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974282

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

January 24, 2019

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 62/415,830

FILING DATE: November 01, 2016

RELATED PCT APPLICATION NUMBER: PCT/US17/59604

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS US62/415,830



Certified by

Michelle K. Lee

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

Provisional Application for Patent Cover Sheet

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c)

Inventor(s)

Inventor 1

[Remove](#)

Given Name	Middle Name	Family Name	City	State	Country i
Andrew	P.	Crew	Guilford	CT	US

Inventor 2

[Remove](#)

Given Name	Middle Name	Family Name	City	State	Country i
John	J.	Flanagan	Guilford	CT	US

Inventor 3

[Remove](#)

Given Name	Middle Name	Family Name	City	State	Country i
Michael		Berlin	Flemington	NJ	US

Inventor 4

[Remove](#)

Given Name	Middle Name	Family Name	City	State	Country i
Hanqing		Dong	Madison	CT	US

All Inventors Must Be Listed – Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

[Add](#)

Title of Invention

TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE

Attorney Docket Number (if applicable)

1513291.121US0

Correspondence Address

Direct all correspondence to (select one):

☒ The address corresponding to Customer Number

☐ Firm or Individual Name

Customer Number

21874

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

Yes, the invention was made by an agency of the United States Government. The U.S. Government agency name is:

Yes, the invention was under a contract with an agency of the United States Government. The name of the U.S. Government agency and Government contract number are:

Doc Code: **TR.PROV**

Document Description: Provisional Cover Sheet (SB16)

PTO/SB/16 (11-08)

Approved for use through 05/31/2015. OMB 0651-0032

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number

Entity Status**Applicant asserts small entity status under 37 CFR 1.27 or applicant certifies micro entity status under 37 CFR 1.29**

- ☒ Applicant asserts small entity status under 37 CFR 1.27
- ☐ Applicant certifies micro entity status under 37 CFR 1.29. Applicant must attach form PTO/SB/15A or B or equivalent.
- ☐ No

Warning

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

Signature

Please see 37 CFR 1.4(d) for the form of the signature.

Signature	Bryan D. Zerhusen, Ph.D./		Date (YYYY-MM-DD)	2016-11-01	
First Name	Bryan	Last Name	Zerhusen	Registration Number (If appropriate)	54566

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **This form can only be used when in conjunction with EFS-Web. If this form is mailed to the USPTO, it may cause delays in handling the provisional application.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that : (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor	1				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Andrew	P.	Crew			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						
City	Guilford	State/Province	CT	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	2 Winterberry Road					
Address 2						
City	Guilford	State/Province	CT			
Postal Code	06437	Country i	US			
Inventor	2				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	John	J.	Flanagan			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						
City	Guilford	State/Province	CT	Country of Residence	US	
Mailing Address of Inventor:						
Address 1	71 High Meadow Road					
Address 2						
City	Guilford	State/Province	CT			
Postal Code	06437	Country i	US			
Inventor	3				Remove	
Legal Name						
Prefix	Given Name	Middle Name	Family Name	Suffix		
	Michael		Berlin			
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service						

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

City	Flemington	State/Province	NJ	Country of Residence ⁱ	US
------	------------	----------------	----	-----------------------------------	----

Mailing Address of Inventor:

Address 1	14 Hendrick Road				
Address 2					
City	Flemington	State/Province	NJ		
Postal Code	08822	Country ⁱ	US		
Inventor	4				Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hanqing		Dong	

Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service

City	Madison	State/Province	CT	Country of Residence ⁱ	US
------	---------	----------------	----	-----------------------------------	----

Mailing Address of Inventor:

Address 1	248 Opening Hill Rd.				
Address 2					
City	Madison	State/Province	CT		
Postal Code	06443	Country ⁱ	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.**Correspondence Information:**Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).☐ An Address is being provided for the correspondence Information of this application.

Customer Number	21874		
Email Address	patent@lockelord.com	Add Email	Remove Email

Application Information:

Title of the Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		
Attorney Docket Number	1513291.121US0	Small Entity Status Claimed	☒
Application Type	Provisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	1	Suggested Figure for Publication (if any)	1

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not be** the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	21874		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status		Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the Add button.			Add

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)ⁱ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ^j (if applicable)	Remove

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant	1 Remove		
If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section. Clear			
Assignee	Legal Representative under 35 U.S.C. 117		Joint Inventor
☒ Person to whom the inventor is obligated to assign.		☐ Person who shows sufficient proprietary interest	
If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:			
Name of the Deceased or Legally Incapacitated Inventor:			
If the Applicant is an Organization check here. ☒			
Organization Name	Arvinas, Inc.		
Mailing Address Information For Applicant:			
Address 1	5 Science Park		
Address 2			
City	New Haven	State/Province	CT
Country	US	Postal Code	06511
Phone Number		Fax Number	
Email Address			
Additional Applicant Data may be generated within this form by selecting the Add button. Add			

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

Assignee	1
-----------------	---

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1				
Address 2				
City		State/Province		
Country i		Postal Code		
Phone Number		Fax Number		
Email Address				

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the **INITIAL** filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Bryan D. Zerhusen, Ph.D./		Date (YYYY-MM-DD)	2016-11-01
First Name	Bryan	Last Name	Zerhusen	Registration Number
				54,566

Additional Signature may be generated within this form by selecting the Add button.

Add

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	1513291.121US0
		Application Number	
Title of Invention	TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE		

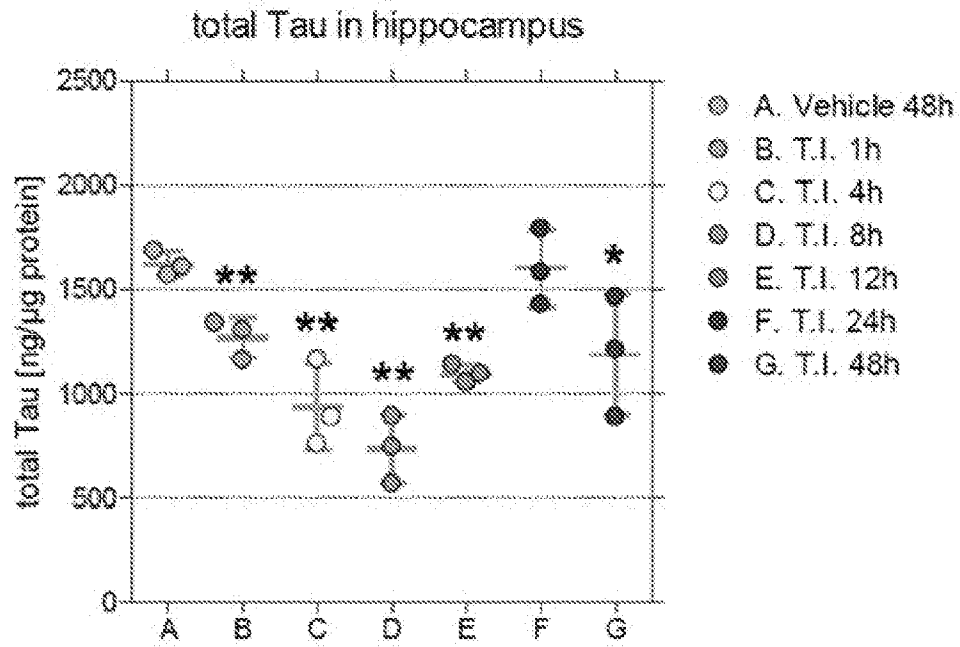
This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

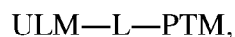
1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

**Figure 1**

CLAIMS

What Is Claimed Is:

1. A bifunctional compound having the chemical structure:



or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph or prodrug thereof,

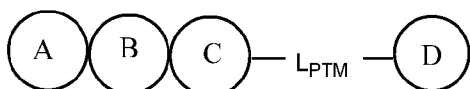
wherein:

the ULM is a small molecule E3 ubiquitin ligase binding moiety that binds an E3 ubiquitin ligase;

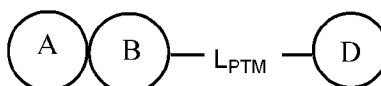
the PTM is a Tau protein targeting moiety; and

the L is a bond or a chemical linking moiety connecting ULM and PTM.

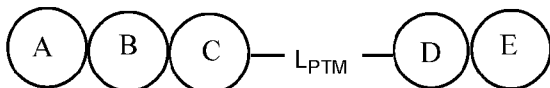
2. The bifunctional compound according to claim 1, wherein the E3 ubiquitin ligase binding moiety that targets a E3 ubiquitin ligase selected from the group consisting of Von Hippel-Lindau (VLM) and cereblon (CLM).
3. The compound according to claim 1 or 2, wherein PTM is represented by Formula I, II, III or IV:



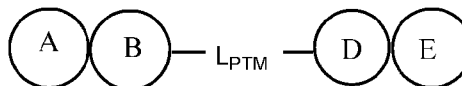
I



II



III



IV

wherein

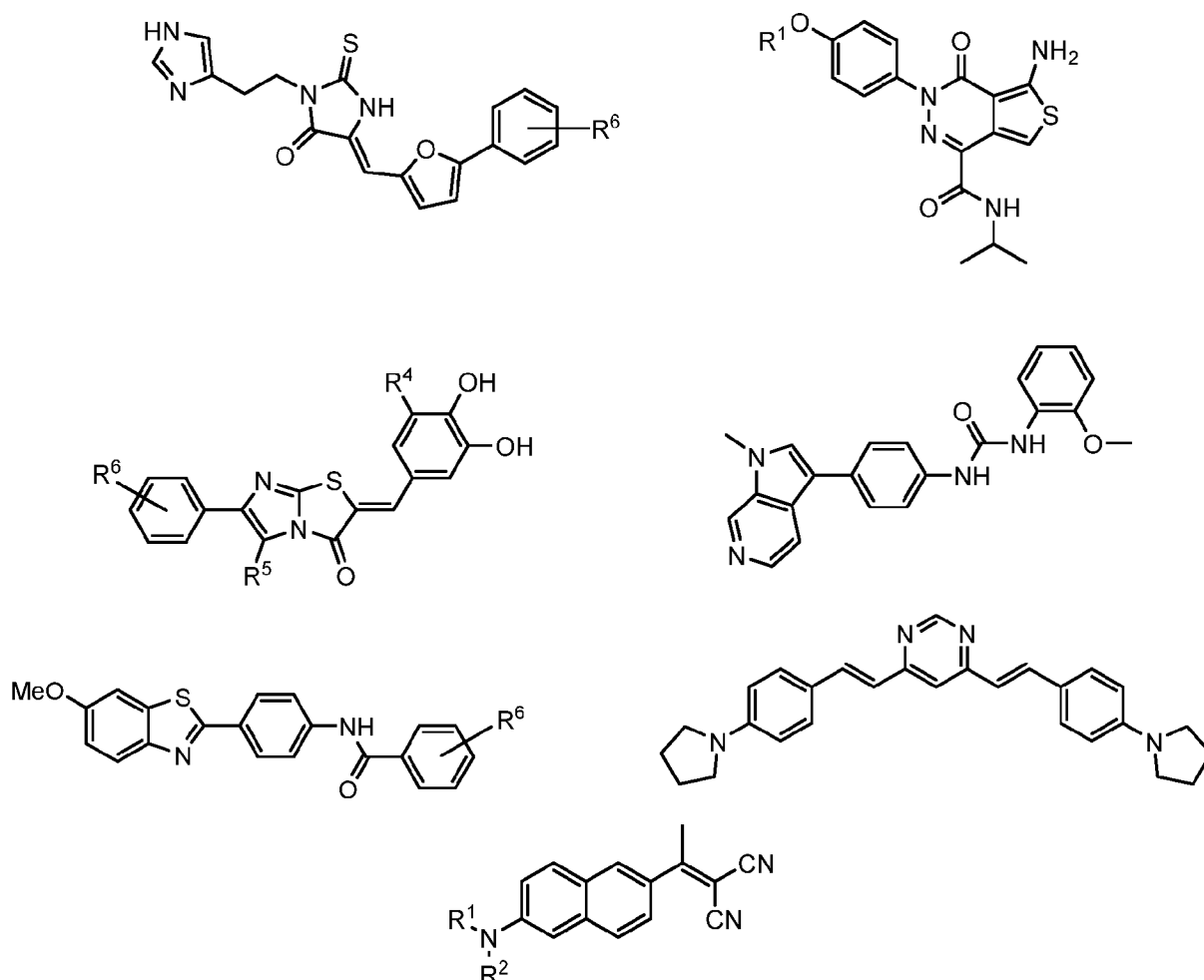
A, B and C are each independently selected from optionally substituted 5- or 6-membered aryl or heteroaryl rings;

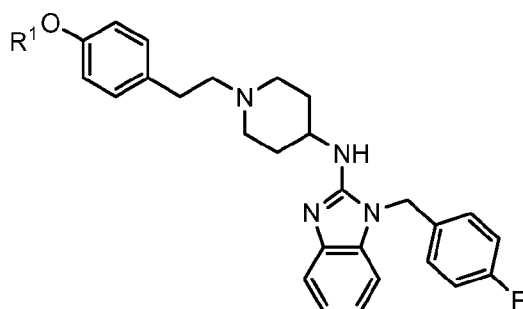
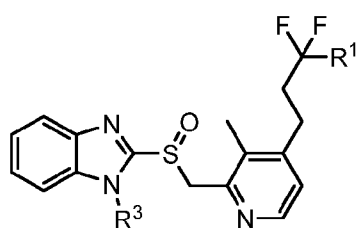
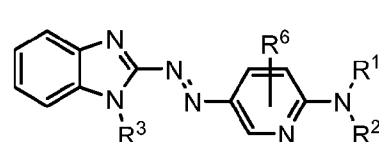
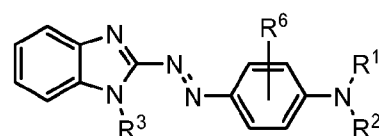
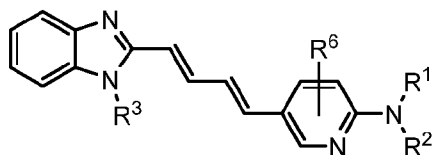
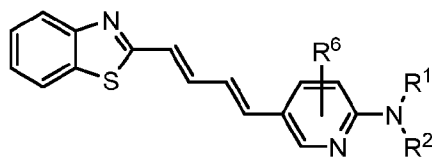
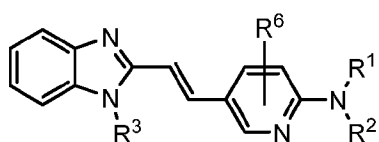
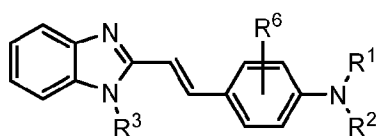
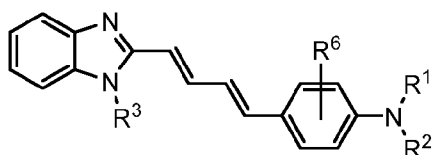
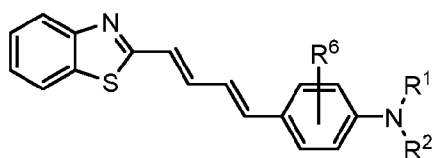
D is selected from an optionally substituted 5- or 6-membered aryl or heteroaryl ring, an optionally substituted 4- to 7-membered cycloalkyl or a heterocycloalkyl, where contact between circles indicates ring fusion.

L_{PTM} is selected from a bond, an alkyl, an alkenyl or an alkynyl, optionally interrupted by one or more rings (i.e., cycloalkyl, heterocycloalkyl, aryl or heteroaryl), or one or more functional groups selected from the groups -O-, -S-, -NR¹_{PTM}- (where R¹_{PTM} is selected from H or alkyl), -S(O)-, -SO₂-, -C(O)-, -NHC(O)-, -C(O)NH-, -NHSO₂-, -NHC(O)NH-, -NHC(O)O-, or -OC(O)NH-, wherein the said functional group are optionally located at either end of the linker.

4. The compound according to claim 3, wherein aryl and heteroaryl rings of A, B, C, D and E of PTM are optionally substituted with 1–3 substituents each independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino and cyano, wherein the said alkyl and alkenyl groups are further optionally substituted.
5. The compound according to claim 3, wherein the PTM is Formula I and:
 A, B and C rings are independently 5- or 6- membered fused aryl or heteroaryl rings;
 L_{PTM} is selected from a bond or an alkyl, and
 D is selected from a 6-membered aryl, heteroaryl or heterocycloalkyl, wherein
 A, B, C and D are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.
6. The compound according to claim 1 or 3; wherein the PTM is Formula I and:
 A and C are a phenyl or a 6-membered heteroaryl ring;
 B is a 5-membered heteroaryl ring;
 L_{PTM} is a bond; and
 D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring;
 wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, and wherein a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

7. The compound according to claim 1 or 3; wherein the PTM is Formula III or IV and:
 A, B and C are 5- or 6- membered fused aryl or heteroaryl rings;
 L_{PTM} is selected from a bond or an alkyl;
 D and E are 5- or 6-membered fused aryl or heteroaryl rings;
 and wherein A, B, C, D and E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.
8. The compound according to any one of claims 1-3, wherein the PTM is represented by a chemical structure selected from the group consisting of:



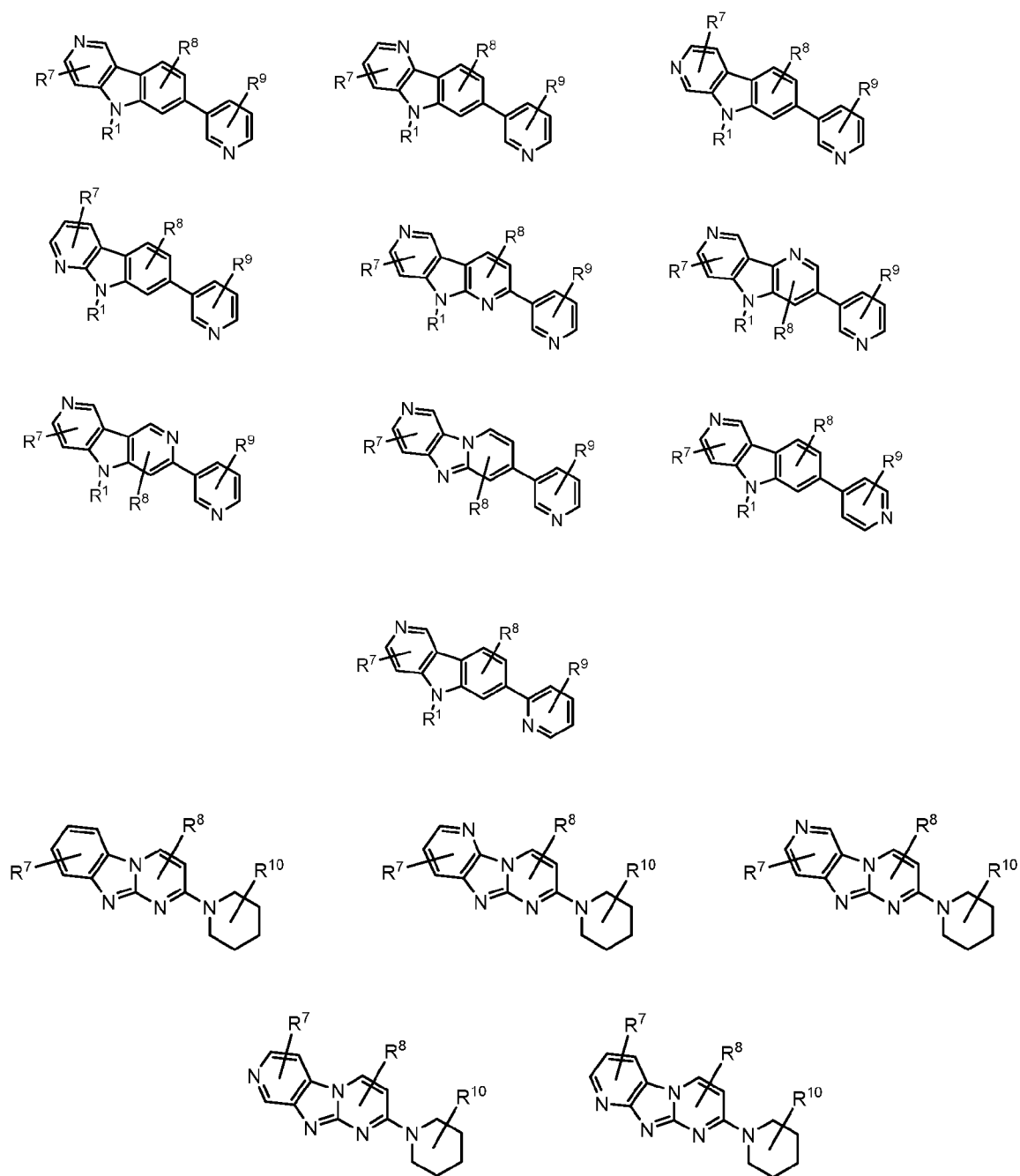


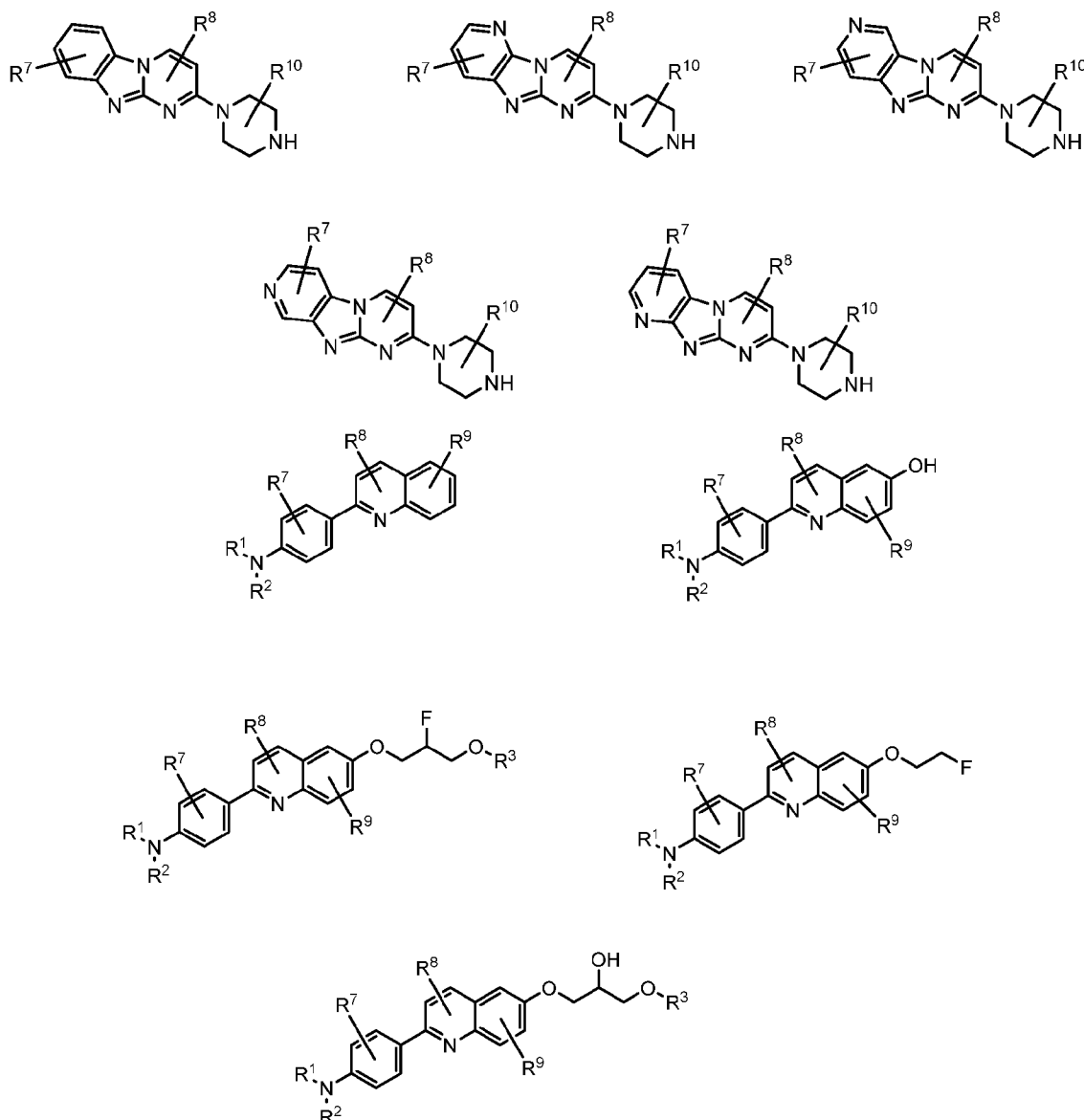
where R^1 , R^2 and R^3 are independently selected from H, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl;

R^4 and R^5 are independently selected from H, methyl, ethyl and halogen; and

R^6 is 1 to 2 substituents independently selected from H, methyl, ethyl and halogen.

9. The compound according to any of claims 1-3, wherein the PTM is represented by a chemical structure selected from the group consisting of:

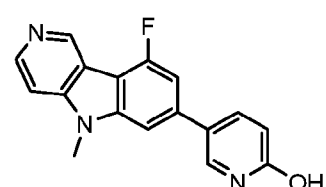
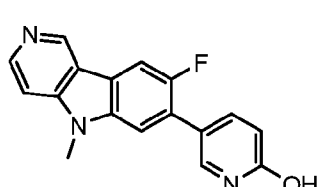
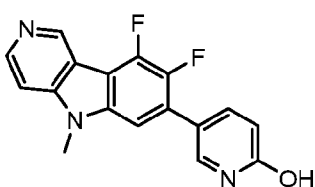
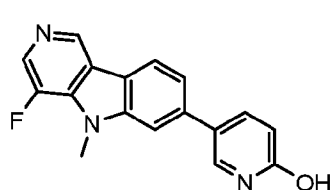
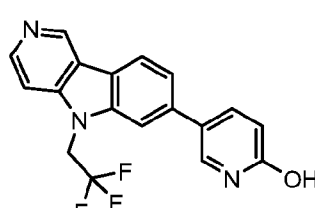
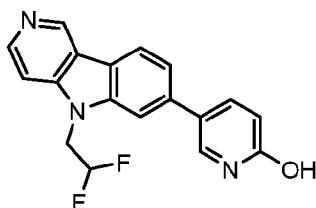
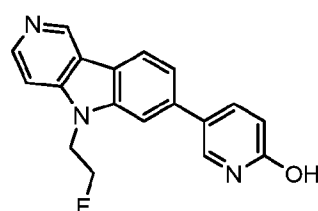
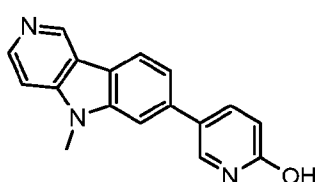
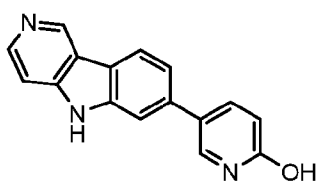
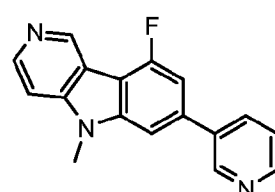
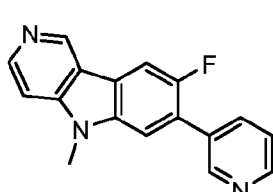
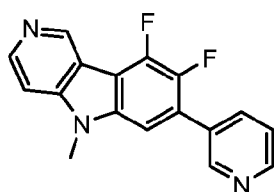
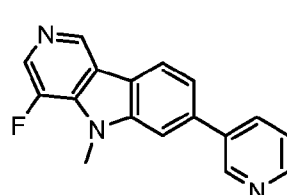
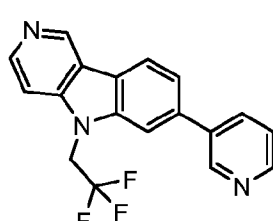
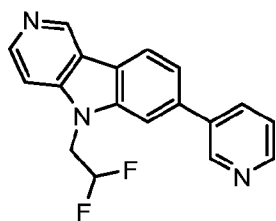
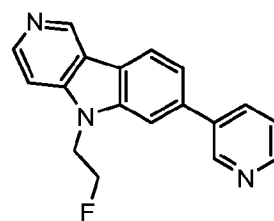
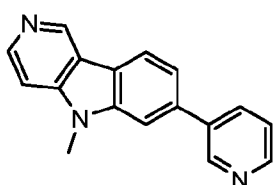
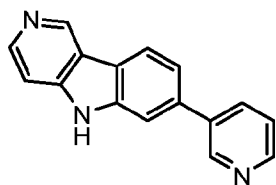


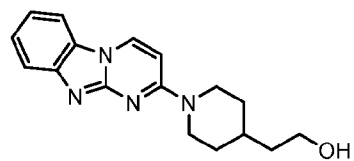
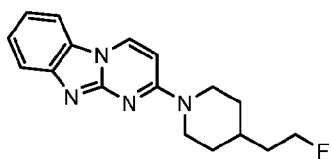
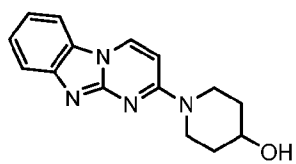
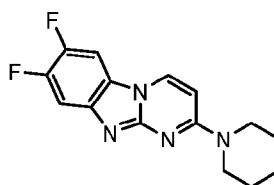
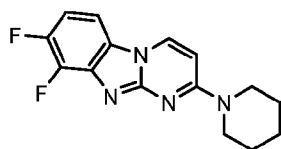
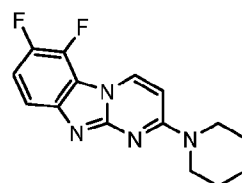
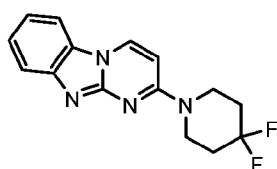
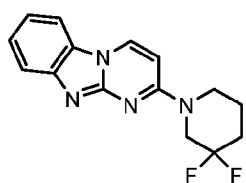
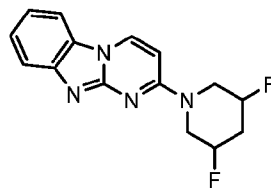
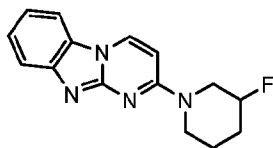
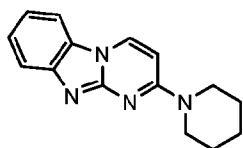
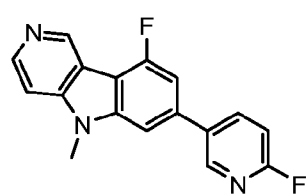
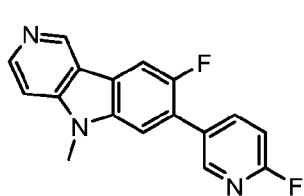
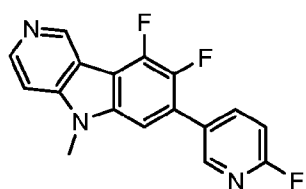
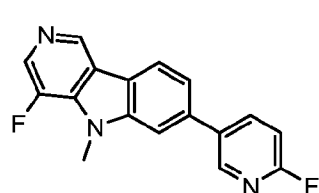
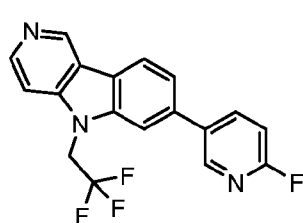
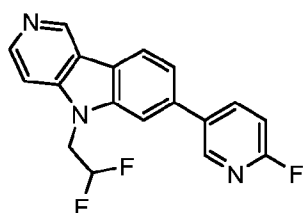
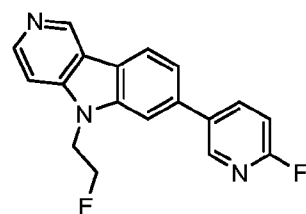
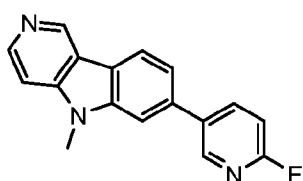
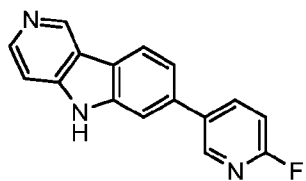


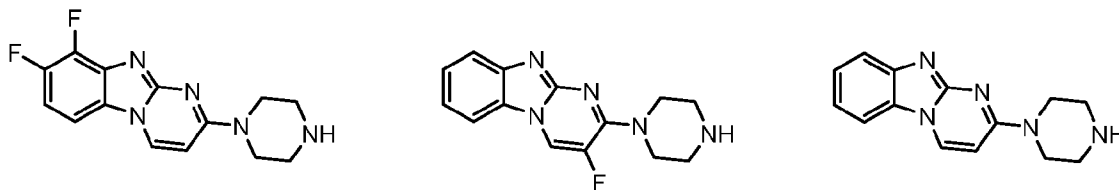
where R^1 , R^2 and R^3 are independently selected from H, optionally substituted alkyl, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; and

R^7 , R^8 , R^9 and R^{10} are 1 to 2 substituents independently selected from H, optionally substituted alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano.

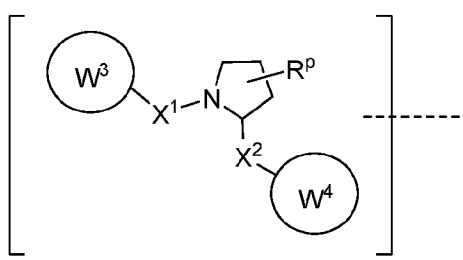
10. The compound according to any of claims 1-3 or 9, wherein the PTM is represented by a chemical structure selected from the group consisting of:







11. The compound according to any of claim 1-10, wherein the ULM is a Von Hippel-Lindau (VHL) ligase-binding moiety (VLM) represented by the structure:



wherein:

X^1 , X^2 are each independently selected from the group of a bond, O, NR^{Y3} , $CR^{Y3}R^{Y4}$, $C=O$, $C=S$, SO , and SO_2 ;

R^{Y3} , R^{Y4} are each independently selected from the group of H, linear or branched C_{1-6} alkyl, optionally substituted by 1 or more halo, C_{1-6} alkoxy optionally substituted by 1-3 R^p groups;

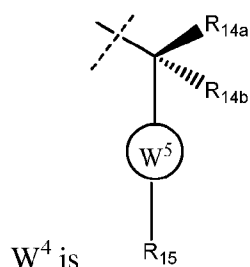
R^p is independently selected from the group H, halo, $-OH$, C_{1-3} alkyl;

W^3 is selected from the group of an optionally substituted $-T-N(R^{1a}R^{1b})X^3$, $-T-Aryl$, an optionally substituted $-T-Heteroaryl$, an optionally substituted $-T-Heterocycle$, an optionally substituted $-NR^1-T-Aryl$, an optionally substituted $-NR^1-T-Heteroaryl$ or an optionally substituted $-NR^1-T-Heterocycle$;

X^3 is $C=O$, R^1 , R^{1a} , R^{1b} are independently selected from the group of H, linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halo or $-OH$ groups, $R^{Y3}C=O$, $R^{Y3}C=S$, $R^{Y3}SO$, $R^{Y3}SO_2$, $N(R^{Y3}R^{Y4})C=O$, $N(R^{Y3}R^{Y4})C=S$, $N(R^{Y3}R^{Y4})SO$, and $N(R^{Y3}R^{Y4})SO_2$;

T is selected from the group of an optionally substituted alkyl, $-(CH_2)_n-$ group, wherein each one of the methylene groups is optionally substituted with one or two substituents selected from the group of halogen, methyl, a linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halogen or $-OH$ groups or an amino acid side chain optionally substituted; and

n is 0 to 6,



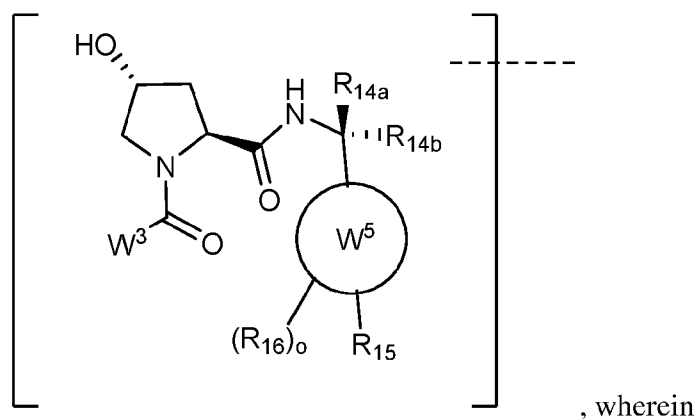
R_{14a}, R_{14b}, are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

W⁵ is selected from the group of a phenyl or a 5-10 membered heteroaryl,

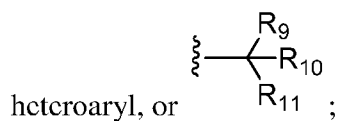
R₁₅ is selected from the group of H, halogen, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a} SO₂R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, or cycloheteroalkyl;

and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

12. The compound according to any of claims 1-10, wherein ULM is a Von Hippel-Lindau (VHL) ligase-binding moiety (VLM) represented by the structure:

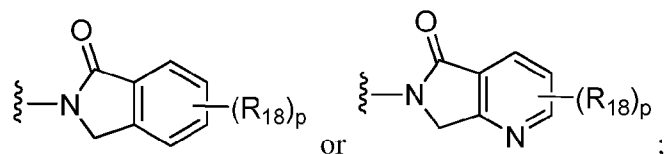
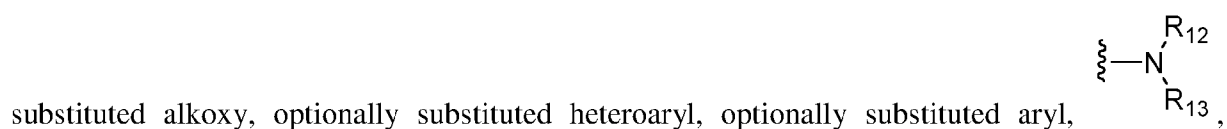


W³ is selected from the group of an optionally substituted aryl, optionally substituted



R₉ and R₁₀ are independently hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl, or R₉, R₁₀, and the carbon atom to which they are attached form an optionally substituted cycloalkyl;

R₁₁ is selected from the group of an optionally substituted heterocyclic, optionally



R₁₂ is selected from the group of H or optionally substituted alkyl;

R₁₃ is selected from the group of H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocycl)carbonyl, or optionally substituted aralkyl;

R_{14a}, R_{14b}, are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

W⁵ is selected from the group of a phenyl or a 5-10 membered heteroaryl,

R₁₅ is selected from the group of H, halogen, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a} SO₂R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, or cycloheteroalkyl;

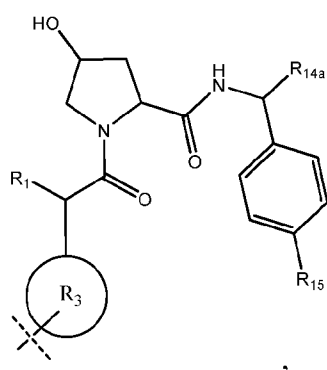
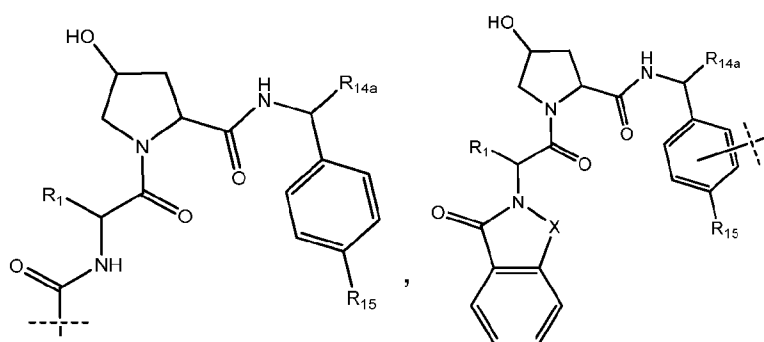
R₁₆ is independently selected from the group of halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy;

o is 0, 1, 2, 3, or 4;

R₁₈ is independently selected from the group of halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

p is 0, 1, 2, 3, or 4, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

13. The compound of any of the claims 1-12, wherein the ULM has a chemical structure selected from the group of:



and

where:

R₁ is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl;

R_{14a} is H, haloalkyl, optionally substituted alkyl, methyl, fluoromethyl, hydroxymethyl, ethyl, isopropyl, or cyclopropyl;

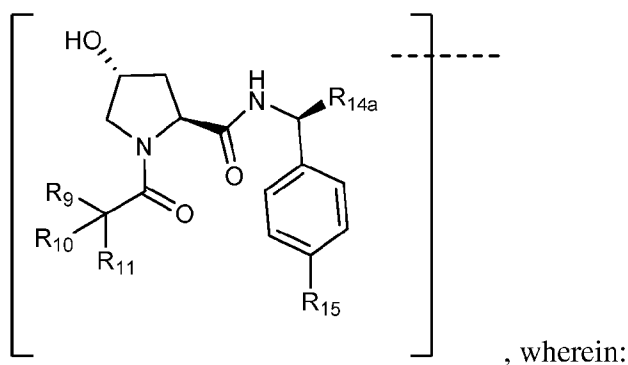
R₁₅ is selected from the group consisting of H, halogen, CN, OH, NO₂, optionally substituted heteroaryl, optionally substituted aryl; optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy, cycloalkyl, or cycloheteroalkyl;

X is C or C=O

R_3 is an optionally substituted 5 or 6 membered heteroaryl; and

wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

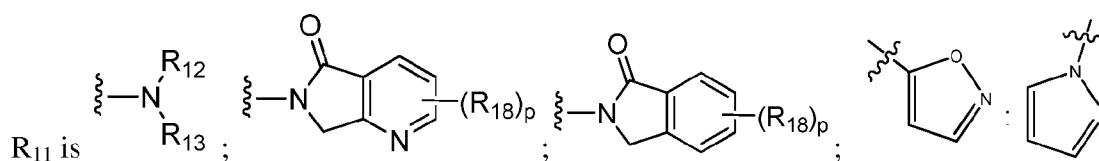
14. The compound according to any one of claims 1-13, wherein the ULM comprises a group according to the chemical structure:



R_{14a} is H, haloalkyl, optionally substituted alkyl, methyl, fluoromethyl, hydroxymethyl, ethyl, isopropyl, or cyclopropyl;

R_9 is H;

R_{10} is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;



or optionally substituted heteroaryl;

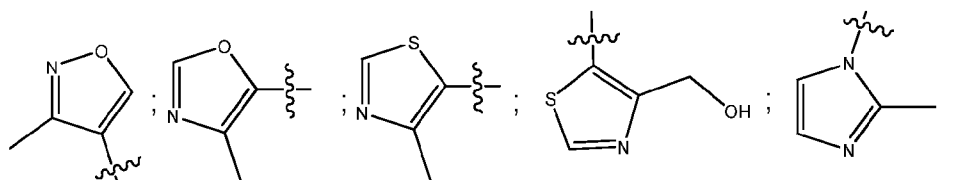
p is 0, 1, 2, 3, or 4;

each R_{18} is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker;

R_{12} is H, C=O;

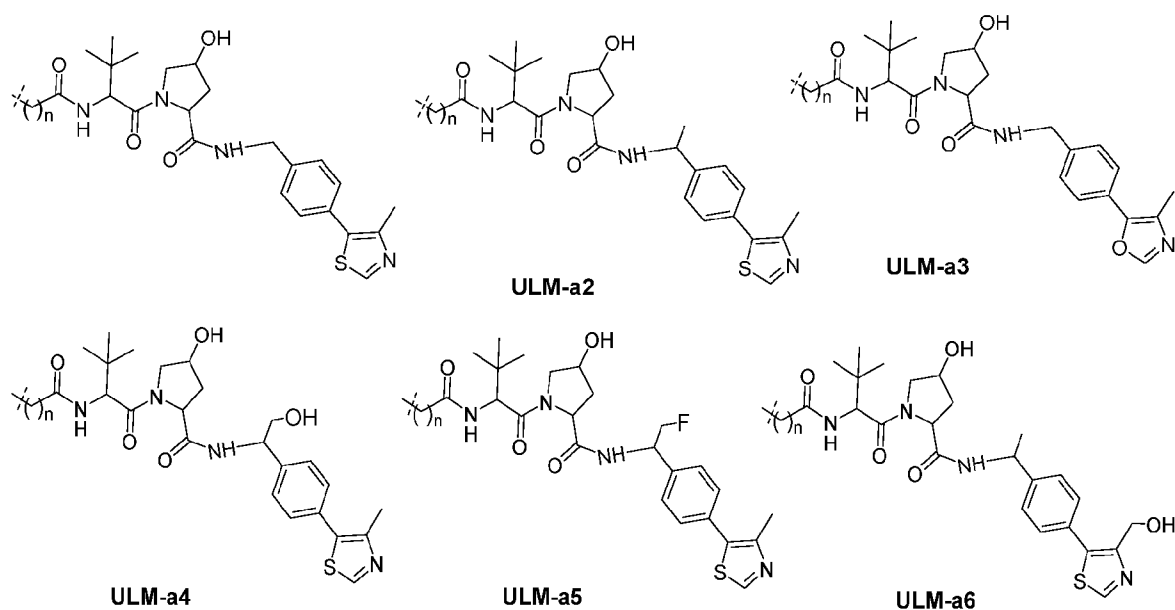
R_{13} is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

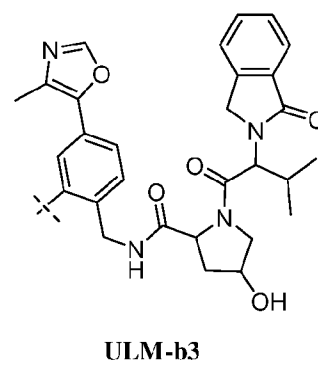
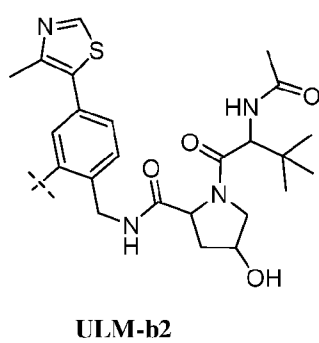
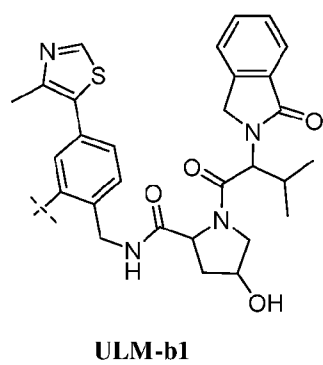
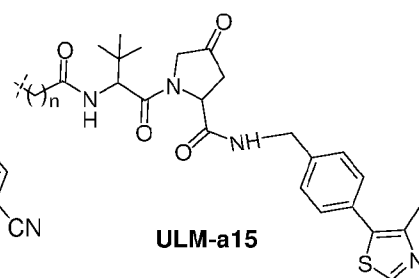
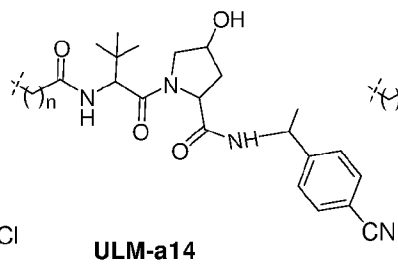
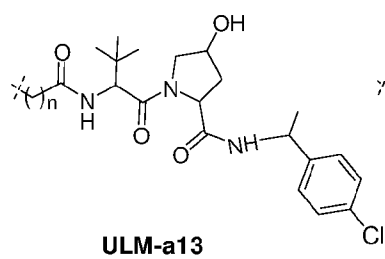
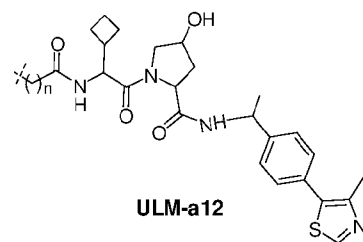
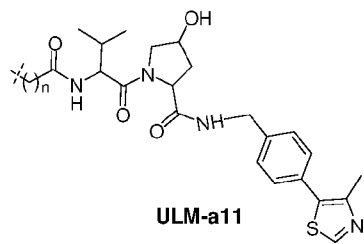
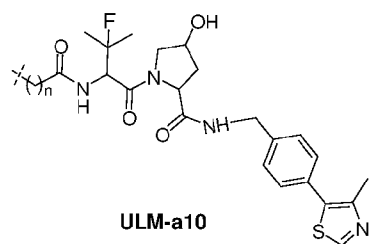
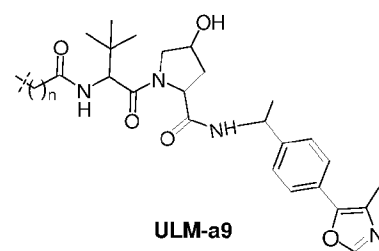
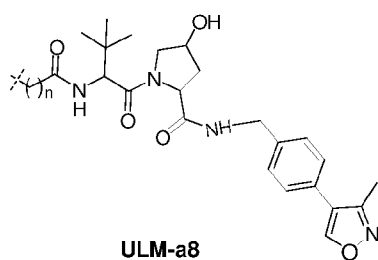
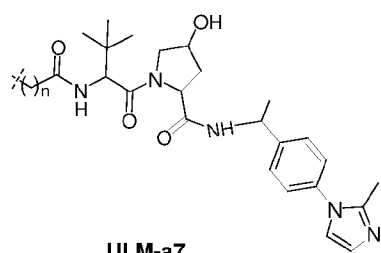
R₁₅ is selected from the group consisting of H, halogen, Cl, CN, OH, NO₂, optionally substituted heteroaryl, optionally substituted aryl;

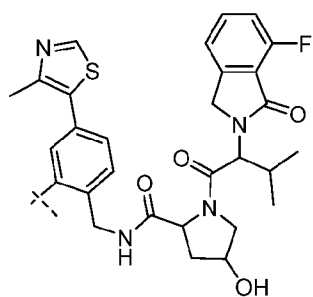


and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

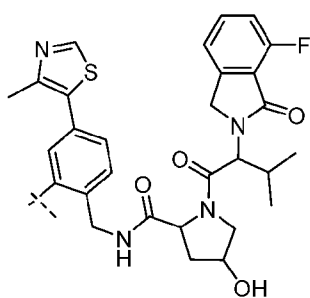
15. The compound according to any one of claims 1-14, wherein the ULM comprises a group selected from the structure consisting of:



