697.9
25		
26	749.7	750.0
27	700.2	700.8
28	703.8	703.6
29	704.8	704.9
30	729.25	729.42
31	715.28	715.33
32	682.77	683.08
33	697.28	697.46
34	670.25	670.41
35	722.27	722.59
36	702.8	702.8

Compound No.	Expected	Observed
	$[M+2H]^{2+}/2$	$[M+2H]^{2+}/2$
37	688.8	688.9
38	681.8	681.7
39	649.25	649.51
40	749.7	750.0
41	700.2	700.8
42	703.8	703.6
43	704.8	704.9
44	660.71	660.95
45	771.80	772.08
46	642.7	642.9
47	649.7	650.1
48	656.7	657.1
49	663.7	664.3
50	670.7	671.1
51	677.7	678.1
52	684.7	685.1
53	691.7	692.1
54	654.7	654.9
55	661.7	662.1
56	668.7	669.0
57	675.7	676.0
58	682.7	683.1
59	689.7	690.1
60	696.7	697.1
61	703.7	704.1

II. Biological Assessment

In vitro Assay:

Cell Viability Assay

[0370] SU-DHL-1 and SUP-M2 cell viability was determined by CellTiter-Glo 2.0 Cell Viability Assay (Promega). SU-DHL-1 cell line was purchased from ATCC (Manassas, VA) and SUP-M2 (ACC-509) was purchased from DSMZ (Germany). RPMI 1640 medium and fetal bovine serum (FBS) were purchased from Gibco/Thermo Fisher Scientific. In a typical procedure, cells seeded at 1000 cells per well in 384-well white plates (Corning) were incubated with serially diluted compounds for 4 days at 37° C with 5% CO₂. At the end of treatment, CellTiter-Glo 2.0 was added to the wells and luminescence was acquired on TECAN SPARK plate reader. Untreated cells were used as control. Data points were fit with a four-parameter equation to generate a concentration-response curve. IC₅₀ values were calculated using a nonlinear regression analysis of the mean ± SD from triplicate.

HiBiT Assay

[0371] STAT3-HiBiT KI HeLa cell line was purchased from Promega. This cell line is a clone created by using CRISPR-Cas9 to fuse HiBiT to the 3' end of STAT3 in HeLa cells. DMEM medium and FBS were purchased from Gibco/Thermo Fisher Scientific. STAT3 degradation was determined based on quantification of luminescent signal using Nano-Glo HiBiT Lytic Detection System. In a typical procedure, cells seeded at 20000 cells per well in 96-well white plates (Corning) were incubated with serially diluted compounds for 24 hours at 37° C with 5% CO₂. At the end of treatment, Nano-Glo HiBiT Lytic Detection reagents was added to the wells and luminescence was acquired on TECAN SPARK plate reader. Untreated cells were used as control. Data points were fit with a four-parameter equation to generate a concentration-response curve. IC₅₀ values were calculated using a nonlinear regression analysis of the mean ± SD from triplicate.

Table E2.

Compound No.	STAT3 Degradation (HeLa 24h HiBiT)		Cell Viability IC ₅₀ (nM)	
	DC ₅₀ (nM)	D _{max} (@1 μM)	SU-DHL-1 (nM)	SUP-M2 (nM)
1	A	A	A	A
2	A	A	A	A
3	B	A	B	B
4	B	A	B	B
5	B	A	B	B
6	A	A	B	B

Compound No.	STAT3 Degradation (HeLa 24h HiBit)		Cell Viability IC50 (nM)	
	DC ₅₀ (nM)	D _{max} (@1 μM)	SU-DHL-1 (nM)	SUP-M2 (nM)
7	A	A	B	A
8	C	A	C	B
9	B	A	B	B
10	B	A	B	B
11	A	A	B	A
12	B	A	C	B
13	B	A	C	B
14	A	A	A	A
15	A	A	B	B
16	B	A	C	C
17	C	A	C	C
18	B	A	B	C
19	A	A	A	A
20	A	A	A	A
21	A	A		A
22	A	A		A
23	A	A	A	A
24	A	A	A	A
25	C	B	B	B
26	A	A		
27	A	A		
28	A	A		
29	A	A		
30	A	A	A	B
31	B	A	B	B
32	B	A	B	C
33	B	A	B	C