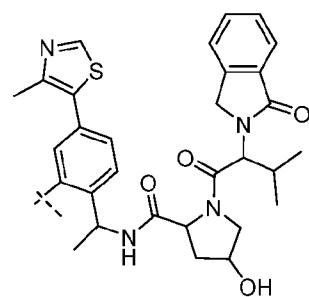




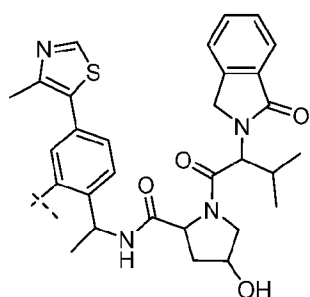
ULM-b4



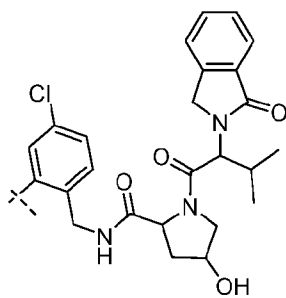
ULM-b5



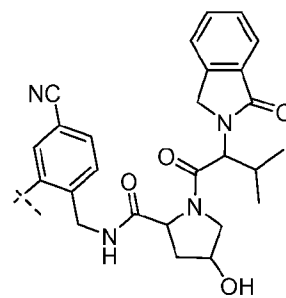
ULM-b6



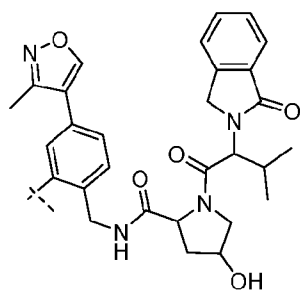
ULM-b7



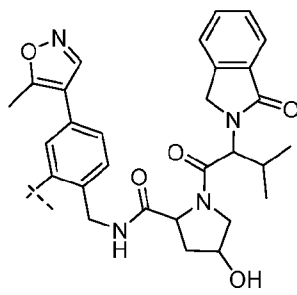
ULM-b8



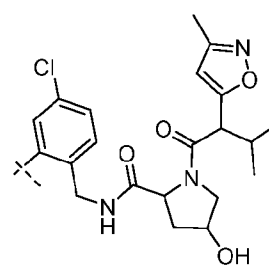
ULM-b9



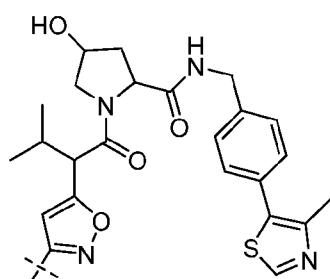
ULM-b10



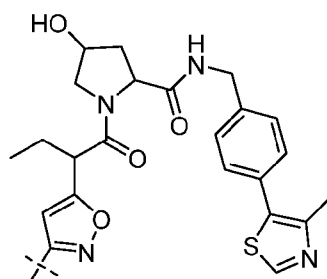
ULM-b11



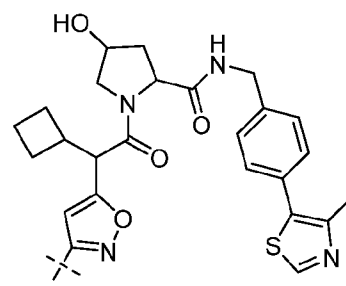
ULM-b12



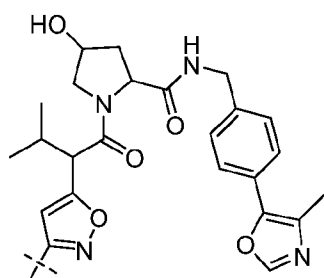
ULM-c1



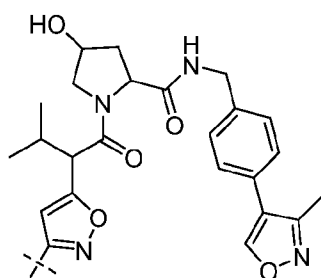
ULM-c2



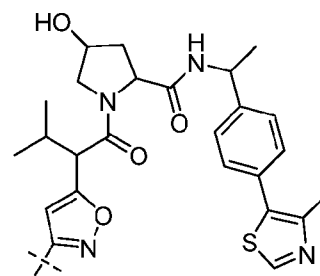
ULM-c3



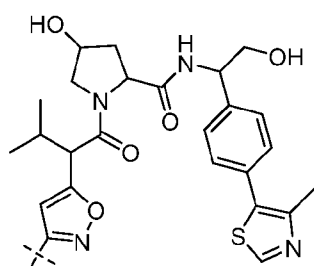
ULM-c4



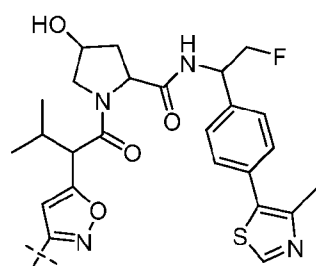
ULM-c5



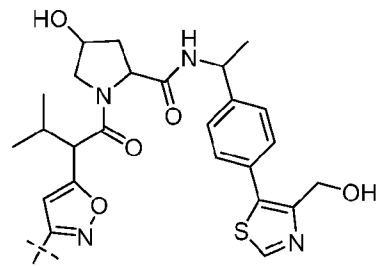
ULM-c6



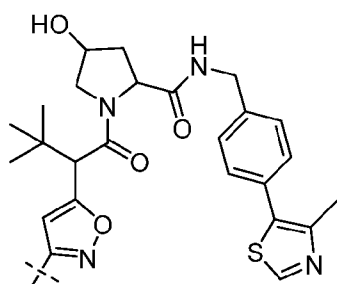
ULM-c7



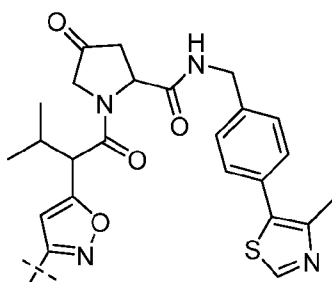
ULM-c8



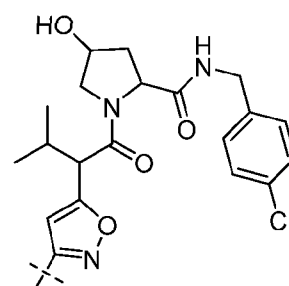
ULM-c9



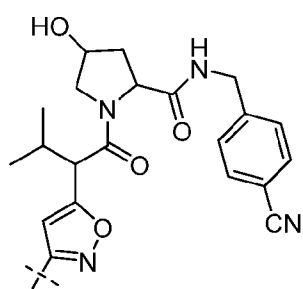
ULM-c10



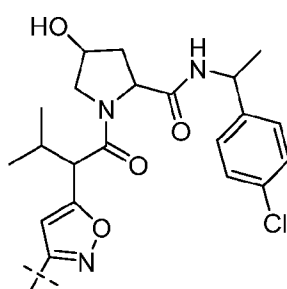
ULM-c11



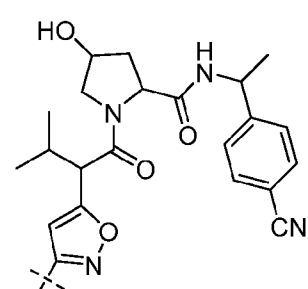
ULM-c12



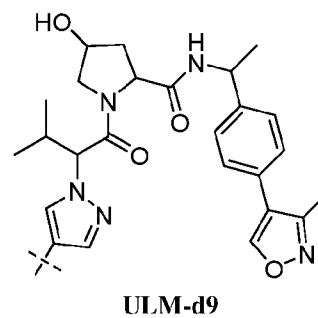
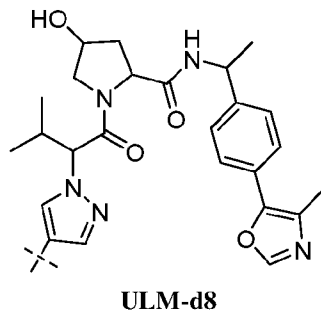
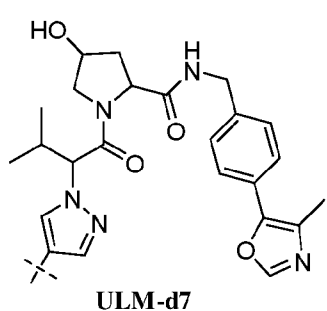
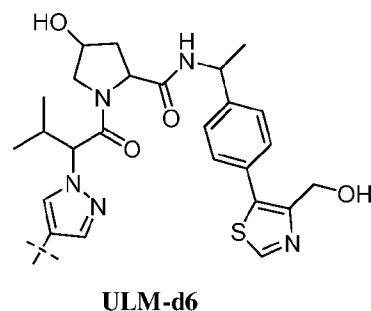
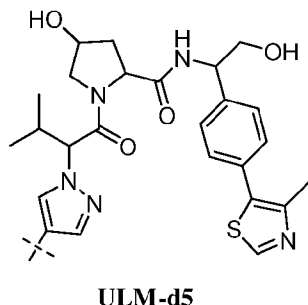
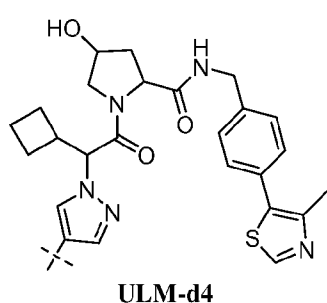
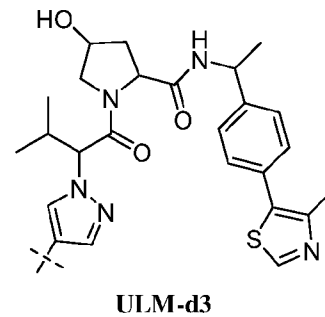
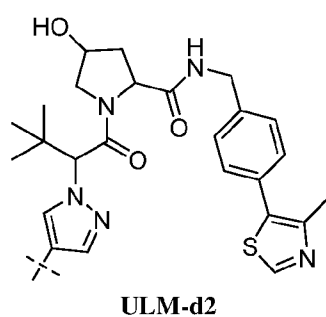
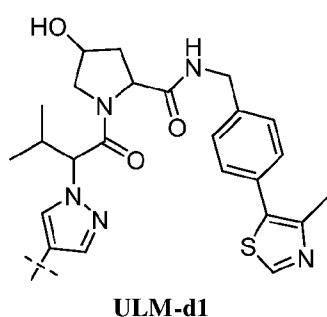
ULM-c13



ULM-c14



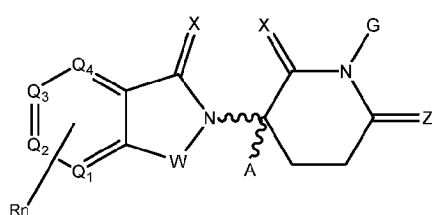
ULM-c15



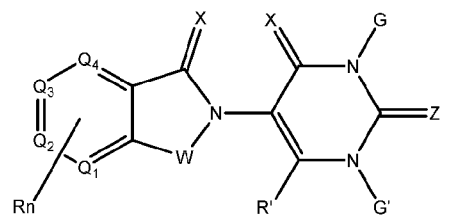
wherein, the phenyl ring in ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 is optionally substituted with fluorine, lower alkyl and alkoxy groups, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM-a.

16. The compound of any of claims 1-10, wherein the ULM is a cereblon ligase-binding moiety (CLM) is a thalidomide, lenalidomide, pomalidomide, analogs thereof, isosteres thereof, or derivatives thereof.

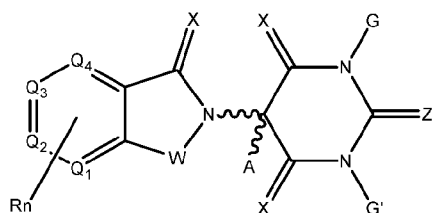
17. The compound of any of claims 1-10, or 16, wherein the CLM has a chemical structure represented by:



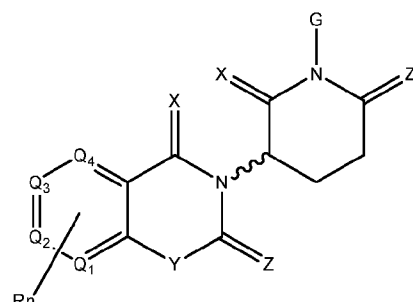
(a)



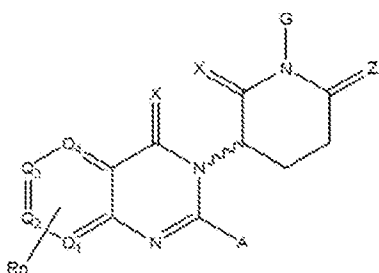
(b)



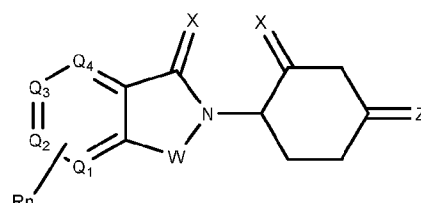
(c)



(d)



(e)



(f)

or

wherein:

W is selected from the group consisting of CH₂, CHR, C=O, SO₂, NH, and N-alkyl;

each X is independently selected from the group consisting of O, S, and H₂;

Y is selected from the group consisting of NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is selected from the group consisting of O, S, and H₂;

G and G' are independently selected from the group consisting of H, alkyl, OH, CH₂-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q₁, Q₂, Q₃, and Q₄ represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A is independently selected from the group H, alkyl, cycloalkyl, Cl and F;

R comprises -CONR'R'', -OR', -NR'R'', -SR', -SO₂R', -SO₂NR'R'', -CR'R''-, -CR'NR'R''-, -aryl, -hetaryl, -alkyl, -cycloalkyl, -heterocyclyl, -P(O)(OR')R'', -P(O)R'R'', -OP(O)(OR')R'', -OP(O)R'R'', -Cl, -F, -Br, -I, -CF₃, -CN, -NR'SO₂NR'R'', -NR'CONR'R'', -CONR'COR'', -NR'C(=N-CN)NR'R'', -C(=N-CN)NR'R'', -NR'C(=N-CN)R'', -NR'C(=C-NO₂)NR'R'', -SO₂NR'COR'', -NO₂, -CO₂R', -C(C=N-OR')R'', -CR'=CR'R'', -CCR', -S(C=O)(C=N-R')R'', -SF₅ and -OCF₃;

R' and R'' are independently selected from the group consisting of a bond, H, alkyl, cycloalkyl, aryl, hetaryl, heterocyclyl, each of which is optionally substituted;

~~~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

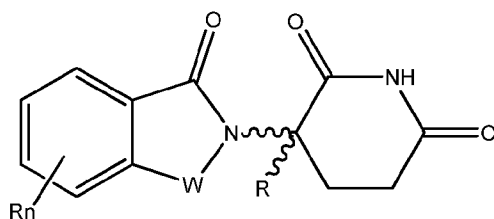
R<sub>n</sub> comprises a functional group or an atom,

wherein n is an integer from 1-4, and wherein

when n is 1, R<sub>n</sub> is modified to be covalently joined to the linker group (L), and

when n is 2, 3, or 4, then one R<sub>n</sub> is modified to be covalently joined to the linker group (L), and any other R<sub>n</sub> is optionally modified to be covalently joined to a PTM, a CLM, a second CLM having the same chemical structure as the CLM, a CLM', a second linker, or any multiple or combination thereof.

18. The compound of any of claims 1-10, 16 or 17, wherein the CLM has a chemical structure represented by:



wherein:

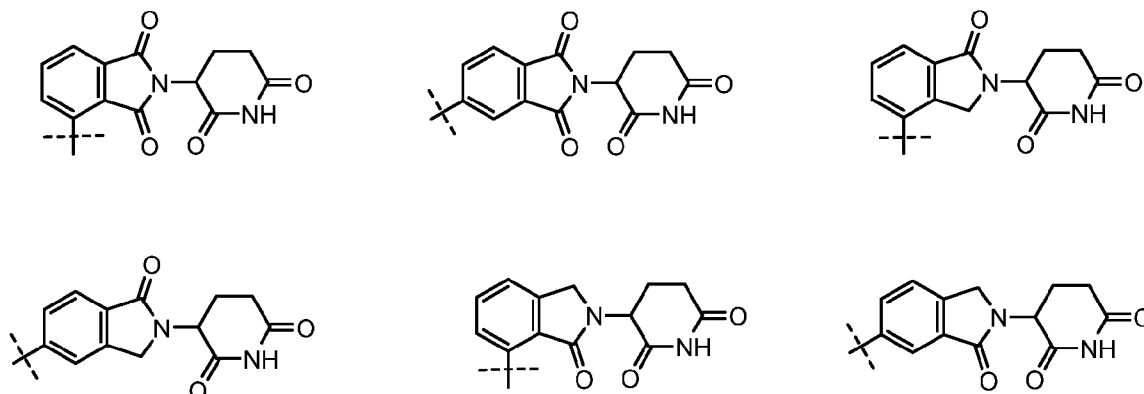
W is independently selected from the group CH<sub>2</sub>, C=O, NH, and N-alkyl;

R is independently selected from a H, methyl, alkyl;

~~~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

R_n comprises 1-4 independently selected functional groups or atoms, and optionally, one of which is modified to be covalently joined to a PTM, a chemical linker group (L), a CLM (or CLM') or combination thereof.

19. The compound of any of claims 1-10, or 16-18, wherein the CLM has a chemical structure represented by:



wherein the dashed lines indicate linker attachment points:

20. The compound of any one of claims 1-19, wherein the linker (L) comprises a chemical structural unit represented by the formula :

-A_q-, wherein

A_q is a group which is connected to the ULM or the PTM moiety; and

q is an integer greater than or equal to 1,

and wherein, A_q is selected from the group consisting of, a bond, CR^{L1}R^{L2}, O, S, SO, SO₂, NR^{L3}, SO₂NR^{L3}, SONR^{L3}, CONR^{L3}, NR^{L3}CONR^{L4}, NR^{L3}SO₂NR^{L4}, CO, CR^{L1}=CR^{L2}, C≡C, SiR^{L1}R^{L2}, P(O)R^{L1}, P(O)OR^{L1}, NR^{L3}C(=NCN)NR^{L4}, NR^{L3}C(=NCN), NR^{L3}C(=CNO₂)NR^{L4}, C₃₋₁₁cycloalkyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, C₃₋₁₁heterocyclyl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, aryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, heteroaryl optionally substituted with 0-6 R^{L1} and/or R^{L2} groups, where R^{L1} or R^{L2}, each independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 0-4 R^{L5} groups;

R^{L1}, R^{L2}, R^{L3}, R^{L4} and R^{L5} are, each independently, H, halo, C₁₋₈alkyl, OC₁₋₈alkyl, SC₁₋₈alkyl, NHC₁₋₈alkyl, N(C₁₋₈alkyl)₂, C₃₋₁₁cycloalkyl, aryl, heteroaryl, C₃₋₁₁heterocyclyl, OC₁₋₈cycloalkyl, SC₁₋₈cycloalkyl, NHC₁₋₈cycloalkyl, N(C₁₋₈cycloalkyl)₂, N(C₁₋₈cycloalkyl)(C₁₋₈alkyl),

OH, NH₂, SH, SO₂C₁₋₈alkyl, P(O)(OC₁₋₈alkyl)(C₁₋₈alkyl), P(O)(OC₁₋₈alkyl)₂, CC-C₁₋₈alkyl, CCH, CH=CH(C₁₋₈alkyl), C(C₁₋₈alkyl)=CH(C₁₋₈alkyl), C(C₁₋₈alkyl)=C(C₁₋₈alkyl)₂, Si(OH)₃, Si(C₁₋₈alkyl)₃, Si(OH)(C₁₋₈alkyl)₂, COC₁₋₈alkyl, CO₂H, halogen, CN, CF₃, CHF₂, CH₂F, NO₂, SF₅, SO₂NHC₁₋₈alkyl, SO₂N(C₁₋₈alkyl)₂, SONHC₁₋₈alkyl, SON(C₁₋₈alkyl)₂, CONHC₁₋₈alkyl, CON(C₁₋₈alkyl)₂, N(C₁₋₈alkyl)CONH(C₁₋₈alkyl), N(C₁₋₈alkyl)CON(C₁₋₈alkyl)₂, NHCONH(C₁₋₈alkyl), NHCON(C₁₋₈alkyl)₂, NHCONH₂, N(C₁₋₈alkyl)SO₂NH(C₁₋₈alkyl), N(C₁₋₈alkyl)SO₂N(C₁₋₈alkyl)₂, NH SO₂NH(C₁₋₈alkyl), NH SO₂N(C₁₋₈alkyl)₂, NH SO₂NH₂.

21. The compound according to any of claims 1-20, wherein the linker (L) comprises a group represented by a general structure selected from the group consisting of:

-N(R)-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-OCH₂-,

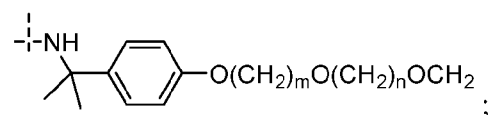
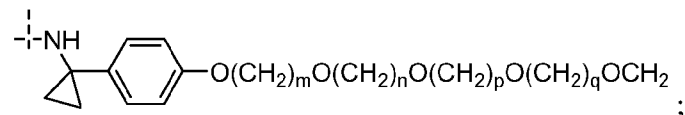
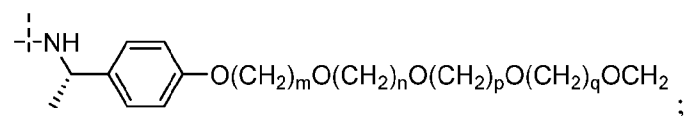
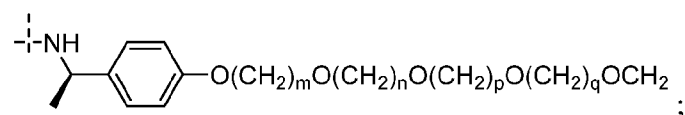
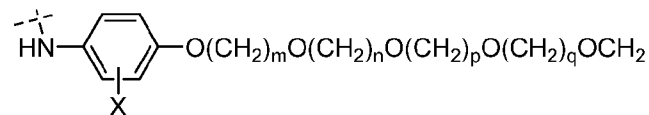
-O-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-OCH₂-,

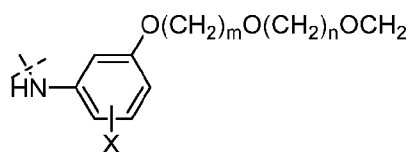
-O-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

-N(R)-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

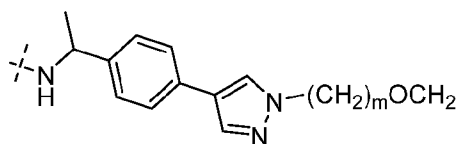
-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-O-;

-(CH₂)_m-O(CH₂)_n-O(CH₂)_o-O(CH₂)_p-O(CH₂)_q-O(CH₂)_r-OCH₂-;



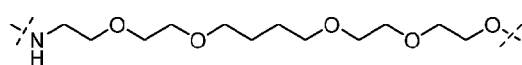
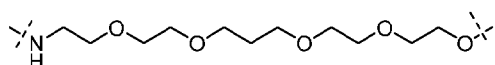
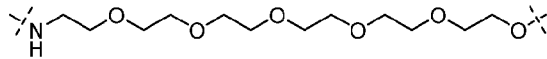
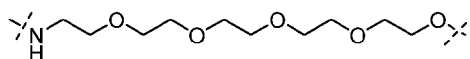
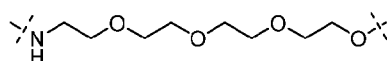
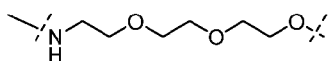
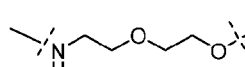
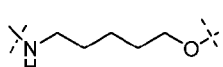
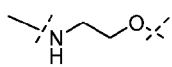


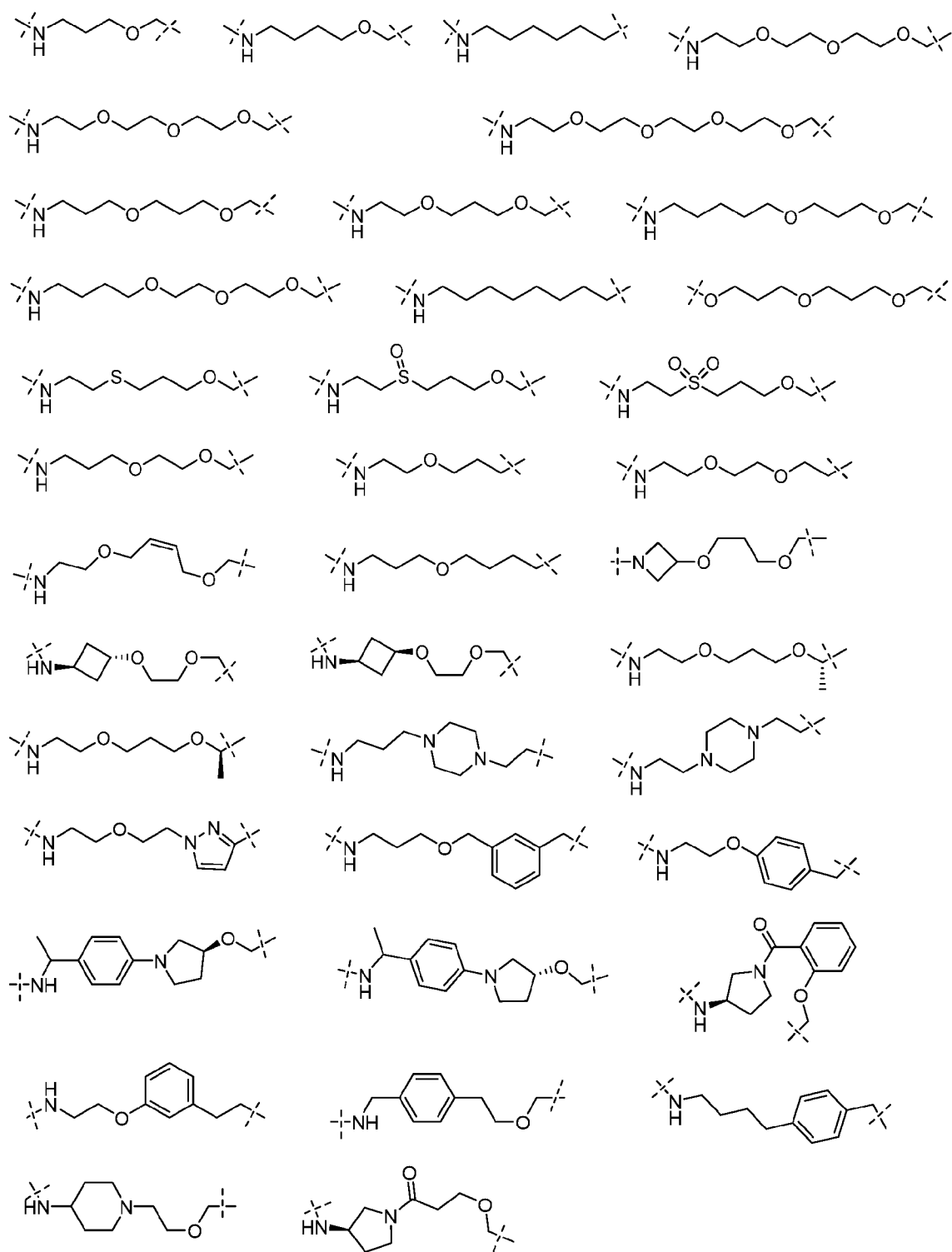
; and

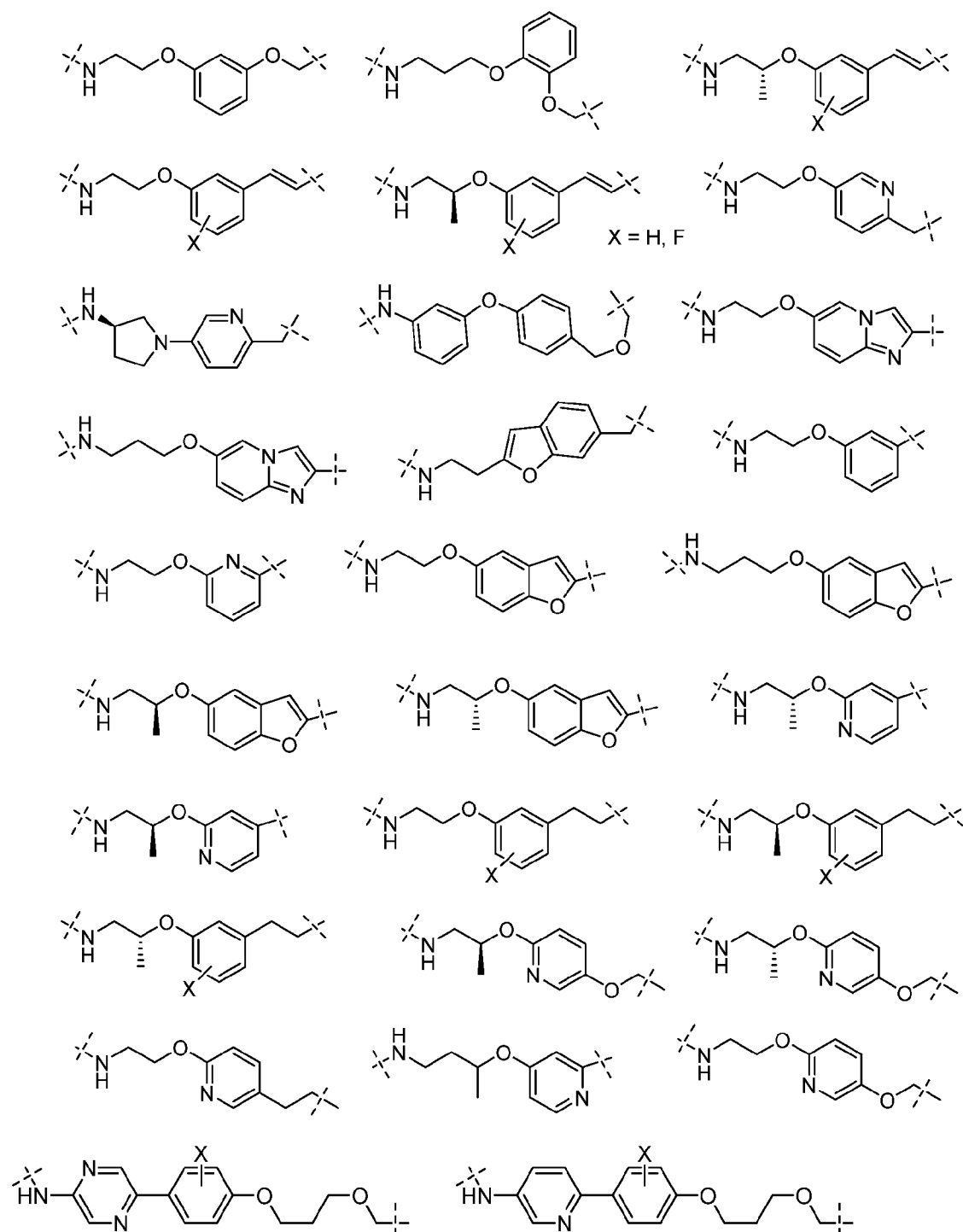


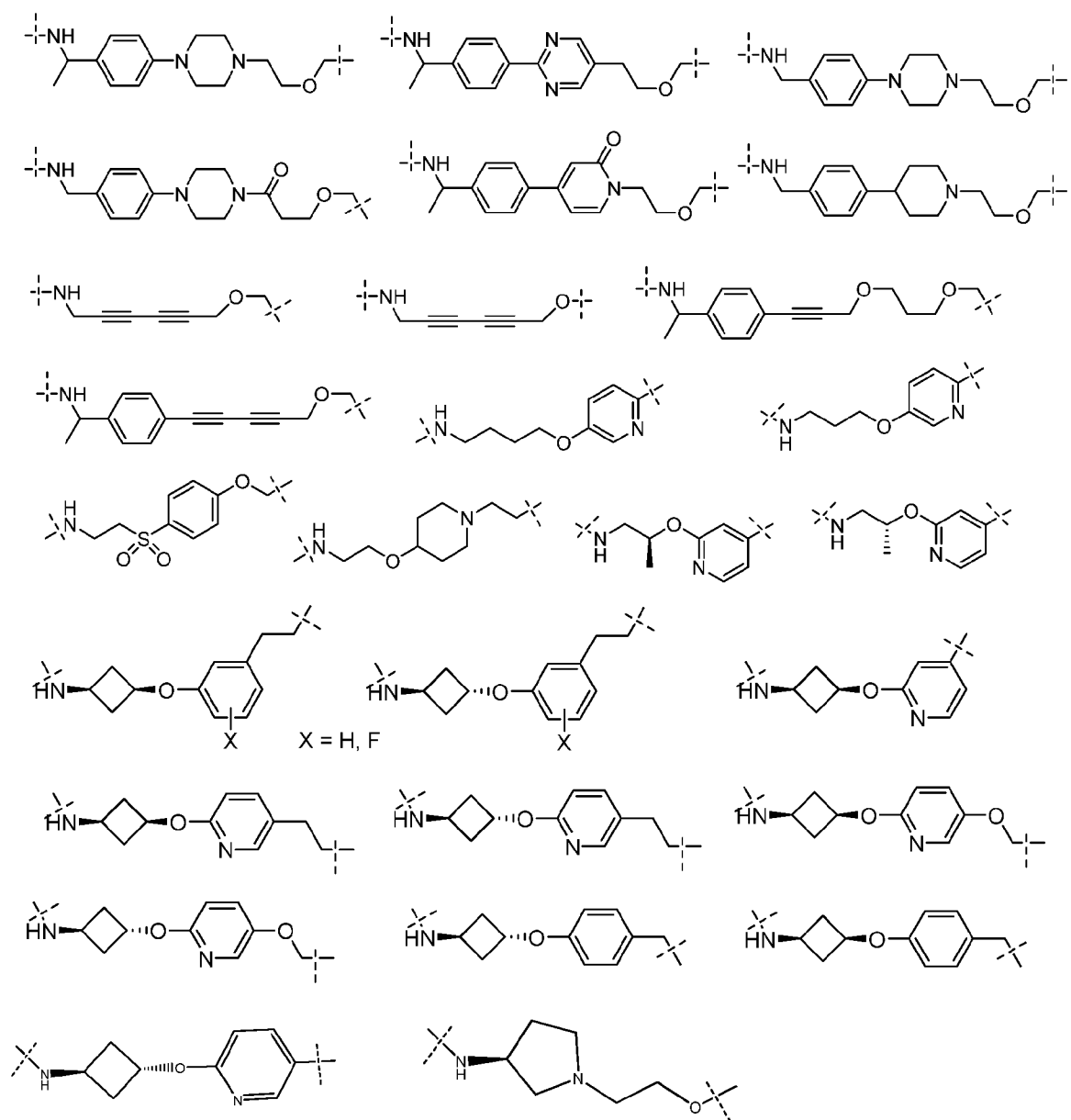
, wherein m, n, o, p, q, and r, are independently 0, 1, 2, 3, 4,

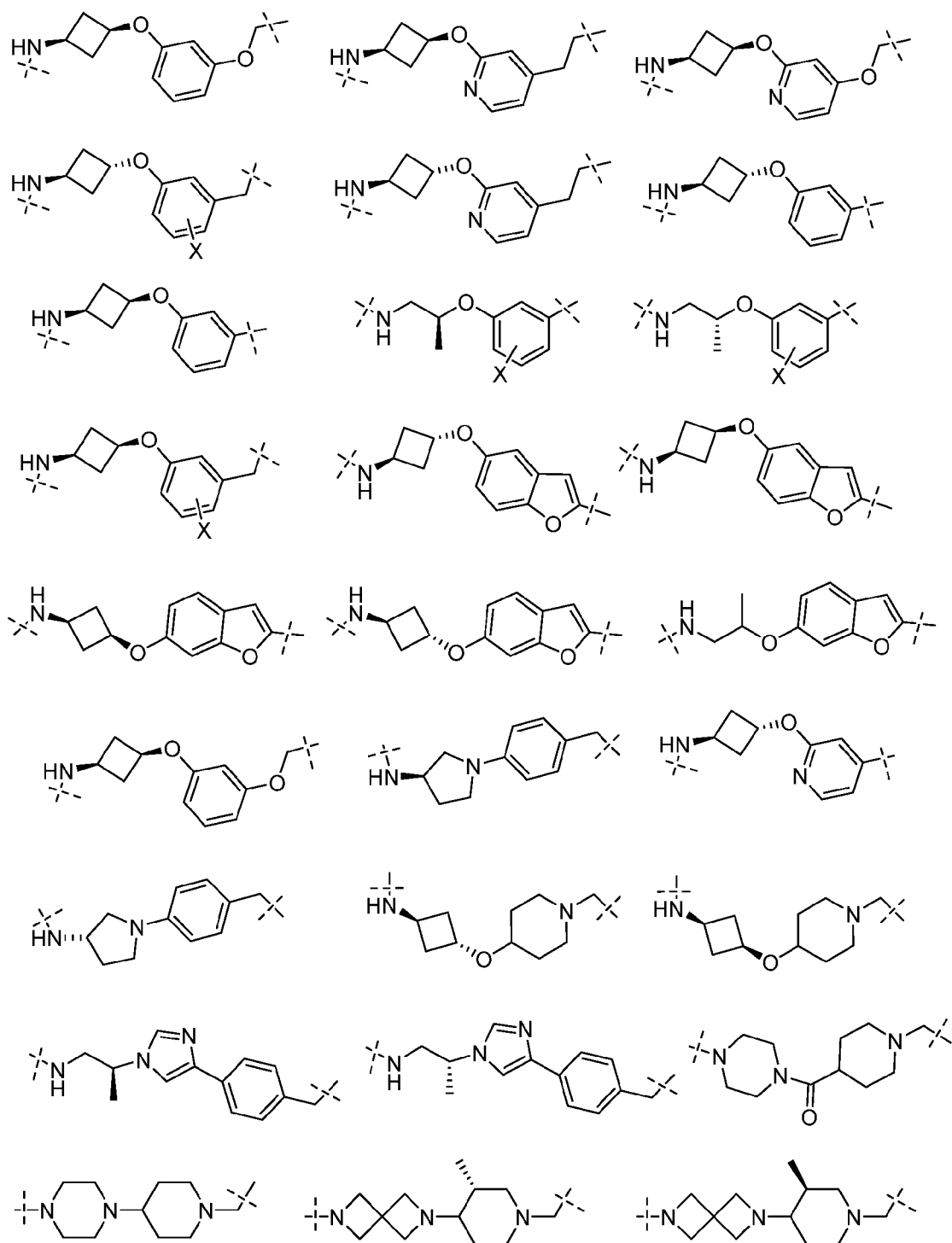
5, with the proviso that when the number is zero, there is no N-O or O-O bond, R is selected from the group H, methyl and ethyl, and X is selected from the group H and F;

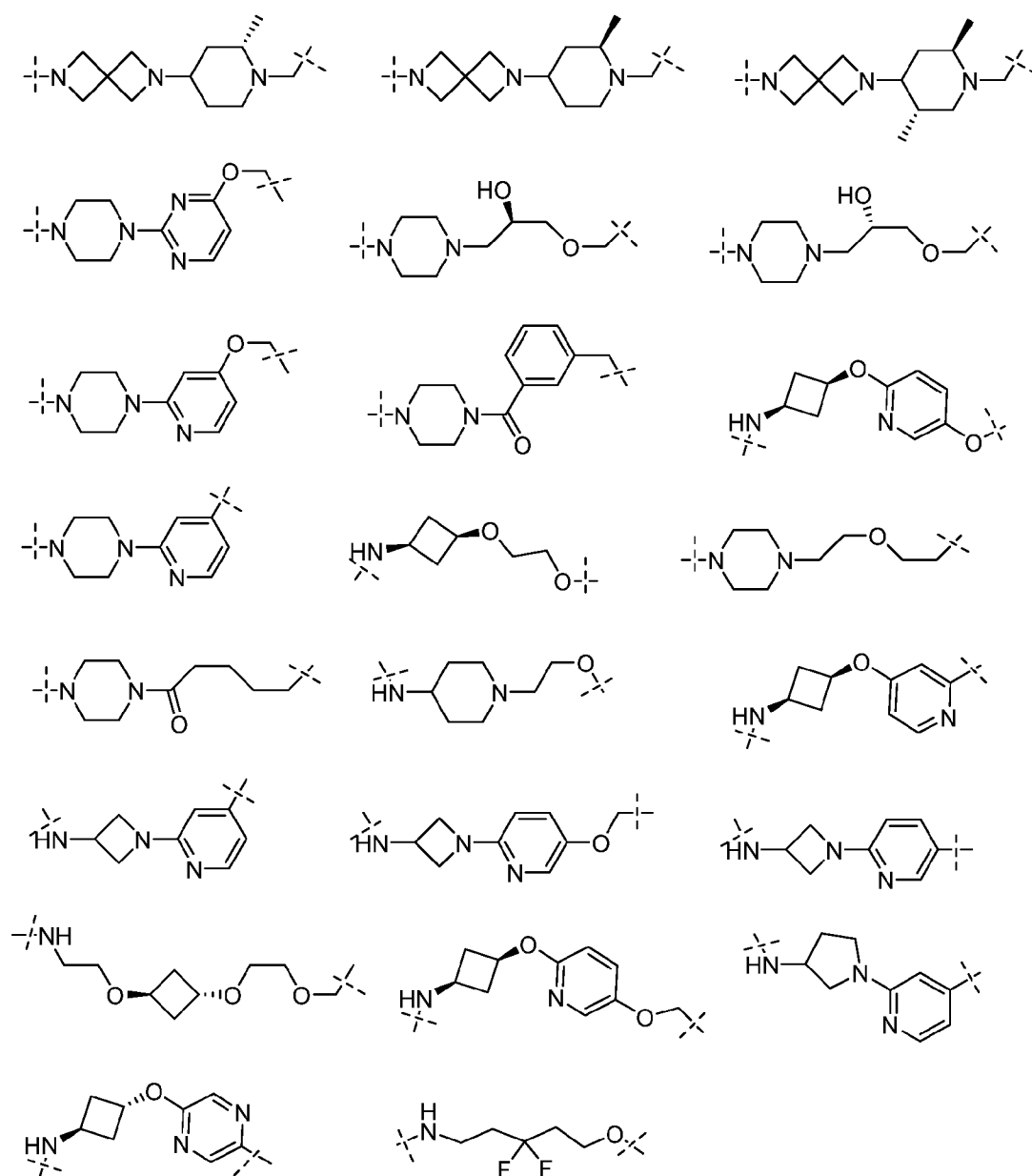




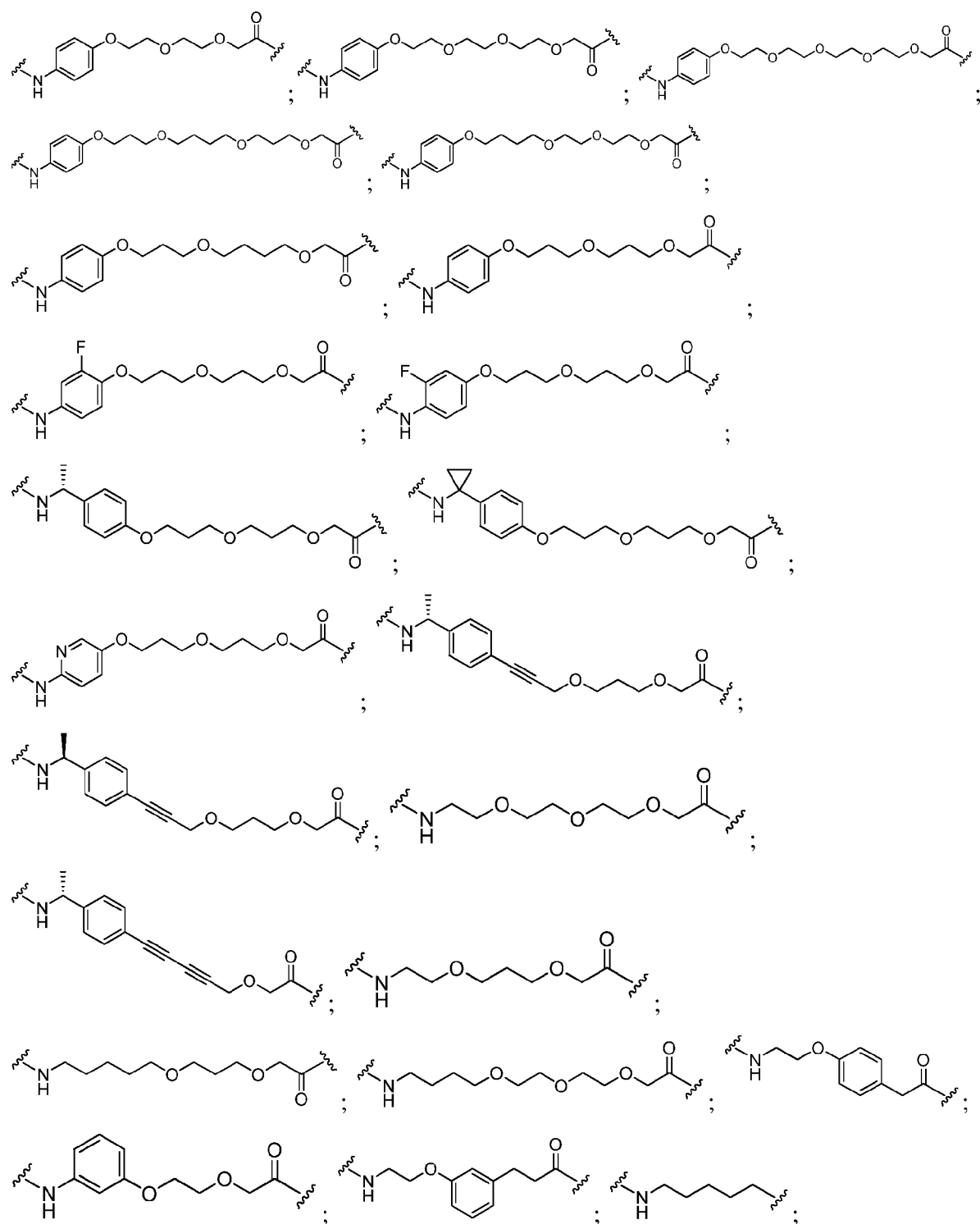


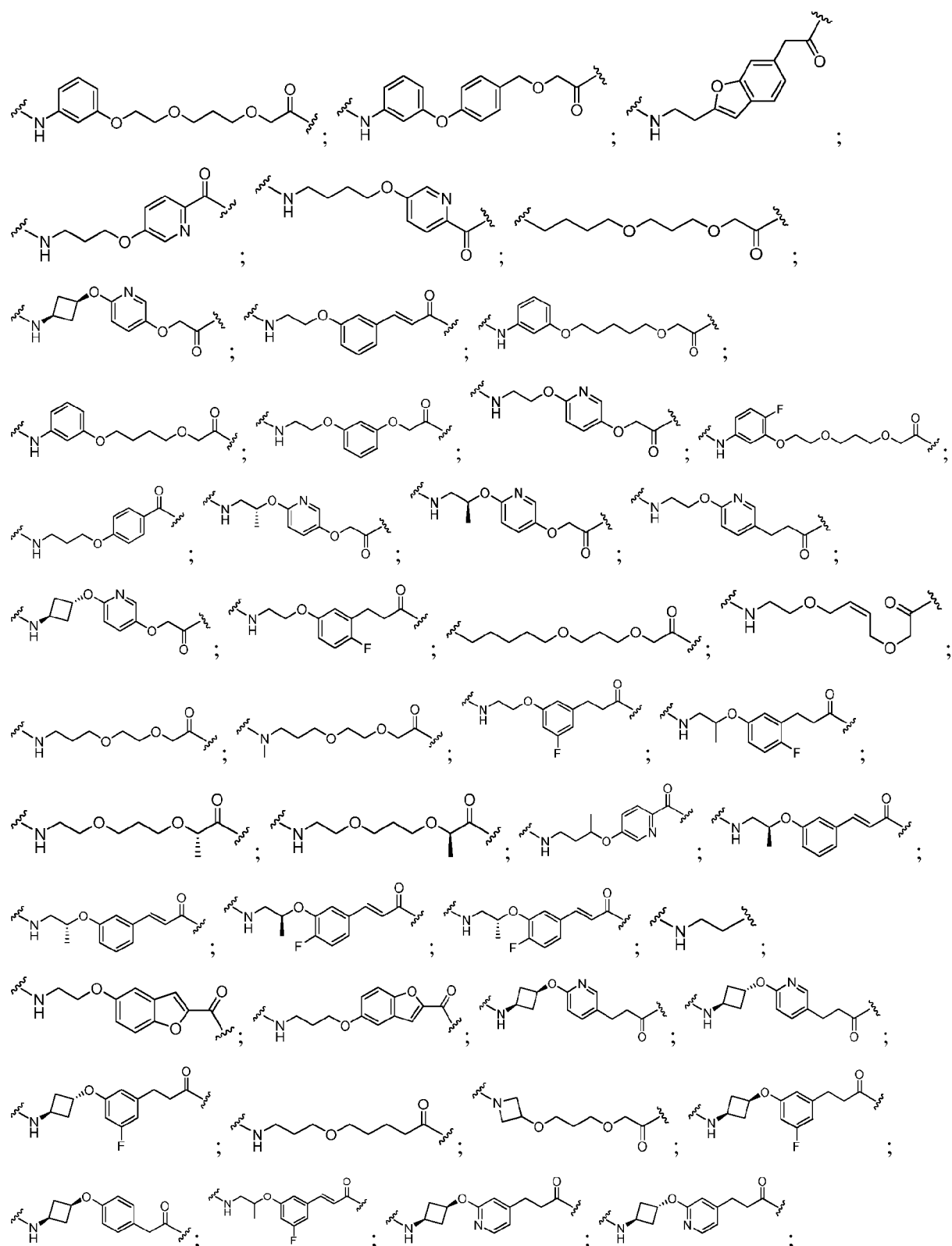


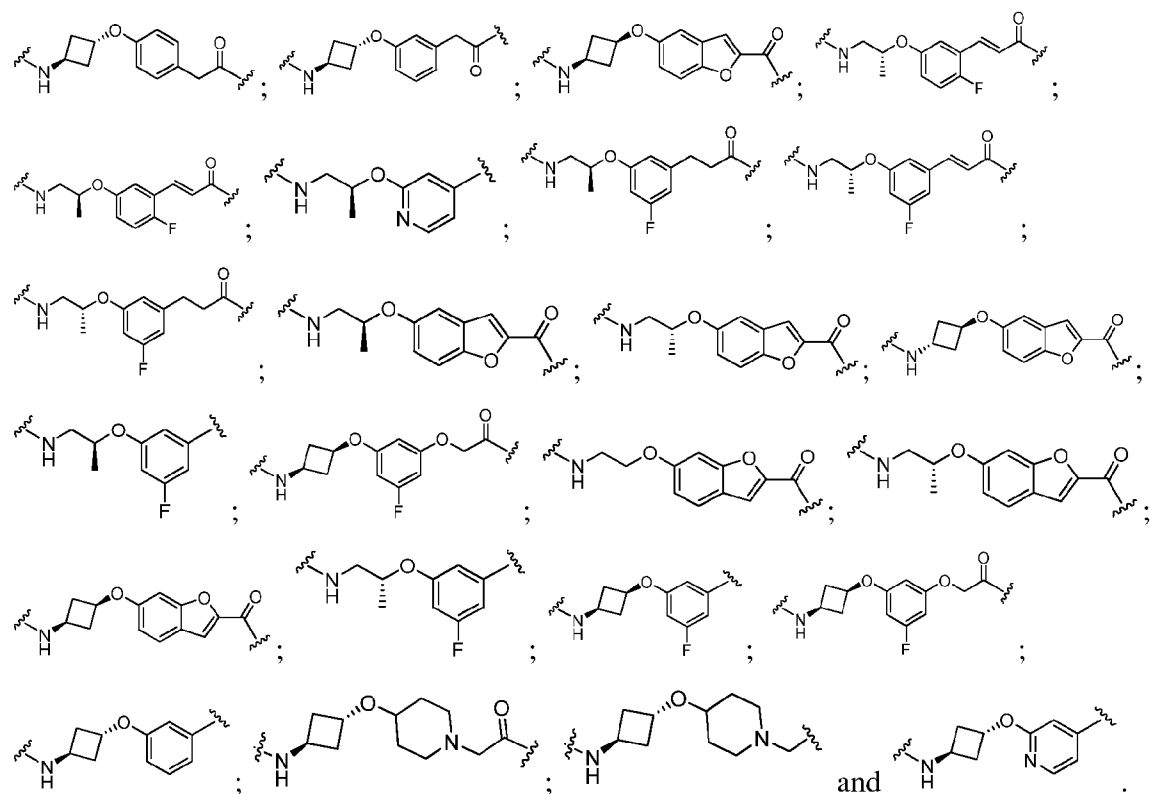




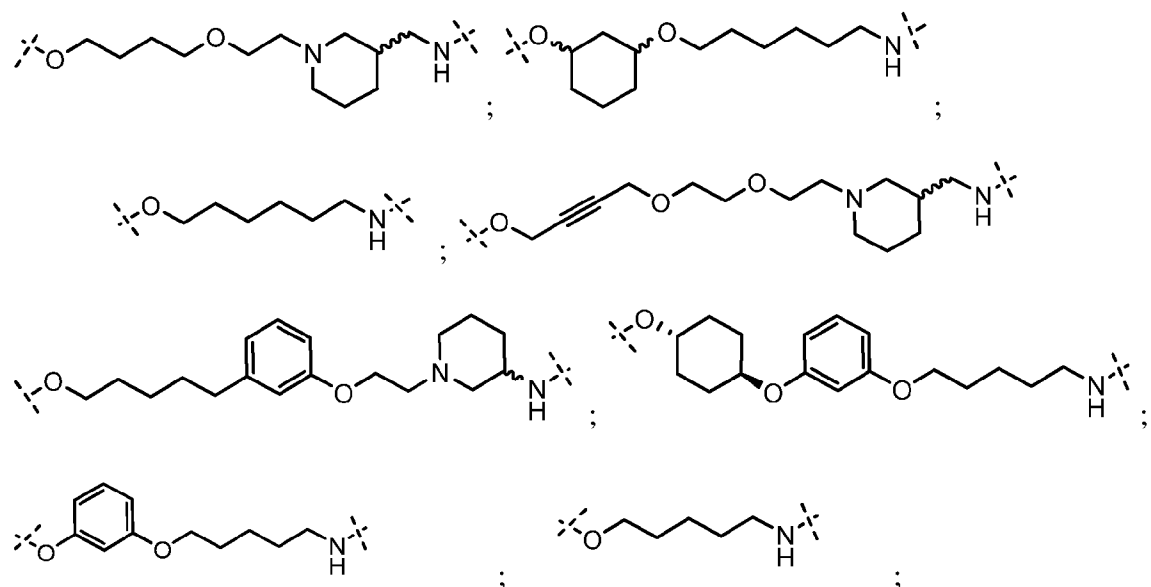
22. The compound according to any of claims 1-20, wherein the linker (L) is selected from the group consisting of:

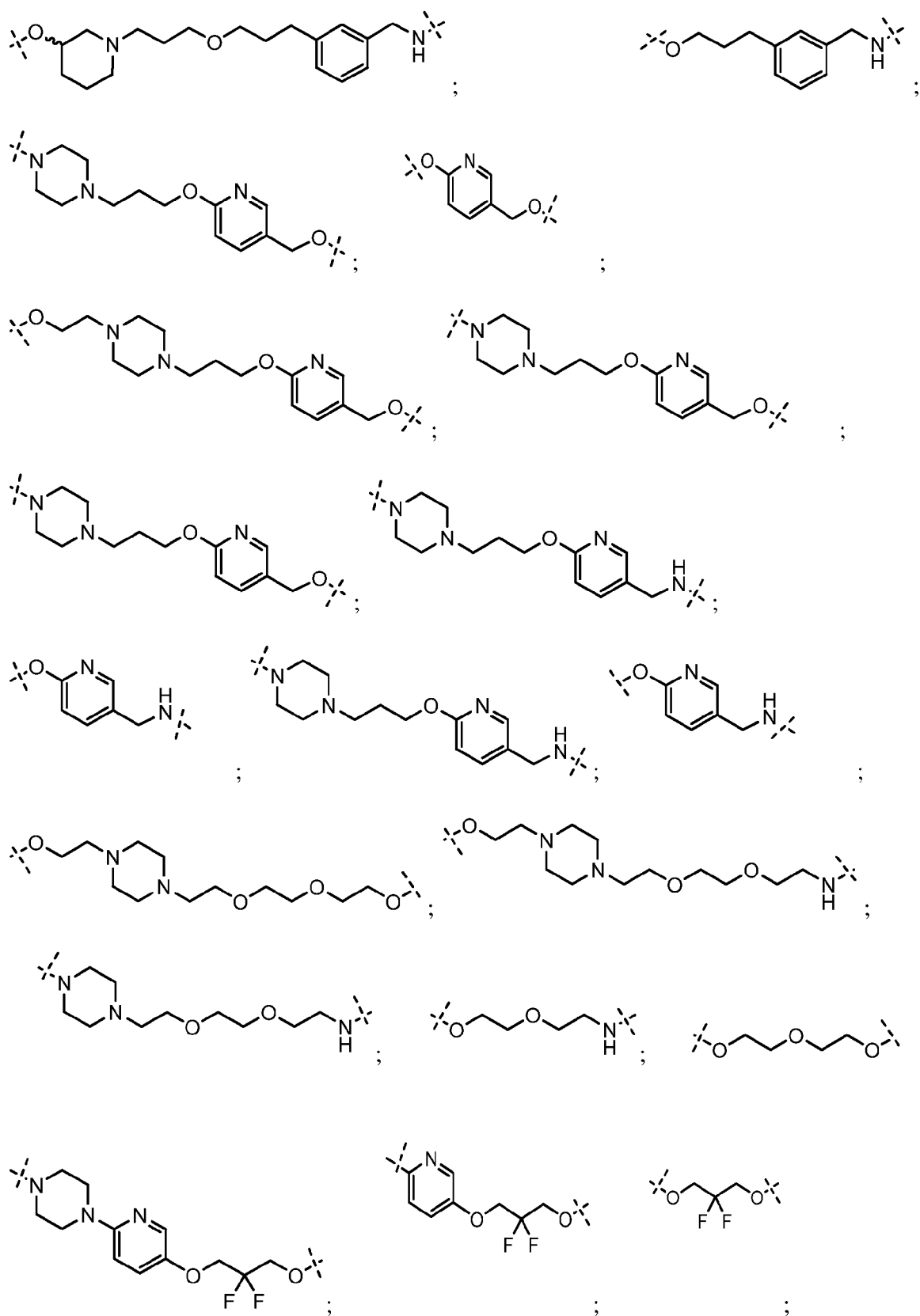


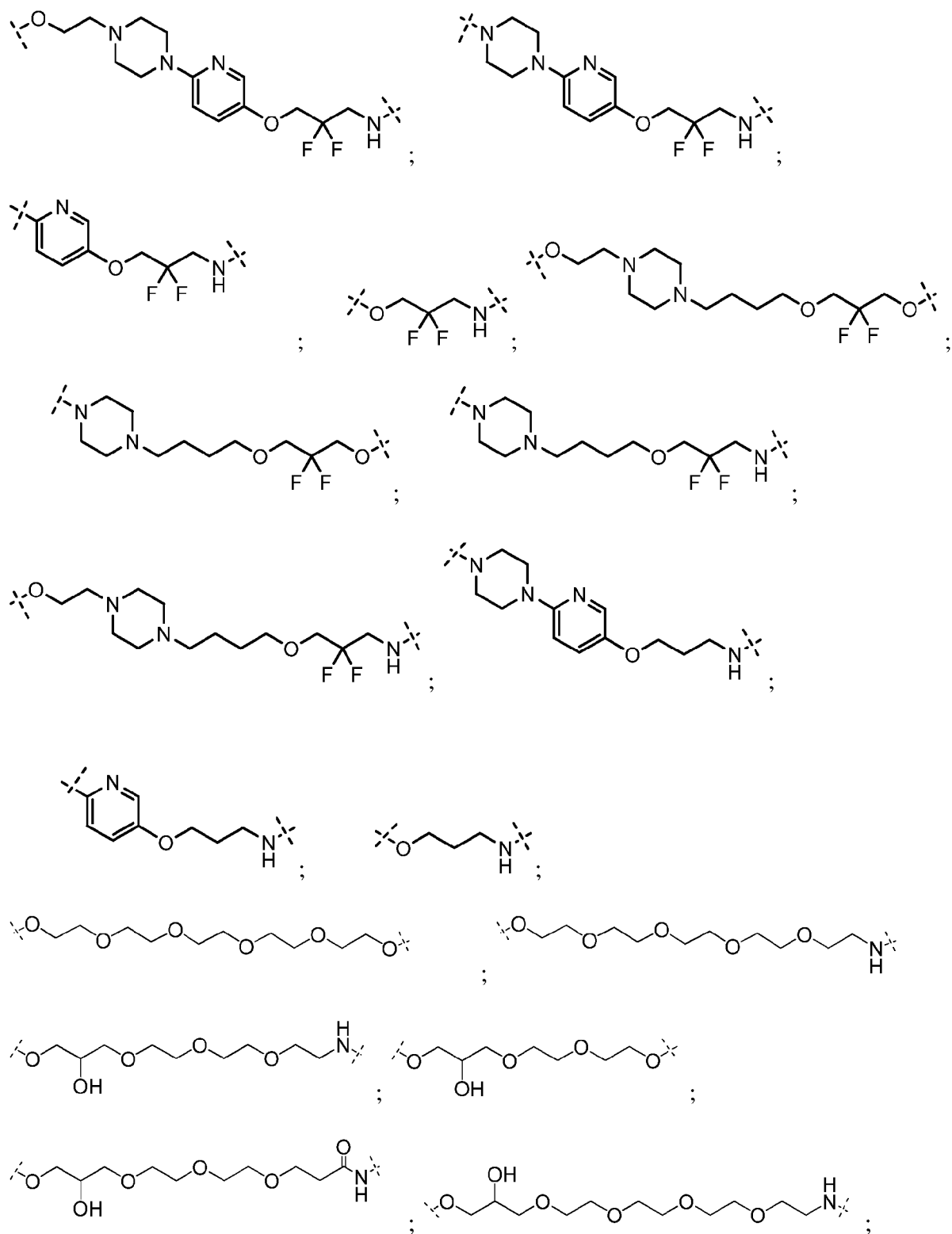


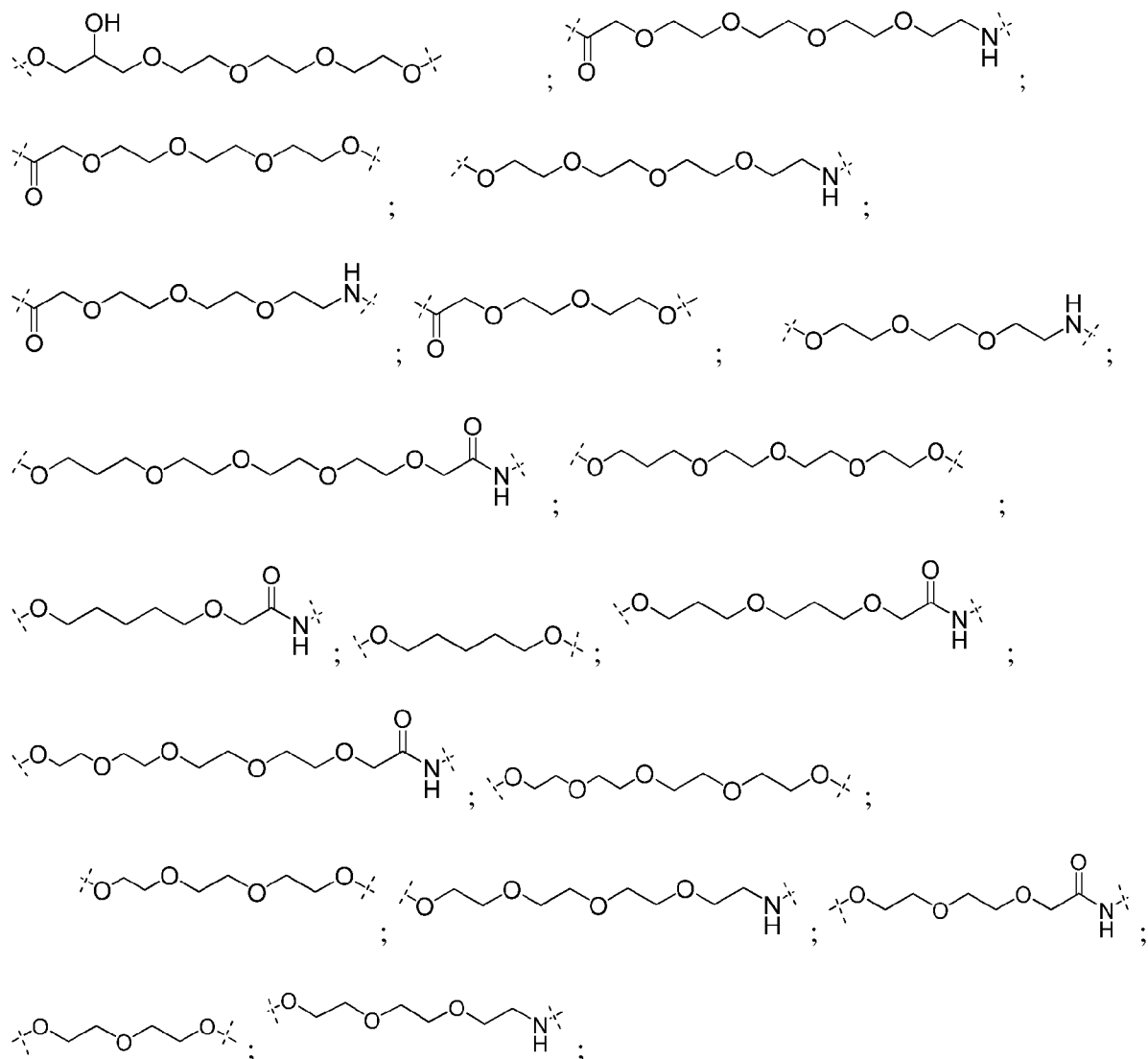


23. The compound according to any of claims 1-20, wherein the linker (L) is selected from the group consisting of:





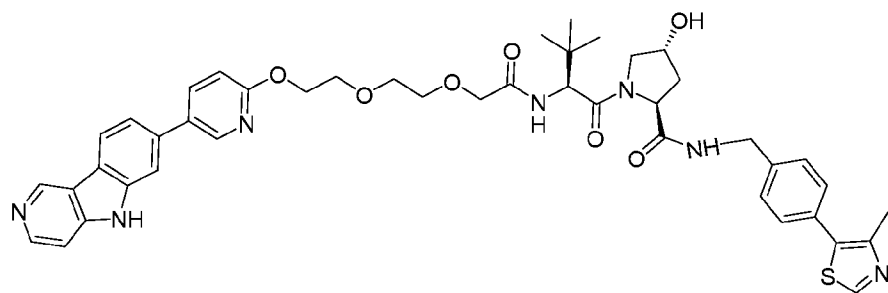
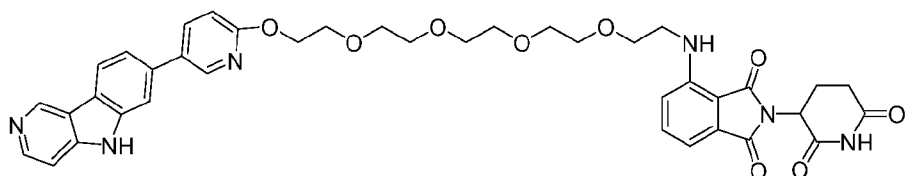
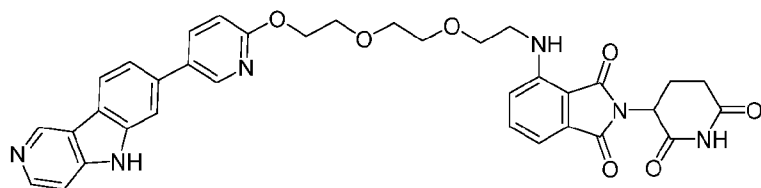
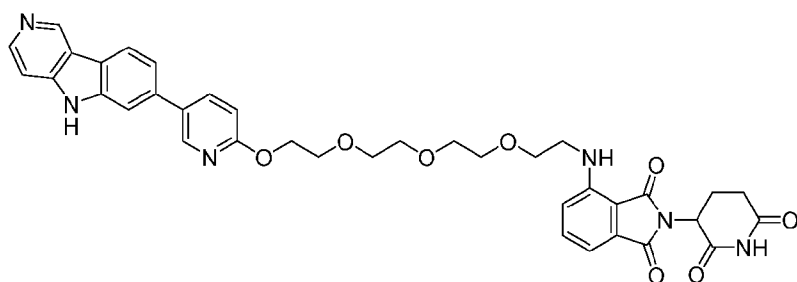
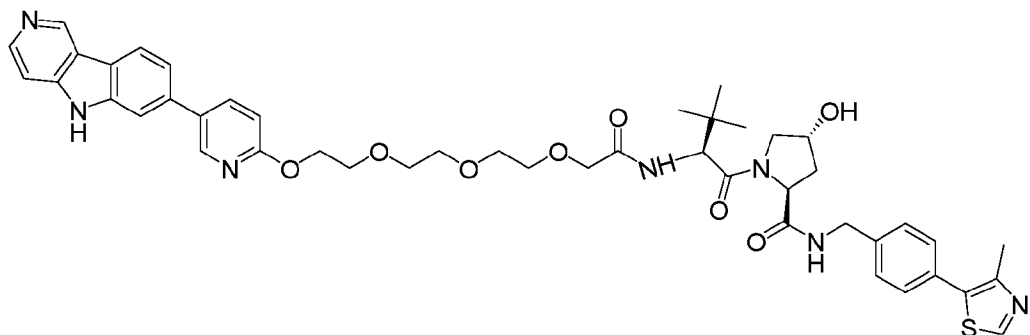


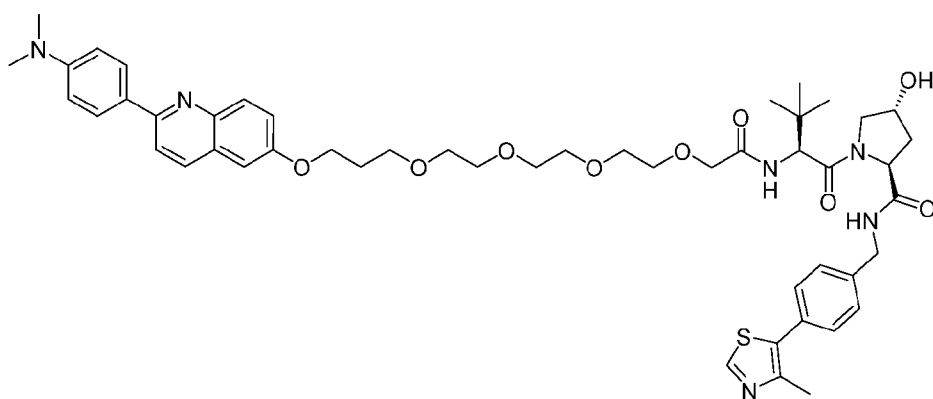
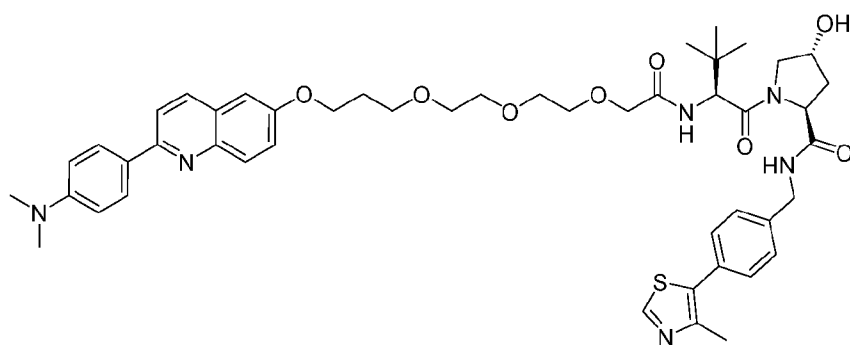
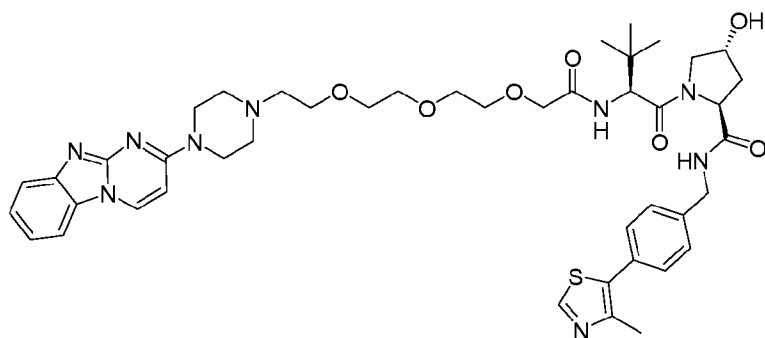
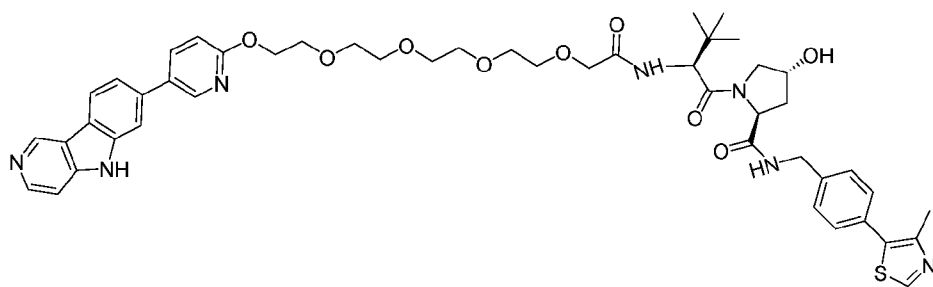


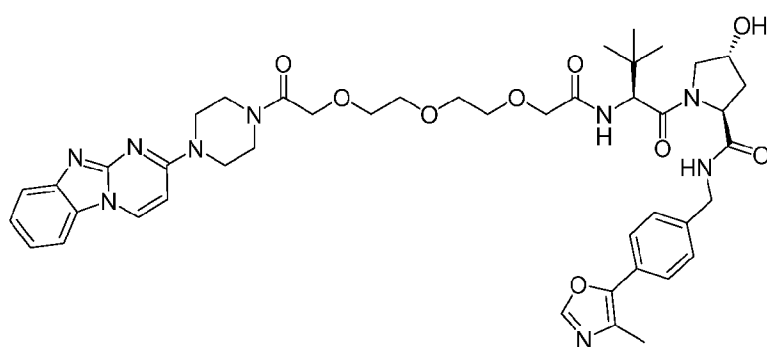
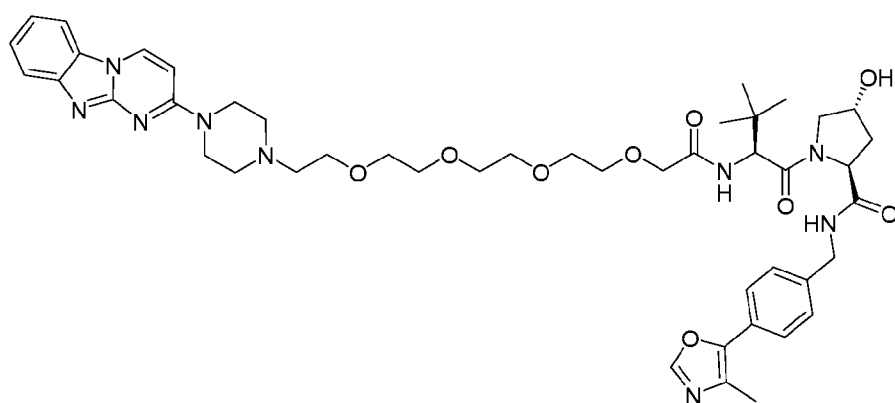
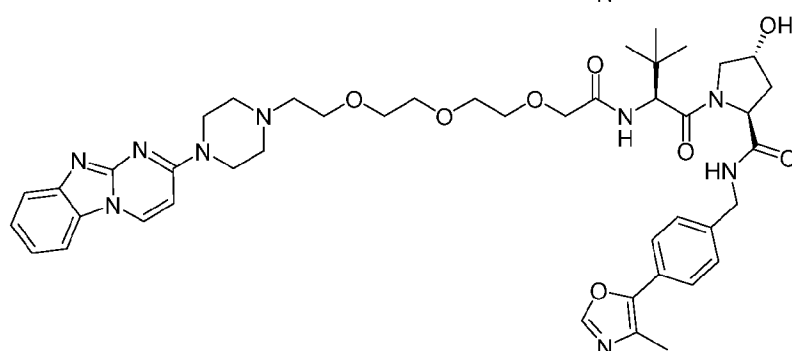
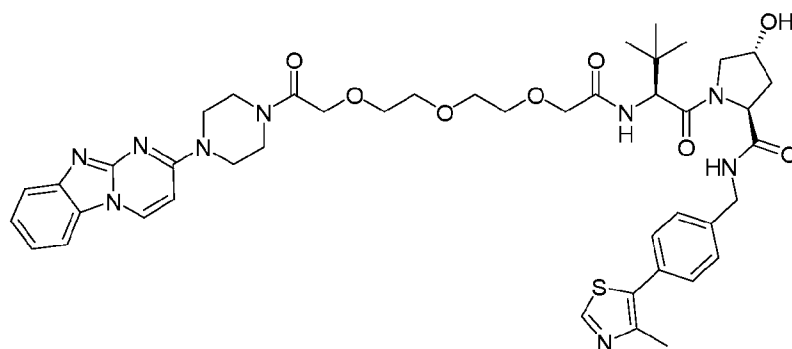
24. The compound according to any of claims 1-20, wherein the L is a polyethylenoxy group optionally substituted with aryl or phenyl comprising from 1 to 10 ethylene glycol units.

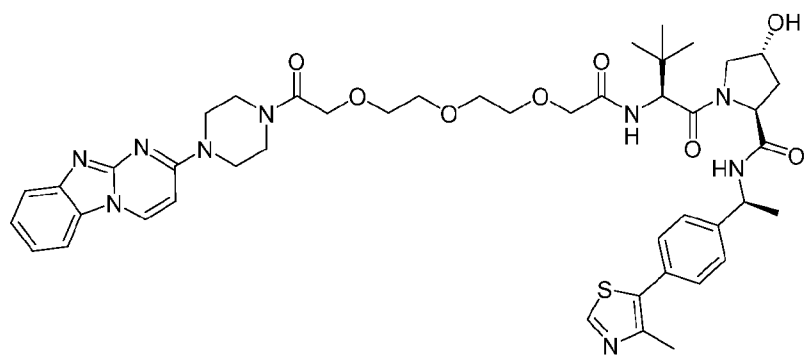
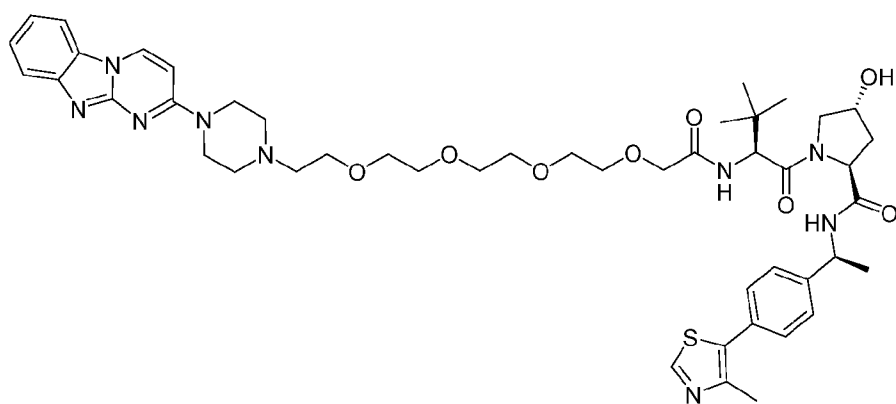
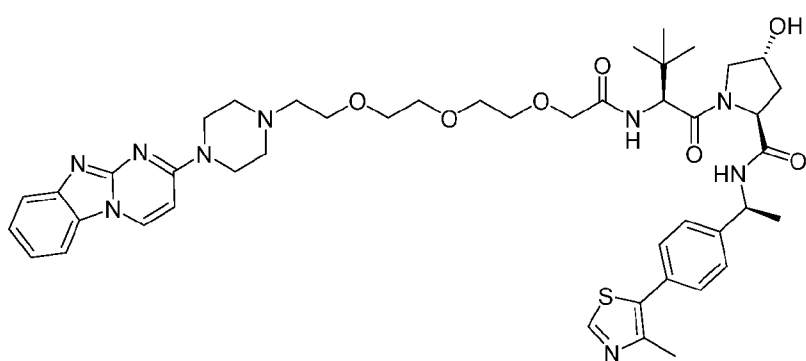
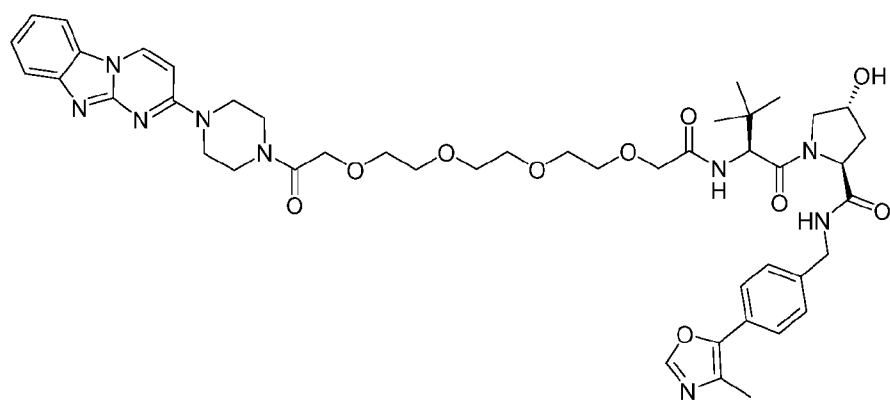
25. The compound according to any one of claims 1-24, wherein the compound comprises multiple ULMs, multiple PTMs, multiple linkers or any combinations thereof.

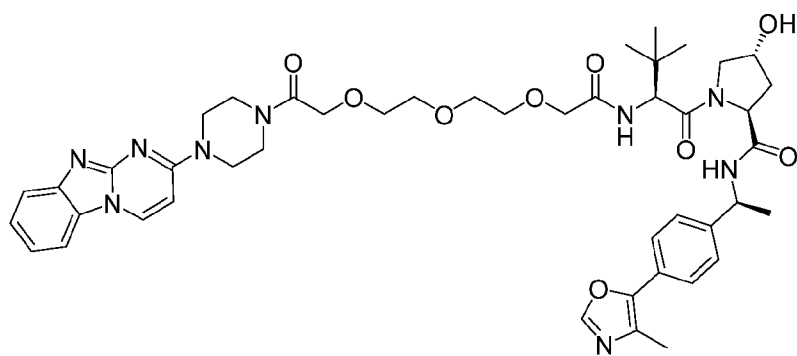
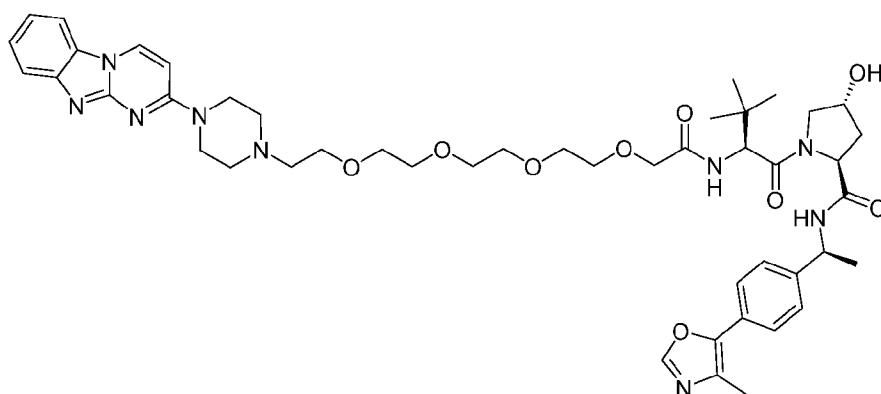
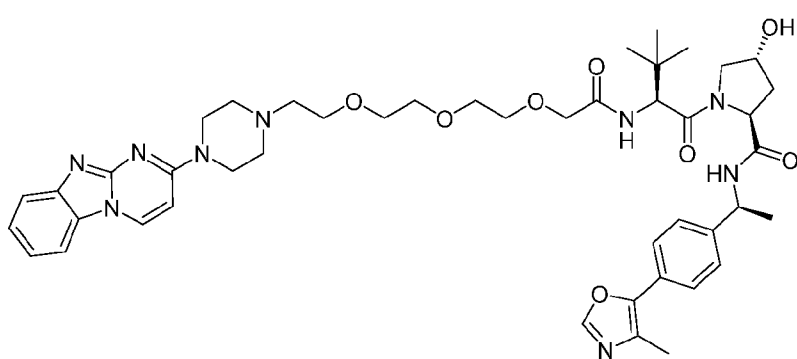
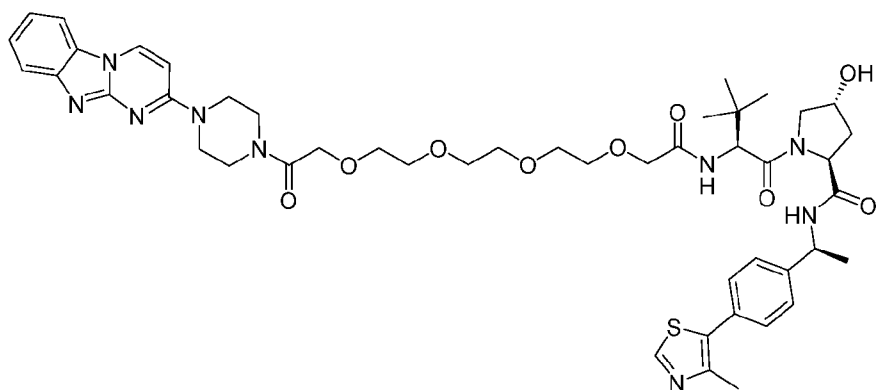
26. The bifunctional compound of claim 1, wherein the compound is selected from the group consisting of:

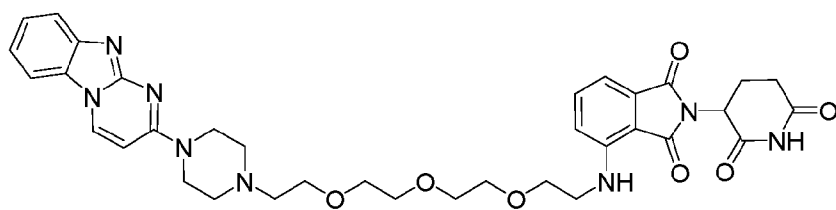
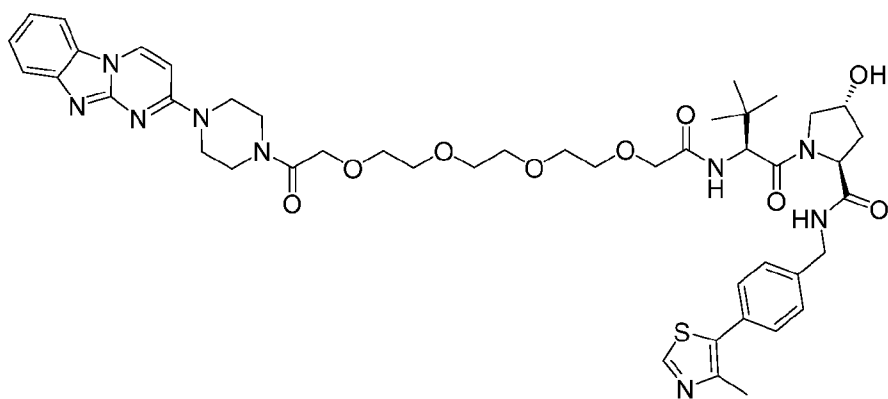
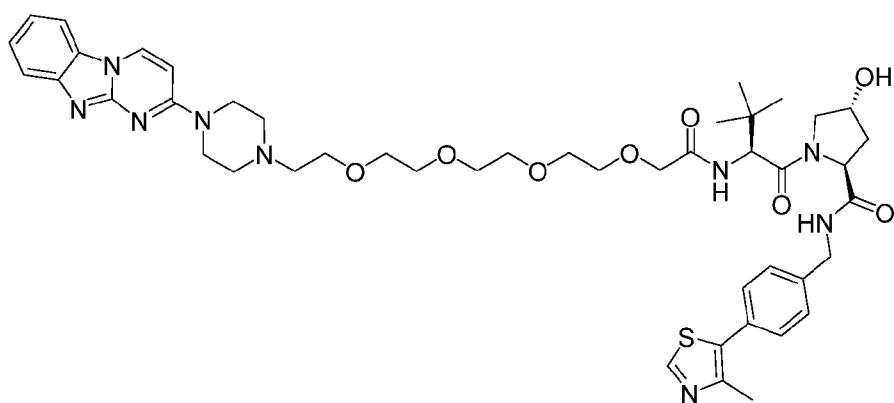
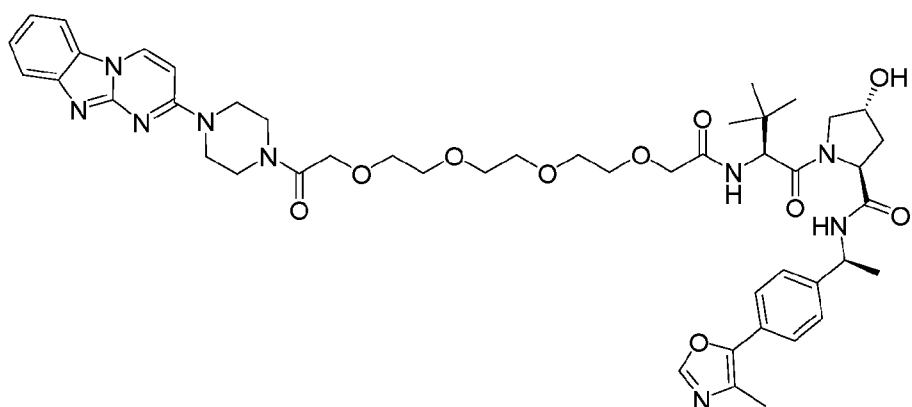


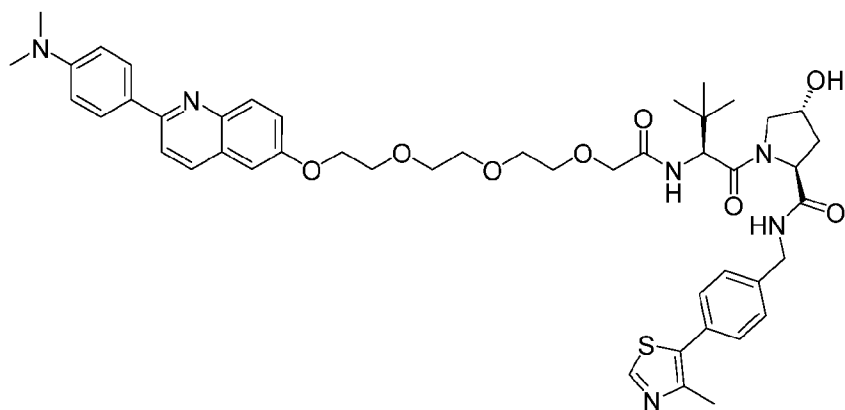
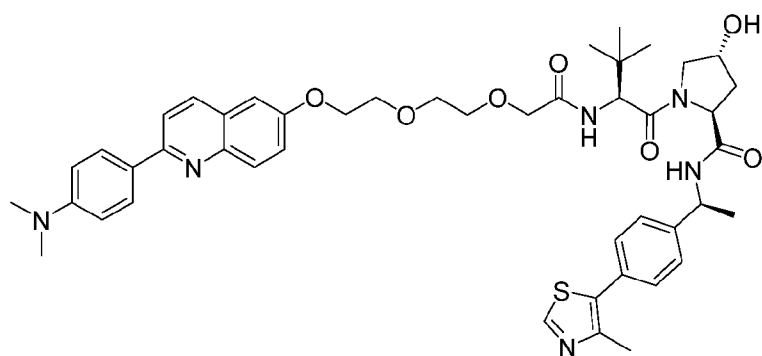
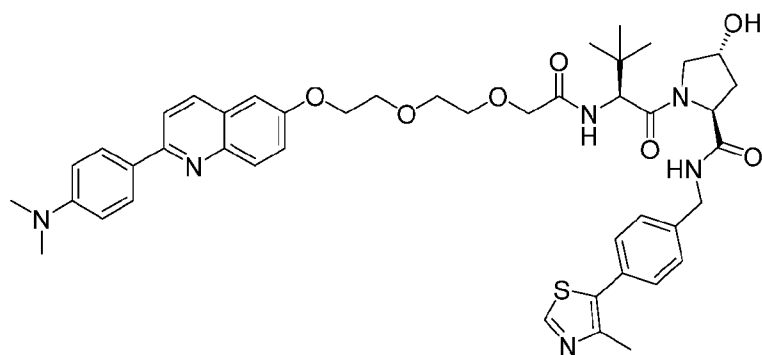
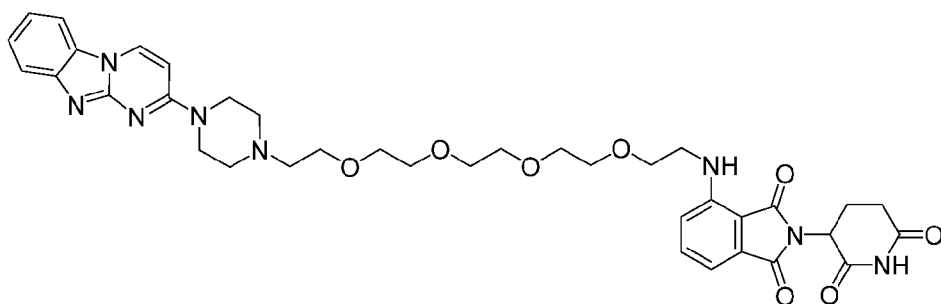


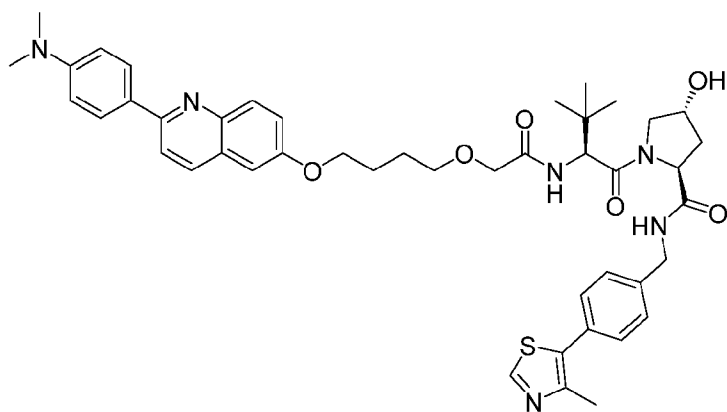
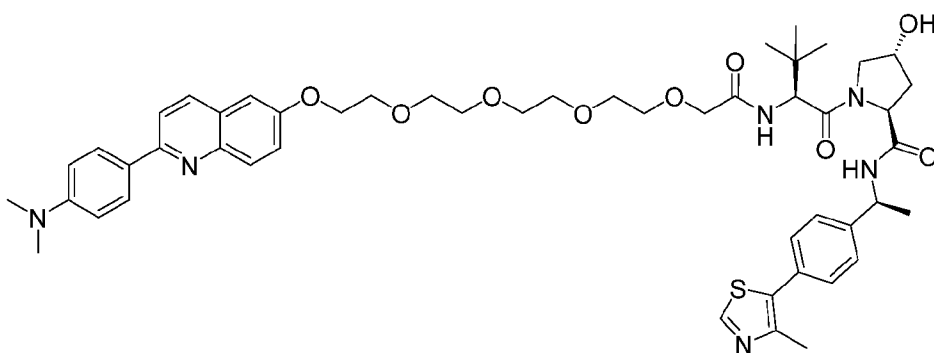
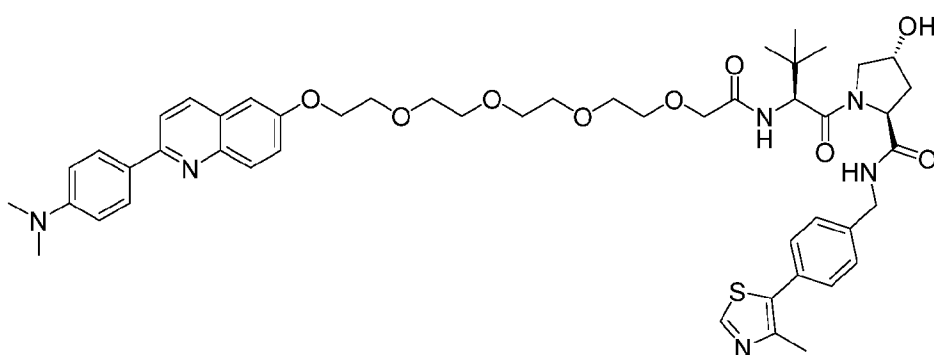
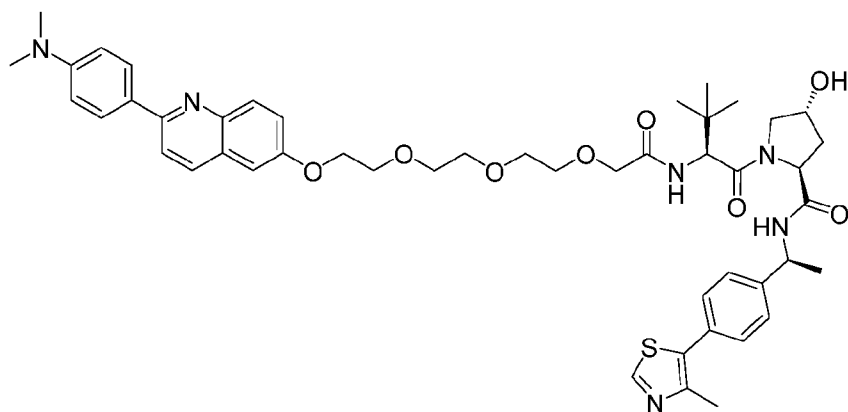