Compound No.	STAT3 Degradation (HeLa 24h HiBit)		Cell Viability IC50 (nM)	
	DC ₅₀ (nM)	D _{max} (@1 μM)	SU-DHL-1 (nM)	SUP-M2 (nM)
34	B	B		
35	B	A		B
36	A	A	A	A
37	C	B	D	B
38	C	B	D	B
39	A	A	A	A
40	B	A		B
41	B	A		B
42	A	A		
43	A	A		
44	A	A		
45	B	A		B
46	D		D	D
47	C		C	C
48	B		B	B
49	B		B	B
50	C		B	B
51	C		C	C
52	C		C	C
53	C		C	C
54	D		D	D
55	D		D	D
56	D		C	C
57	C		C	C
58	D		D	C
59	D		D	D
60	D		D	D

Compound No.	STAT3 Degradation (HeLa 24h HiBit)		Cell Viability IC ₅₀ (nM)	
	DC ₅₀ (nM)	D _{max} (@1 μM)	SU-DHL-1 (nM)	SUP-M2 (nM)
61	D		D	D

DC₅₀: A: < 10 nM; B: ≥10 nM and <100 nM; C: ≥100 nM and < 1000 nM ; D: ≥1000 nM.

D_{max}: A(>=80%), B(>=60% and <80%), C (>=40% and <60%), and D(<40%);

IC₅₀ for SU-DHL-1 and SUP-M2: A: < 10 nM; B: ≥10 nM and <100 nM; C: ≥100 nM and < 1000 nM ; D: ≥1000 nM.

INCORPORATION BY REFERENCE

[0372] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0373] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, and reference to “the cell” includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth.

[0374] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

CLAIMS

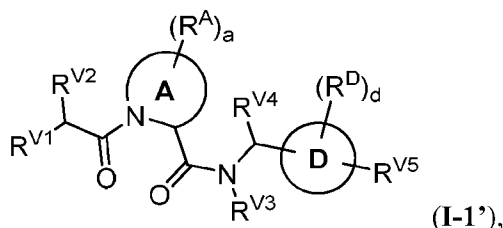
WHAT IS CLAIMED IS:

1. A compound of Formula I:

T-L-V (I),

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

V is of Formula **I-1'**



wherein:

Ring A is 5- to 7-membered heterocycle;

each R^A is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

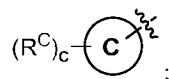
a is an integer selected from 0 to 10, as valency permits;

Ring D' is C₆ aryl or 5- to 6-membered heteroaryl;

each R^D is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

d is an integer selected from 0 to 4;

R^{V1} is $\text{---NR}^{V1'}$, ---O--- , or



$R^{V1'}$ is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

Ring C is C₆ aryl or 5- to 6-membered heteroaryl;

each R^C is independently $-\xi^{**}$, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

** denotes attachment to **L**;

c is an integer selected from 0 to 5, as valency permits;

R^{V2} is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

R^{V2} is C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is attached to **L** and optionally substituted with one or more R^u ;

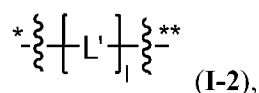
R^{V3} is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

R^{V4} is -(C₁₋₃ alkylene)-**; wherein the alkylene is optionally substituted with one or more R^u and ** denotes attachment to **L**; or

R^{V4} is hydrogen, C₁₋₆ alkyl, C₁₋₈ heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted with one or more R^u ; and

R^{V5} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

L is of Formula **I-2**



wherein:

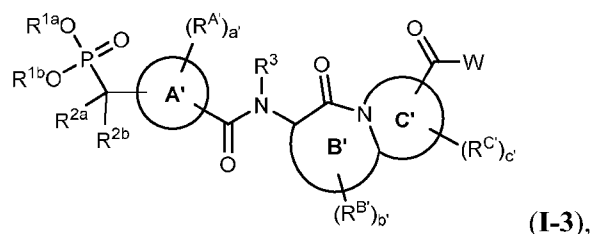
* denotes attachment to **T** and ** denotes attachment to **V**;

each L' is independently C₁₋₆ alkylene, C₁₋₆ heteroalkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₃₋₁₂ carbocyclylene, 3- to 12-membered heterocyclylene, C₆₋₁₀ arylene, 5- to 10-membered heteroarylene, -C(=O)-, -C(=O)N(R^{L'})-, -C(=O)O-, -N(R^{L'})-, -O-, -S-, or -S(=O)₂-, wherein the alkylene, alkenylene, carbocyclylene, heterocyclylene, arylene, or heteroarylene is optionally substituted with one or more R^u ;

each occurrence of $R^{L'}$ is independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

l is an integer selected from 0 to 6,

T is of Formula **I-3**



wherein:

R^{1a} and R^{1b} are independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

R^{2a} and R^{2b} are independently hydrogen or halogen;

R^{2a} and R^{2b} together form an oxo; or

R^{2a} and R^{2b} , together with the carbon atom to which they are attached, form C_{3-6} carbocycle or 3- to 6-membered heterocycle, wherein the carbocycle or heterocycle is optionally substituted with one or more R^u ;

Ring A' is C_{6-10} aryl or 5- to 10-membered heteroaryl;

each $R^{A'}$ is independently halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

a' is an integer selected from 0 to 6, as valency permits;

R^3 is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkenyl,

alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

Ring B' is 3- to 12-membered heterocycle;

each R^{B'} is independently $-\frac{s}{x}^*$, oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

* denotes attachment to L;

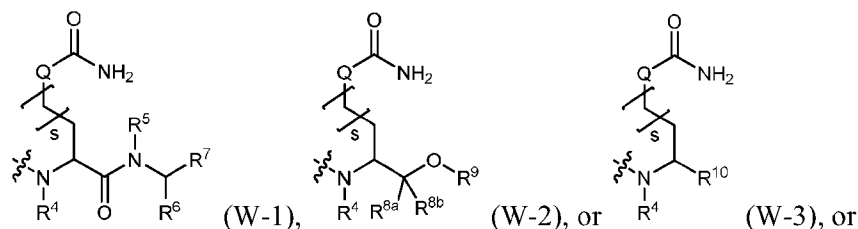
b' is an integer selected from 0 to 6, as valency permits;

Ring C' is 3- to 8-membered heterocycle;

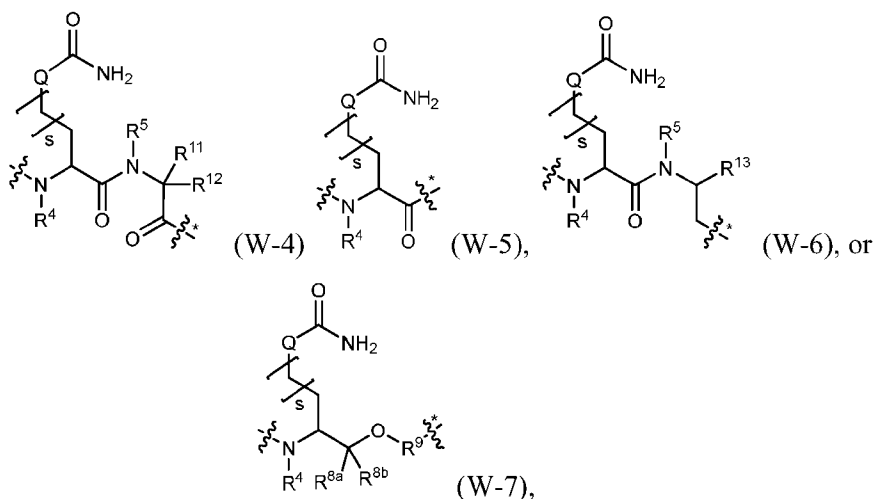
each R^{C'} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

c' is an integer selected from 0 to 6, as valency permits;

W is



W is



wherein:

* denotes attachment to **L**;

Q is absent; or

Q is $-\text{C}(\text{R}^Q)_2-$, $-\text{O}-$, and $-\text{N}(\text{R}^Q)-$;

each R^Q is independently hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{3-6} carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ; or

two R^Q , together with the carbon atom to which they are attached, form C_{3-6} carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

R^Q is hydrogen, C_{1-6} alkyl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

s is an integer selected from 0 to 4;

R^4 and R^5 are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^6 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a} ;