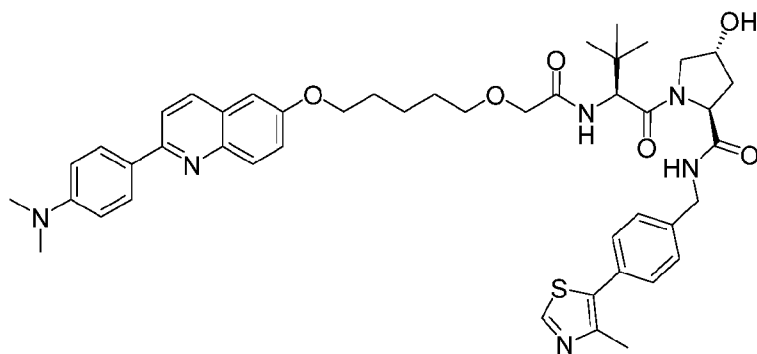
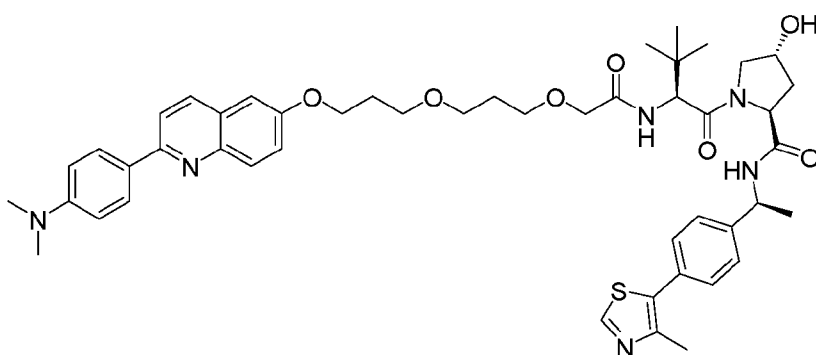
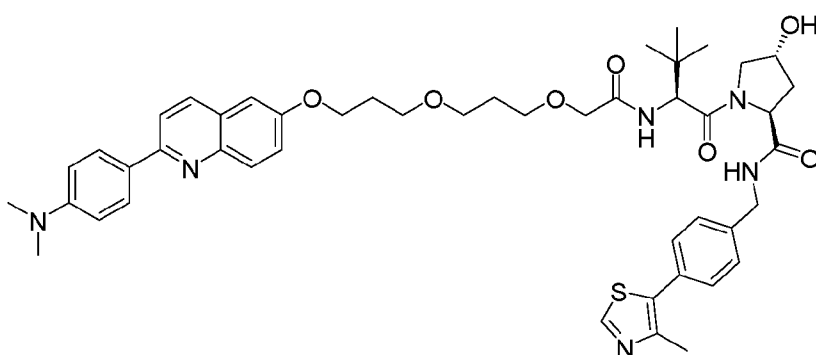
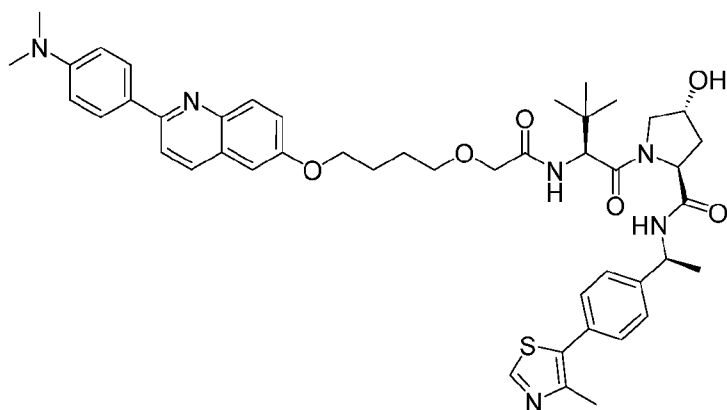


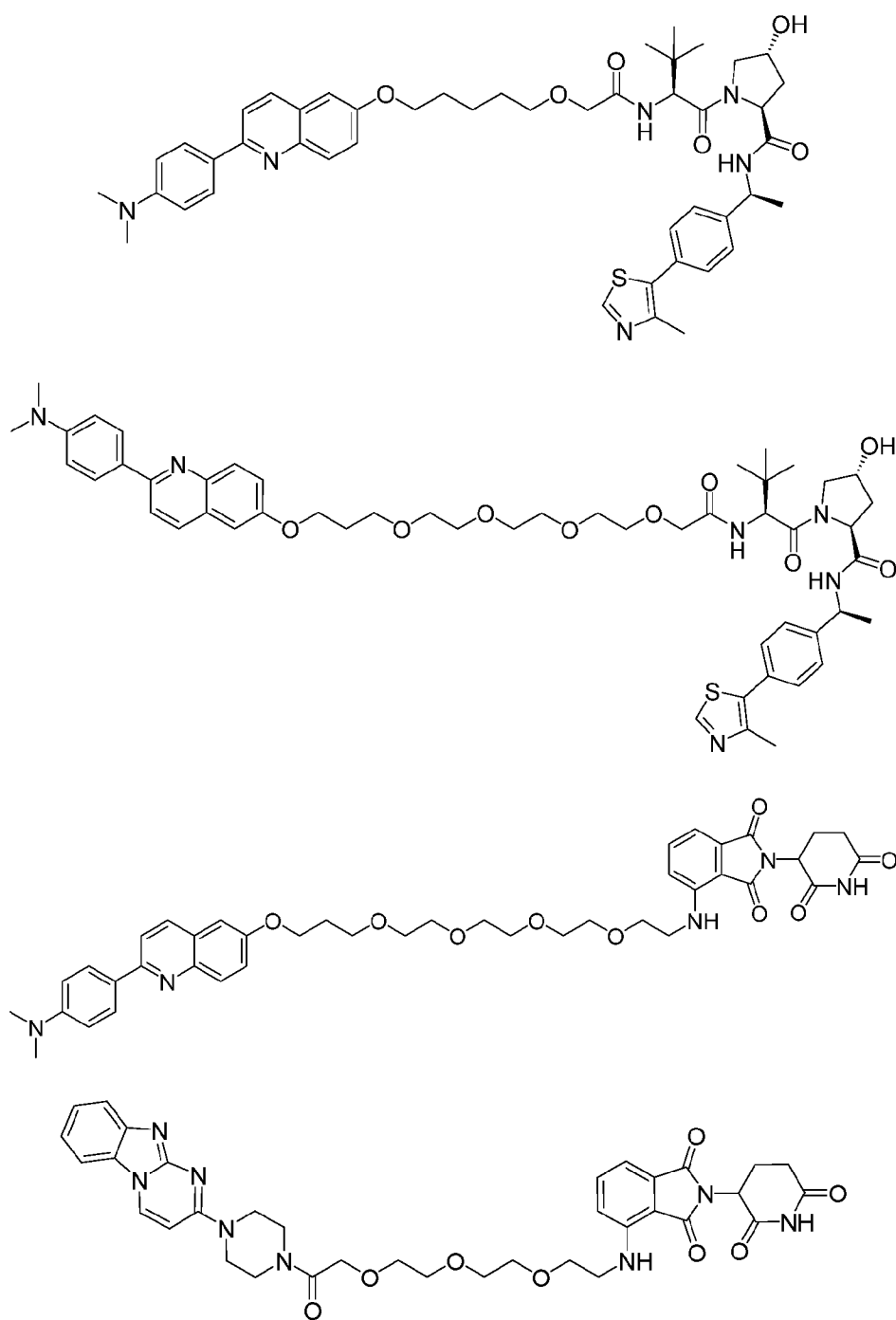


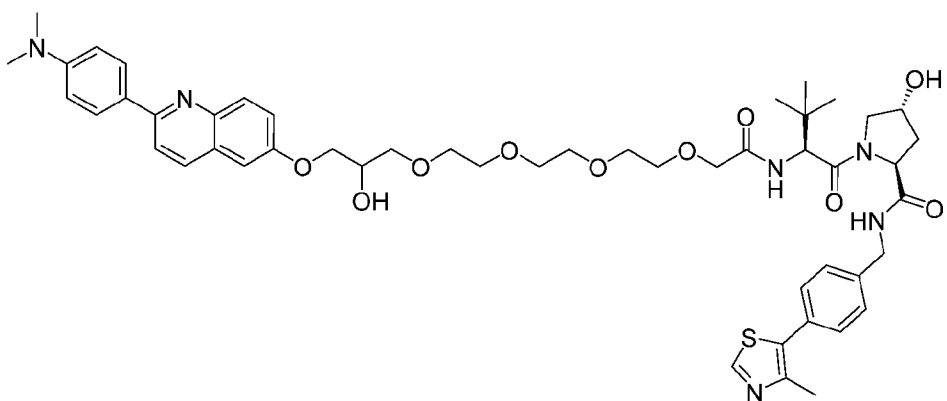
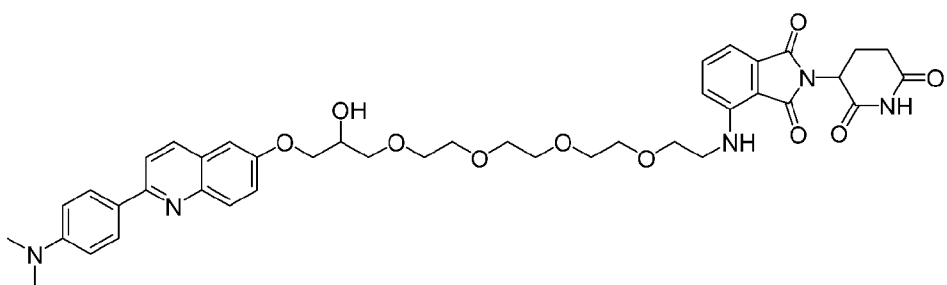
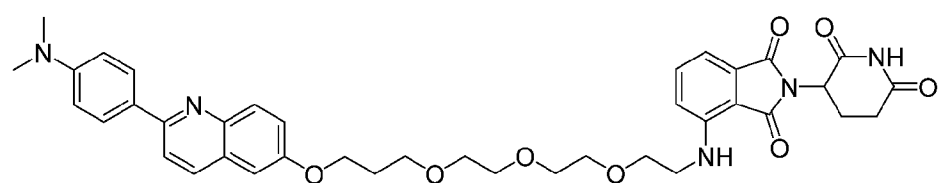
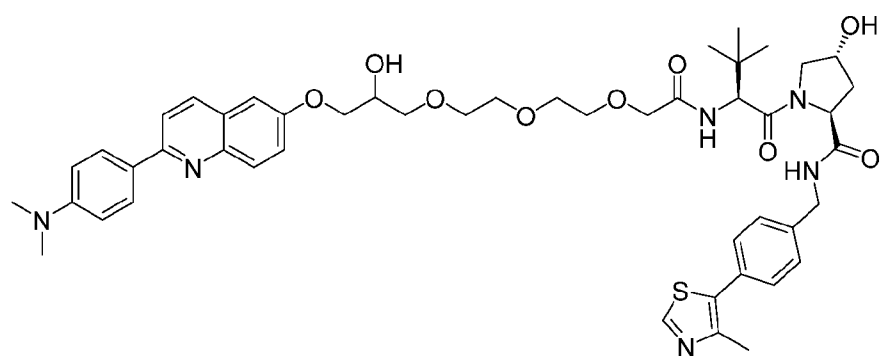
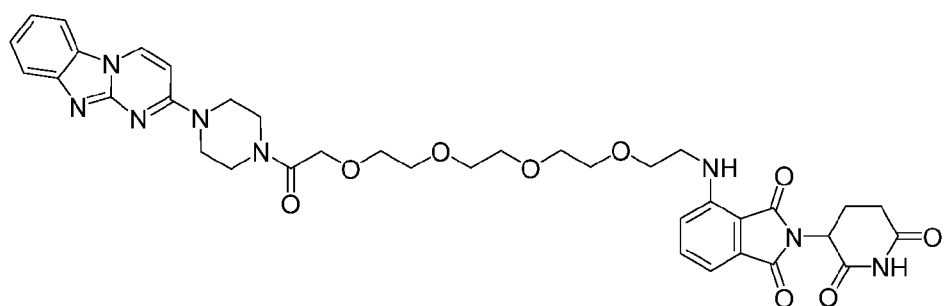


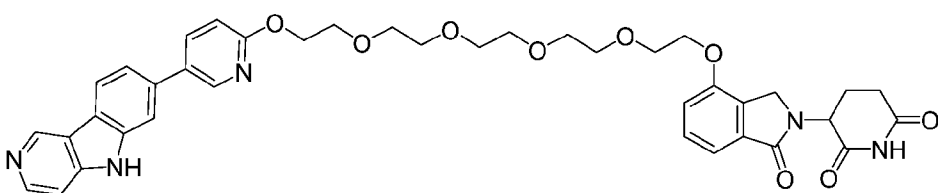
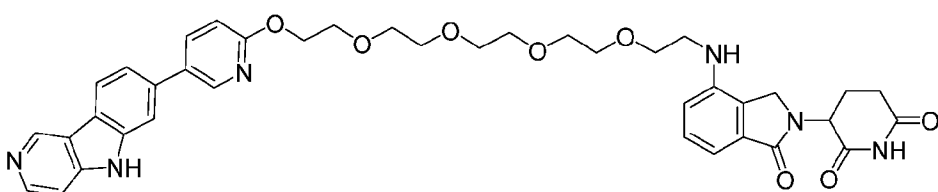
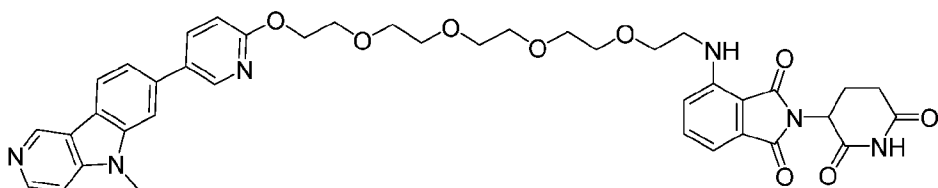
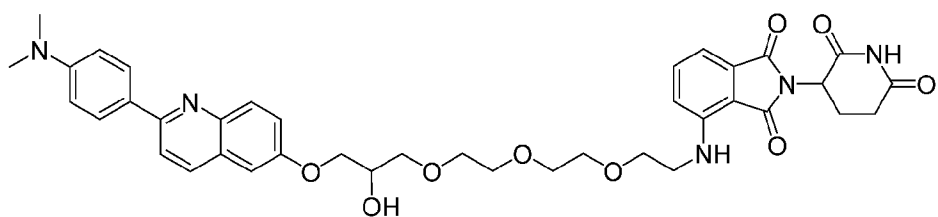




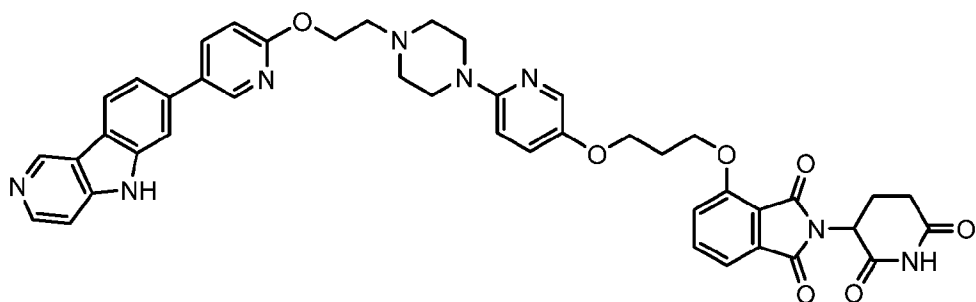


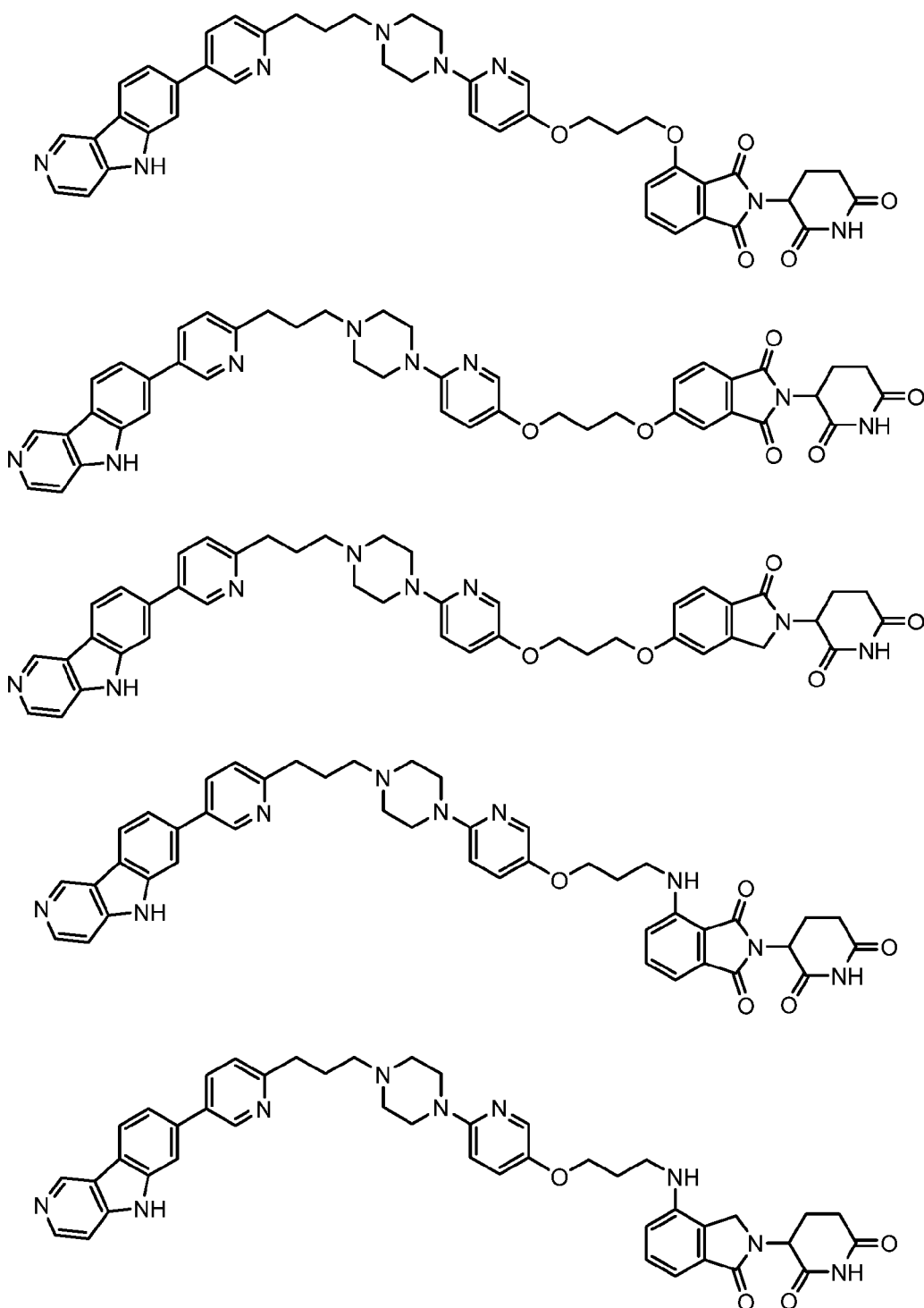


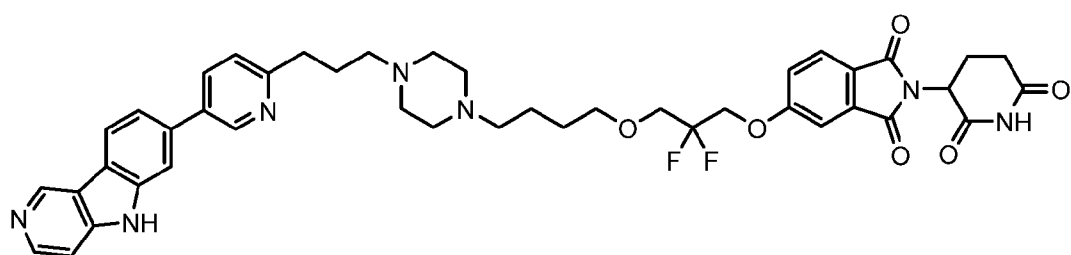
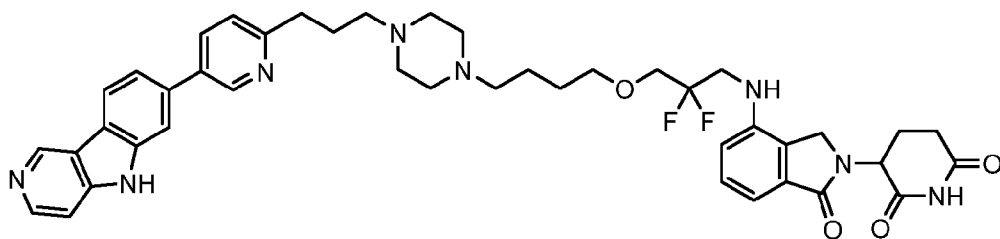
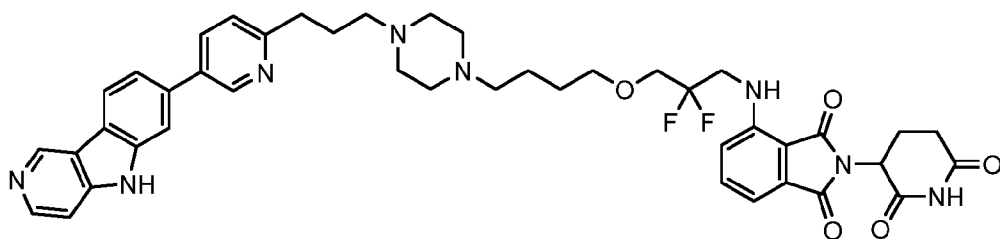
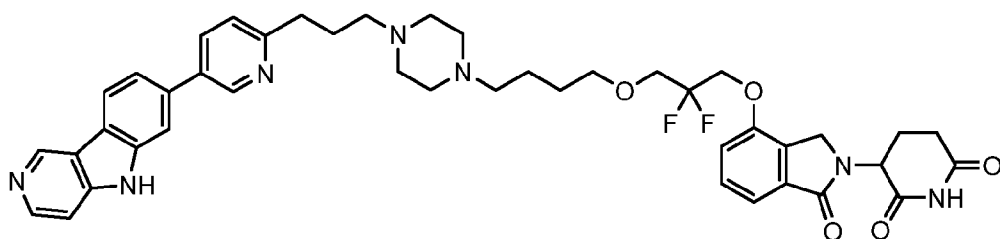
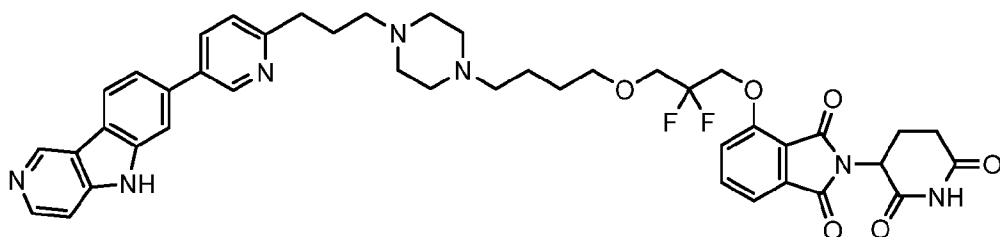
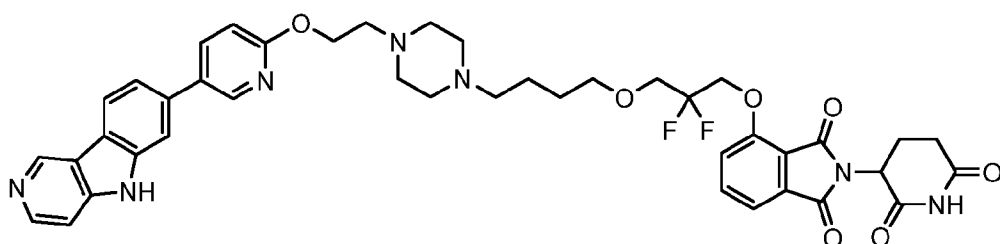


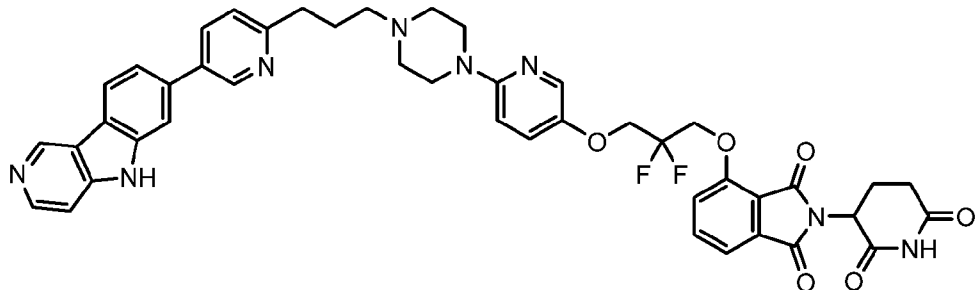
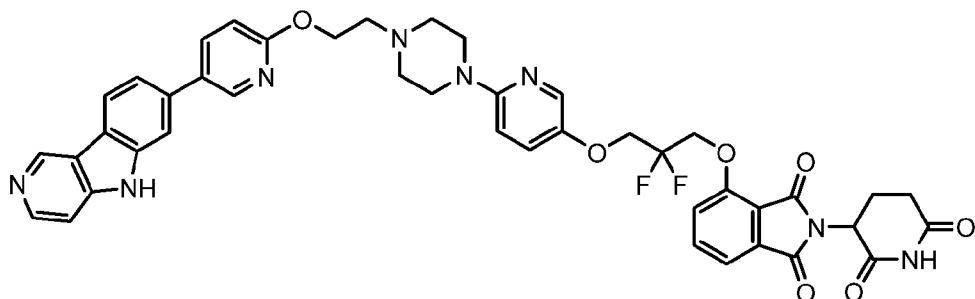
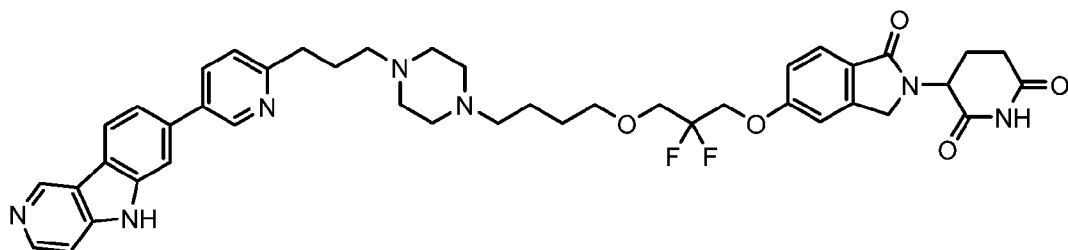
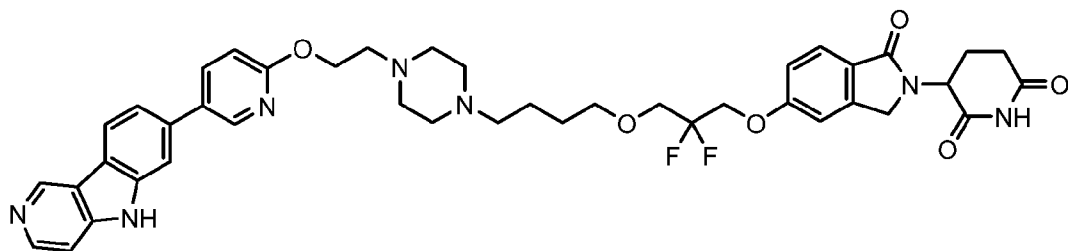
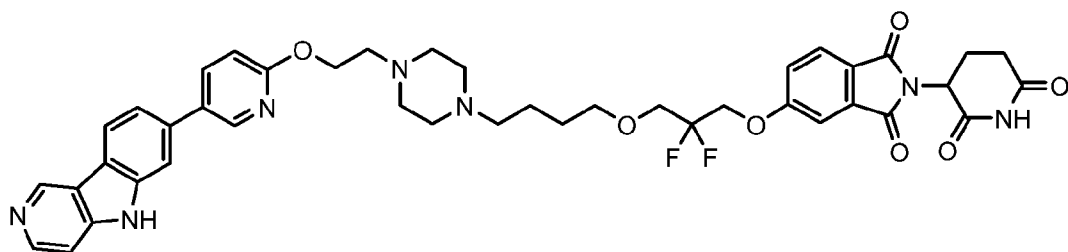


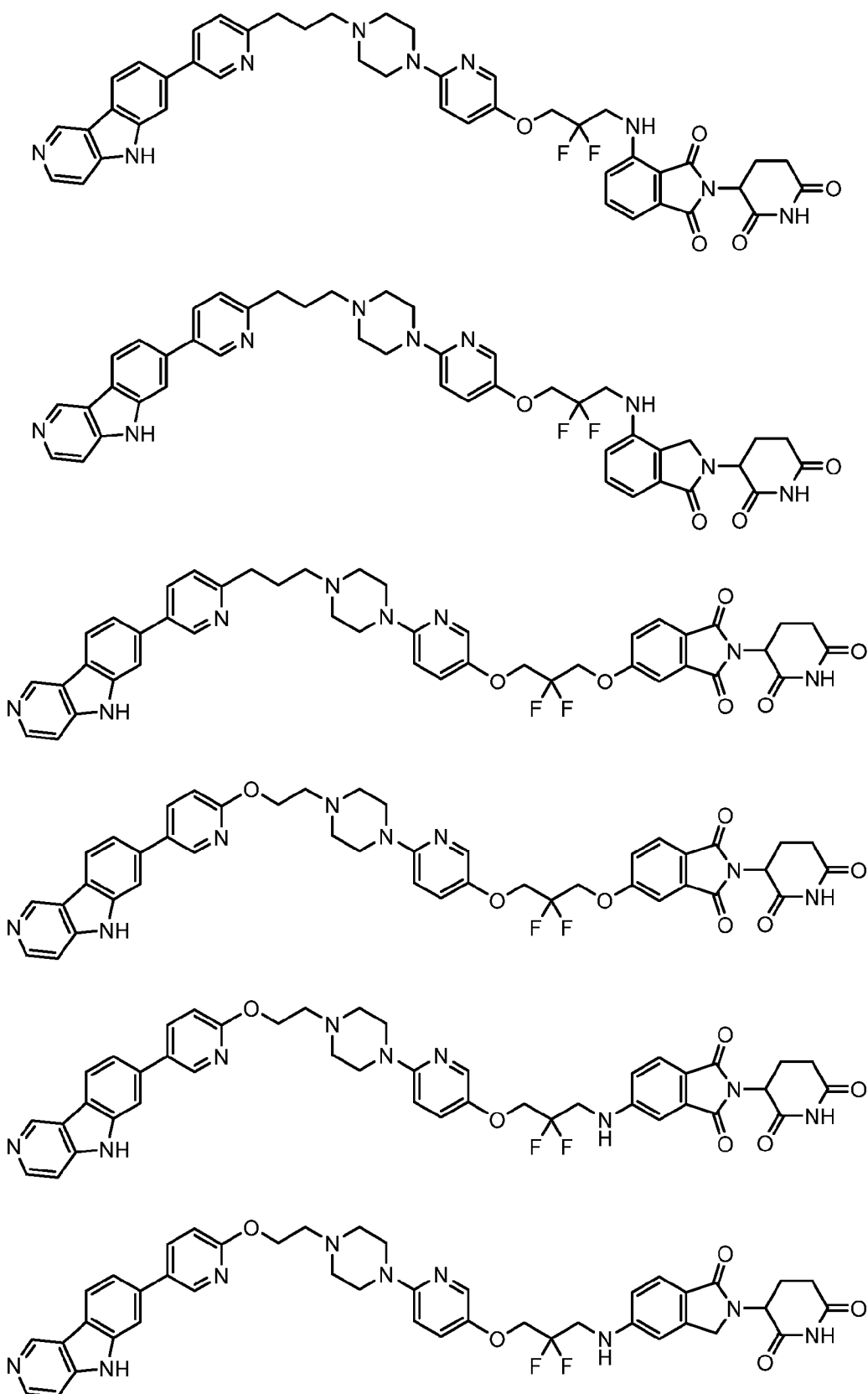
27. The bifunctional compound of claim 1, wherein the compound is selected from the group consisting of:

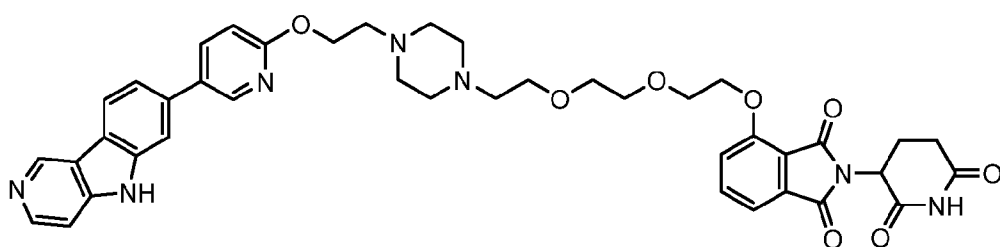
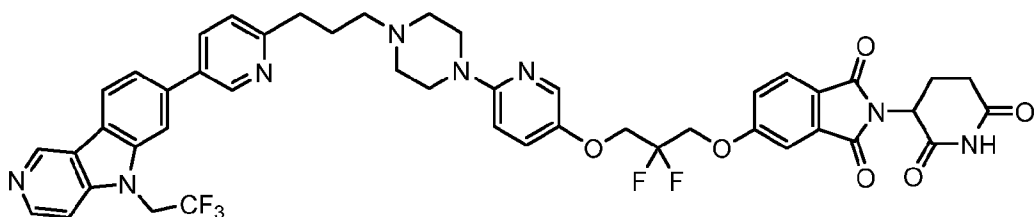
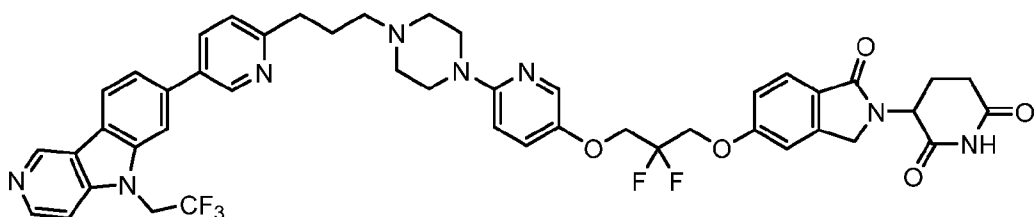
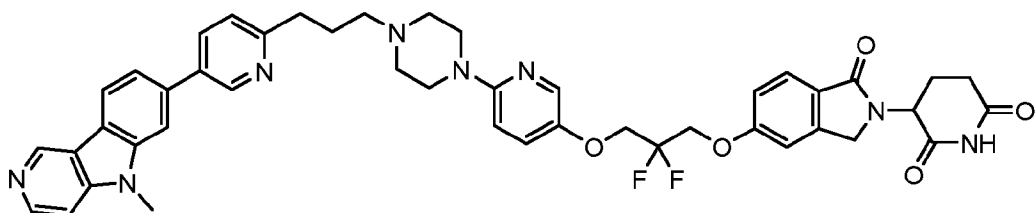
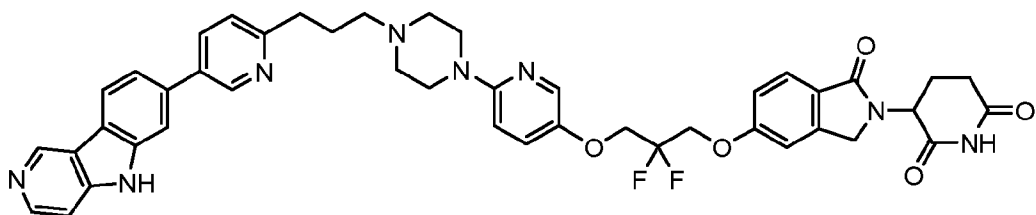


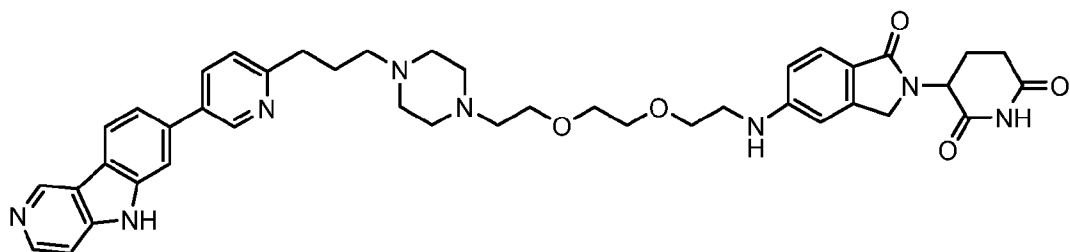
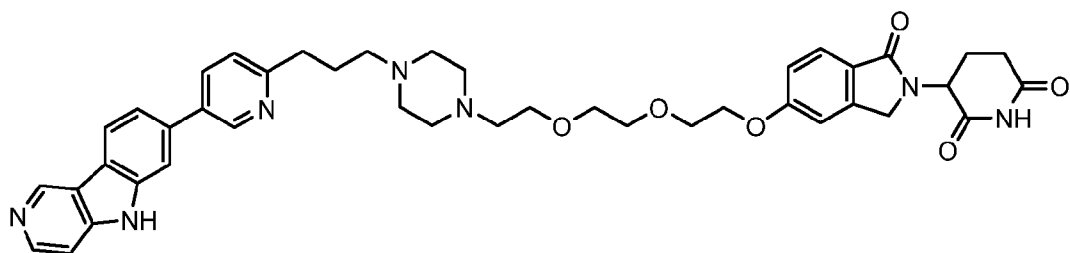
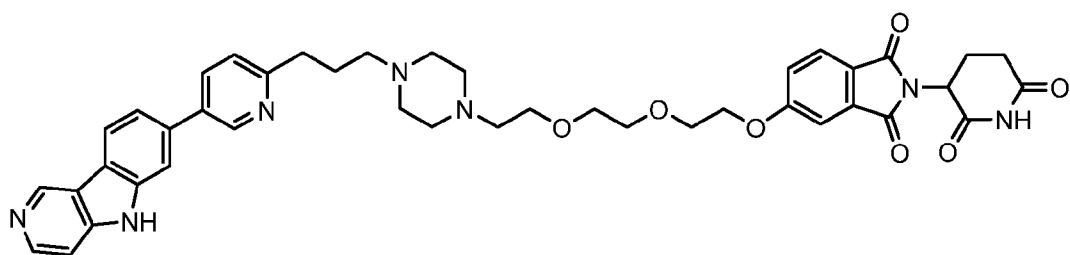
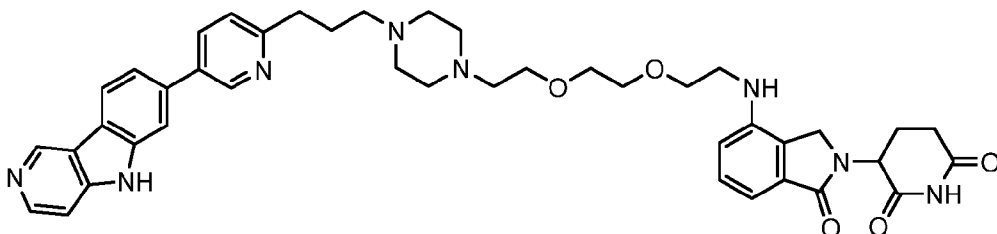
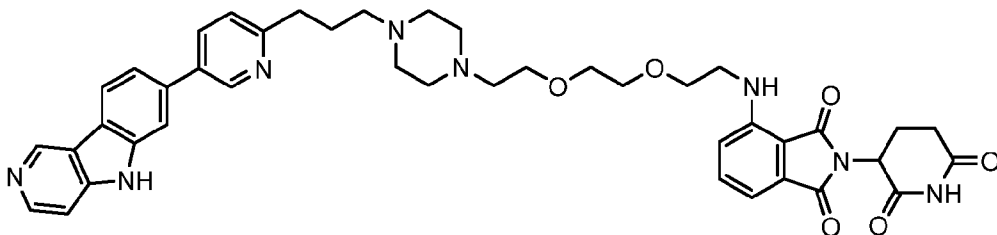


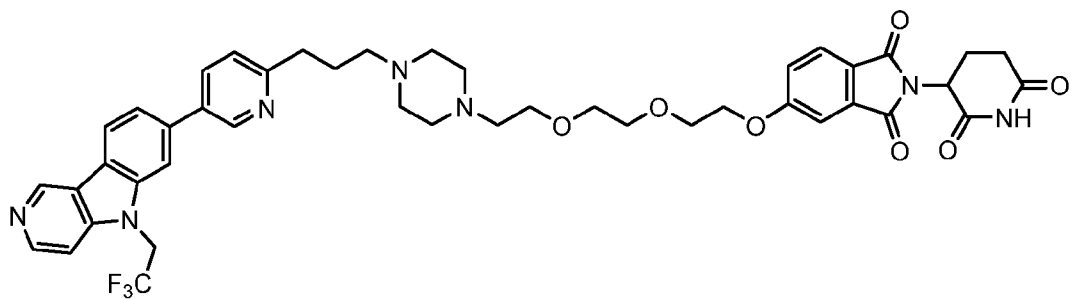
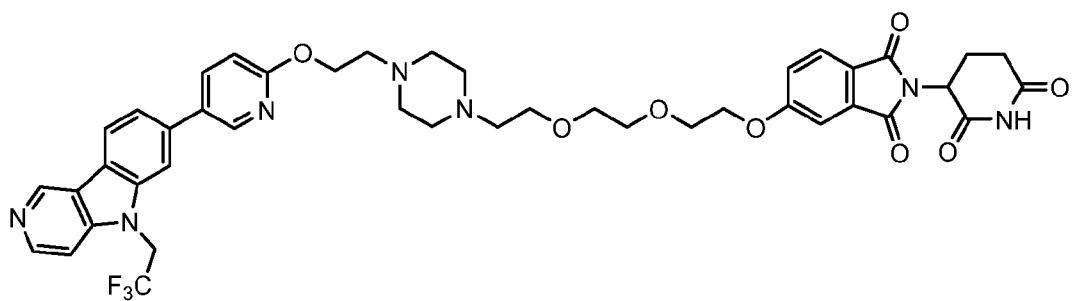
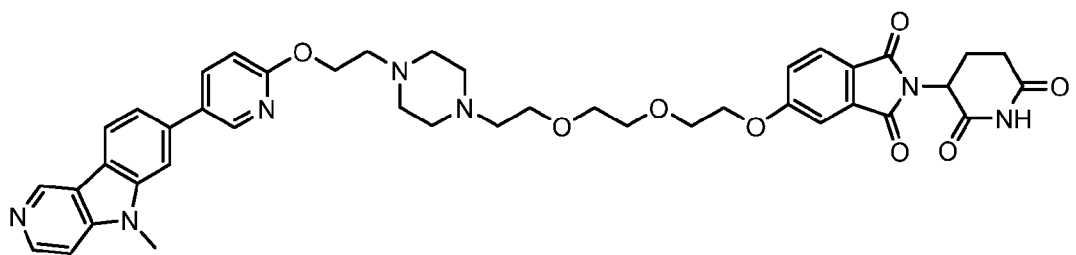
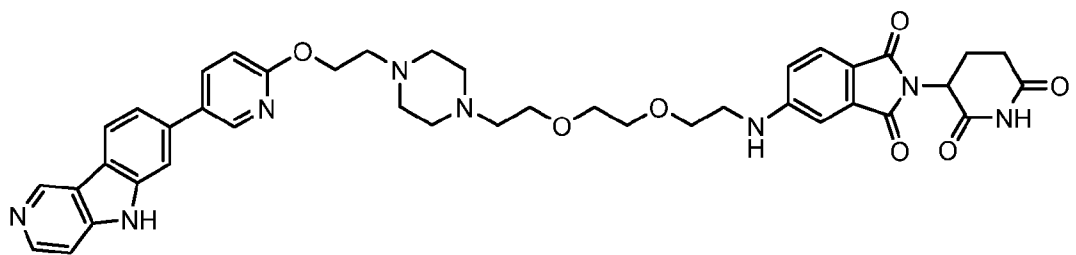


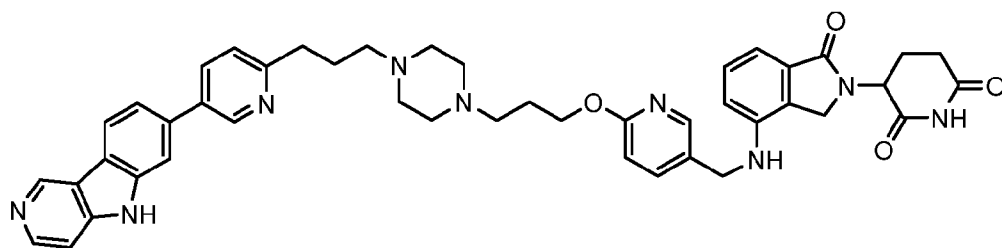
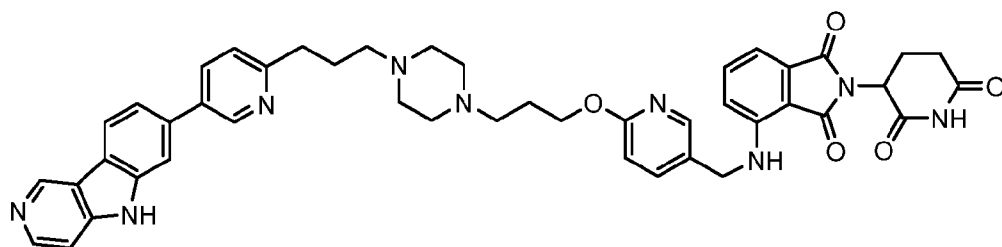
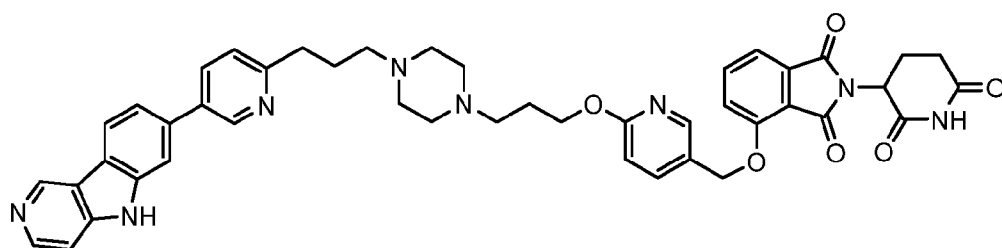
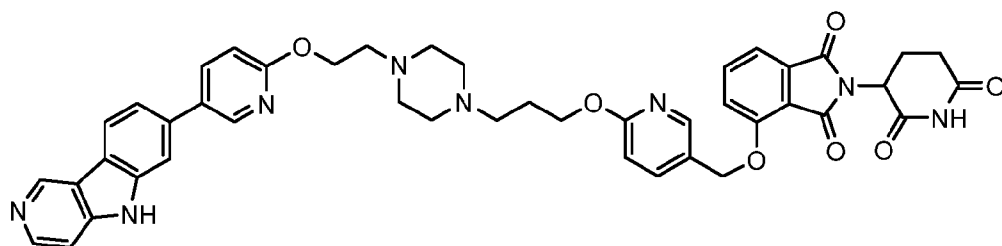
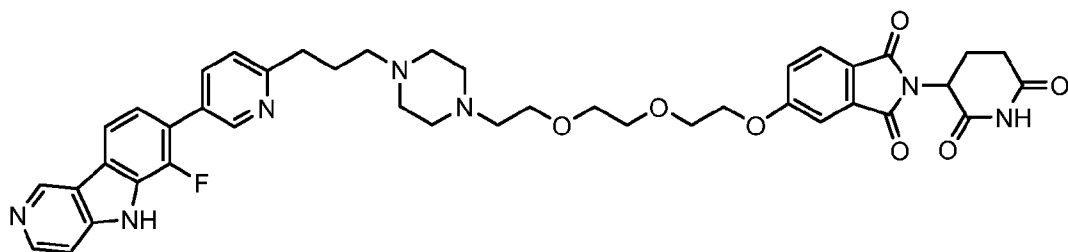


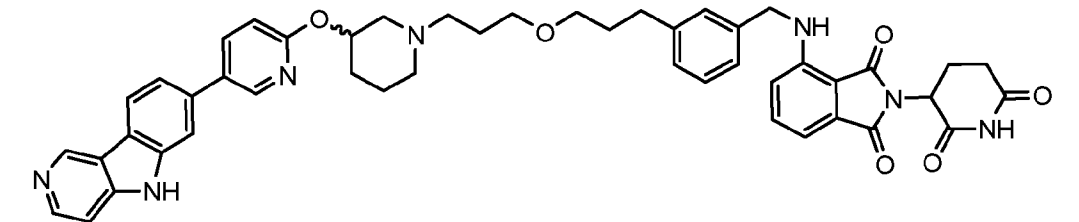
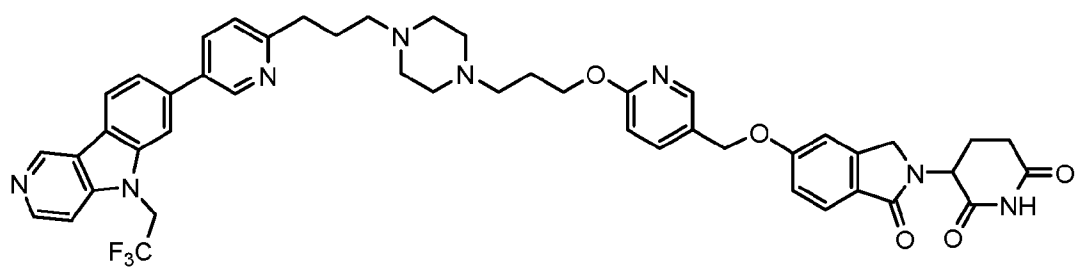
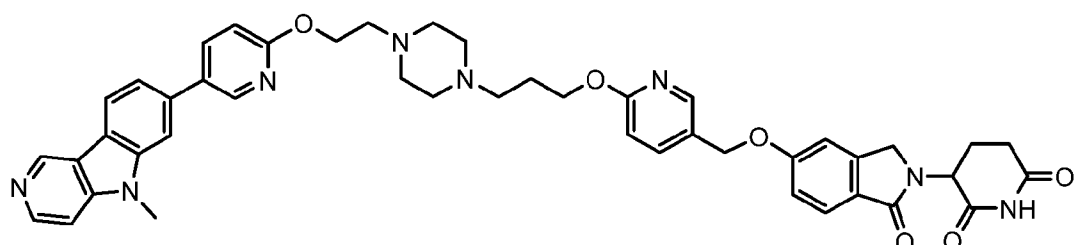
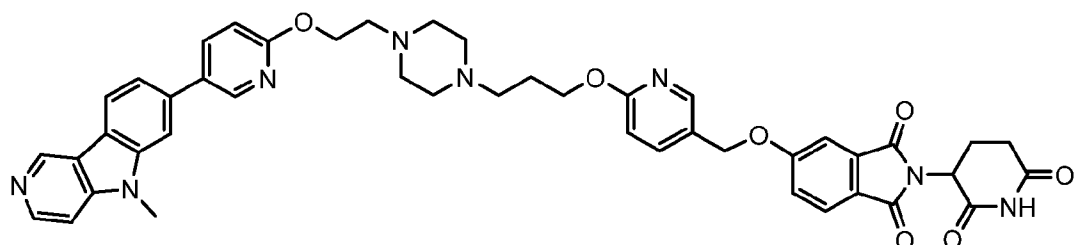
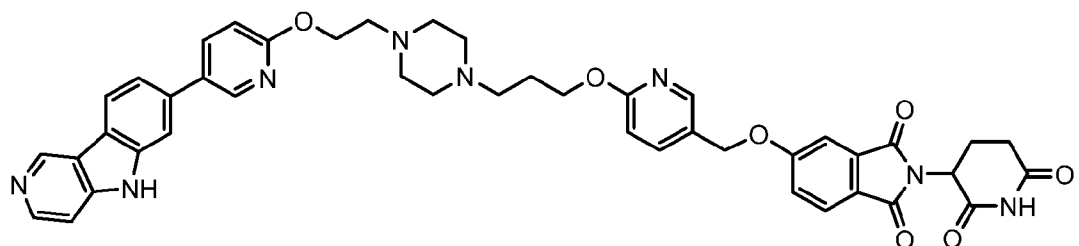
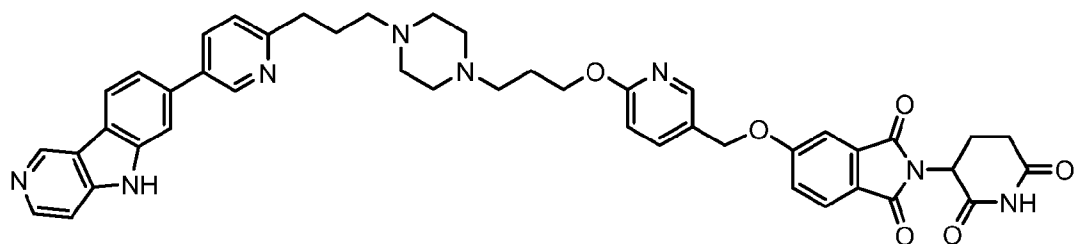


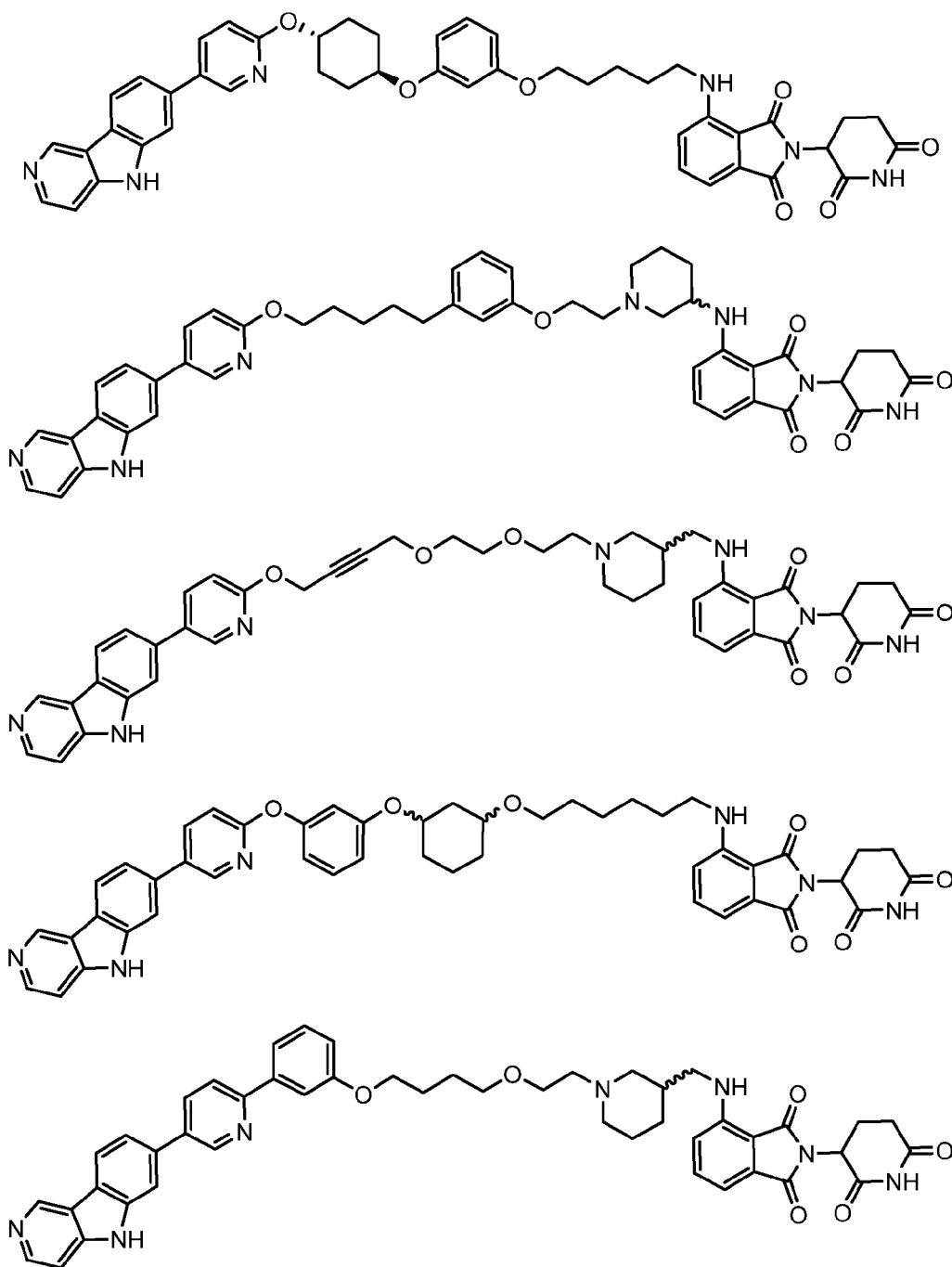












28. A composition comprising an effective amount of a bifunctional compound of any of claims 1-27, and a pharmaceutically acceptable carrier.