R^7 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{7a} ; or

R^7 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^{7b} ;

each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

or

R^6 and R^7 , together with the carbon atom to which they are attached, form C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkylamino, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

R^9 is C_{6-10} aryl or 5- to 10-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{9a} ;

each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -

- $C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{10} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ alkylamino, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{11} is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u ;
- R^{12} is hydrogen, C₁₋₆ alkyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -(C₁₋₆ alkylene)-(C₃₋₁₂ carbocyclyl), -(C₁₋₆ alkylene)-(3- to 12-membered heterocyclyl), -(C₁₋₆ alkylene)-(C₆₋₁₀ aryl), or -(C₁₋₆ alkylene)-(5- to 10-membered heteroaryl), wherein the alkyl, alkylene, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^{12a} ;
- each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;
- R^{11} and R^{12} , together with the carbon atom to which they are attached, form C₃₋₆ carbocyclyl or 3- to 6-membered heterocyclyl, wherein carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ; or
- R^{11} and R^5 , together with the intervening atoms, form 4- to 8-membered heterocyclyl optionally substituted with one or more R^u ; and
- R^{13} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ,

wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -

$S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl;

each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

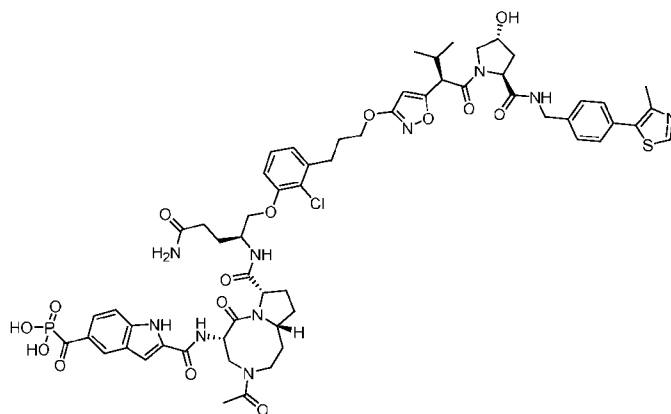
or

R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,

wherein each occurrence of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

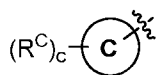
each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

2. The compound of claim 1, wherein the compound is not

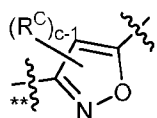


3. The compound of claim 1, wherein R^{V1} is $-NR^{V1}-\frac{5}{2}-^{**}$.

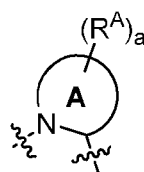
4. The compound of claim 1 or 2, wherein R^{V1} is



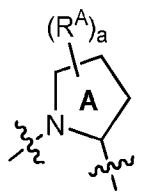
5. The compound of claim 4, wherein $(R^C)_c$ is not



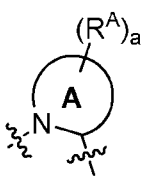
6. The compound of claim 4, wherein Ring C is not isoxazoly.
7. The compound of any one of claims 1-6, wherein Ring C is 5- to 6-membered heteroaryl comprising at least two nitrogen atoms.
8. The compound of claim 7, wherein Ring C is triazolyl.
9. The compound of claim 8, wherein Ring C is 1,2,3-triazolyl.
10. The compound of any one of claims 1-9, wherein c is 0.

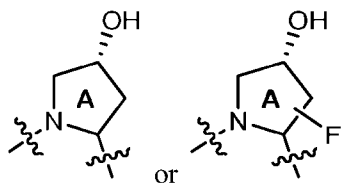


11. The compound of any one of claims 1-10, wherein

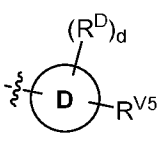


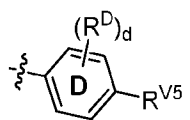
12. The compound of any one of claims 1-11, wherein a is 1 or 2, and at least one of R^A is -OH.

13. The compound any one of claims 1-12, wherein  is



14. The compound of any one of claims 1-13, wherein Ring D is phenyl.

15. The compound of claim 14, wherein  is



16. The compound of any one of claims 1-15, wherein d is 0 or 1.
17. The compound of any one of claims 1-16, wherein R^{V2} is 2-propyl or *t*-butyl.
18. The compound of any one of claims 1-16, wherein R^{V2} is 3- to 12-membered heterocyclyl attached to L and optionally substituted with one or more R^u .
19. The compound of any one of claims 1-16, wherein one R^C and R^{V2} , together with the intervening atoms, form 3- to 12-membered heterocyclyl optionally substituted with one or more R^u .
20. The compound of any one of claims 1-19, wherein R^{V3} is hydrogen.
21. The compound of any one of claims 1-20, wherein R^{V4} is hydrogen or methyl.

22. The compound of any one of claims 1-21, wherein R^{V5} is halogen or 5- to 6-membered heteroaryl optionally substituted with one or more R^u .
23. The compound of claim 22, wherein R^{V5} is thiazolyl.
24. The compound of any one of claims 1-23, wherein each L' is independently C_{1-6} alkylene, C_{1-6} heteroalkylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, $-C(=O)-$, $-C(=O)N(R^{L'})-$, $-C(=O)O-$, $-N(R^{L'})-$, $-O-$, or $-S(=O)_2-$, wherein the alkylene, heteroalkylene, carbocyclylene, or heterocyclylene is optionally substituted with one or more R^u , l is an integer selected from 1 to 4.
25. The compound of any one of claims 1-23, wherein L is C_{1-6} alkylene, C_{3-12} carbocyclylene, 3- to 12-membered heterocyclylene, $-C(=O)-$, $-N(R^{L'})-$, or $-O-$, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted with one or more R^u .
26. The compound of any one of claims 1-23, wherein L is C_{1-6} alkylene, $*(C_{1-6} \text{ alkylene})-N(R^{L'})-C(=O)-$, $*-C(=O)-(3\text{- to }12\text{-membered carbocyclylene})-$, $-O-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-O-$, $-N(R^{L'})-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-N(R^{L'})-$, $-C(=O)-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-C(=O)-$, $-C(=O)-(3\text{- to }12\text{-membered heterocyclylene})-$, $-(3\text{- to }12\text{-membered heterocyclylene})-C(=O)-$, $-(3\text{- to }12\text{-membered heterocyclylene})-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered heterocyclylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered carbocyclylene})-$, or $-(3\text{- to }12\text{-membered carbocyclylene})-(C_{1-6} \text{ alkylene})-$, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted with one or more R^u .
27. The compound of any one of claims 1-23, wherein L is C_{1-6} alkylene, $*(C_{1-6} \text{ alkylene})-N(R^{L'})-C(=O)-$, $*-C(=O)-(3\text{- to }12\text{-membered carbocyclylene})-$, $-(3\text{- to }12\text{-membered heterocyclylene})-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered heterocyclylene})-$, $-(3\text{- to }12\text{-membered carbocyclylene})-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered carbocyclylene})-$, $-(3\text{- to }12\text{-membered heterocyclylene})-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered carbocyclylene})-$, $-(3\text{- to }12\text{-membered carbocyclylene})-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered heterocyclylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered heterocyclylene})-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered carbocyclylene})-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered heterocyclylene})-(C(=O))-$, $-(C(=O))-(3\text{- to }12\text{-membered heterocyclylene})-(C_{1-6} \text{ alkylene})-$, $-(C_{1-6} \text{ alkylene})-(3\text{- to }12\text{-membered carbocyclylene})-(C(=O))-$, $-(C(=O))-(3\text{- to }12\text{-membered carbocyclylene})-$

(C₁₋₆ alkylene)-, -(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-(C(=O))-, -(C(=O))-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene)-, -(3- to 12-membered carbocyclylene)-(C₁₋₆ alkylene)-(C(=O))-, -(C(=O))-(C₁₋₆ alkylene)-(3- to 12-membered carbocyclylene)-, -(C₁₋₆ alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, -(3- to 12-membered heterocyclylene)-(C(=O))-(C₁₋₆ alkylene)-, -(C₁₋₆ alkylene)-(C(=O))-(3- to 12-membered carbocyclylene)-, -(3- to 12-membered carbocyclylene)-(C(=O))-(C₁₋₆ alkylene)-, -(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-(3- to 12-membered carbocyclylene), -(3- to 12-membered heterocyclylene)-C(=O)-(3- to 12-membered carbocyclylene), -(3- to 12-membered heterocyclylene)-O-(3- to 12-membered carbocyclylene), -(3- to 12-membered heterocyclylene)-N(R^L)-(3- to 12-membered carbocyclylene), -(3- to 12-membered carbocyclylene)-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene), -(3- to 12-membered carbocyclylene)-C(=O)-(3- to 12-membered heterocyclylene), -(3- to 12-membered carbocyclylene)-O-(3- to 12-membered heterocyclylene), -(3- to 12-membered carbocyclylene)-N(R^L)-(3- to 12-membered heterocyclylene), or -(C(=O))-(C₁₋₆ alkylene)-(C(=O))-, wherein the alkylene, carbocyclylene, or heterocyclylene is optionally substituted with one or more R^u.