29. The composition of claim 28, wherein the composition further comprises at least one of additional bioactive agent or another bifunctional compound of claim 1.
30. The composition of claim 29, wherein the additional bioactive agent is anti-neurodegenerative agent.
31. The composition of claim 29, wherein the additional bioactive agent is P-gp inhibitor.
32. The composition of claim 31, wherein P-gp inhibitor is Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Piperine, Quercetin, Quinidine, Quinine, Reserpine, Ritonavir, Tariquidar, Elacridar or Verapamil.
33. A composition comprising a pharmaceutically acceptable carrier and an effective amount of at least one compound of any of claims 1-27 for treating a disease or disorder in a subject, the method comprising administering the composition to a subject in need thereof, wherein the compound is effective in treating or ameliorating at least one symptom of the disease or disorder.
34. The composition of claim 33, wherein the disease or disorder is associated with Tau accumulation and aggregation.
35. The composition of claim 32 or 33, wherein the disease or disorder is a neurodegenerative disease associated with Tau accumulation and aggregation.
36. The composition of claim 34, wherein the disease or disorder is Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS—Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten

Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choroacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralysis, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion

Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome, Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Stroke, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucopolidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological

Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralysis, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT

Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

37. The composition of claim 33, 34 or 35, wherein the disease or disorder is a neurological disorder with at least one of Huntington's disease, muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor and Stroke.

38. The composition of claim 33, 34 or 35, wherein the disease or disorder is Alzheimer's disease.

TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE

INCORPORATION BY REFERENCE

[001] U.S. Patent Application Serial No. 15/230,354, filed on August 5, 2016 (116US2); and U.S. Patent Application Serial No. 62/406,888, filed on October 11, 2016 (122US0); and U.S. Patent Application Serial No. 14/686,640, filed on April 14, 2015 (100US2), published as U.S. Patent Application Publication No. 2015/0291562; and U.S. Patent Application Serial No. 14/792,414, filed on July 6, 2015 (100US4), published as U.S. Patent Application Publication No. 2016/0058872; and U.S. Patent Application Serial No. 14/371,956, filed on July 11, 2014 (103US9), published as U.S. Patent Application Publication No. 2014/0356322; and U.S. Patent Application Serial No. 15/074,820, filed on March 18, 2016 (111US9), published as U.S. Patent Application Publication No. 2016/0272639, are incorporated herein by reference in their entirety. Furthermore, all references cited herein are incorporated by reference herein in their entirety.

BACKGROUND

1. Field of the discovery

[002] The present description relates to bifunctional compounds, which are useful for modifying intracellular ubiquitination and subsequent degradation of target polypeptides and proteins, in particular, Tau protein. Compounds of the present disclosure place target protein/polypeptide in proximity to a ubiquitin ligase to effect the ubiquitination and degradation (and inhibition) of Tau protein.

2. Background information

[003] Most small molecule drugs bind enzymes or receptors in tight and well-defined pockets. On the other hand, protein-protein interactions are notoriously difficult to target using small molecules due to their large contact surfaces and the shallow grooves or flat interfaces involved. E3 ubiquitin ligases (of which hundreds are known in humans) confer substrate specificity for ubiquitination, and therefore, are more attractive therapeutic targets than general proteasome inhibitors due to their specificity for certain protein substrates. The development of ligands of E3 ligases has proven challenging, in part due to the fact that they must disrupt protein-protein interactions. However, recent developments have provided specific ligands which bind to these ligases. For example, since the discovery of nutlins, the first small molecule E3 ligase inhibitors,

additional compounds have been reported that target E3 ligases, but the field remains underdeveloped.

[004] One E3 ligase with exciting therapeutic potential is the von Hippel-Lindau (VHL) tumor suppressor, the substrate recognition subunit of the E3 ligase complex VCB, which also consists of elongins B and C, Cul2 and Rbx1. The primary substrate of VHL is Hypoxia Inducible Factor 1 α (HIF-1 α), a transcription factor that upregulates genes such as the pro-angiogenic growth factor VEGF and the red blood cell inducing cytokine erythropoietin in response to low oxygen levels. The first small molecule ligands of Von Hippel Lindau (VHL) to the substrate recognition subunit of the E3 ligase were generated, and crystal structures were obtained confirming that the compound mimics the binding mode of the transcription factor HIF-1 α , the major substrate of VHL.

[005] Cereblon is a protein that in humans is encoded by the CRBN gene. CRBN orthologs are highly conserved from plants to humans, which underscores its physiological importance. Cereblon forms an E3 ubiquitin ligase complex with damaged DNA binding protein 1 (DDB1), Cullin-4A (CUL4A), and regulator of cullins 1 (ROC1). This complex ubiquitinates a number of other proteins. Through a mechanism which has not been completely elucidated, cereblon ubiquitination of target proteins results in increased levels of fibroblast growth factor 8 (FGF8) and fibroblast growth factor 10 (FGF10). FGF8 in turn regulates a number of developmental processes, such as limb and auditory vesicle formation. The net result is that this ubiquitin ligase complex is important for limb outgrowth in embryos. In the absence of cereblon, DDB1 forms a complex with DDB2 that functions as a DNA damage-binding protein.

[006] The Tau protein is an abundant protein in the central nervous system primarily found in neuronal cells, although Tau is expressed at lower levels in other cells of the central nervous system. In a healthy neuron, Tau binds to microtubules and regulates microtubule stability, which is critical for axonal outgrowth and neuronal plasticity. When pathologically altered, Tau molecules are not able to stabilize microtubules and are prone to form insoluble aggregates. Once the Tau protein forms insoluble aggregates in cells, cellular dysfunction occurs, axonal transport is compromised, and neuronal loss ensues. Accumulation of abnormal Tau aggregates in neurons is an important pathological signature in multiple neurodegenerative disorders including Alzheimer's disease. In certain pathological conditions, Tau aggregation results in paired-helical filaments (PHFs) and/or neurofibrillary tangles (NFTs). The accumulation of PHFs and NFTs in neurons

directly correlates with microtubule dysfunction and neuronal degeneration. Neurons containing tau PHFs or NFTs tangles activate diverse cellular mechanisms to try and rid the cell of the abnormal protein aggregates.

[007] More recent studies suggest that, instead of the large insoluble filaments, soluble Tau oligomers might play a more critical role in the onset and progression of disease prior to the development of PHF- or NFT-induced neurotoxicity. Oligomeric species of Tau may act as seeds for the aggregation of native Tau, thereby promoting neurotoxic Tau aggregation. Accumulating evidence has suggested that Tau aggregates can be transmitted from one cell to another by propagating in a prion-like manner.

[008] Tau alteration and dysfunction and extensive neuron loss has long been associated with several neurodegenerative diseases now collectively called tauopathies.

[009] The term "taupathy" or "tauopathies" refers herein to a class of neurodegenerative diseases associated with the pathological aggregation of Tau protein in neurofibrillary or gliofibrillary tangles in the human brain. Examples of tauopathies include but are not limited to AD, Down's syndrome, frontotemporal lobular dementia (FTLD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP)

[0010] Due to its pathological significance in multiple neurodegenerative diseases, Tau is an important therapeutic target. Preventing Tau aggregation becomes a potential strategy to treat neurodegenerative disorders associated with Tau. So far, great effort has been made to identify molecular mechanisms of Tau aggregation and find therapeutics to halt the progression of neurodegeneration. .

[0011] Tau aggregation inhibitors which demonstrated promising pre-clinical data have proven ineffective in recent clinical trials for the treatment of various tauopathies.

[0012] Therefore, a need exists in the art for effective treatments of diseases and conditions that are related to the aggregation of Tau in neurodegenerative disorders such as tauopathies.

SUMMARY

[0013] The present disclosure describes bifunctional compounds, including compositions comprising the same, which function to recruit endogenous proteins to an E3 ubiquitin ligase for ubiquitination and subsequent degradation, and methods of using the same. In particular, the present disclosure provides bifunctional or proteolysis targeting chimeric (PROTAC) compounds, which find utility as modulators of targeted ubiquitination and degradation of Tau protein

aggregates. In addition, the description provides methods of using an effective amount of the compounds as described herein for the treatment or amelioration of disease conditions due to accumulation or aggregation of Tau proteins such as tauopathies. These diseases or disorders include but are not limited to neurological or neurodegenerative disorders.

[0014] Thus, in one aspect, the disclosure provides compounds which function to recruit endogenous proteins, e.g., Tau, to E3 Ubiquitin Ligase for ubiquitination and degradation.

[0015] In any of the embodiments, the compounds have the following general structures

PTM-L-ULM

[0016] In certain embodiments, the compounds have the following general structures (A)

PTM-L-VLM (A)

[0017] In certain embodiments, the compounds have the following general structures (B)

PTM-L-CLM (B)

wherein, PTM represents protein targeting moiety, ULM represents E3 ubiquitin ligase targeting moiety including but not limited to VLM (VHL ligase-binding moiety and CLM (cereblon ligase-binding moiety) and L represents a linker, e.g., a bond or a chemical linker moiety. As would be understood by the skilled artisan, the bifunctional compounds as described herein can be synthesized such that the number and position of the respective functional moieties can be varied as desired.

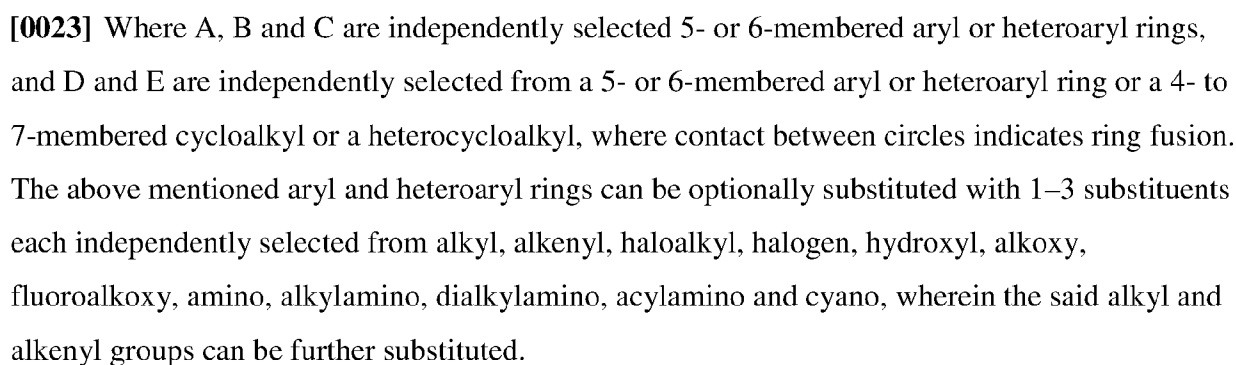
[0018] In certain embodiments, the PTMs in structure (A) are the ligands that bind to Tau as well as VHL E3 ubiquitin ligase.

[0019] In certain embodiments, the PTMs in structure (B) are the ligands that bind to Tau as well as CLM E3 ubiquitin ligase.

[0020] In certain embodiments, the compounds as described herein comprise multiple ULMs, multiple PTMs, multiple chemical linkers or a combination thereof. In an additional aspect, the description provides therapeutic compositions comprising an effective amount of a compound as described herein or salt form thereof, and a pharmaceutically acceptable carrier. The therapeutic compositions modulate protein degradation in a patient or subject, for example, an animal such as a human, and can be used for treating or ameliorating disease states or conditions which are modulated through the degraded protein. In certain embodiments, the therapeutic compositions as described herein may be used to effectuate the degradation of proteins of interest for the treatment or amelioration of a disease, e.g., neuronal disease. In yet another aspect, the present invention provides a method of ubiquitinating/degrading a target protein in a cell. In certain embodiments,

[0021] In particular, PTM are molecules that bind to Tau protein(TAU), and ULM are molecules that bind to VHL E3 ubiquitin ligase and/or to CLM E3 ubiquitin ligase with the following general structures:

[0022] The PTM (protein-targeting moiety) of the PROTACs of current disclosure is represented by the general formulas I, II, III and IV.



[0024] L_{PTM} is selected from a bond, an alkyl, an alkenyl or an alkynyl, optionally interrupted by one or more rings (i.e., cycloalkyl, heterocycloalkyl, aryl or heteroaryl), or one or more functional groups which could include -O-, -S-, $-NR^1_{PTM}-$ (where R^1_{PTM} is selected from H or alkyl), -S(O)-, -SO₂-, -C(O)-, -NHC(O)-, -C(O)NH-, -NHSO₂-, -NHC(O)NH-, -NHC(O)O-, -OC(O)NH-, wherein the said functional group can be optionally located at either end of the linker (i.e., directly adjacent to the B, C or D rings).

[0025] Preferred PTM embodiments of the current disclosure are represented by the structures I and II, where A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D is selected from a 6-membered aryl, heteroaryl or heterocycloalkyl, wherein A, B, C and D are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0026] Other preferred PTM embodiments are represented by the structures III and IV wherein A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D and E are 5- or 6-membered fused aryl or heteroaryl rings and wherein A, B, C, D and E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0027] Most preferred PTM embodiments of the current disclosure are represented by the structure I, where A is a phenyl or a 6-membered heteroaryl ring, B is a 5-membered heteroaryl ring, C is a phenyl or a 6-membered heteroaryl ring, L_{PTM} is a bond, and D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring, wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, with the proviso that a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

[0028] It will be understood that the general structures are exemplary and the respective moieties can be arranged spatially in any desired order, number or configuration.

[0029] In further embodiments, the description provides a bifunctional compound having a structure selected from the group consisting of Exemplary compounds 1-50 of Table 1, a salt, a polymorph, and a prodrug thereof.

[0030] In another aspect, the description provides compositions comprising compounds as described herein, and a pharmaceutically acceptable carrier. In certain embodiments, the compositions are therapeutic or pharmaceutical compositions comprising an effective amount of a compound as described herein and a pharmaceutically acceptable carrier. In certain embodiments,

the therapeutic or pharmaceutical compositions comprise an additional biologically active agent, e.g., an agent effective for the treatment of neuronal disease.

[0031] In any of the aspects or embodiments described herein, the therapeutic compositions comprising compounds described herein can be in any suitable dosage form, e.g., solid, or liquid, and configured to be delivered by any suitable route, e.g., oral, parenteral, intravenous, intraperitoneal, subcutaneous, intramuscular, etc.

[0032] In another aspect, the description provides methods of modulating Tau protein, their ubiquitination and the subsequent degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating Tau ubiquitination and degradation in the subject.

[0033] In yet another aspect, the description provides methods of treating or ameliorating a symptom of a disease related to TAU activity in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject in need thereof, wherein the compound or composition comprising the same is effective in treating or ameliorating a symptom of a disease related to TAU activity in the subject. In certain embodiments, the disease to be treated is neurological or neurodegenerative disease, e.g. Alzheimer, Parkinson, Dementia etc.

[0034] In a preferred embodiment, the subject is a human.

[0035] In an additional aspect, the description provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present disclosure.

[0036] Where applicable or not specifically disclaimed, any one of the embodiments described herein are contemplated to be able to combine with any other one or more embodiments, even though the embodiments are described under different aspects of the disclosure. As such, the preceding general areas of utility are given by way of example only and are not intended to be limiting on the scope of the present disclosure and appended claims. Additional objects and advantages associated with the compositions, methods, and processes of the present disclosure will be appreciated by one of ordinary skill in the art in light of the instant claims, description, and examples. For example, the various aspects and embodiments of the disclosure may be utilized in numerous combinations, all of which are expressly contemplated by the present description. These

additional advantages, objects, and embodiments are expressly included within the scope of the present disclosure. The publications and other materials used herein to illuminate the background of the disclosure, and in particular cases, to provide additional details respecting the practice, are incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0037] The accompanying drawings, which are incorporated into and form a part of the specification, illustrate several embodiments of the present disclosure and, together with the description, serve to explain the principles of the invention. The drawings are only for the purpose of illustrating an embodiment of the disclosure and are not to be construed as limiting the invention. Further objects, features and advantages of the invention will become apparent from the following detailed description taken in conjunction with the accompanying figures showing illustrative embodiments of the disclosure, in which:

[0038] **Figure 1** shows total tau levels in hippocampal homogenates. Data are displayed as scattered dot blot. Statistically significant differences between the test item (TI) treated groups versus the vehicle control group according to One-way ANOVA followed by Dunnett's Multiple Comparison Test are indicated by asterisk ** $p < 0.01$, * $p < 0.05$.

DETAILED DESCRIPTION

[0039] The following is a detailed description provided to aid those skilled in the art in practicing the present disclosure. Those of ordinary skill in the art may make modifications and variations in the embodiments described herein without departing from the spirit or scope of the present disclosure. All publications, patent applications, patents, figures and other references mentioned herein are expressly incorporated by reference in their entirety.

[0040] The present description relates to the surprising and unexpected discovery that an E3 ubiquitin ligase protein can ubiquitinate a target protein once the E3 ubiquitin ligase protein and the target protein are brought into proximity by a chimeric construct (e.g., PROTAC) as described herein, which binds the E3 ubiquitin ligase protein (e.g., VHL and cereblon) and the target protein e.g., TAU. Accordingly, the present description provides compounds, compositions comprising the same and associated methods of use for ubiquitination and degradation of a chosen target protein.

[0041] The following terms are used to describe the present disclosure. In instances where a term is not specifically defined herein, that term is given an art-recognized meaning by those of ordinary skill applying that term in context to its use in describing the present disclosure.

[0042] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise (such as in the case of a group containing a number of carbon atoms in which case each carbon atom number falling within the range is provided), between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also included in the invention.

[0043] The term “compound”, as used herein, unless otherwise indicated, refers to any specific chemical compound disclosed herein and includes tautomers, regioisomers, geometric isomers, and where applicable, stereoisomers, including optical isomers (enantiomers) and other stereoisomers (diastereomers) thereof, as well as pharmaceutically acceptable salts and derivatives (including prodrug forms) thereof where applicable, in context. Within its use in context, the term compound generally refers to a single compound, but also may include other compounds such as stereoisomers, regioisomers and/or optical isomers (including racemic mixtures) as well as specific enantiomers or enantiomerically enriched mixtures of disclosed compounds. The term also refers, in context to prodrug forms of compounds which have been modified to facilitate the administration and delivery of compounds to a site of activity. It is noted that in describing the present compounds, numerous substituents and variables associated with same, among others, are described. It is understood by those of ordinary skill that molecules which are described herein are stable compounds as generally described hereunder.

[0044] When the bond  is shown, both a double bond and single bond are represented within the context of the compound shown.

[0045] The term “patient” or “subject” is used throughout the specification to describe an animal, preferably a human or a domesticated animal, to whom treatment, including prophylactic treatment, with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human

patient, the term patient refers to that specific animal, including a domesticated animal such as a dog or cat or a farm animal such as a horse, cow, sheep, etc. In general, in the present invention, the term patient refers to a human patient unless otherwise stated or implied from the context of the use of the term.

[0046] The term “effective” is used to describe an amount of a compound, composition or component which, when used within the context of its intended use, effects an intended result. The term effective subsumes all other effective amount or effective concentration terms, which are otherwise described or used in the present application.

[0047] The term “Ubiquitin Ligase” refers to a family of proteins that facilitate the transfer of ubiquitin to a specific substrate protein, targeting the substrate protein for degradation. For example, cereblon is an E3 Ubiquitin Ligase protein that alone or in combination with an E2 ubiquitin-conjugating enzyme causes the attachment of ubiquitin to a lysine on a target protein, and subsequently targets the specific protein substrates for degradation by the proteasome. Thus, E3 ubiquitin ligase alone or in complex with an E2 ubiquitin conjugating enzyme is responsible for the transfer of ubiquitin to targeted proteins. In general, the ubiquitin ligase is involved in polyubiquitination such that a second ubiquitin is attached to the first; a third is attached to the second, and so forth. Polyubiquitination marks proteins for degradation by the proteasome. However, there are some ubiquitination events that are limited to mono-ubiquitination, in which only a single ubiquitin is added by the ubiquitin ligase to a substrate molecule. Mono-ubiquitinated proteins are not targeted to the proteasome for degradation, but may instead be altered in their cellular location or function, for example, via binding other proteins that have domains capable of binding ubiquitin. Further complicating matters, different lysines on ubiquitin can be targeted by an E3 to make chains. The most common lysine is Lys48 on the ubiquitin chain. This is the lysine used to make polyubiquitin, which is recognized by the proteasome.

[0048] The term “protein target moiety” or PTM is used to describe a small molecule which binds to a target protein or other protein or polypeptide of interest and places/presents that protein or polypeptide in proximity to an ubiquitin ligase such that degradation of the protein or polypeptide by ubiquitin ligase may occur. Non-limiting examples of small molecule target protein binding moieties include compounds targeting Tau protein.

[0049] The term “target protein” is used to describe a protein or polypeptide, which is a target for binding to a compound according to the present invention and degradation by ubiquitin ligase hereunder. Such small molecule target protein binding moieties also include pharmaceutically

acceptable salts, enantiomers, solvates and polymorphs of these compositions, as well as other small molecules that may target a protein of interest. These binding moieties are linked to ULM groups through linker groups L.

[0050] Tau protein target may be used in screens that identify compound moieties which bind to the protein and by incorporation of the moiety into compounds according to the present disclosure, the level of activity of the protein may be altered for therapeutic end result.

[0051] The term “disease state or condition” is used to describe any disease state or condition wherein protein dysregulation (i.e., the amount of protein expressed in a patient is elevated) occurs and where degradation of Tau protein in a patient may provide beneficial therapy or relief of symptoms to a patient in need thereof. In certain instances, the disease state or condition may be cured.

[0052] Disease states or conditions which may be treated using compounds according to the present invention include neuronal disease, for example, neurodegeneration, Huntington's disease and muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, Neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor, Stroke.

[0053] The term “neurological disorder” or “neurological disorders”, as used herein, refers to any disorder, disease, and/or syndrome due to or resulting from neurologic, psychiatric, psychological, and/or cerebrovascular symptomology or origin. The term “neurological disorder” or “neurological disorders”, as used herein, also refers to diseases, disorder or condition of the brain and nervous system or psychiatric disorders or conditions. Neurological disorders include, but are not limited to Absence of the Septum Pellucidum, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adrenoleukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS—Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's

Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis, Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralysis, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm,

Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia
 Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-
 Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease,
 Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity,
 Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated
 Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile
 Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease,
 Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial
 Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome,
 Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome,
 Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome,
 Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome,
 Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary
 Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan
 Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage
 Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological,
 Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly,
 Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and
 Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy,
 Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Stroke, Mitochondrial Myopathies,
 Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease,
 Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia,
 Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic
 Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic
 Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—
 Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy,
 Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis,
 Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological
 Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection,
 Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis
 Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders,
 Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick

Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralysis, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension, Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia,

Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

[0054] The term “bioactive agent” is used to describe an agent, other than a compound according to the present disclosure, which is used in combination with the compounds of the present disclosure as an agent with biological activity to assist in effecting an intended therapy, inhibition and/or prevention/prophylaxis for which the present compounds are used.

[0055] The term "pharmaceutically acceptable salt" is used throughout the specification to describe, where applicable, a salt form of one or more of the compounds described herein which are presented to increase the solubility of the compound in the gastric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids and bases well known in the pharmaceutical art. Sodium and potassium salts are particularly preferred as neutralization salts of the phosphates according to the present invention.

[0056] The term "pharmaceutically acceptable derivative" is used throughout the specification to describe any pharmaceutically acceptable prodrug form (such as an ester, amide or other prodrug group), which, upon administration to a patient, provides directly or indirectly the present compound or an active metabolite of the present compound.

[0057] The term “independently” is used herein to indicate that the variable, which is independently applied, varies independently from application to application.

[0058] The term “hydrocarbyl” shall mean a compound which contains carbon and hydrogen and which may be fully saturated, partially unsaturated or aromatic and includes aryl groups, alkyl groups, alkenyl groups and alkynyl groups.

[0059] The term “alkyl” shall mean within its context a linear, branch-chained or cyclic fully saturated hydrocarbon radical or alkyl group, preferably a C₁-C₁₀, more preferably a C₁-C₆, alternatively a C₁-C₃ alkyl group, which may be optionally substituted. Examples of alkyl groups are methyl, ethyl, n-butyl, sec-butyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, isopropyl, 2-

methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl, cyclohexylethyl and cyclohexyl, among others.

[0060] The term "lower alkyl" means the alkyl groups with no more than six carbon atoms.

[0061] The term "unsubstituted" shall mean substituted only with hydrogen atoms. A range of carbon atoms which includes C₀ means that carbon is absent and is replaced with H. Thus, a range of carbon atoms which is C₀-C₆ includes carbon atoms of 1, 2, 3, 4, 5 and 6 and for C₀, H stands in place of carbon. The term "substituted" or "optionally substituted" shall mean independently (i.e., where more than substituent occurs, each substituent is independent of another substituent) one or more substituents (independently up to five substituents, preferably up to three substituents, often 1 or 2 substituents on a moiety in a compound according to the present invention and may include substituents which themselves may be further substituted) at a carbon (or nitrogen) position anywhere on a molecule within context, and includes as substituents hydroxyl, thiol, carboxyl, cyano (C≡N), nitro (NO₂), halogen (preferably, 1, 2 or 3 halogens, especially on an alkyl, especially a methyl group such as a trifluoromethyl), an alkyl group (preferably, C₁-C₁₀, more preferably, C₁-C₆), aryl (especially phenyl and substituted phenyl for example benzyl or benzoyl), alkoxy group (preferably, C₁-C₆ alkyl or aryl, including phenyl and substituted phenyl), thioether (C₁-C₆ alkyl or aryl), acyl (preferably, C₁-C₆ acyl), ester or thioester (preferably, C₁-C₆ alkyl or aryl) including alkylene ester (such that attachment is on the alkylene group, rather than at the ester function which is preferably substituted with a C₁-C₆ alkyl or aryl group), preferably, C₁-C₆ alkyl or aryl, halogen (preferably, F or Cl), amine (including a five- or six-membered cyclic alkylene amine, further including a C₁-C₆ alkyl amine or a C₁-C₆ dialkyl amine which alkyl groups may be substituted with one or two hydroxyl groups) or an optionally substituted -N(C₀-C₆ alkyl)C(O)(O-C₁-C₆ alkyl) group (which may be optionally substituted with a polyethylene glycol chain to which is further bound an alkyl group containing a single halogen, preferably chlorine substituent), hydrazine, amido, which is preferably substituted with one or two C₁-C₆ alkyl groups (including a carboxamide which is optionally substituted with one or two C₁-C₆ alkyl groups), alkanol (preferably, C₁-C₆ alkyl or aryl), or alkanoic acid (preferably, C₁-C₆ alkyl or aryl).

Substituents according to the present invention may include, for example -SiR₁R₂R₃ groups where each of R₁ and R₂ is as otherwise described herein and R₃ is H or a C₁-C₆ alkyl group, preferably R₁, R₂, R₃ in this context is a C₁-C₃ alkyl group (including an isopropyl or t-butyl group). Each of the above-described groups may be linked directly to the substituted moiety or alternatively, the substituent may be linked to the substituted moiety (preferably in the case of an aryl or heteroaryl

moiety) through an optionally substituted $-(CH_2)_m-$ or alternatively an optionally substituted $-(OCH_2)_m-$, $-(OCH_2CH_2)_m-$ or $-(CH_2CH_2O)_m-$ group, which may be substituted with any one or more of the above-described substituents. Alkylene groups $-(CH_2)_m-$ or $-(CH_2)_n-$ groups or other chains such as ethylene glycol chains, as identified above, may be substituted anywhere on the chain. Preferred substituents on alkylene groups include halogen or C_1 - C_6 (preferably C_1 - C_3) alkyl groups, which may be optionally substituted with one or two hydroxyl groups, one or two ether groups (O - C_1 - C_6 groups), up to three halo groups (preferably F), or a sidechain of an amino acid as otherwise described herein and optionally substituted amide (preferably carboxamide substituted as described above) or urethane groups (often with one or two C_0 - C_6 alkyl substituents, which group(s) may be further substituted). In certain embodiments, the alkylene group (often a single methylene group) is substituted with one or two optionally substituted C_1 - C_6 alkyl groups, preferably C_1 - C_4 alkyl group, most often methyl or O-methyl groups or a sidechain of an amino acid as otherwise described herein. In the present invention, a moiety in a molecule may be optionally substituted with up to five substituents, preferably up to three substituents. Most often, in the present invention moieties which are substituted are substituted with one or two substituents.

[0062] The term “substituted” (each substituent being independent of any other substituent) shall also mean within its context of use C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halogen, amido, carboxamido, sulfone, including sulfonamide, keto, carboxy, C_1 - C_6 ester (oxyester or carbonylester), C_1 - C_6 keto, urethane $-O-C(O)-NR_1R_2$ or $-N(R_1)-C(O)-O-R_1$, nitro, cyano and amine (especially including a C_1 - C_6 alkylene- NR_1R_2 , a mono- or di- C_1 - C_6 alkyl substituted amines which may be optionally substituted with one or two hydroxyl groups). Each of these groups contain unless otherwise indicated, within context, between 1 and 6 carbon atoms. In certain embodiments, preferred substituents will include for example, $-NH-$, $-NHC(O)-$, $-O-$, $=O$, $-(CH_2)_m-$ (here, m and n are in context, 1, 2, 3, 4, 5 or 6), $-S-$, $-S(O)-$, SO_2- or $-NH-C(O)-NH-$, $-(CH_2)_nOH$, $-(CH_2)_nSH$, $-(CH_2)_nCOOH$, C_1 - C_6 alkyl, $-(CH_2)_nO-(C_1$ - C_6 alkyl), $-(CH_2)_nC(O)-(C_1$ - C_6 alkyl), $-(CH_2)_nOC(O)-(C_1$ - C_6 alkyl), $-(CH_2)_nC(O)O-(C_1$ - C_6 alkyl), $-(CH_2)_nNHC(O)-R_1$, $-(CH_2)_nC(O)-NR_1R_2$, $-(OCH_2)_nOH$, $-(CH_2O)_nCOOH$, C_1 - C_6 alkyl, $-(OCH_2)_nO-(C_1$ - C_6 alkyl), $-(CH_2O)_nC(O)-(C_1$ - C_6 alkyl), $-(OCH_2)_nNHC(O)-R_1$, $-(CH_2O)_nC(O)-NR_1R_2$, $-S(O)_2-R_S$, $-S(O)-R_S$ (R_S is C_1 - C_6 alkyl or a $-(CH_2)_m-NR_1R_2$ group), NO_2 , CN or halogen (F, Cl, Br, I, preferably F or Cl), depending on the context of the use of the substituent. R_1 and R_2 are each, within context, H or a C_1 - C_6 alkyl group (which may be optionally substituted with one or two hydroxyl groups or up to three halogen groups, preferably fluorine). The term “substituted” shall also mean, within the chemical context

of the compound defined and substituent used, an optionally substituted aryl or heteroaryl group or an optionally substituted heterocyclic group as otherwise described herein. Alkylene groups may also be substituted as otherwise disclosed herein, preferably with optionally substituted C₁-C₆ alkyl groups (methyl, ethyl or hydroxymethyl or hydroxyethyl is preferred, thus providing a chiral center), a sidechain of an amino acid group as otherwise described herein, an amido group as described hereinabove, or a urethane group O-C(O)-NR₁R₂ group where R₁ and R₂ are as otherwise described herein, although numerous other groups may also be used as substituents. Various optionally substituted moieties may be substituted with 3 or more substituents, preferably no more than 3 substituents and preferably with 1 or 2 substituents. It is noted that in instances where, in a compound at a particular position of the molecule substitution is required (principally, because of valency), but no substitution is indicated, then that substituent is construed or understood to be H, unless the context of the substitution suggests otherwise.

[0063] The term "aryl" or "aromatic", in context, refers to a substituted (as otherwise described herein) or unsubstituted monovalent aromatic radical having a single ring (*e.g.*, benzene, phenyl, benzyl) or condensed rings (*e.g.*, naphthyl, anthracenyl, phenanthrenyl, etc.) and can be bound to the compound according to the present invention at any available stable position on the ring(s) or as otherwise indicated in the chemical structure presented. Other examples of aryl groups, in context, may include heterocyclic aromatic ring systems "heteroaryl" groups having one or more nitrogen, oxygen, or sulfur atoms in the ring (monocyclic) such as imidazole, furyl, pyrrole, furanyl, thiene, thiazole, pyridine, pyrimidine, pyrazine, triazole, oxazole or fused ring systems such as indole, quinoline, indolizine, azaindolizine, benzofurazan, etc., among others, which may be optionally substituted as described above. Among the heteroaryl groups which may be mentioned include nitrogen-containing heteroaryl groups such as pyrrole, pyridine, pyridone, pyridazine, pyrimidine, pyrazine, pyrazole, imidazole, triazole, triazine, tetrazole, indole, isoindole, indolizine, azaindolizine, purine, indazole, quinoline, dihydroquinoline, tetrahydroquinoline, isoquinoline, dihydroisoquinoline, tetrahydroisoquinoline, quinolizine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, imidazopyridine, imidazotriazine, pyrazinopyridazine, acridine, phenanthridine, carbazole, carbazoline, perimidine, phenanthroline, phenacene, oxadiazole, benzimidazole, pyrrolopyridine, pyrrolopyrimidine and pyridopyrimidine; sulfur-containing aromatic heterocycles such as thiophene and benzothiophene; oxygen-containing aromatic heterocycles such as furan, pyran, cyclopentapyran, benzofuran and isobenzofuran; and aromatic heterocycles comprising 2 or more hetero atoms selected from among nitrogen, sulfur and oxygen,

such as thiazole, thiadizole, isothiazole, benzoxazole, benzothiazole, benzothiadiazole, phenothiazine, isoxazole, furazan, phenoxazine, pyrazoloxazole, imidazothiazole, thienofuran, furopyrrole, pyridoxazine, furopyridine, fuopyrimidine, thienopyrimidine and oxazole, among others, all of which may be optionally substituted.

[0064] The term “heterocycle” refers to a cyclic group which contains at least one heteroatom, i.e., O, N or S, and may be aromatic (heteroaryl) or non-aromatic. Thus, the heteroaryl moieties are subsumed under the definition of heterocycle, depending on the context of its use. Exemplary heteroaryl groups are described hereinabove. Exemplary non-aromatic heterocyclic groups for use in the present invention include, for example, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, N-methylpiperazinyl, pyrazolidinyl, imidazolidinyl, morpholinyl, tetrahydropyranyl, azetidiny, oxetanyl, oxathiolanyl, pyridone, 2-pyrrolidone, ethyleneurea, 1,3-dioxolane, 1,3-dioxane, 1,4-dioxane, phthalimide and succinimide, among others, as described herein.

[0065] The term “co-administration” or “combination therapy” shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present invention may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all co-administered compounds or compositions are found in the subject at a given time. In certain preferred aspects of the present invention, one or more of the present compounds described above, are coadministered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects of the invention, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy

[0066] The present disclosure describes bifunctional compounds which function to recruit endogenous proteins to an E3 ubiquitin ligase for degradation, and methods of using the same. In particular, the present disclosure provides bifunctional or proteolysis targeting chimeric (PROTAC) compounds, which find utility as modulators of targeted ubiquitination of Tau proteins. An advantage of the compounds provided herein is that a broad range of pharmacological activities is possible, consistent with the degradation/inhibition of Tau protein.

[0067] As such, the present invention provides such compounds and compositions comprising an E3 ubiquitin ligase targeting moiety (“ULM”) coupled to a Tau protein target binding moiety (“PTM”), which result in the ubiquitination of Tau protein, which leads to degradation (and/or

inhibition) of the Tau protein. The present disclosure also provides a library of compositions and the use thereof.

[0068] The present description provides compounds which comprise a ligand, e.g., a small molecule ligand (i.e., having a molecular weight of below 2,000, 1,000, 500, or 200 Daltons), which is capable of binding to a ubiquitin ligase, such as VHL or cereblon. The compounds also comprise a moiety that is capable of binding to target protein, in such a way that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and/or inhibition) of that protein. Small molecule can mean, in addition to the above, that the molecule is non-peptidyl, that is, it is not generally considered a peptide, e.g., comprises fewer than 4, 3, or 2 amino acids. In accordance with the present description, the PTM, ULM or PROTAC molecule can be a small molecule.

[0069] In one embodiment, the description provides a composition useful for regulating protein activity. The composition comprises a ubiquitin pathway protein binding moiety (preferably for VHL or cereblon) according to a defined chemical structure and a Tau protein targeting moiety which are linked together, preferably through a linker, wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein and the targeting moiety recognizes Tau target protein and wherein the ubiquitin pathway protein binding moiety is coupled to the Tau targeting moiety.

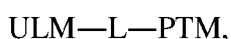
[0070] In another embodiment, the present invention provides a library of compounds. The library comprises more than one compound wherein each composition has a ubiquitin pathway protein binding moiety (preferably, VHL or cereblon) and a Tau protein binding moiety, wherein ULM is coupled (preferably, through a linker moiety) to Tau, and wherein the ubiquitin pathway protein binding moiety recognizes an ubiquitin pathway protein, in particular, an E3 ubiquitin ligase.

[0071] In another embodiment, the present disclosure provides a method of ubiquitinating/degrading a target protein (e.g. Tau) in a cell. The method comprises administering a bifunctional composition comprising an ubiquitin pathway protein binding moiety and a targeting moiety, preferably linked through a linker moiety, as otherwise described herein, wherein the ubiquitin pathway protein binding moiety is coupled to the targeting moiety and wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein (e.g., VHL, cereblon) and the targeting moiety recognizes the target protein (e.g., Tau) such that degradation of the target protein will occur when the target protein is placed in proximity to the ubiquitin ligase, thus resulting in degradation/inhibition of the effects of the target protein and the control of protein

levels. The control of protein levels afforded by the present invention provides treatment of a disease state or condition, which is modulated through the target protein by lowering the level of that protein in the cells of a patient.

[0072] In yet another embodiment, the present invention is directed to a method of treating a patient in need for a disease state or condition modulated through a protein (e.g., Tau) where the degradation of that protein will produce a therapeutic effect in that patient, the method comprising administering to a patient in need an effective amount of a compound according to the present disclosure, optionally in combination with another bioactive agent. The disease state or condition may be a disease caused by a microbial agent or other exogenous agent such as a virus, bacteria, fungus, protozoa or other microbe or may be a disease state, which is caused by overexpression of a protein i.e. accumulation or aggregation of Tau protein, which leads to a disease state and/or condition.

[0073] In one aspect, the present disclosure provides compounds useful for regulating protein activity. The composition comprises an E3 ubiquitin ligase, a ubiquitin pathway protein binding moiety, and a protein targeting moiety which are linked or coupled together, preferably through a linker, wherein the ubiquitin pathway protein binding moiety recognizes a ubiquitin pathway protein and the targeting moiety recognizes a target protein (e.g., Tau). Such compounds may be referred to herein as PROTAC compounds or PROTACs with the following general chemical structure:



or a pharmaceutically acceptable salt, enantiomer, stereoisomer, solvate, polymorph or prodrug thereof,

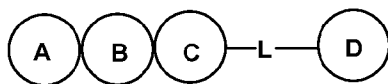
wherein ULM is a small molecule E3 ubiquitin ligase binding moiety that binds an E3 ubiquitin ligase;

PTM is a small molecule comprising a Tau protein targeting moiety that degrades the Tau protein; and

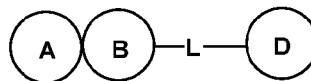
L is a bond or a chemical linking moiety connecting ULM and PTM.

[0074] In certain embodiments, the E3 ubiquitin ligase binding moiety targets a member of the group consisting of Von Hippel-Lindau (VLM), cereblon (CLM), mouse double-minute homolog2 (MLM), and IAP (ILM).

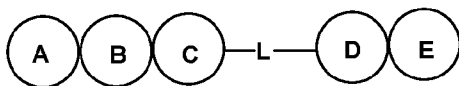
[0075] In one aspect, the description provides Tau protein binding moieties (PTM). In certain embodiments, PTM is represented by formula I, formula II, formula III or formula IV:



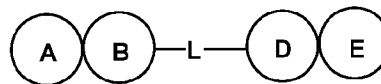
I



II



III



IV

wherein

A, B and C are each independently selected from optionally substituted 5- or 6-membered aryl or heteroaryl rings;

D and E are independently selected from a 5- or 6-membered aryl or heteroaryl ring or a 4- to 7-membered cycloalkyl or a heterocycloalkyl, where contact between circles indicates ring fusion.

L_{PTM} is selected from a bond, an alkyl, an alkenyl or an alkynyl, optionally interrupted by one or more rings (i.e., cycloalkyl, heterocycloalkyl, aryl or heteroaryl), or one or more functional groups selected from the groups -O-, -S-, $-NR^1_{PTM}-$ (where R^1_{PTM} is selected from H or alkyl), -S(O)-, $-SO_2-$, -C(O)-, -NHC(O)-, -C(O)NH-, $-NHSO_2-$, -NHC(O)NH-, -NHC(O)O-, or -OC(O)NH-, wherein the said functional group are optionally located at either end of the linker.

[0076] In certain embodiments, aryl and heteroaryl rings of A, B, C and D of PTM are optionally substituted with 1–3 substituents each independently selected from alkyl, alkenyl, haloalkyl, halogen, hydroxyl, alkoxy, fluoroalkoxy, amino, alkylamino, dialkylamino, acylamino and cyano, wherein the said alkyl and alkenyl groups are further optionally substituted.

[0077] In certain embodiments, formula I of PTM is:

A, B and C rings are independently 5- or 6- membered fused aryl or heteroaryl rings;

L_{PTM} is selected from a bond or an alkyl, and

D is selected from a 6-membered aryl, heteroaryl or heterocycloalkyl, wherein

A, B, C and D are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0078] In certain additional embodiments, formula I of PTM is:

A and C are a phenyl or a 6-membered heteroaryl ring;

B is a 5-membered heteroaryl ring;

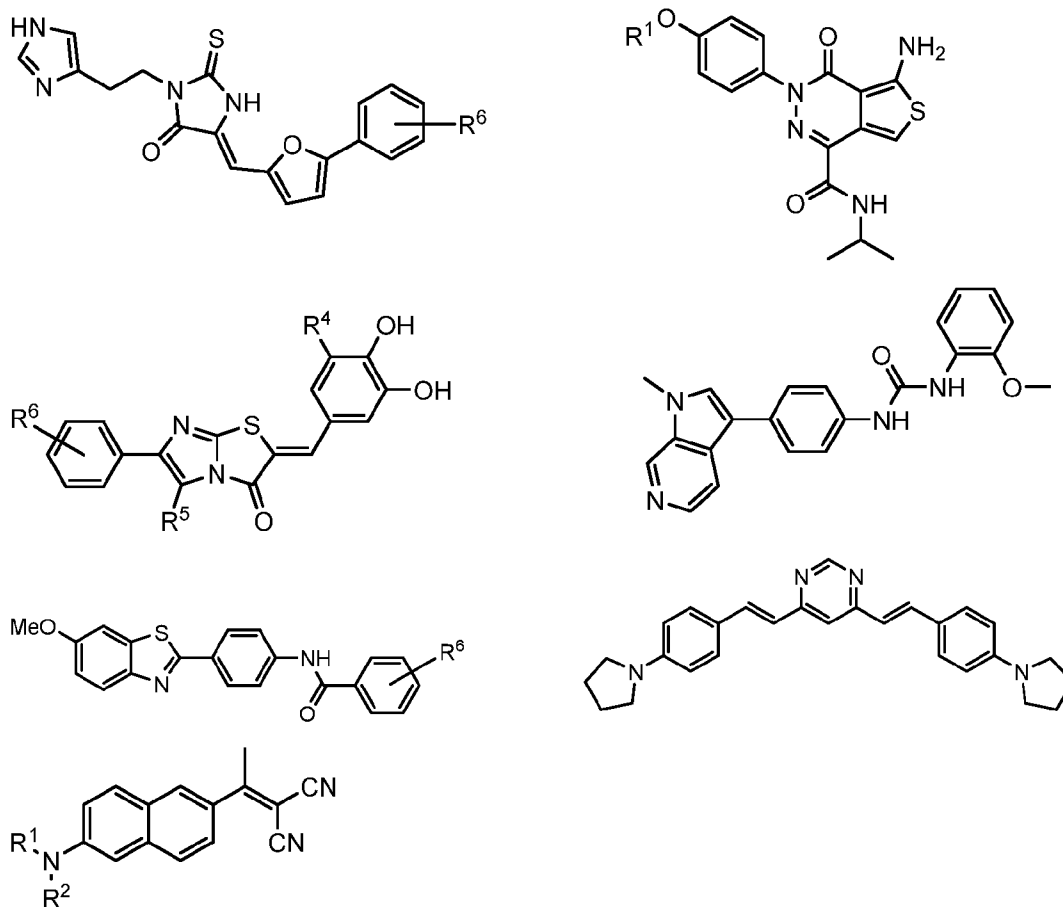
L_{PTM} is a bond; and

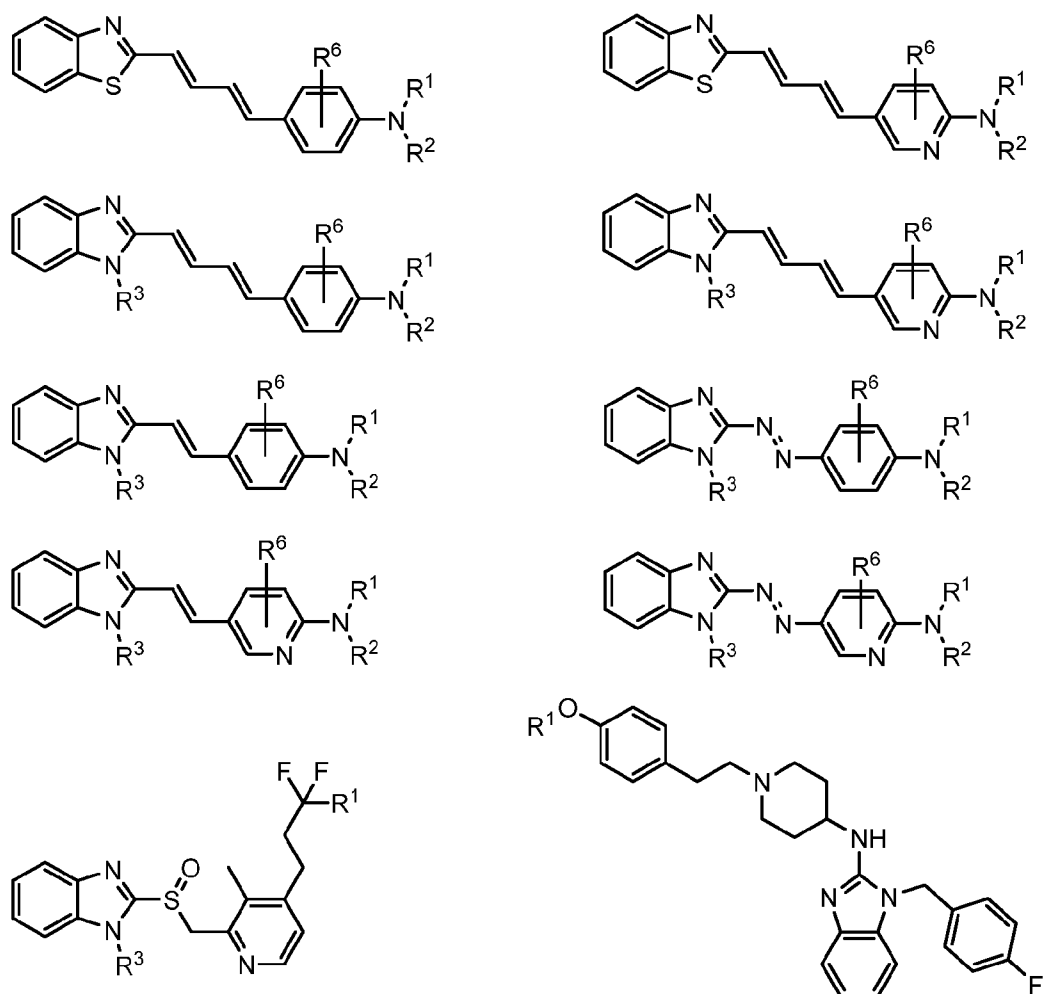
D is a 6-membered heteroaryl or a 6-membered heterocycloalkyl ring;

wherein each A, B, C and D is optionally independently substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, and wherein a nitrogen atom of any of the A, B, C and D rings is not directly connected to a heteroatom or to a carbon atom, to which another heteroatom is directly attached.