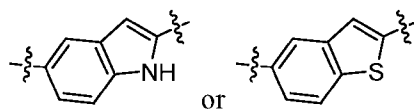
28. The compound of any one of claims 1-23, wherein L is C₁₋₆ alkylene, *(C₁₋₆ alkylene)-N(R^L)-C(=O)-, *-C(=O)-(3- to 12-membered carbocyclylene)-, *(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, *(3- to 12-membered heterocyclylene)-C(=O)-, *(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-(C(=O))-, *-C(=O)-(C₁₋₆ alkylene)-, *(C(=O))-(C₁₋₆ alkylene)-(C(=O))-, *(C₁₋₆ alkylene)-C(=O)-, C₁₋₆ alkylene, *-N(R^L)-(C₁₋₆ alkylene)-C(=O)-, or *-C(=O)-(3- to 12-membered carbocyclylene)-C(=O)-, wherein the alkylene, heterocyclylene, or carbocyclylene is optionally substituted with one or more R^u, and *denotes attachment to T.

29. The compound of any one of claims 1-28, wherein each R^L is hydrogen.

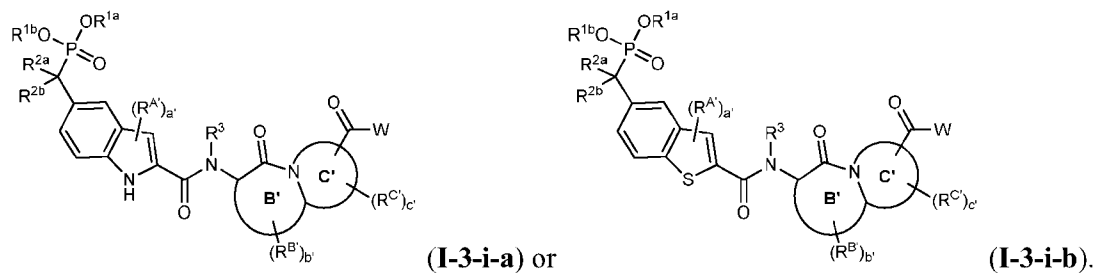
30. The compound of any one of claims 1-29, wherein Ring A' is 5- to 10-membered heteroaryl.

31. The compound of claim 30, wherein Ring A' is indolyl or benzo[b]thiophenyl.

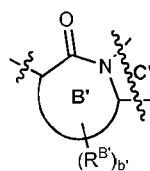
32. The compound of claim 31, wherein Ring A' is



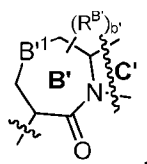
33. The compound of claim 1, wherein T is of Formula **I-3-i-a** or **I-3-i-b**



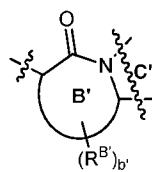
34. The compound of any one of claims 1-33, wherein Ring B' is 7- to 9-membered heterocycle.



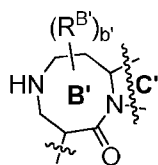
35. The compound of any one of claims 1-34, wherein



wherein B'¹ is -NHCH₂-, -CH₂NH-, or -CH₂CH₂-.