[0079] Other preferred PTM embodiments are represented by the structures III and IV wherein A, B and C are 5- or 6- membered fused aryl or heteroaryl rings, L_{PTM} is selected from a bond or an alkyl, and D and E are 5- or 6-membered fused aryl or heteroaryl rings and wherein A, B, C, D and E are optionally substituted with alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, alkylamino, dialkylamino or cyano.

[0080] In certain embodiments, PTM is represented by following chemical structure:





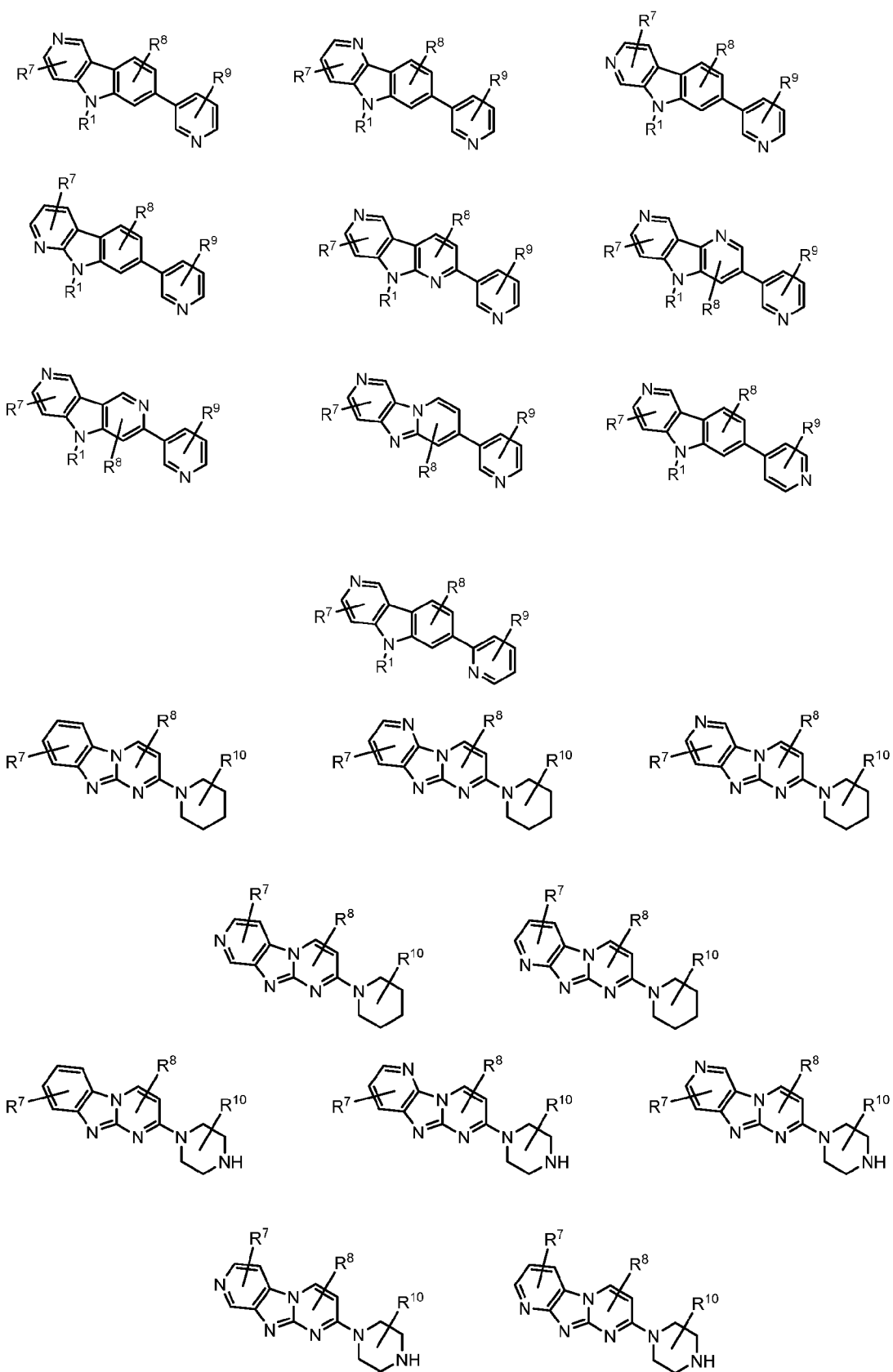
where R¹, R² and R³ are independently selected from H, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl;

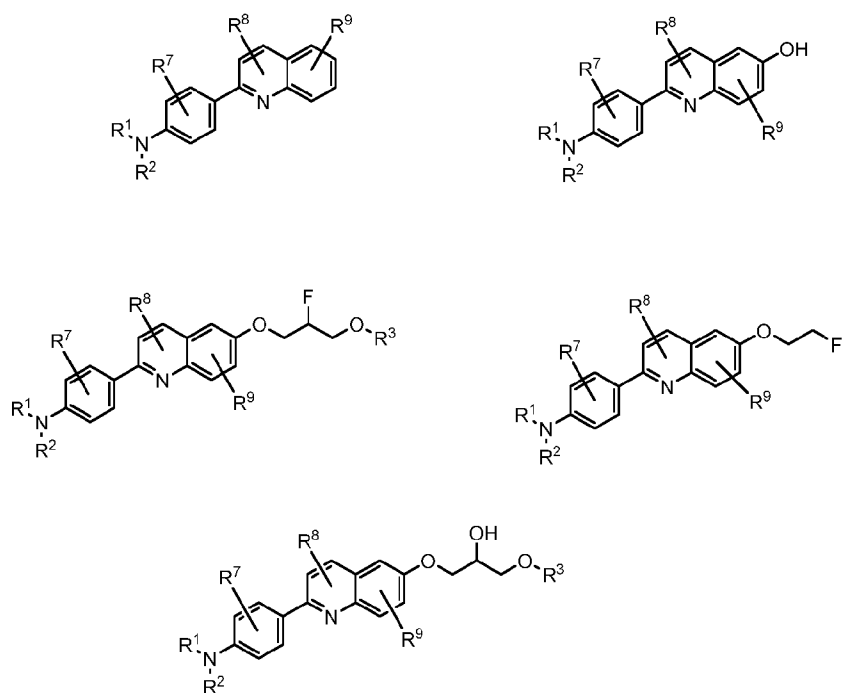
R⁴ and R⁵ are independently selected from H, methyl, ethyl and halogen; and

R⁶ is 1 to 2 substituents independently selected from H, methyl, ethyl and halogen, and wherein the PTM is coupled to a ULM via L.

[0081] In any of the embodiments described herein, PTM is covalently coupled to one or more ULM (VLM or CLM) groups, or a linker to which is attached one or more ULM (VLM or CLM) groups as described herein.

[0082] In certain embodiments, PTM is represented by chemical structure:

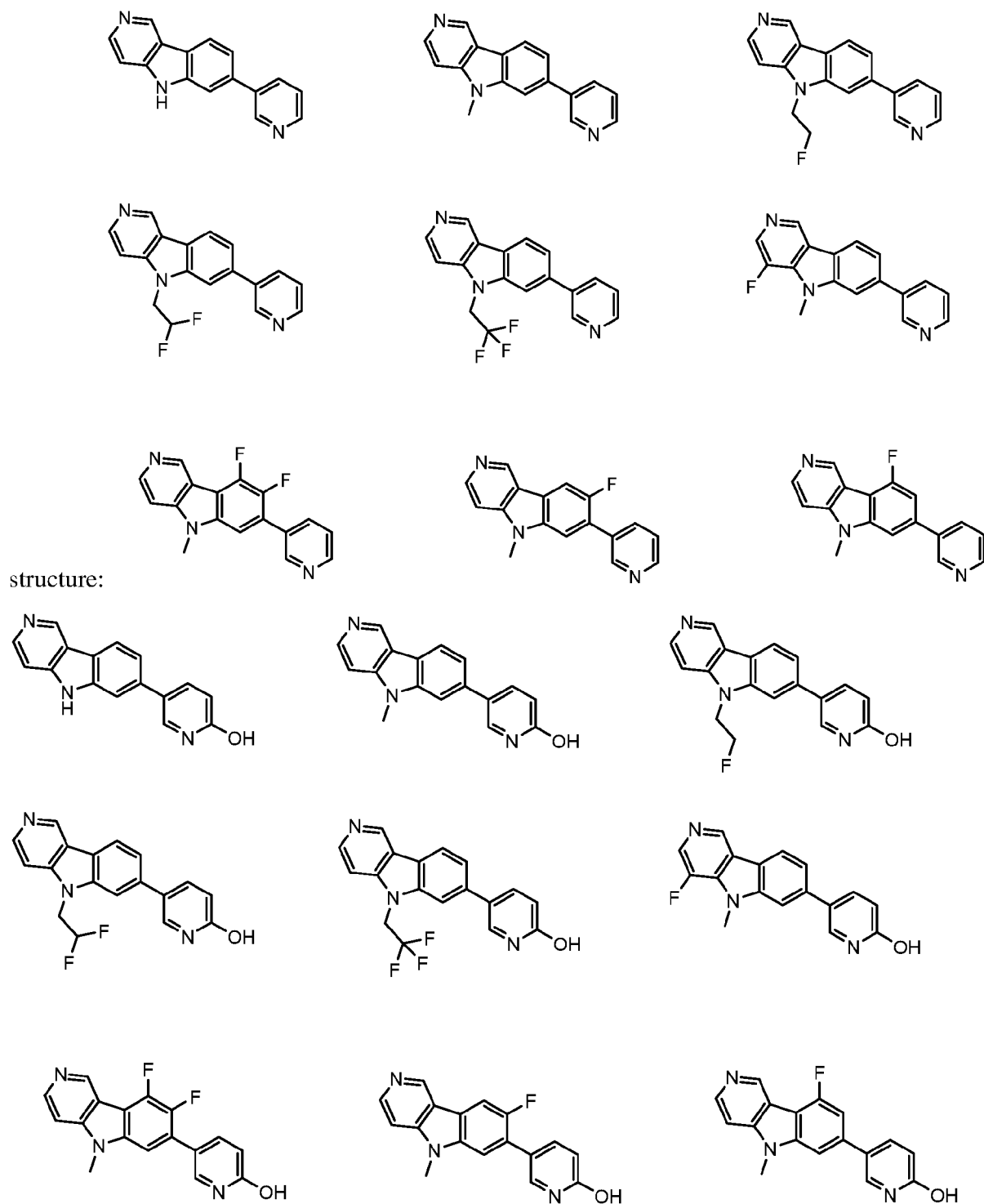


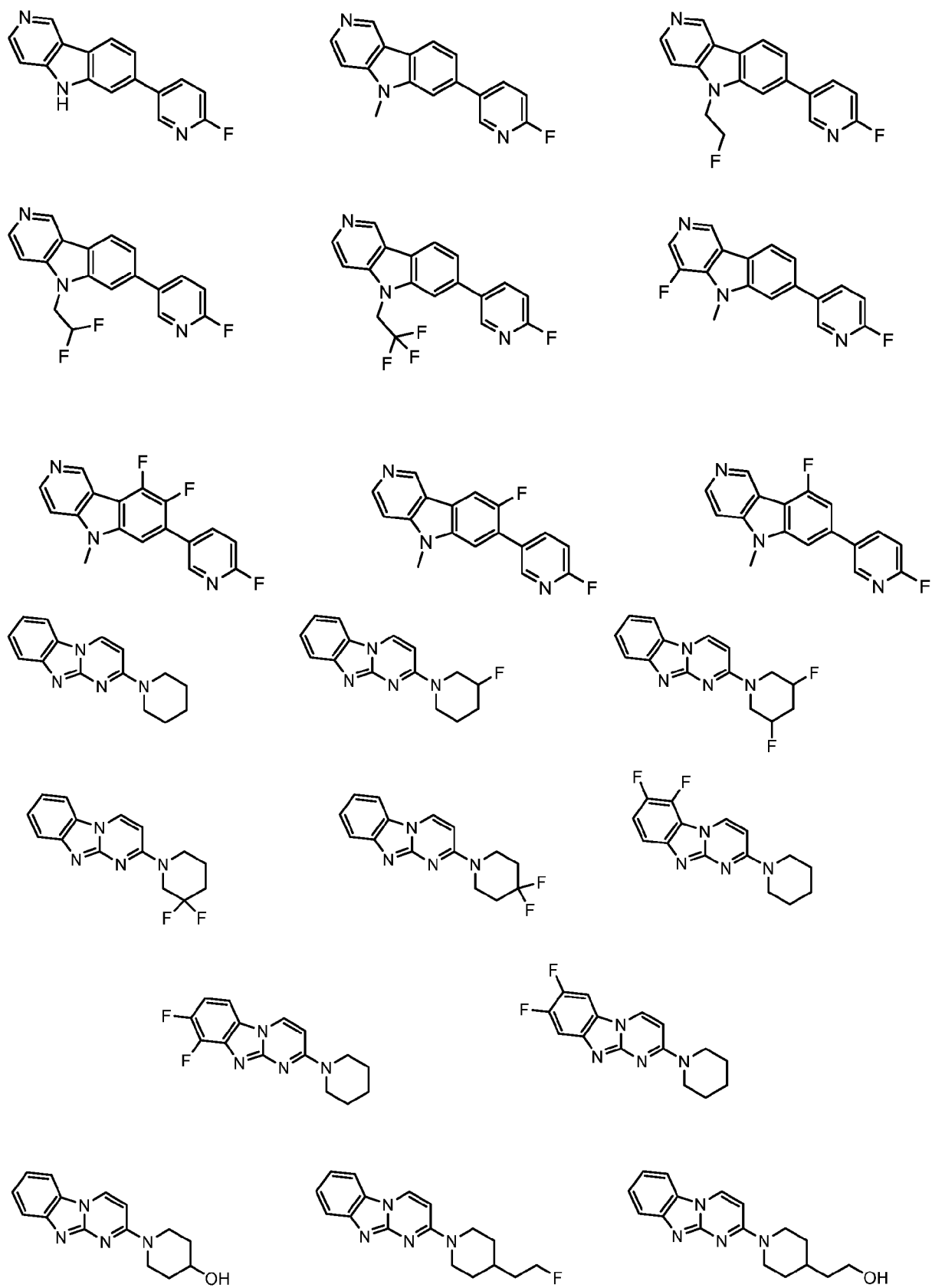


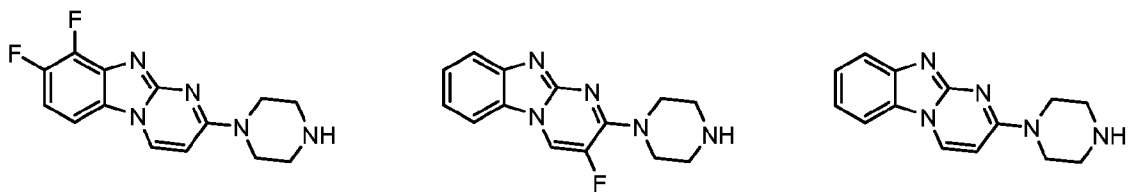
where R^1 , R^2 and R^3 are independently selected from H, optionally substituted alkyl, methyl, ethyl, 2-fluoroethyl and 2,2,2-trifluoroethyl; and

R^7 , R^8 , R^9 and R^{10} are 1 to 2 substituents independently selected from H, optionally substituted alkyl, haloalkyl, halogen, hydroxyl, alkoxy, amino, dialkylamino or cyano, and wherein the PTM is coupled to a ULM (VLM or CLM) via L.

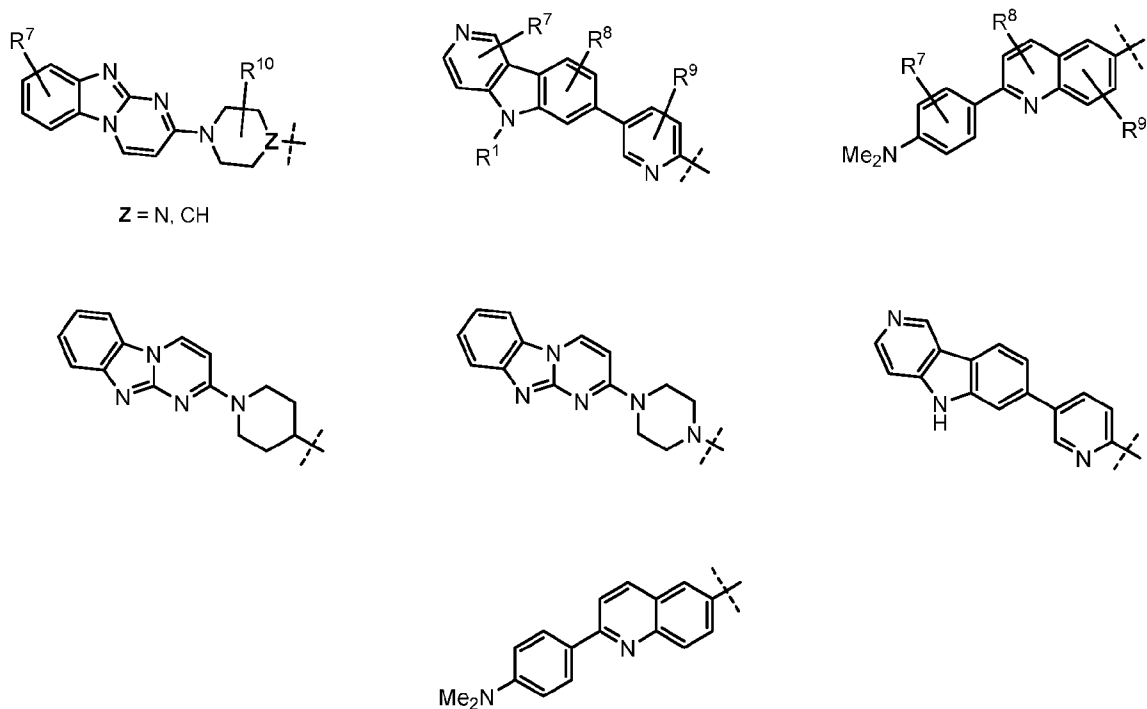
[0083] In certain additional embodiments, PTM is represented by chemical







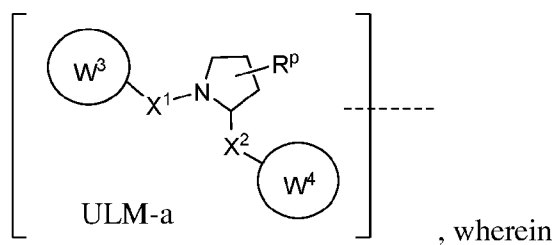
[0084] In certain embodiments linker attachment point to PTM is as indicated by the dotted line:



Exemplary ULMs:

[0085] In one aspect ULM is VHL.

[0086] In certain embodiments of the compounds as described herein, ULM is VLM and comprises a chemical structure selected from the group ULM-a:



where a dashed line indicates the attachment of at least one PTM, another ULM or VLM or CLM (i.e., ULM' or VLM' or CLM'), or a chemical linker moiety coupling at least one PTM, a ULM' or VLM' or CLM' to the other end of the linker;

X^1 , X^2 are each independently selected from the group of a bond, O, NR^{Y3} , $CR^{Y3}R^{Y4}$, $C=O$, $C=S$, SO, and SO_2 ;

R^{Y3} , R^{Y4} are each independently selected from the group of H, linear or branched C_{1-6} alkyl, optionally substituted by 1 or more halo, C_{1-6} alkoxy optionally substituted by 1-3 R^P groups;

R^P is independently selected from the group H, halo, -OH, C_{1-3} alkyl;

W^3 is selected from the group of an optionally substituted $-T-N(R^{1a}R^{1b})X^3$, $-T$ -Aryl, an optionally substituted $-T$ -Heteroaryl, an optionally substituted $-T$ -Heterocycle, an optionally substituted $-NR^1-T$ -Aryl, an optionally substituted $-NR^1-T$ -Heteroaryl or an optionally substituted $-NR^1-T$ -Heterocycle;

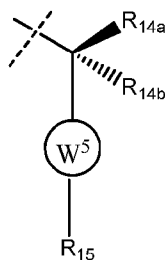
X^3 is $C=O$, R^1 , R^{1a} , R^{1b} are independently selected from the group of H, linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halo or -OH groups, $R^{Y3}C=O$, $R^{Y3}C=S$, $R^{Y3}SO$, $R^{Y3}SO_2$, $N(R^{Y3}R^{Y4})C=O$, $N(R^{Y3}R^{Y4})C=S$, $N(R^{Y3}R^{Y4})SO$, and $N(R^{Y3}R^{Y4})SO_2$;

where T is covalently bonded to X^1 ;

W^4 is an optionally substituted $-NR^1-T$ -Aryl, an optionally substituted $-NR^1-T$ -Heteroaryl group or an optionally substituted $-NR^1-T$ -Heterocycle, where $-NR^1$ is covalently bonded to X^2 where R^1 is H or CH_3 , preferably H.

[0087] In any of the embodiments described herein, T is selected from the group of an optionally substituted alkyl, $-(CH_2)_n-$ group, wherein each one of the methylene groups is optionally substituted with one or two substituents selected from the group of halogen, methyl, a linear or branched C_1-C_6 alkyl group optionally substituted by 1 or more halogen or -OH groups or an amino acid side chain optionally substituted; and

n is 0 to 6, often 0, 1, 2, or 3, preferably 0 or 1.



[0088] In certain embodiments, W^4 is

R_{14a} , R_{14b} , are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

[0089] In any of the embodiments, W^5 is selected from the group of a phenyl or a 5-10 membered heteroaryl,

R_{15} is selected from the group of H, halogen, CN, OH, NO_2 , $N R_{14a}R_{14b}$, OR_{14a} , $CONR_{14a}R_{14b}$, $NR_{14a}COR_{14b}$, $SO_2NR_{14a}R_{14b}$, $NR_{14a}SO_2R_{14b}$, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, or cycloheteroalkyl;

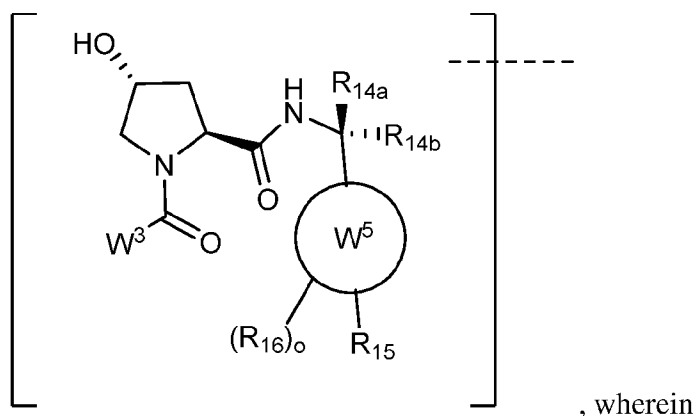
[0090] In additional embodiments, W^4 substituents for use in the present invention also include specifically (and without limitation to the specific compound disclosed) the W^4 substituents which are found in the identified compounds disclosed herein. Each of these W^4 substituents may be used in conjunction with any number of W^3 substituents which are also disclosed herein.

[0091] In certain additional embodiments, ULM-a, is optionally substituted by 1-3 R^P groups in the pyrrolidine moiety. Each R^P is independently H, halo, -OH, C1-3alkyl.

[0092] In any of the embodiments described herein, the W^3 , W^4 can independently be covalently coupled to a linker which is attached one or more PTM groups.

and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

[0093] In certain embodiments, ULM is VHL and is represented by the structure:

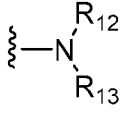


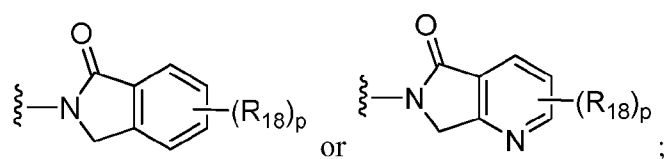
W^3 is selected from the group of an optionally substituted aryl, optionally substituted

heteroaryl, or ;

R₉ and R₁₀ are independently hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl, or R₉, R₁₀, and the carbon atom to which they are attached form an optionally substituted cycloalkyl;

R₁₁ is selected from the group of an optionally substituted heterocyclic, optionally

substituted alkoxy, optionally substituted heteroaryl, optionally substituted aryl, ,



R₁₂ is selected from the group of H or optionally substituted alkyl;

R₁₃ is selected from the group of H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl;

R_{14a}, R_{14b}, are each independently selected from the group of H, haloalkyl, or optionally substituted alkyl;

W⁵ is selected from the group of a phenyl or a 5-10 membered heteroaryl,

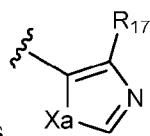
R₁₅ is selected from the group of H, halogen, CN, OH, NO₂, N R_{14a}R_{14b}, OR_{14a}, CONR_{14a}R_{14b}, NR_{14a}COR_{14b}, SO₂NR_{14a}R_{14b}, NR_{14a} SO₂R_{14b}, optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy; aryl, heteroaryl, cycloalkyl, or cycloheteroalkyl;

R₁₆ is independently selected from the group of halo, optionally substituted alkyl, optionally substituted haloalkyl, hydroxy, or optionally substituted haloalkoxy;

o is 0, 1, 2, 3, or 4;

R₁₈ is independently selected from the group of halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker; and

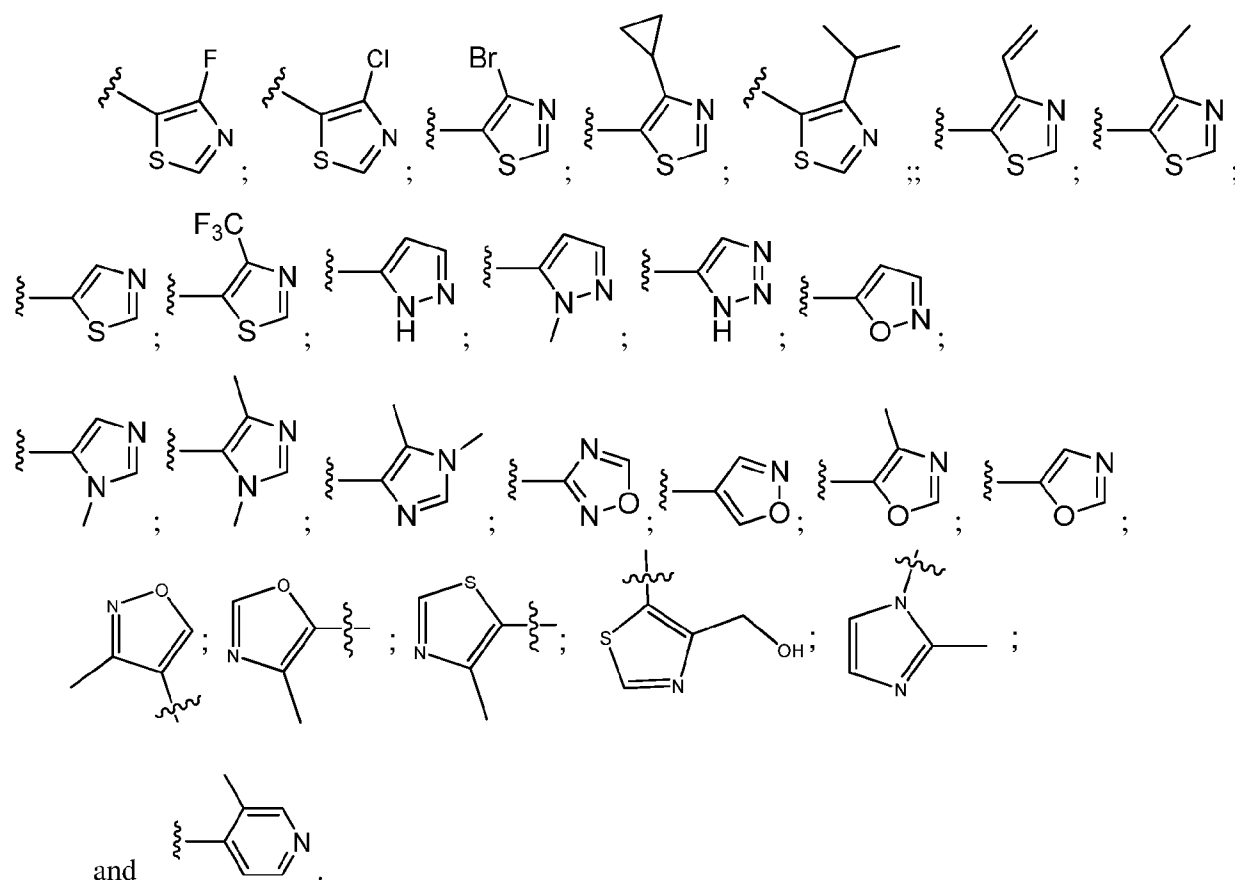
p is 0, 1, 2, 3, or 4, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.



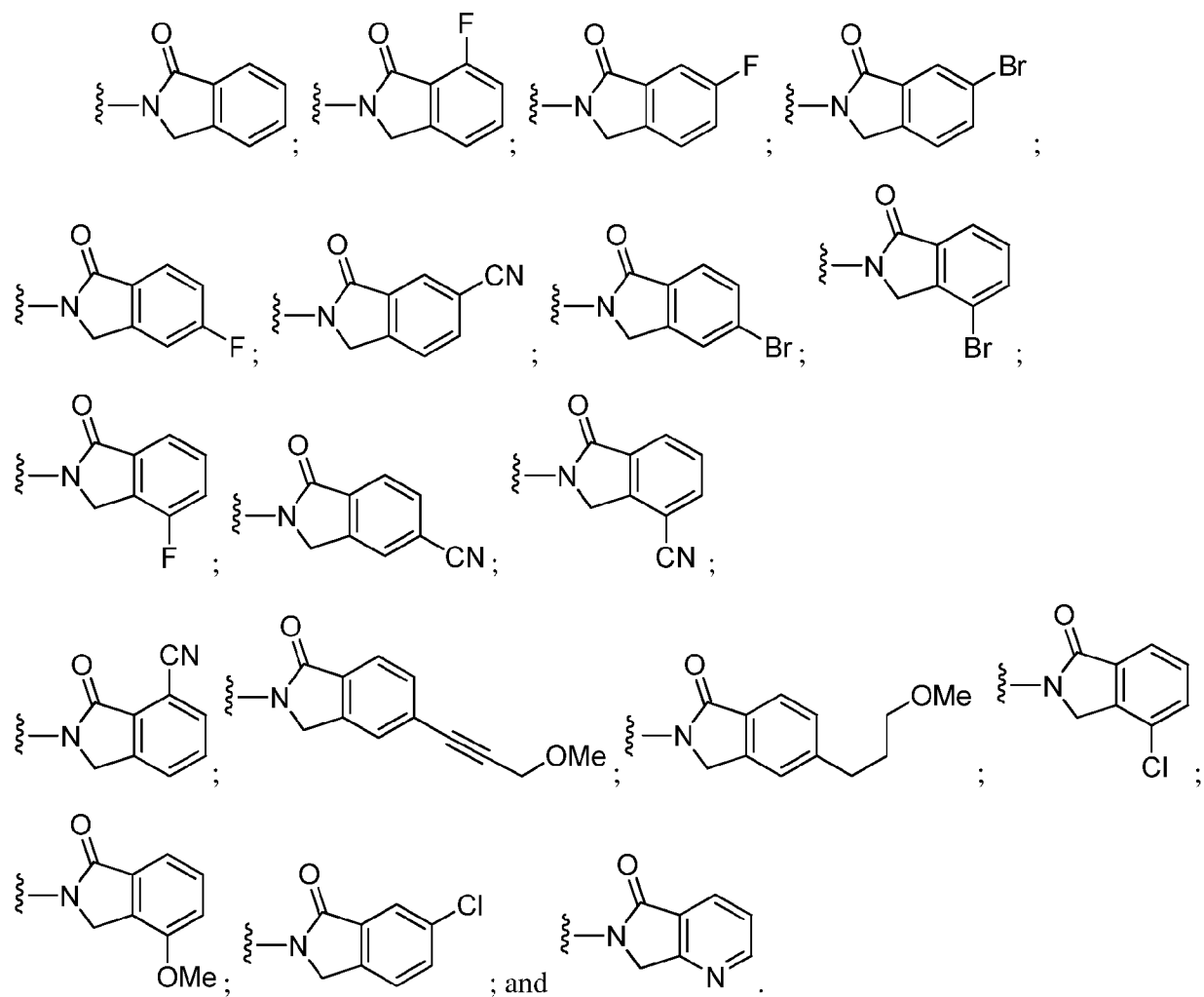
[0094] In certain embodiments, R_{15} is wherein R_{17} is H, halo, optionally substituted C_{3-6} cycloalkyl, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkenyl, and C_{1-6} haloalkyl; and Xa is S or O.

[0095] In certain embodiments, R_{17} is selected from the group methyl, ethyl, isopropyl, and cyclopropyl.

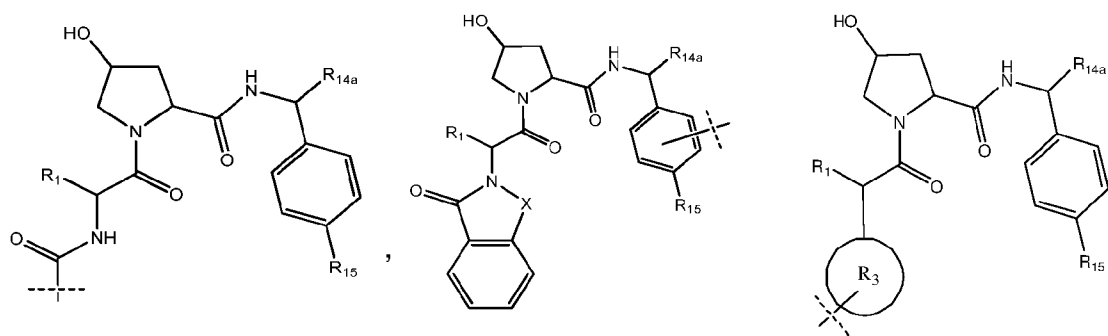
[0096] In certain additional embodiments, R_{15} is selected from the group consisting of:



[0097] In certain embodiments, R_{11} is selected from the group consisting of:



[0098] In certain embodiments, ULM has a chemical structure selected from the group of:



wherein, R₁ is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; optionally substituted alkyl, optionally substituted hydroxyalkyl, optionally substituted heteroaryl, or haloalkyl;

R_{14a} is H, haloalkyl, optionally substituted alkyl, methyl, fluoromethyl, hydroxymethyl, ethyl, isopropyl, or cyclopropyl;

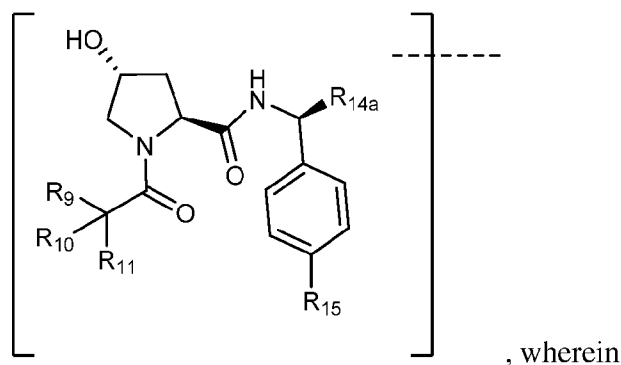
R₁₅ is selected from the group consisting of H, halogen, CN, OH, NO₂, optionally substituted heteroaryl, optionally substituted aryl; optionally substituted alkyl, optionally substituted haloalkyl, optionally substituted haloalkoxy, cycloalkyl, or cycloheteroalkyl;

X is C or C=O

R₃ is an optionally substituted 5 or 6 membered heteroaryl; and

wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM (ULM-a).

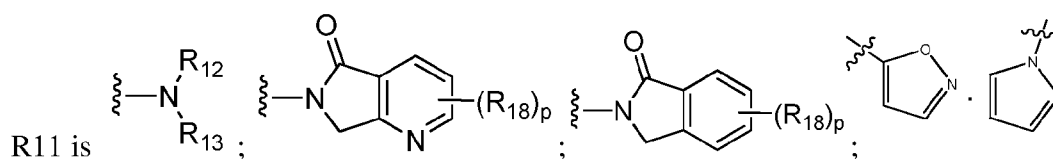
[0099] In certain embodiments, ULM comprises a group according to the chemical structure:



R_{14a} is H, haloalkyl, optionally substituted alkyl, methyl, fluoromethyl, hydroxymethyl, ethyl, isopropyl, or cyclopropyl;

R₉ is H;

R₁₀ is H, ethyl, isopropyl, tert-butyl, sec-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;



or optionally substituted heteroaryl;

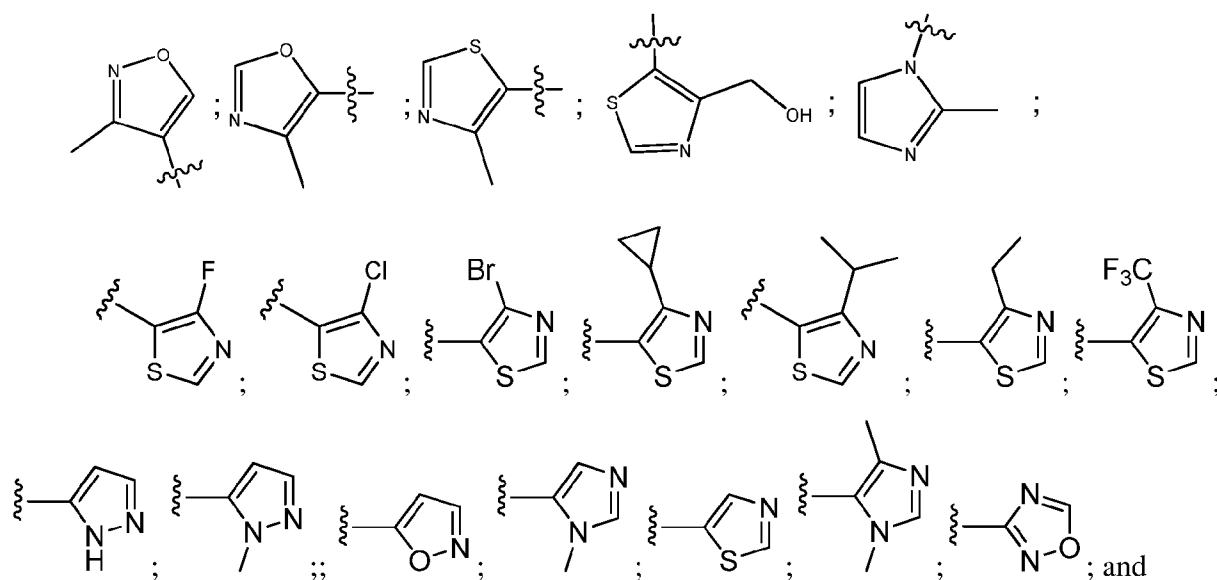
p is 0, 1, 2, 3, or 4;

each R₁₈ is independently halo, optionally substituted alkoxy, cyano, optionally substituted alkyl, haloalkyl, haloalkoxy or a linker;

R₁₂ is H, C=O;

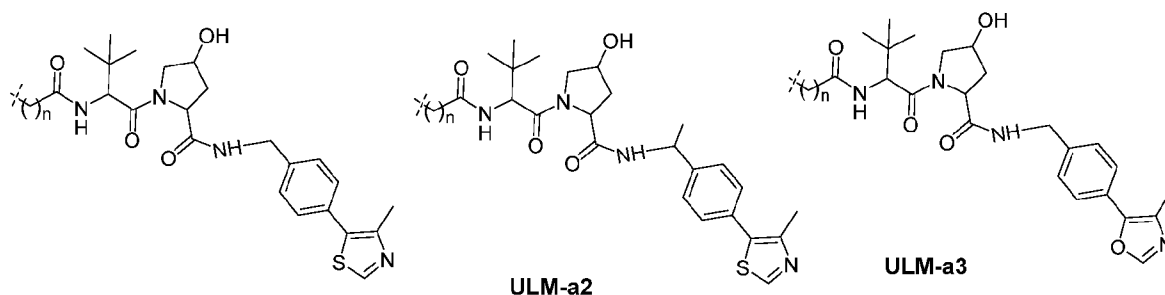
R₁₃ is H, optionally substituted alkyl, optionally substituted alkylcarbonyl, optionally substituted (cycloalkyl)alkylcarbonyl, optionally substituted aralkylcarbonyl, optionally substituted arylcarbonyl, optionally substituted (heterocyclyl)carbonyl, or optionally substituted aralkyl,

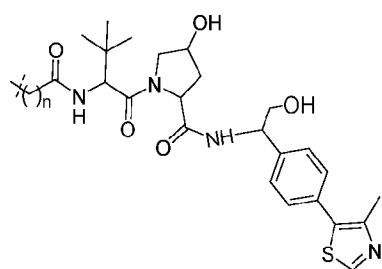
R₁₅ is selected from the group consisting of H, halogen, Cl, CN, OH, NO₂, optionally substituted heteroaryl, optionally substituted aryl;



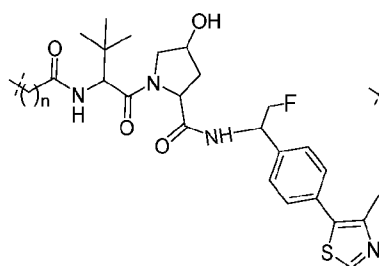
wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM.

[00100] In certain embodiments, the ULM is selected from the following structures:

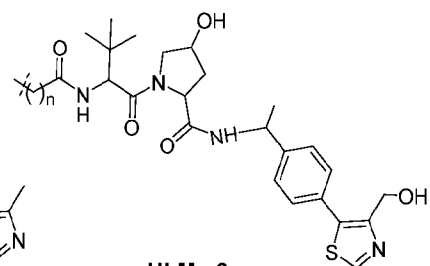




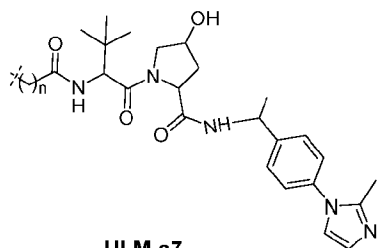
ULM-a4



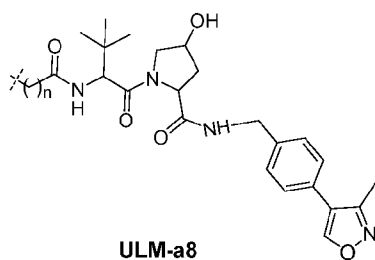
ULM-a5



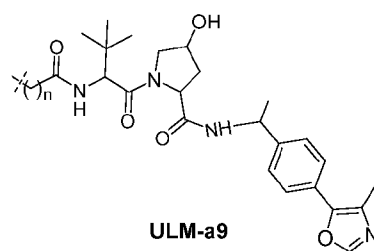
ULM-a6



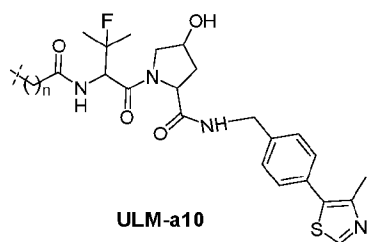
ULM-a7



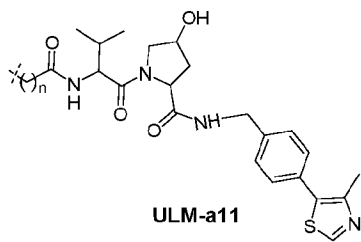
ULM-a8



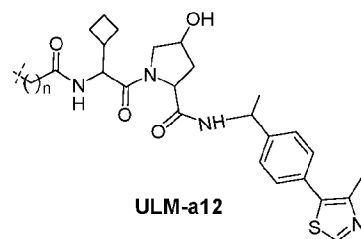
ULM-a9



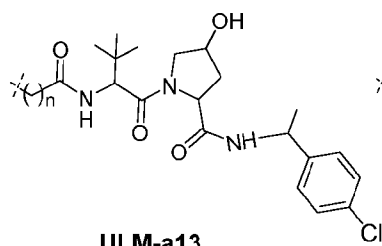
ULM-a10



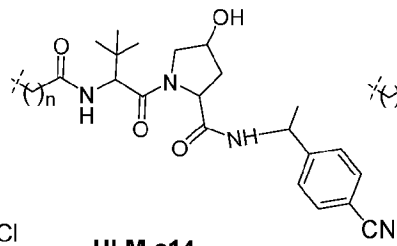
ULM-a11



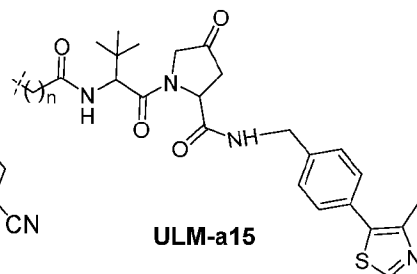
ULM-a12



ULM-a13



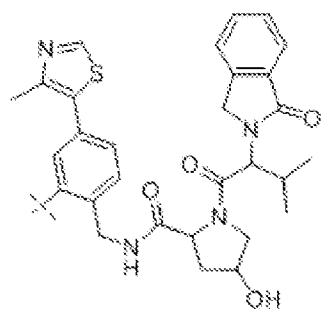
ULM-a14



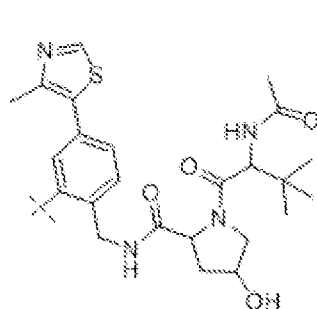
ULM-a15

where n is 0 or 1.

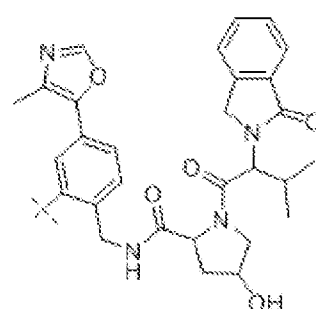
[00101] In certain embodiments, the ULM is selected from the following structures:



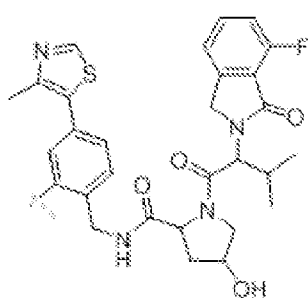
ULM-b1



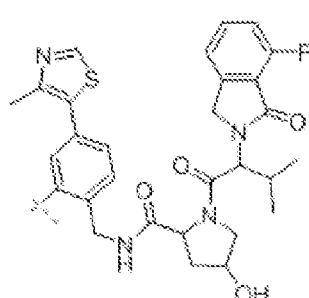
ULM-b2



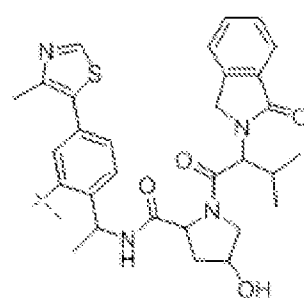
ULM-b3



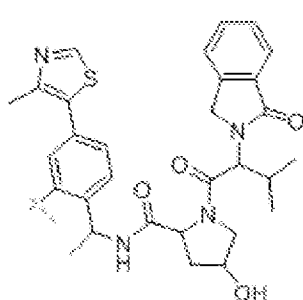
ULM-b4



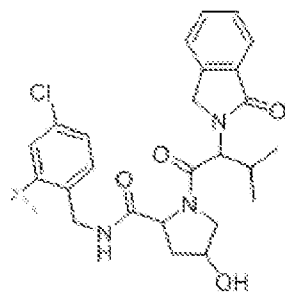
ULM-b5



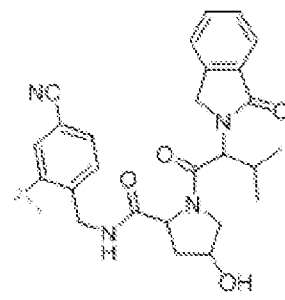
ULM-b6



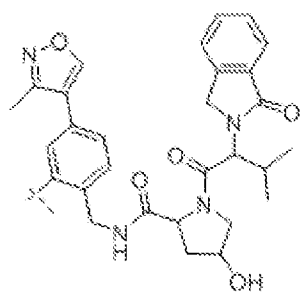
ULM-b7



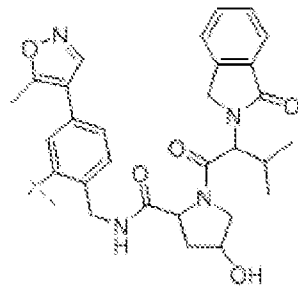
ULM-b8



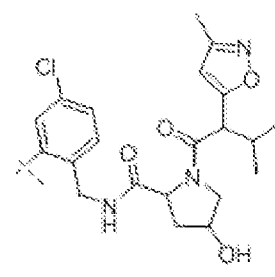
ULM-b9



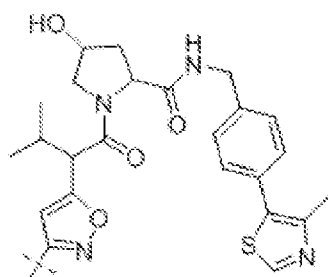
ULM-b7



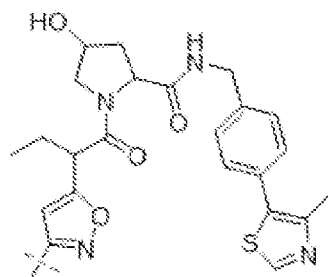
ULM-b8



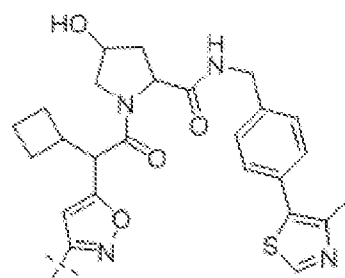
ULM-b9



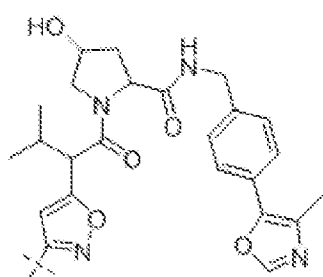
ULM-c1



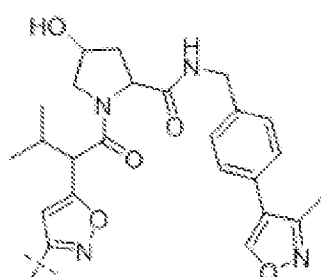
ULM-c2



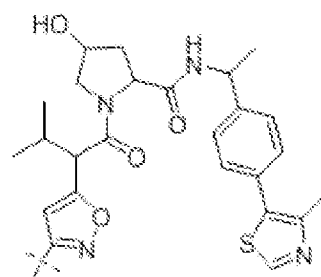
ULM-c3



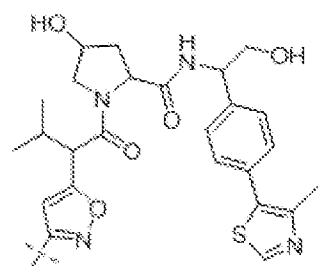
ULM-c4



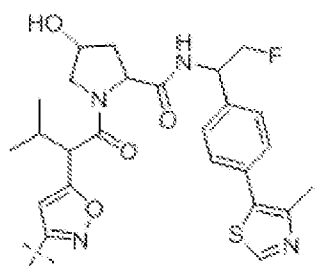
ULM-c5



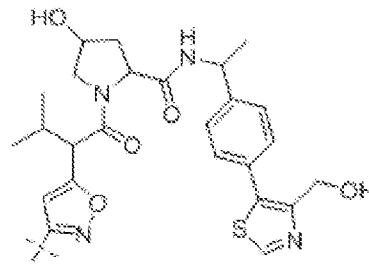
ULM-c6



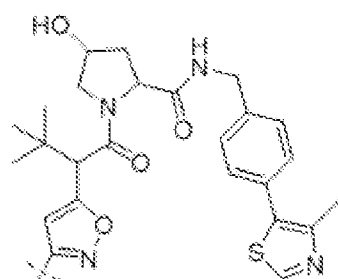
ULM-c7



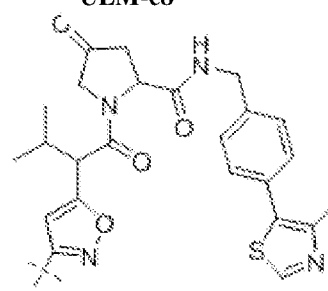
ULM-c8



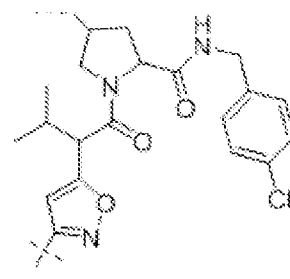
ULM-c9



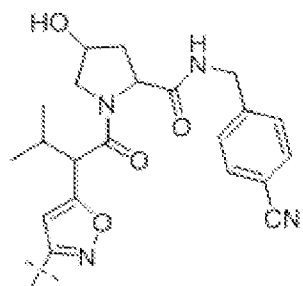
ULM-c10



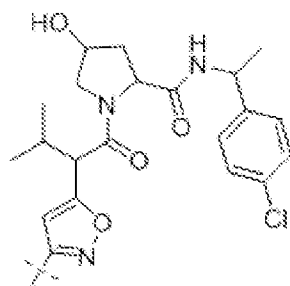
ULM-c11



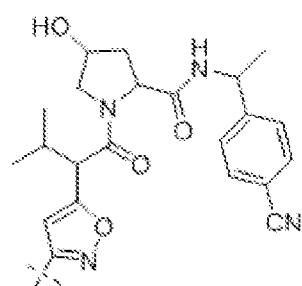
ULM-c12



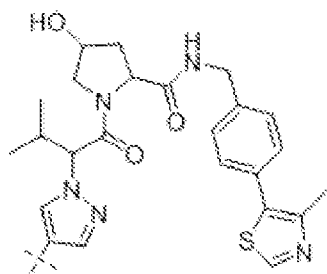
ULM-c13



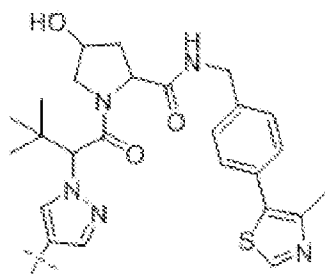
ULM-c14



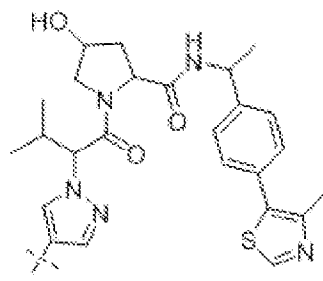
ULM-c15



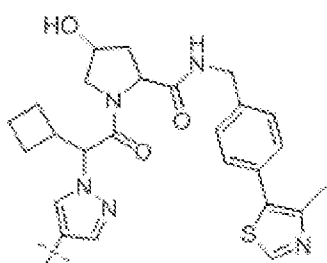
ULM-d1



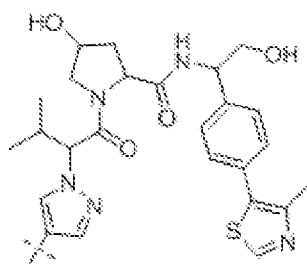
ULM-d2



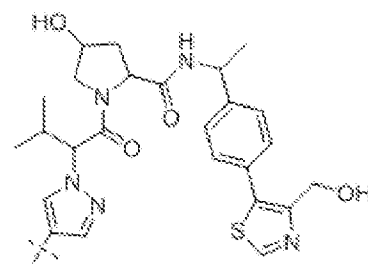
ULM-d3



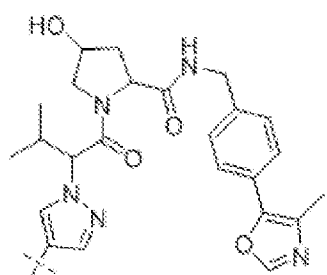
ULM-d4



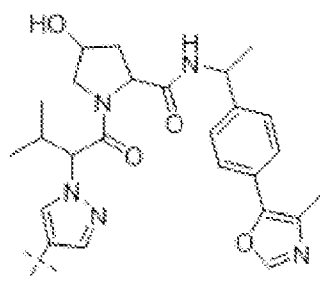
ULM-d5



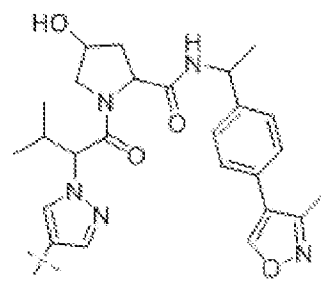
ULM-d6



ULM-d7



ULM-d8



ULM-d9

wherein, the phenyl ring in ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 is optionally substituted with fluorine, lower alkyl and alkoxy groups, and wherein the dashed line indicates the site of attachment of at least one PTM, another ULM (ULM') or a chemical linker moiety coupling at least one PTM or a ULM' or both to ULM-a.

[00102] In one embodiment, the phenyl ring in ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9 can be functionalized as the ester to make it a part of the prodrug.

[00103] In certain embodiments, the hydroxyl group on the pyrrolidine ring of ULM-a1 through ULM-a15, ULM-b1 through ULM-b12, ULM-c1 through ULM-c15 and ULM-d1 through ULM-d9, respectively, comprises an ester-linked prodrug moiety.

Exemplary CLMs:

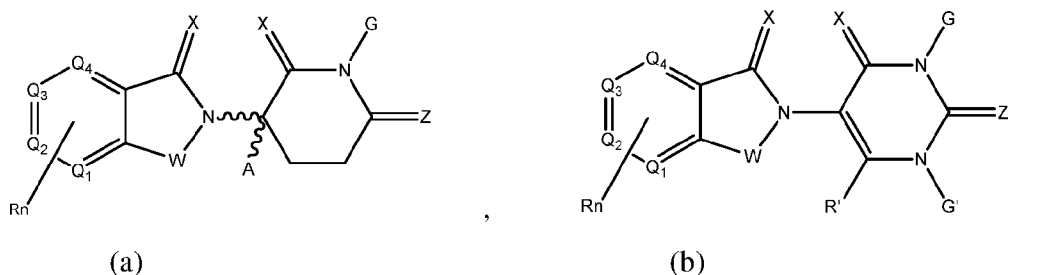
[00104] In one aspect the description provides compounds useful for binding and/or inhibiting cereblon.

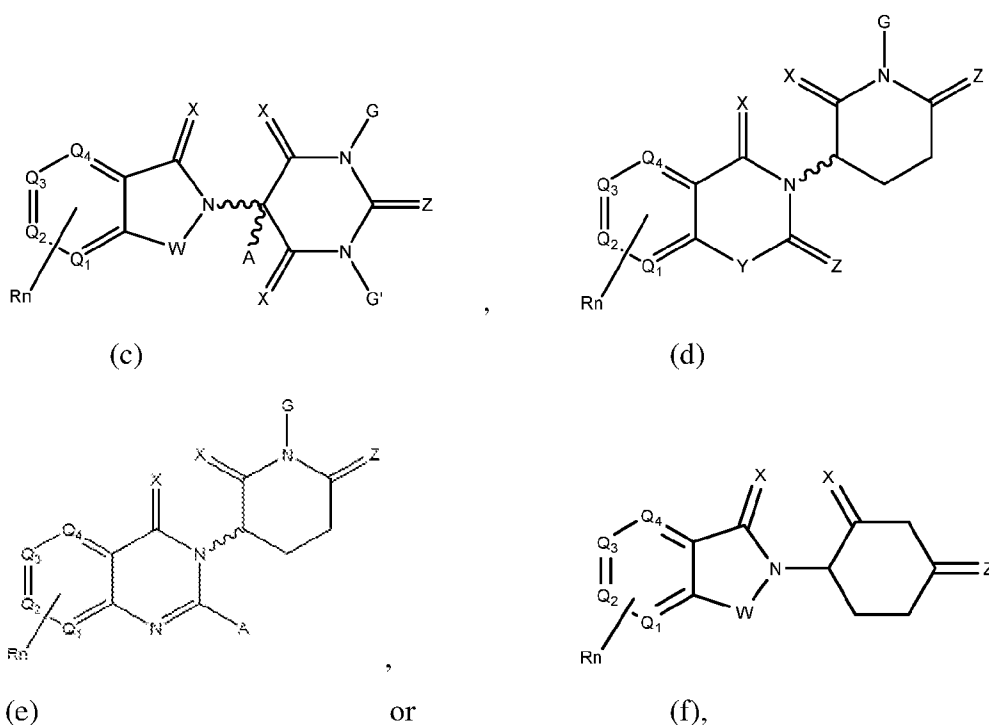
[00105] In some embodiments, ULM is CLM and is represented by:

a thalidomide, lenalidomide, pomalidomide, analogs thereof, isosteres thereof, or derivatives thereof.

Neo-imide Compounds

[00106] In certain embodiments, the compound is selected from the group consisting of chemical structures:





Wherein, W is selected from the group consisting of CH₂, CHR, C=O, SO₂, NH, and N-alkyl;

each X is independently selected from the group consisting of O, S, and H₂;

Y is selected from the group consisting of NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is selected from the group consisting of O, S, and H₂;

G and G' are independently selected from the group consisting of H, alkyl, OH, CH₂-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q₁, Q₂, Q₃, and Q₄ represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A is independently selected from the group H, alkyl, cycloalkyl, Cl and F;

R comprises but is not limited to: -CONR'R'', -OR', -NR'R'', -SR', -SO₂R', -SO₂NR'R'', -CR'R'', -CR'NR'R'', -aryl, -hetaryl, -alkyl, -cycloalkyl, -heterocyclyl, -P(O)(OR')R'', -P(O)R'R'', -OP(O)(OR')R'', -OP(O)R'R'', -Cl, -F, -Br, -I, -CF₃, -CN, -NR'SO₂NR'R'', -NR'CONR'R'', -CONR'COR'', -NR'C(=N-CN)NR'R'', -C(=N-CN)NR'R'', -NR'C(=N-CN)R'', -NR'C(=C-NO₂)NR'R'', -SO₂NR'COR'', -NO₂, -CO₂R', -C(C=N-OR')R'', -CR'=CR'R'', -CCR', -S(C=O)(C=N-R')R'', -SF₅ and -OCF₃;

R' and R'' are independently selected from the group consisting of a bond, H, alkyl, cycloalkyl, aryl, hetaryl, heterocyclyl, each of which is optionally substituted;

~~~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

R<sub>n</sub> comprises a functional group or an atom,

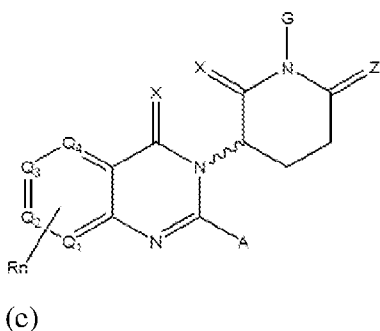
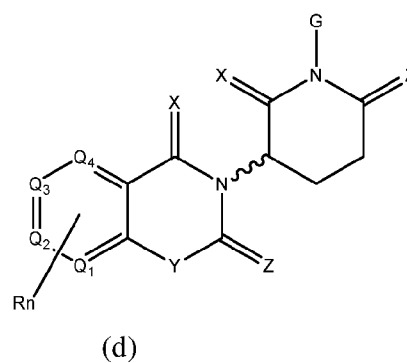
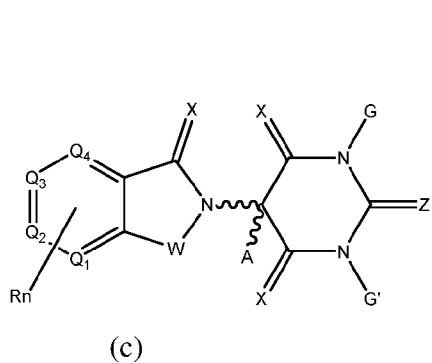
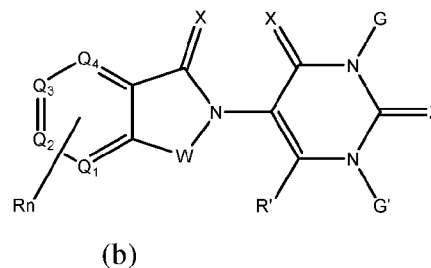
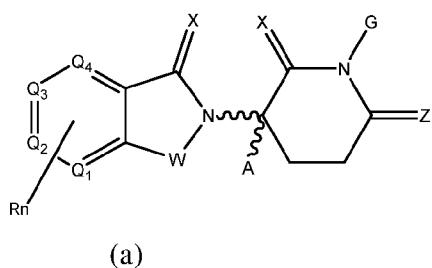
wherein n is an integer from 1-4, and wherein

when n is 1, R<sub>n</sub> is modified to be covalently joined to the linker group (L), and

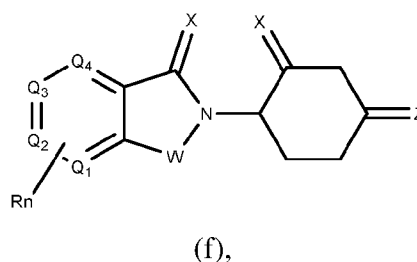
when n is 2, 3, or 4, then one R<sub>n</sub> is modified to be covalently joined to the linker group (L), and any other R<sub>n</sub> is optionally modified to be covalently joined to a PTM, a CLM, a second CLM having the same chemical structure as the CLM, a CLM', a second linker, or any multiple or combination thereof.

### Exemplary CLMs

**[00107]** In any of the compounds described herein, the CLM comprises a chemical structure selected from the group:



and



Wherein, W is independently selected from the group CH<sub>2</sub>, CHR, C=O, SO<sub>2</sub>, NH, and N-alkyl;

X is independently selected from the group O, S and H<sub>2</sub>;

Y is independently selected from the group NH, N-alkyl, N-aryl, N-hetaryl, N-cycloalkyl, N-heterocyclyl, O, and S;

Z is independently selected from the group O, and S or H<sub>2</sub> except that both X and Z cannot be H<sub>2</sub>;

G and G' are independently selected from the group H, alkyl, OH, CH<sub>2</sub>-heterocyclyl optionally substituted with R', and benzyl optionally substituted with R';

Q1 – Q4 represent a carbon C substituted with a group independently selected from R', N or N-oxide;

A is independently selected from the group alkyl, cycloalkyl, Cl and F;

R comprises, but is not limited to: -CONR'R'', -OR', -NR'R'', -SR', -SO<sub>2</sub>R', -SO<sub>2</sub>NR'R'', -CR'R'', -CR'NR'R'', -aryl, -hetaryl, -alkyl, -cycloalkyl, -heterocyclyl, -P(O)(OR')R'', -P(O)R'R'', -OP(O)(OR')R'', -OP(O)R'R'', -Cl, -F, -Br, -I, -CF<sub>3</sub>, -CN, -NR'SO<sub>2</sub>NR'R'', -NR'CONR'R'', -CONR'COR'', -NR'C(=N-CN)NR'R'', -C(=N-CN)NR'R'', -NR'C(=N-CN)R'', -NR'C(=C-NO<sub>2</sub>)NR'R'', -SO<sub>2</sub>NR'COR'', -NO<sub>2</sub>, -CO<sub>2</sub>R', -C(C=N-OR')R'', -CR'=CR'R'', -CCR', -S(C=O)(C=N-R')R'', -SF<sub>5</sub> and -OCF<sub>3</sub>

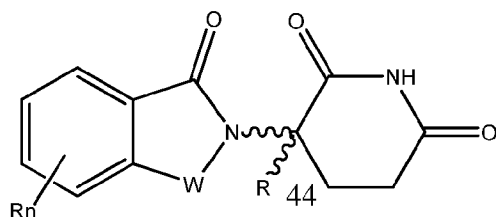
R' and R'' are independently selected from a bond, H, alkyl, cycloalkyl, aryl, hetaryl, heterocyclyl, each of which is optionally substituted;

n is an integer from 1-4;

~~~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

R_n comprises 1-4 independent functional groups or atoms, and optionally, one of which is modified to be covalently joined to a ABM, a chemical linker group (L), a ULM, CLM (or CLM') or combination thereof.

[00108] In certain embodiments described herein, the CLM or ULM comprises a chemical structure selected from the group:



wherein:

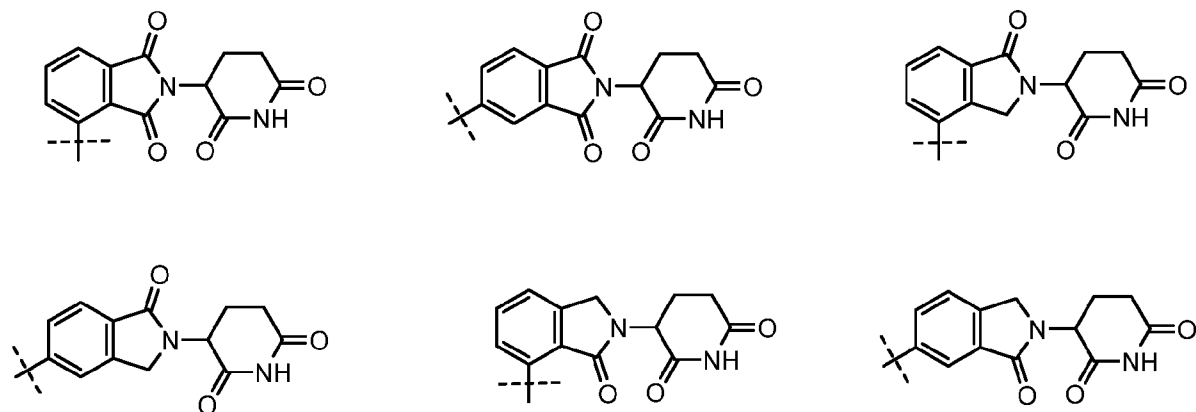
W is independently selected from the group CH₂, C=O, NH, and N-alkyl;