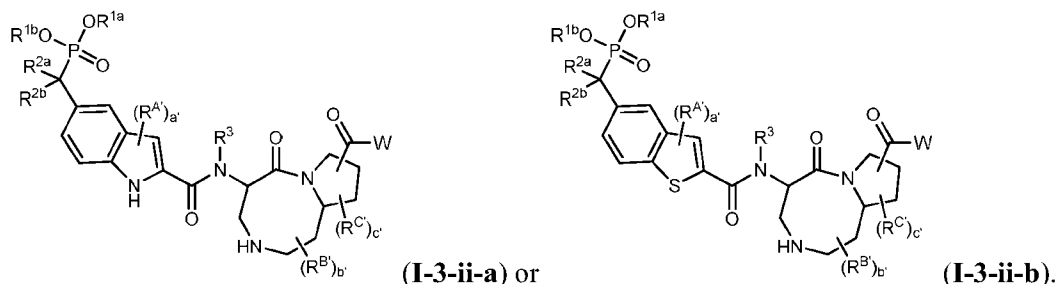


36. The compound of claim 35, wherein



37. The compound of any one of claims 1-36, wherein Ring C' is 4- to 7-membered heterocycle.

38. The compound of claim 1, wherein T is of Formula **I-3-ii-a** or **I-3-ii-b**



39. The compound of any one of claims 1-38, wherein R^{1a} and R^{1b} are both hydrogen.

40. The compound of any one of claims 1-39, wherein R^{2a} and R^{2b} are independently halogen.

41. The compound of claim 40, wherein R^{2a} and R^{2b} are both -F.

42. The compound of any one of claims 1-39, wherein R^{2a} and R^{2b} together form an oxo.

43. The compound of any one of claims 1-42, wherein each R^{A'} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

44. The compound of any one of claims 1-43, wherein a' is 0.

45. The compound of any one of claims 1-44, wherein R³ is hydrogen or C₁₋₆ alkyl.

46. The compound of any one of claims 1-45, wherein each R^{B'} is independently $-\frac{5}{2}$, oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₁₂ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-

membered heteroaryl, or $-C(=O)R^a$, wherein the alkyl, heteroalkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

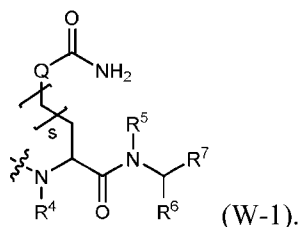
47. The compound of any one of claims 1-45, wherein each $R^{B'}$ is independently $-\xi^*$, C_{1-12} heteroalkyl, or $-C(=O)R^a$, wherein the heteroalkyl is optionally substituted with one or more R^u .

48. The compound of any one of claims 1-47, wherein b' is 0 or 1.

49. The compound of any one of claims 1-48, wherein each $R^{C'}$ is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, C_{6-10} aryl, or 5- to 10-membered heteroaryl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u .

50. The compound of any one of claims 1-49, wherein c' is 0.

51. The compound of any one of claims 1-50, wherein W is

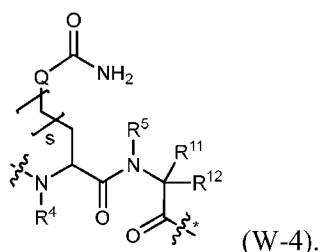


52. The compound of claim 51, wherein R^6 is C_6 aryl or 5- to 6-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a} , and R^7 is C_6 aryl or 5- to 6-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{7a} ; or R^6 is C_6 aryl or 5- to 6-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{6a} , and R^7 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^{7b} .

53. The compound of claim 52, wherein each R^{6a} and each R^{7a} are independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, or -S(=O)₂R^a, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or each R^{7b} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

54. The compound of claim 52, wherein each R^{6a} and each R^{7a} are independently halogen, C₁₋₆ alkyl, C₁₋₆ alkylamino, or -S(=O)₂R^a, wherein the alkyl or alkylamino is optionally substituted with one or more R^u; or each R^{7b} is C₃₋₆ carbocyclyl or 3- to 6-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

55. The compound of any one of claims 1-50, wherein W is



56. The compound of claim 55, wherein R^{12} is -(C₁₋₆ alkylene)-(C₆₋₁₀ aryl) or -(C₁₋₆ alkylene)-(5- to 10-membered heteroaryl), wherein the alkylene is optionally substituted with one or more R^u, and the aryl or heteroaryl is optionally substituted with one or more R^{12a}.

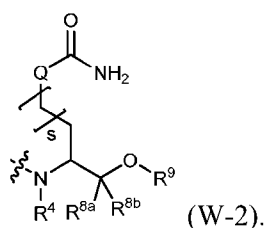
57. The compound of claim 56, wherein each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, or -S(=O)₂R^a, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

58. The compound of claim 56, wherein each R^{12a} is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

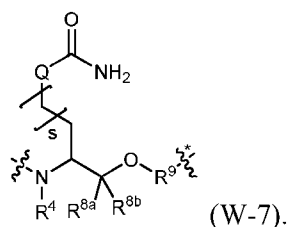
59. The compound of any one of claims 55-58, wherein R⁵ is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

60. The compound of claim 59, wherein R⁵ is hydrogen.

61. The compound of any one of claims 1-50, wherein W is



62. The compound of any one of claims 1-50, wherein W is



63. The compound of claim 62, wherein R^{8a} and R^{8b} are independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-

membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

64. The compound of claim 63, wherein R^{8a} and R^{8b} are both hydrogen.

65. The compound of any one of claims 62-64, wherein R⁹ is C₆ aryl or 5- to 6-membered heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more R^{9a}.

66. The compound of claim 65, wherein each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, or -S(=O)₂R^a, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

67. The compound of claim 65, wherein each R^{9a} is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u.

68. The compound of any one of claims 50-67, wherein R⁴ is hydrogen, C₁₋₆ alkyl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

69. The compound of claim 68, wherein R⁴ is hydrogen.

70. The compound of any one of claims 50-69, wherein Q is absent.

71. The compound of any one of claims 50-70, wherein s is 1.

72. A compound selected from compounds described in Table 1 and pharmaceutically acceptable salts thereof.
73. A pharmaceutical composition comprising the compound of any one of claims 1-72, and a pharmaceutically acceptable excipient.
74. A method of degrading STAT3 protein in a patient or biological sample comprising contacting said patient or biological sample with a compound of any one of claims 1-72.
75. Use of a compound of any one of claims 1-72 in the manufacture of a medicament for degrading STAT3 protein in a patient or biological sample.
76. A compound of any one of claims 1-72 for use in degrading STAT3 protein in a patient or biological sample.
77. A method of treating a STAT3-mediated disease or disorder comprising administering to a patient in need thereof a compound of any one of claims 1-72.
78. Use of a compound of any one of claims 1-72 in the manufacture of a medicament for treating a STAT3-mediated disease or disorder.
79. A compound of any one of claims 1-72 for use in treating a STAT3-mediated disease or disorder.
80. The method, use, or compound for use of any one of claims 77-79, wherein the STAT3-mediated disorder is cancer, an autoimmune disease, an inflammatory disorder, a neurodegenerative disease, a viral disease, a hereditary disorder, a hormone-related disease, a metabolic disorder, a condition associated with organ transplantation, an immunodeficiency disorder, a destructive bone disorder, a proliferative disorder, an infectious disease, a condition associated with cell death, thrombin-induced platelet aggregation, liver disease, a pathologic immune condition involving T cell activation, a cardiovascular disorder, and a CNS disorder.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2024/015462

A. CLASSIFICATION OF SUBJECT MATTER INV. C07F9/38 C07D519/00 A61P29/00 A61P35/00 ADD.		
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) C07F C07D A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2021/188696 A1 (KYMERA THERAPEUTICS INC [US]) 23 September 2021 (2021-09-23) compounds (Id); compounds I-1 to I-10, I-23, I-24, I-42, I-53, I-54, I-59, I-60, I-63, I-77 to I-80, I-82 to I-89; paragraph [0002]; claims -----	1 - 80
X	WO 2020/198435 A1 (UNIV MICHIGAN REGENTS [US]) 1 October 2020 (2020-10-01) paragraph [0001]; examples 125-127 -----	1 - 80
A	WO 2020/205467 A1 (UNIV MICHIGAN REGENTS [US]) 8 October 2020 (2020-10-08) paragraph [0001]; examples 1-188 -----	1 - 80
A	WO 2021/195481 A1 (UNIV MICHIGAN REGENTS [US]) 30 September 2021 (2021-09-30) claims; examples 1-64 -----	1 - 80
☐ 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 1 July 2024		Date of mailing of the international search report 15/07/2024
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schmid, Arnold

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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