R is independently selected from a H, methyl, alkyl;

~~~~~ represents a bond that may be stereospecific ((R) or (S)) or non-stereospecific; and

R<sub>n</sub> comprises 1-4 independently selected functional groups or atoms, and optionally, one of which is modified to be covalently joined to a PTM, a chemical linker group (L), a CLM (or CLM') or combination thereof.

**[00109]** In some embodiments, the CLM is represented by the following structures with the dashed lines indicating linker attachment points:



**[00110]** In any of the embodiments comprising the structure ULM-L-PTM, wherein the linker (L) comprises a chemical structural unit represented by the formula :

-A<sub>q</sub>-, wherein

A<sub>q</sub> is a group which is connected to a ULM or PTM moiety; and

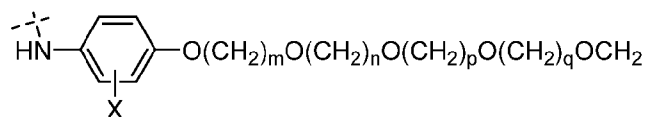
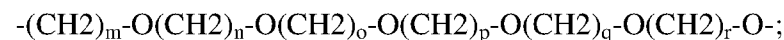
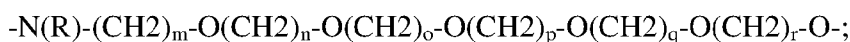
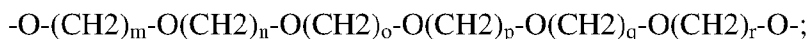
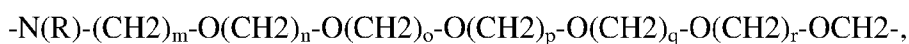
q is an integer greater than or equal to 1,

and wherein, A<sub>q</sub> is selected from the group consisting of a bond, CR<sup>L1</sup>R<sup>L2</sup>, O, S, SO, SO<sub>2</sub>, NR<sup>L3</sup>, SO<sub>2</sub>NR<sup>L3</sup>, SONR<sup>L3</sup>, CONR<sup>L3</sup>, NR<sup>L3</sup>CONR<sup>L4</sup>, NR<sup>L3</sup>SO<sub>2</sub>NR<sup>L4</sup>, CO, CR<sup>L1</sup>=CR<sup>L2</sup>, C≡C, SiR<sup>L1</sup>R<sup>L2</sup>, P(O)R<sup>L1</sup>, P(O)OR<sup>L1</sup>, NR<sup>L3</sup>C(=NCN)NR<sup>L4</sup>, NR<sup>L3</sup>C(=NCN), NR<sup>L3</sup>C(=CNO<sub>2</sub>)NR<sup>L4</sup>, C<sub>3-11</sub>cycloalkyl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, C<sub>3-11</sub>heterocyclyl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, aryl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, heteroaryl optionally substituted with 0-6 R<sup>L1</sup> and/or R<sup>L2</sup> groups, where R<sup>L1</sup> or R<sup>L2</sup>, each

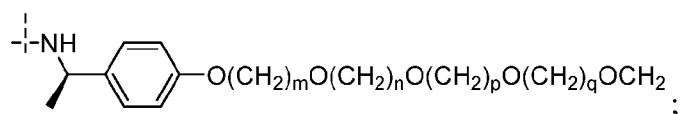
independently are optionally linked to other groups to form cycloalkyl and/or heterocyclyl moiety, optionally substituted with 0-4  $R^{L5}$  groups;

$R^{L1}$ ,  $R^{L2}$ ,  $R^{L3}$ ,  $R^{L4}$  and  $R^{L5}$  are, each independently, H, halo,  $C_{1-8}$ alkyl,  $OC_{1-8}$ alkyl,  $SC_{1-8}$ alkyl,  $NHC_{1-8}$ alkyl,  $N(C_{1-8}alkyl)_2$ ,  $C_{3-11}$ cycloalkyl, aryl, heteroaryl,  $C_{3-11}$ heterocyclyl,  $OC_{1-8}$ cycloalkyl,  $SC_{1-8}$ cycloalkyl,  $NHC_{1-8}$ cycloalkyl,  $N(C_{1-8}cycloalkyl)_2$ ,  $N(C_{1-8}cycloalkyl)(C_{1-8}alkyl)$ , OH,  $NH_2$ , SH,  $SO_2C_{1-8}alkyl$ ,  $P(O)(OC_{1-8}alkyl)(C_{1-8}alkyl)$ ,  $P(O)(OC_{1-8}alkyl)_2$ ,  $CC-C_{1-8}alkyl$ , CCH,  $CH=CH(C_{1-8}alkyl)$ ,  $C(C_{1-8}alkyl)=CH(C_{1-8}alkyl)$ ,  $C(C_{1-8}alkyl)=C(C_{1-8}alkyl)_2$ ,  $Si(OH)_3$ ,  $Si(C_{1-8}alkyl)_3$ ,  $Si(OH)(C_{1-8}alkyl)_2$ ,  $COC_{1-8}alkyl$ ,  $CO_2H$ , halogen, CN,  $CF_3$ ,  $CHF_2$ ,  $CH_2F$ ,  $NO_2$ ,  $SF_5$ ,  $SO_2NHC_{1-8}alkyl$ ,  $SO_2N(C_{1-8}alkyl)_2$ ,  $SONHC_{1-8}alkyl$ ,  $SON(C_{1-8}alkyl)_2$ ,  $CONHC_{1-8}alkyl$ ,  $CON(C_{1-8}alkyl)_2$ ,  $N(C_{1-8}alkyl)CONH(C_{1-8}alkyl)$ ,  $N(C_{1-8}alkyl)CON(C_{1-8}alkyl)_2$ ,  $NHCONH(C_{1-8}alkyl)$ ,  $NHCON(C_{1-8}alkyl)_2$ ,  $NHCONH_2$ ,  $N(C_{1-8}alkyl)SO_2NH(C_{1-8}alkyl)$ ,  $N(C_{1-8}alkyl)SO_2N(C_{1-8}alkyl)_2$ ,  $NH SO_2NH(C_{1-8}alkyl)$ ,  $NH SO_2N(C_{1-8}alkyl)_2$ ,  $NH SO_2NH_2$ .

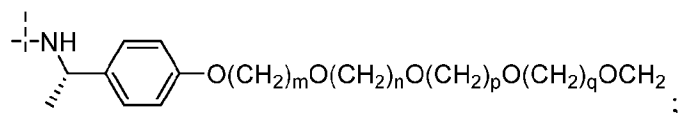
**[00111]** In some of the embodiments, linker (L) comprises a group represented by a general structure selected from the group consisting of:



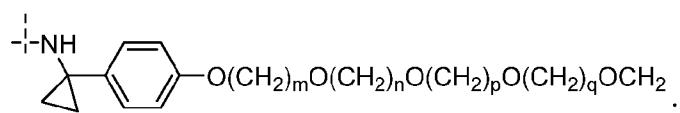
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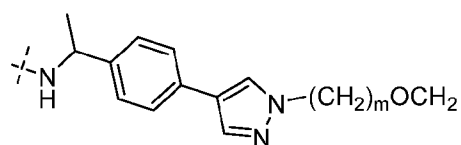
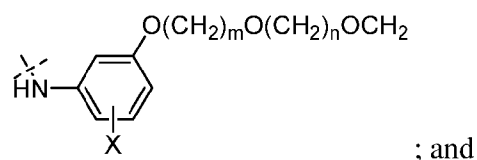
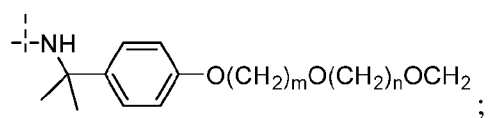
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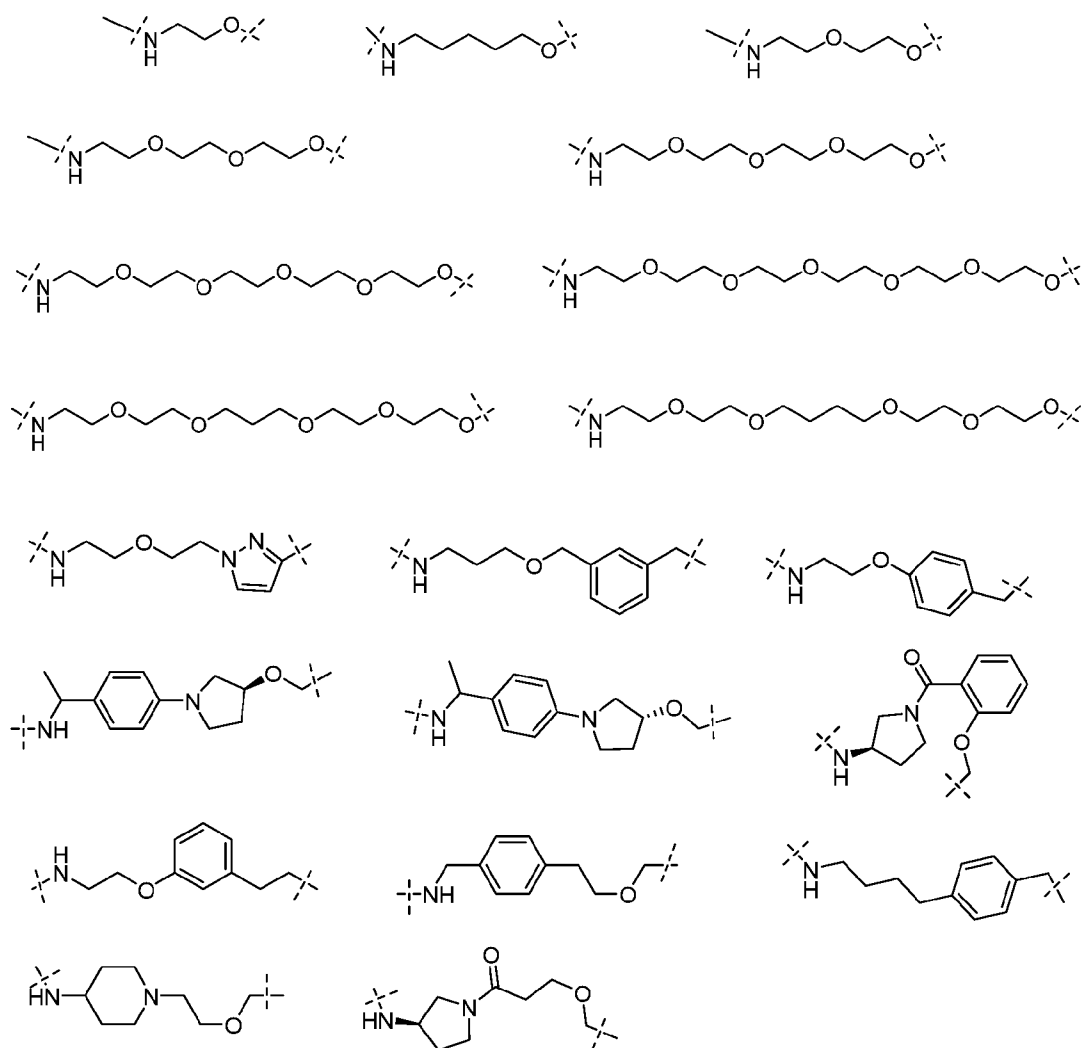
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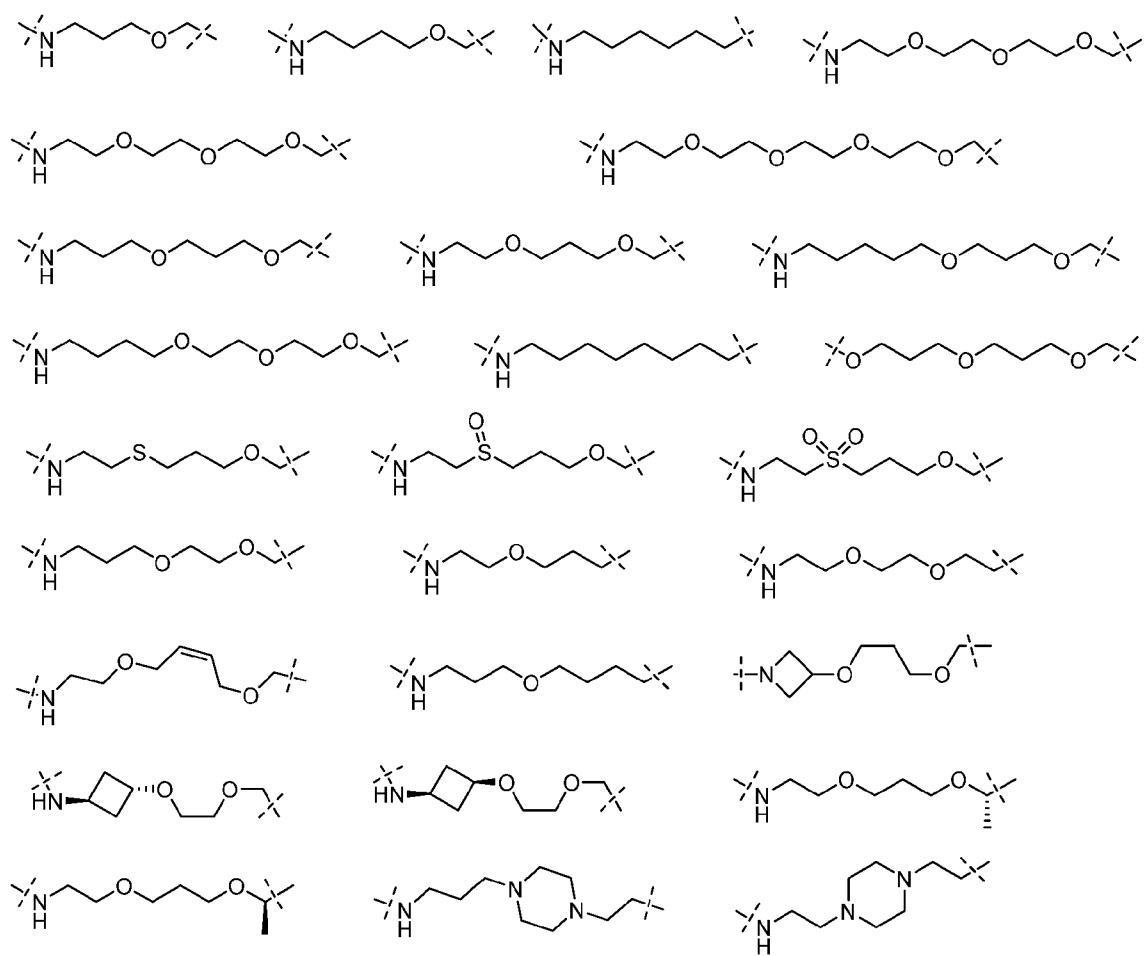


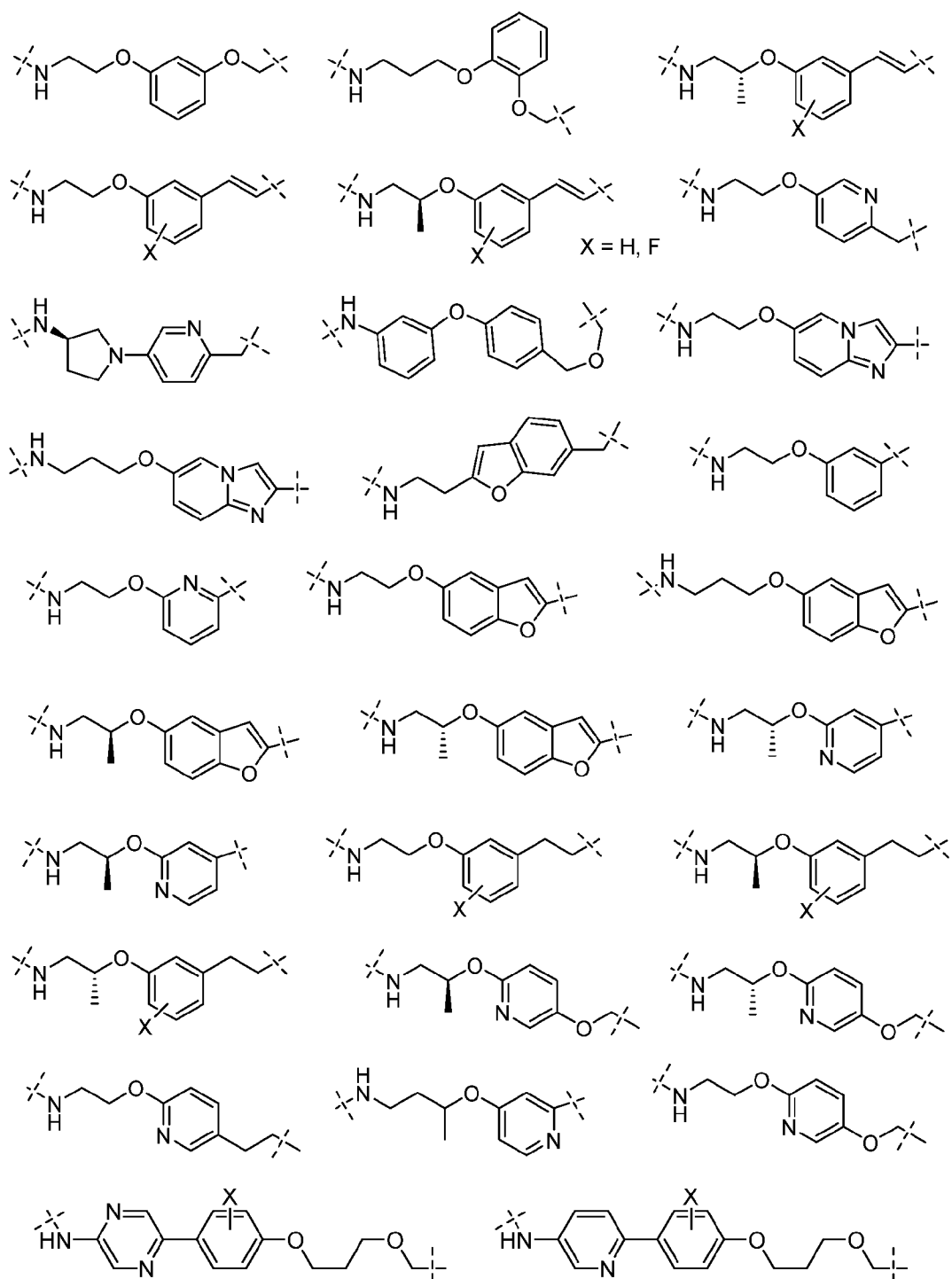
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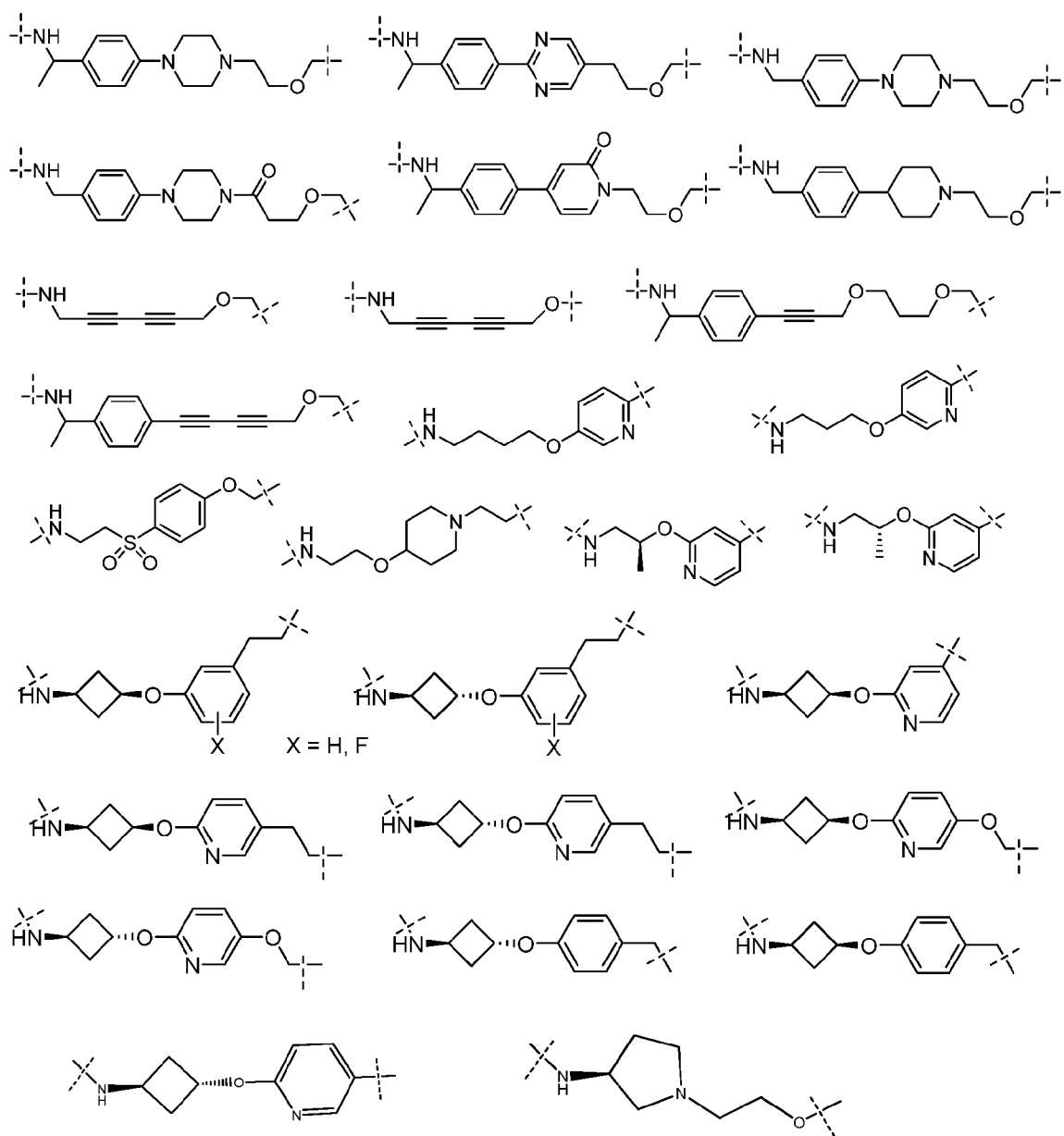


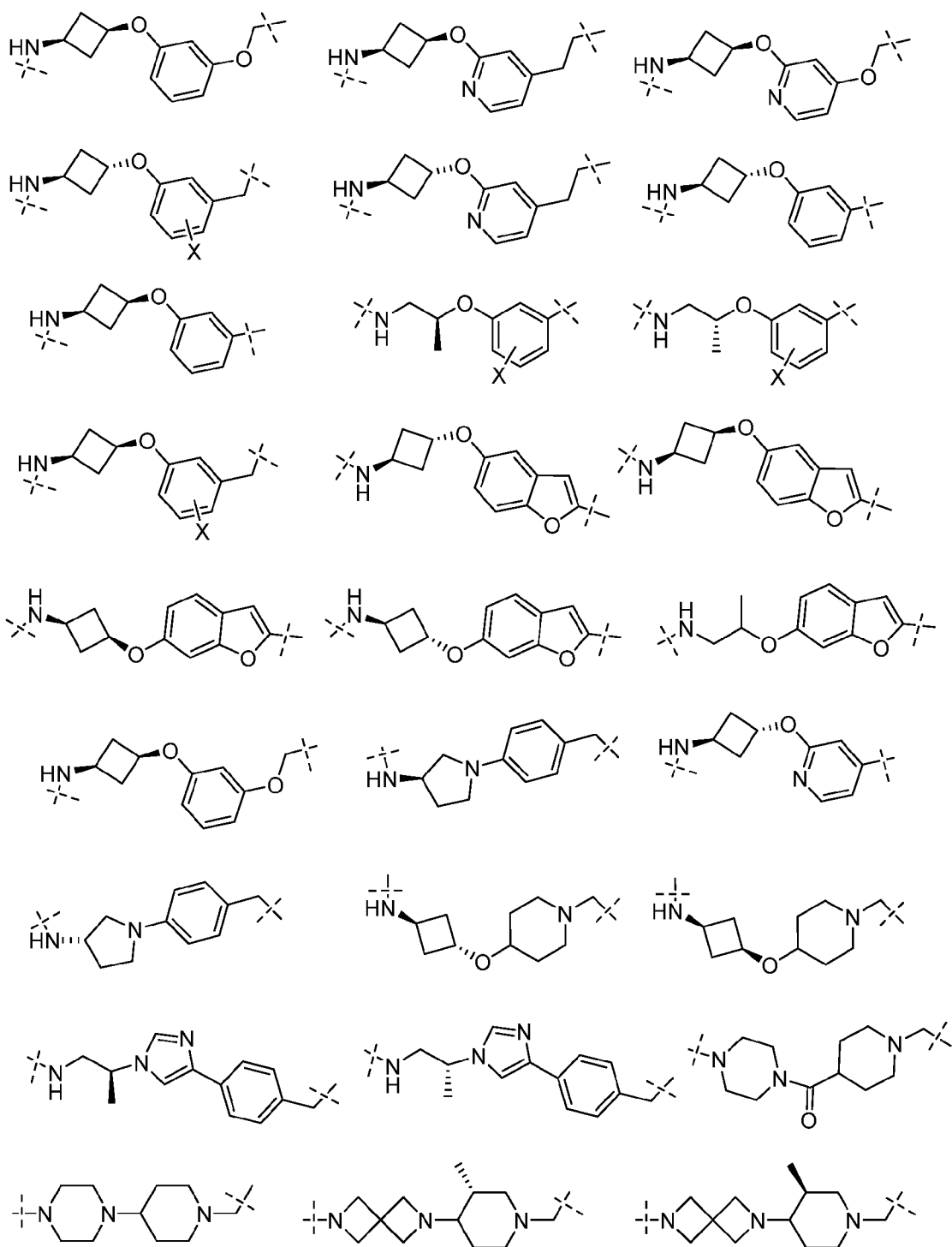
, wherein m, n, o, p, q, and r, are independently 0, 1, 2, 3, 4, 5, with the provision that when the number is zero, there is no N-O or O-O bond, R is selected from the group H, methyl and ethyl, and X is selected from the group H and F;

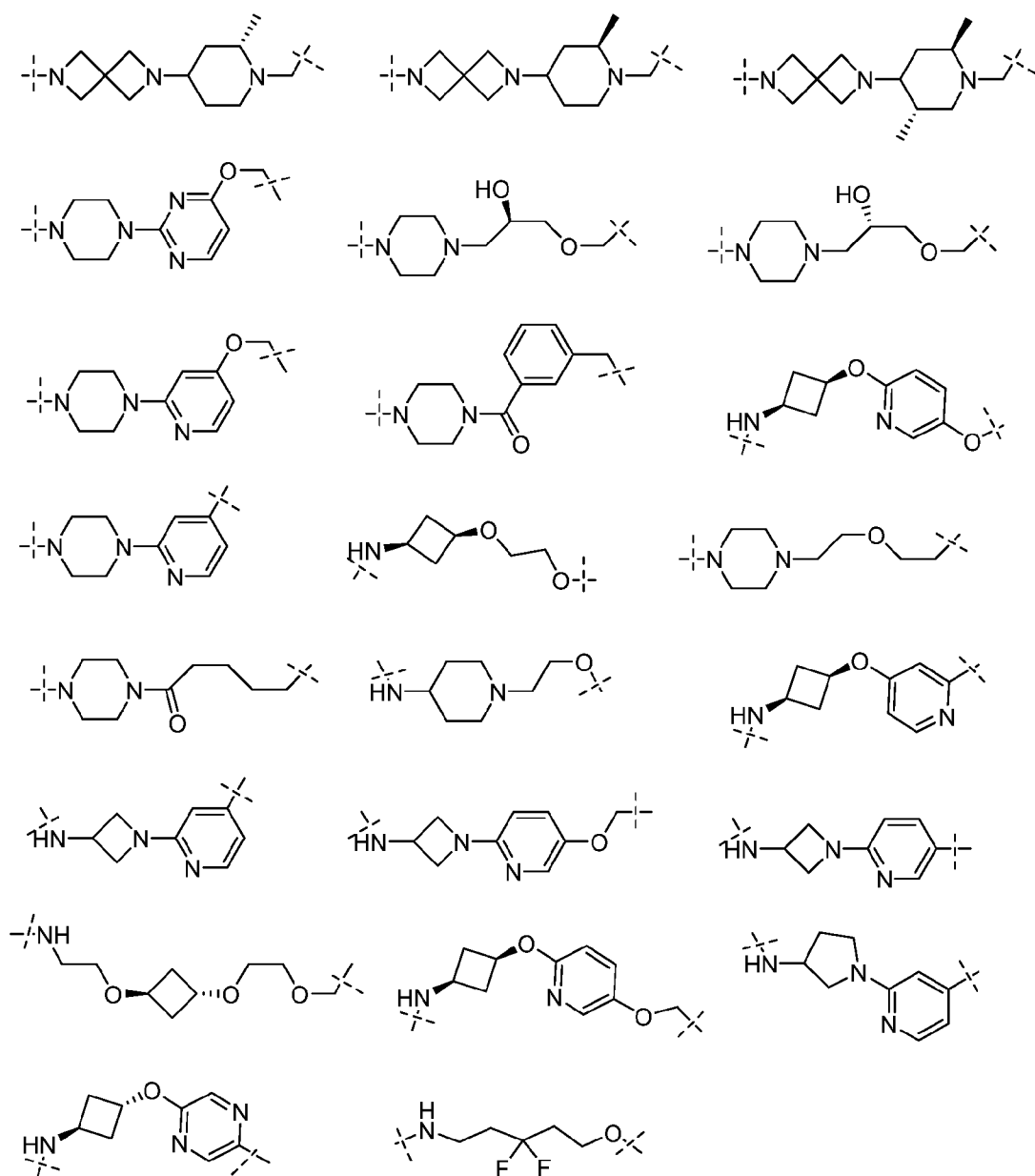




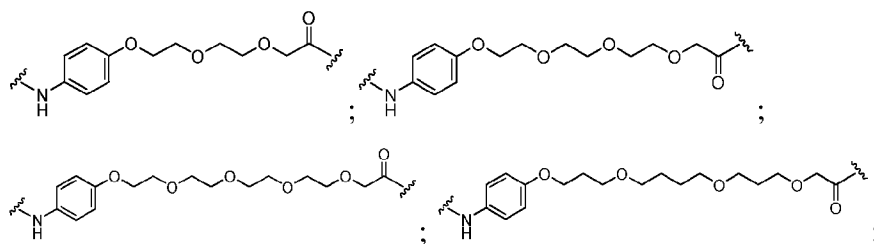


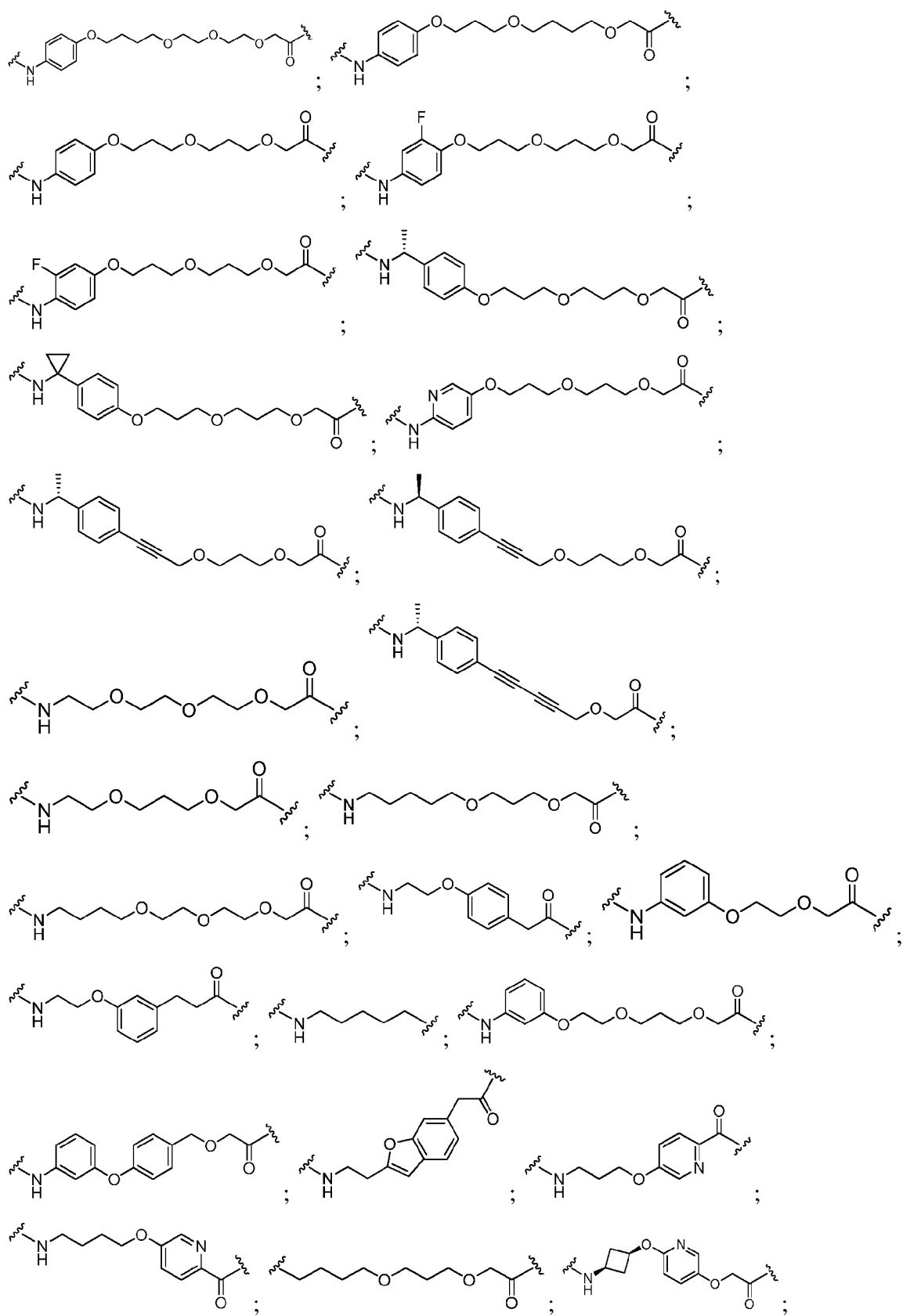


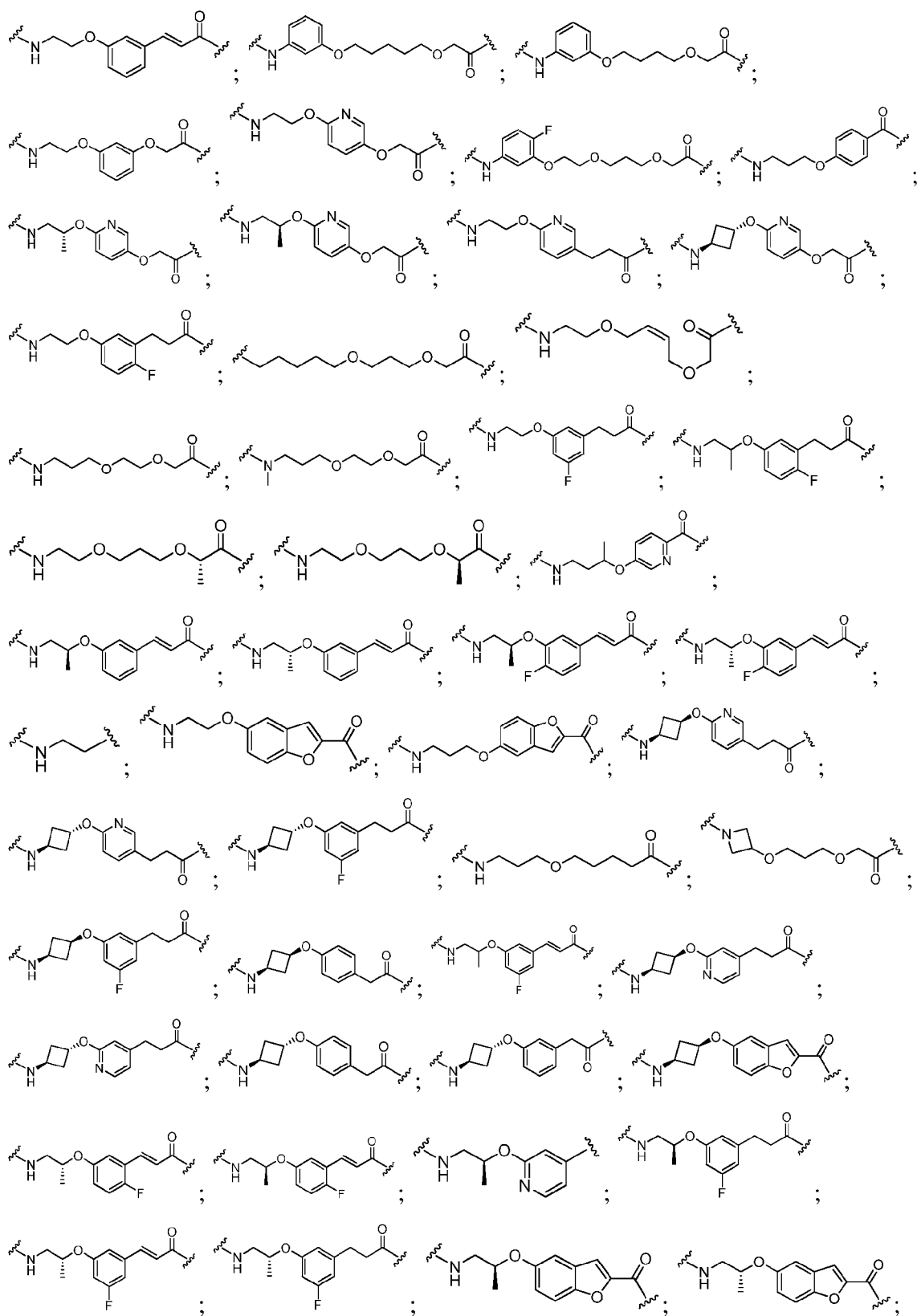


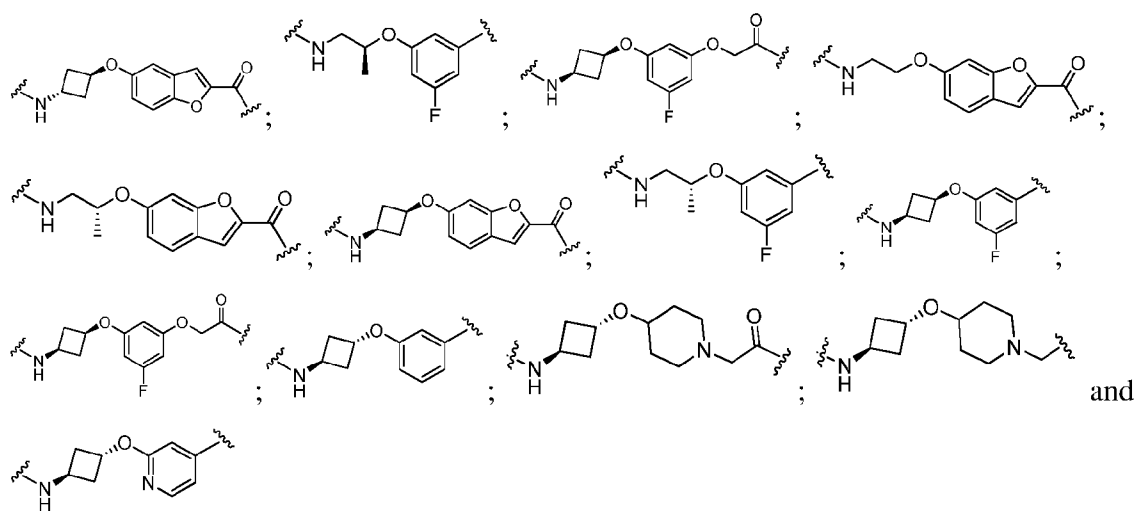


**[00112]** In some additional embodiments, linker (L) is selected from the group consisting of:

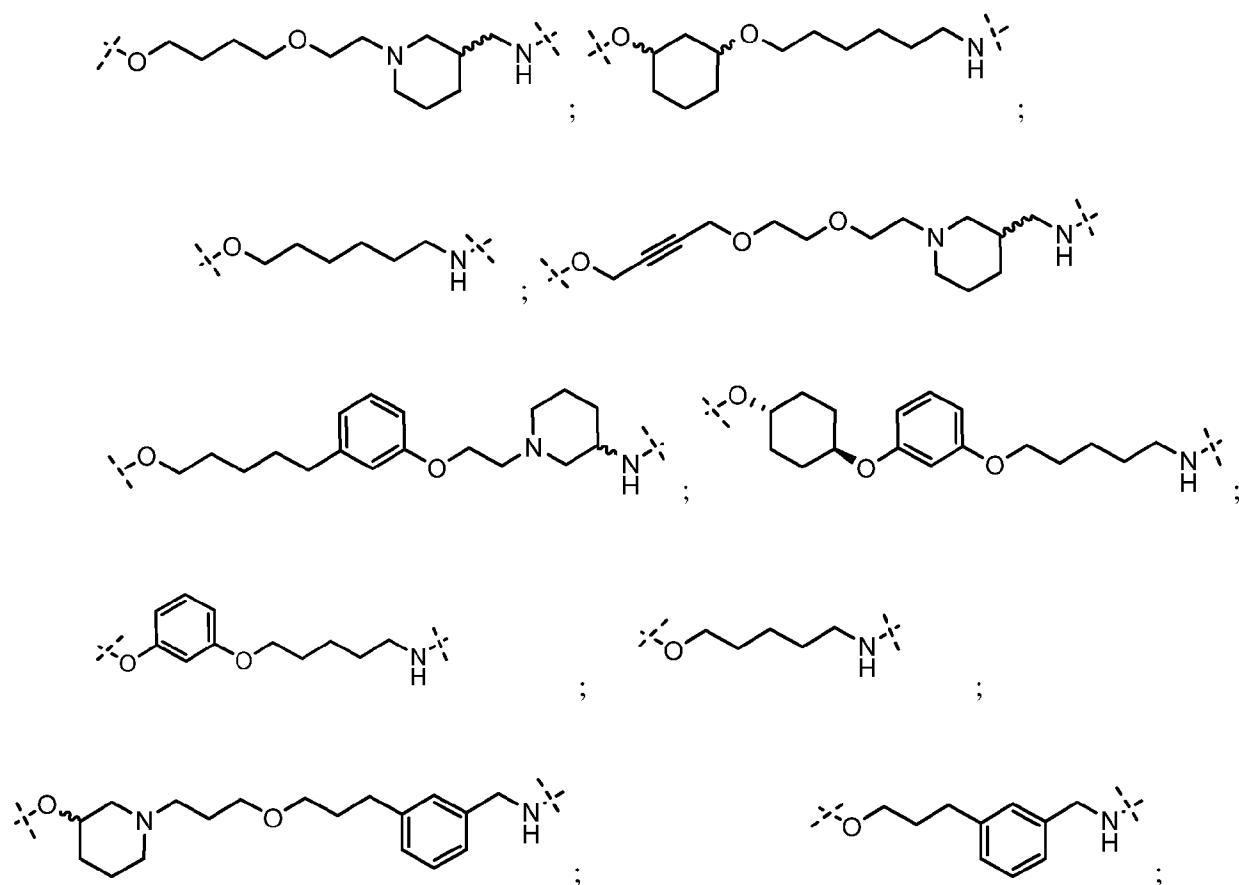


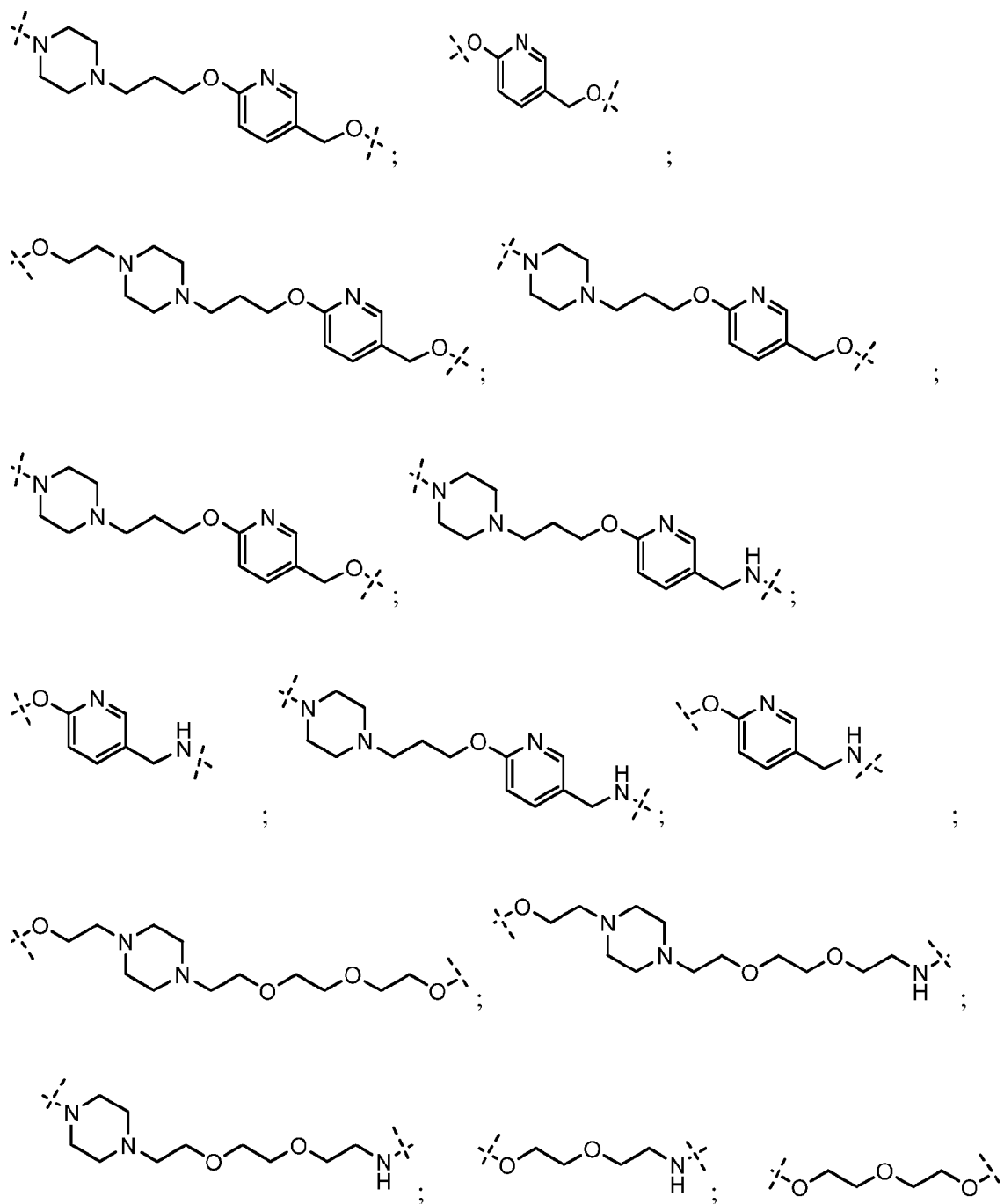


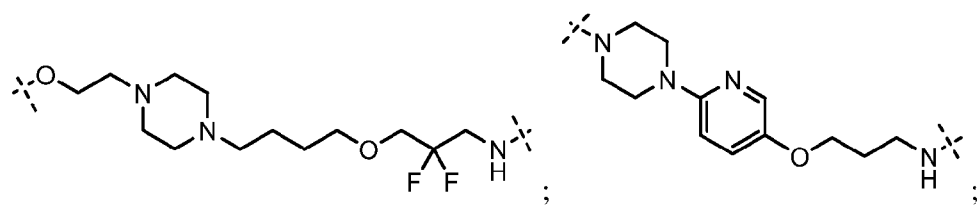
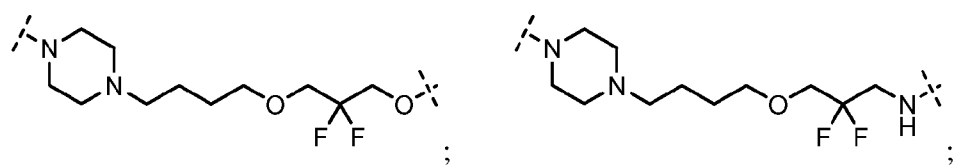
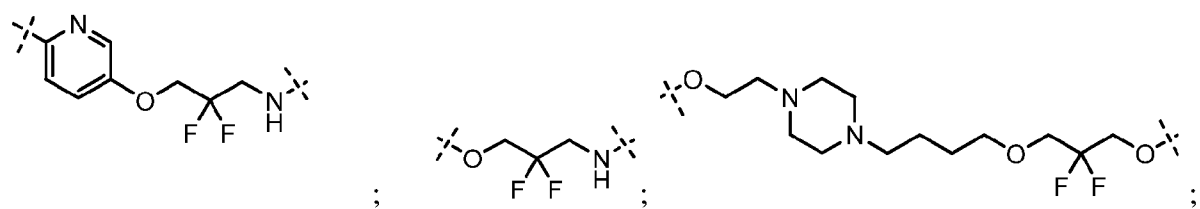
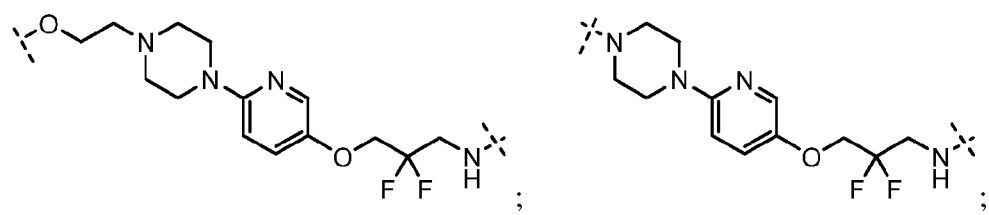
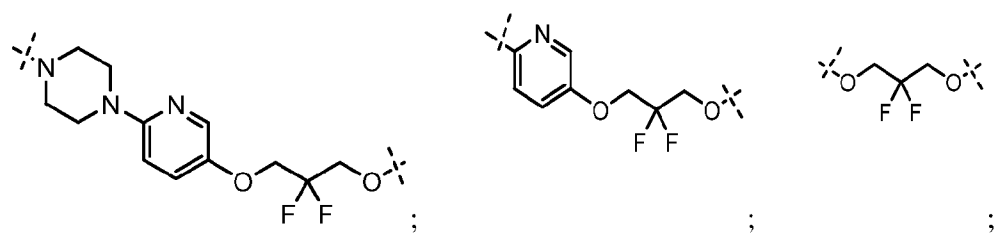


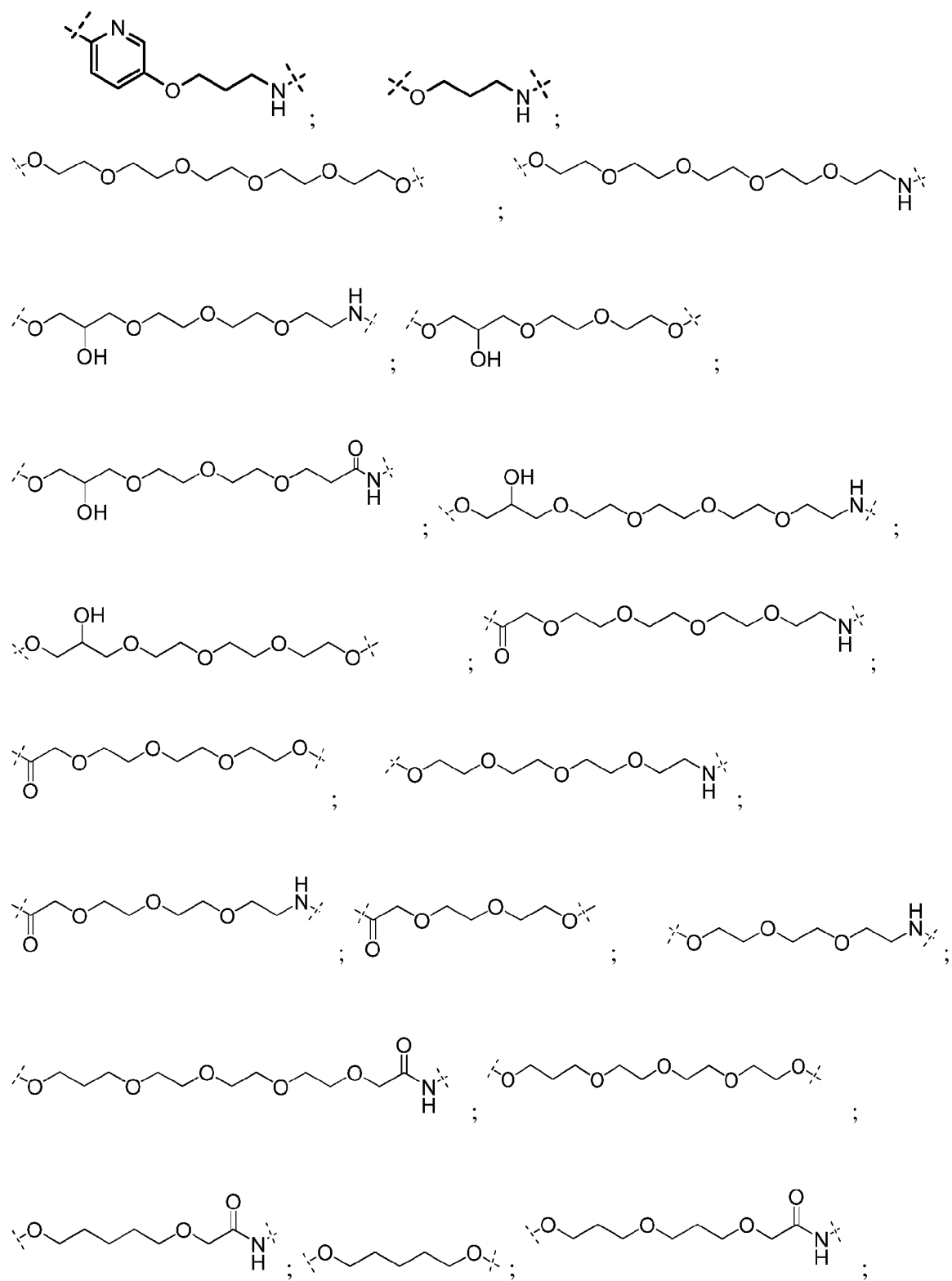


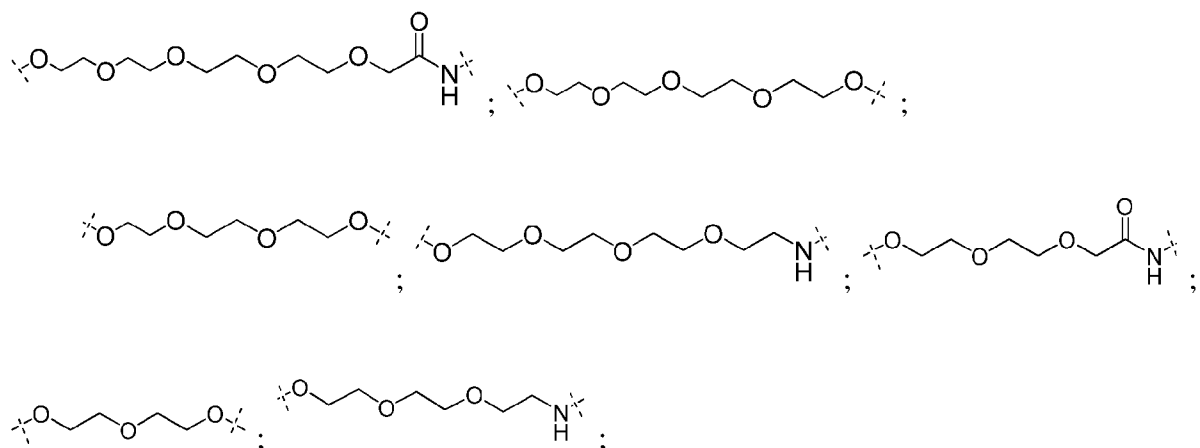
**[00113]** In some preferred embodiments, linker (L) is selected from the group consisting of:











**[00114]** In some embodiments, L is an optionally substituted polyethylenoxy group comprising from 1 to 10 units.

**[00115]** In some additional embodiments, L is a polyethylene group optionally substituted with aryl or phenyl comprising from 1 to 10 ethylene glycol units.

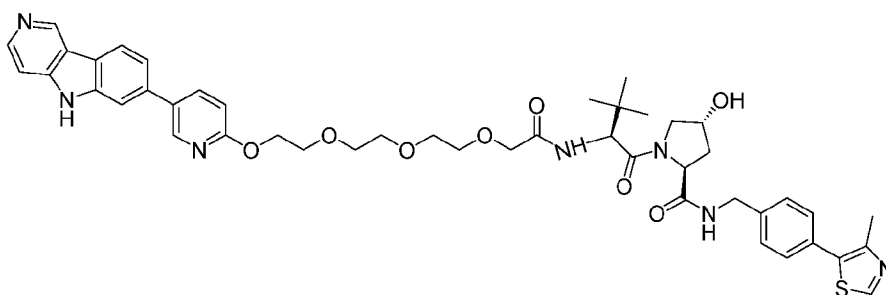
**[00116]** In any of the embodiments, the compound comprises multiple ULMs, multiple PTMs, multiple linkers or any combinations thereof.

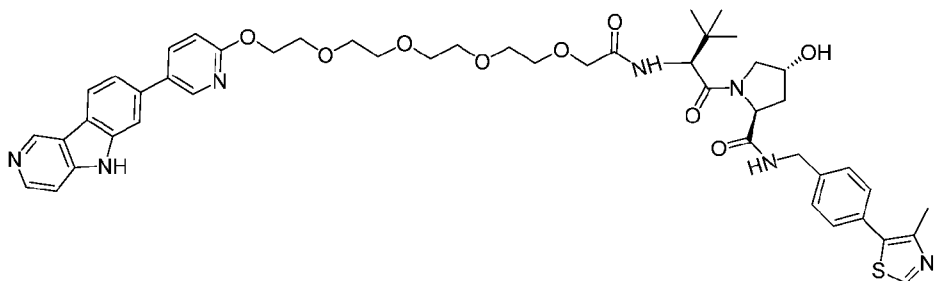
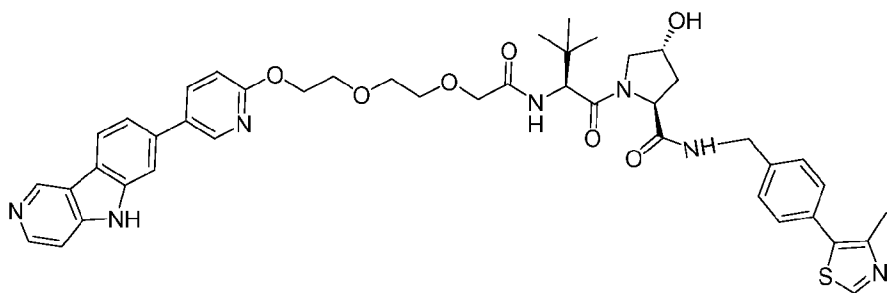
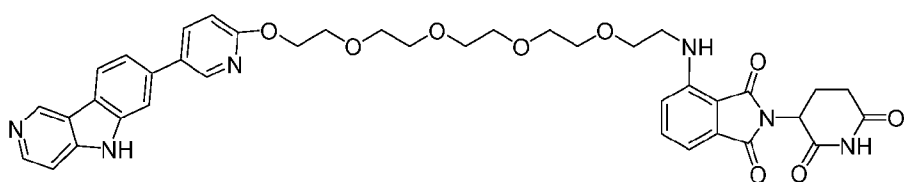
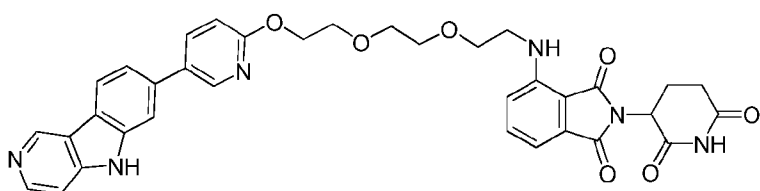
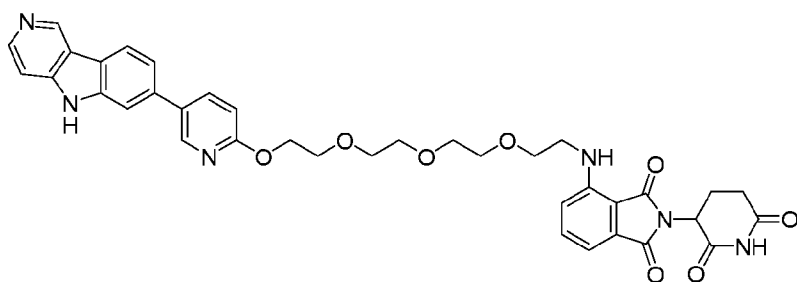
### **Exemplary Tau-PROTAC Compounds**

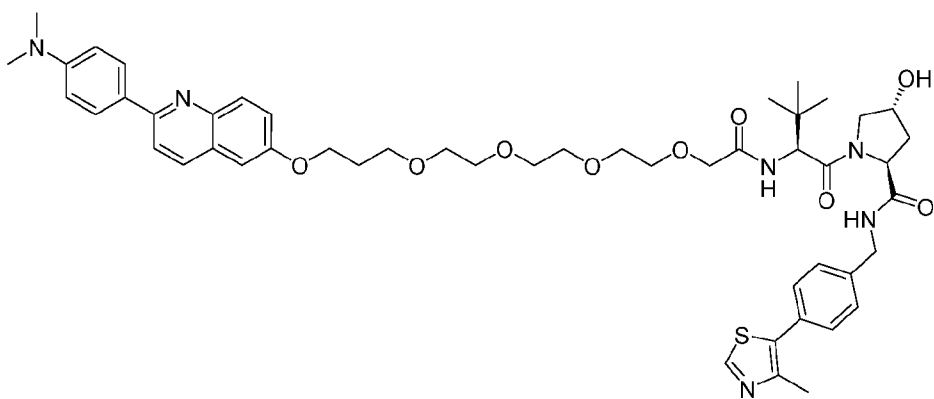
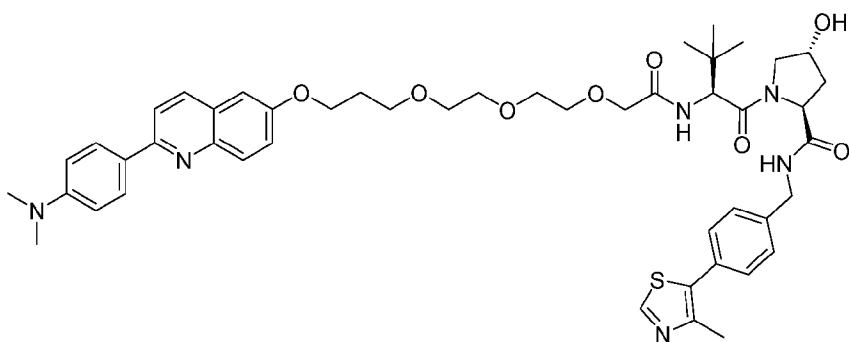
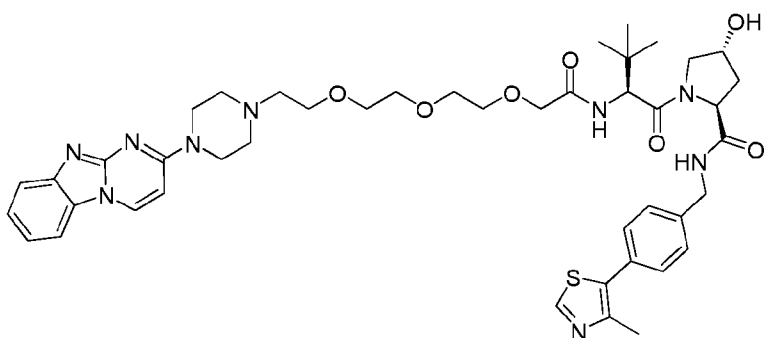
**[00117]** As described above, in certain aspects, the description provides bifunctional PROTAC compounds comprising at least one PTM group, a linker, and at least one ULM (VLM or CLM) group as described herein.

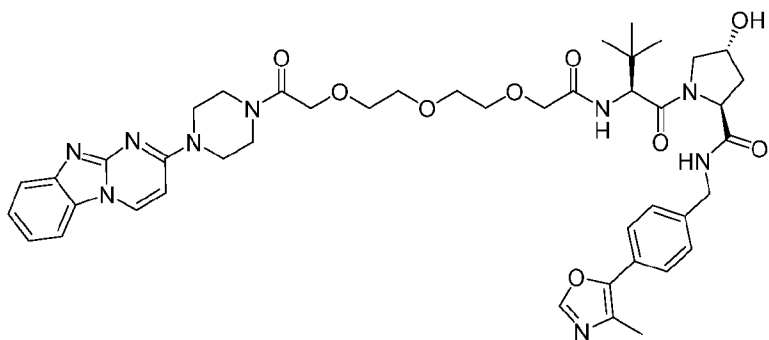
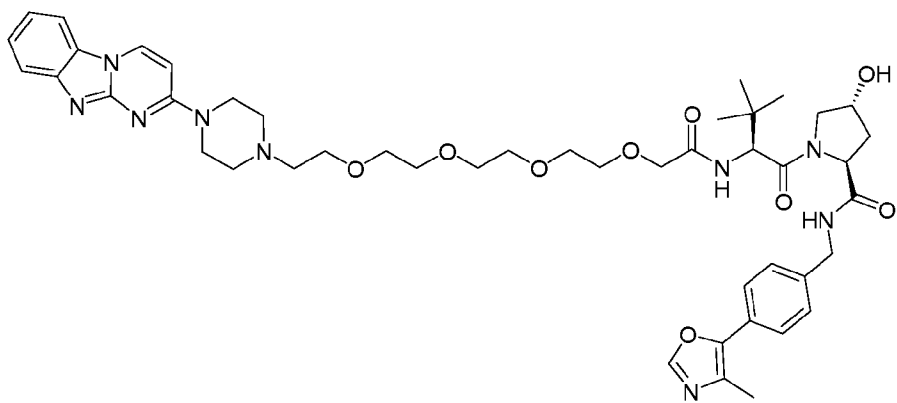
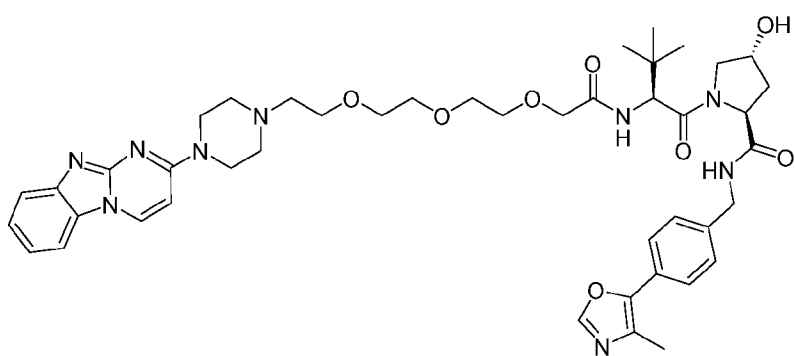
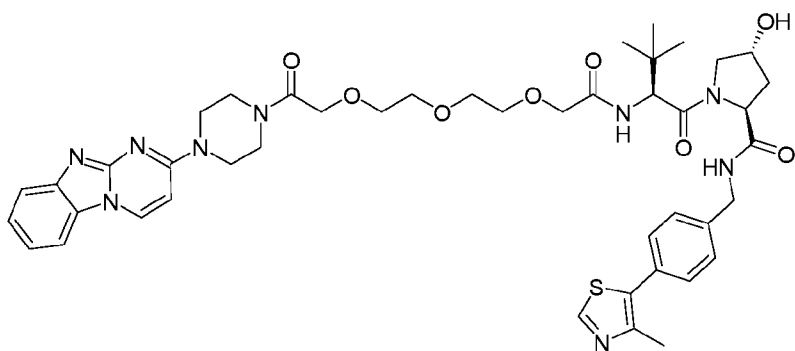
**[00118]** In certain embodiments, the compound is selected from the group consisting of compounds 1-50 (as described in Table 1), and salts and polymorphs thereof.

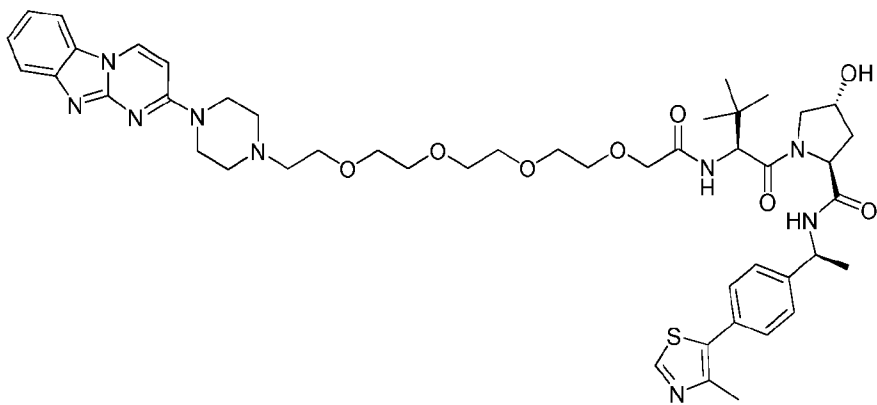
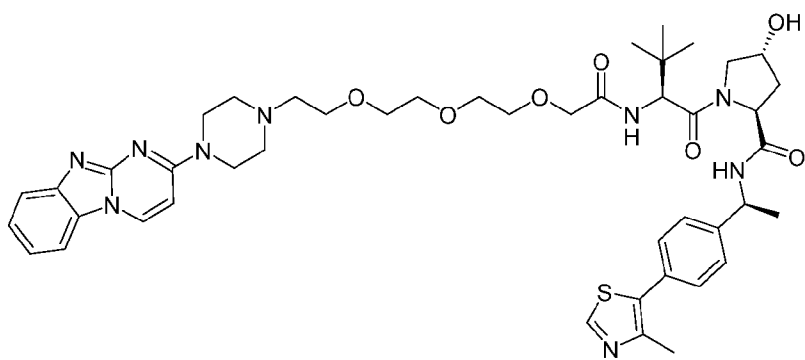
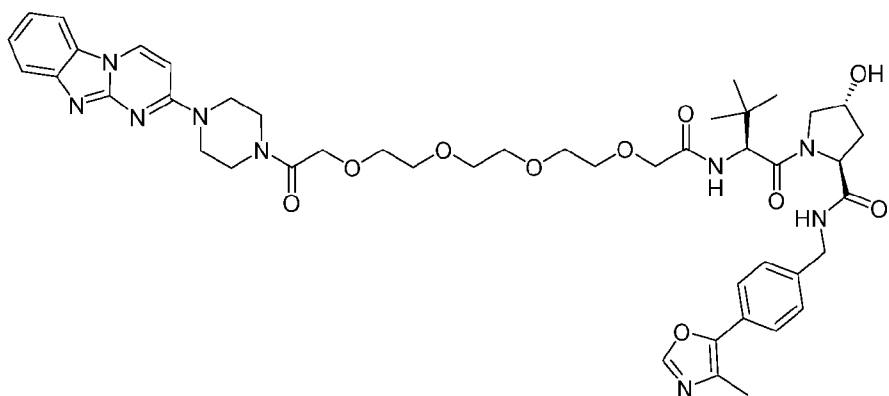
**[00119]** In certain embodiments, the compound is selected from the group consisting of:

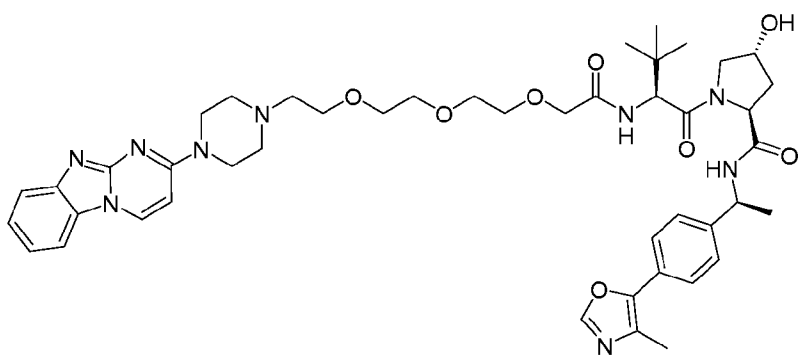
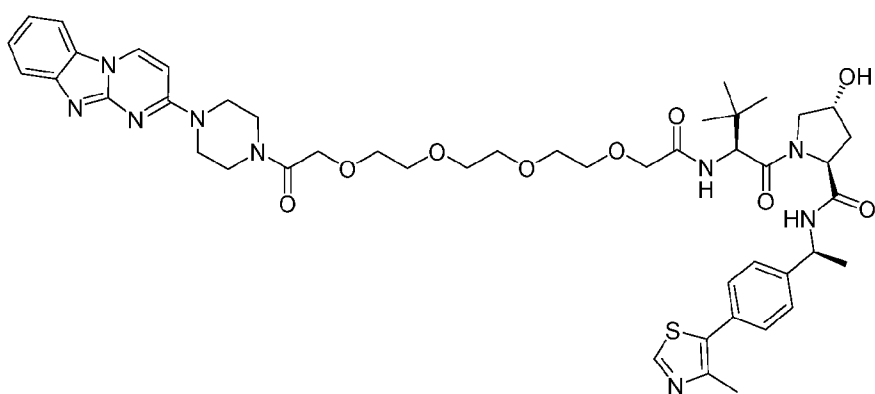
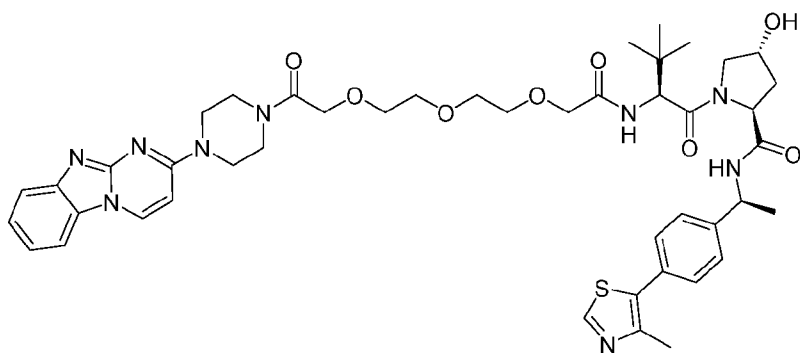


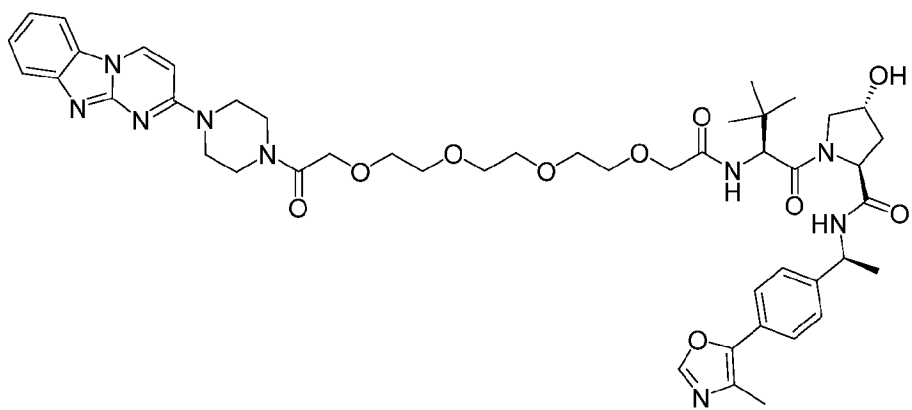
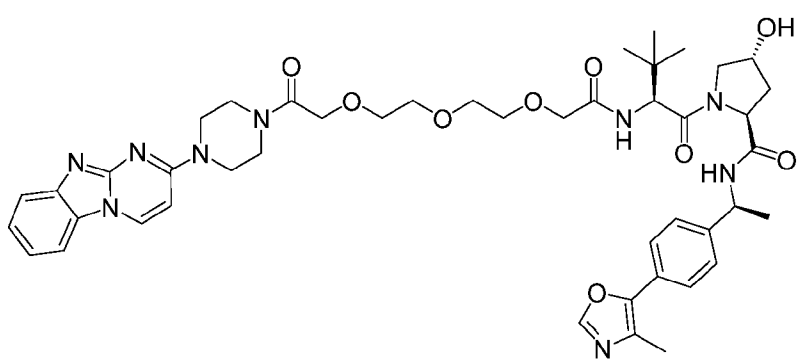
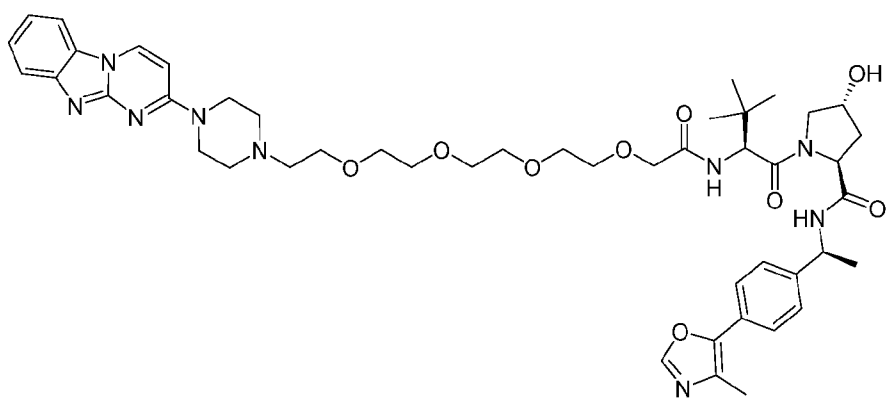




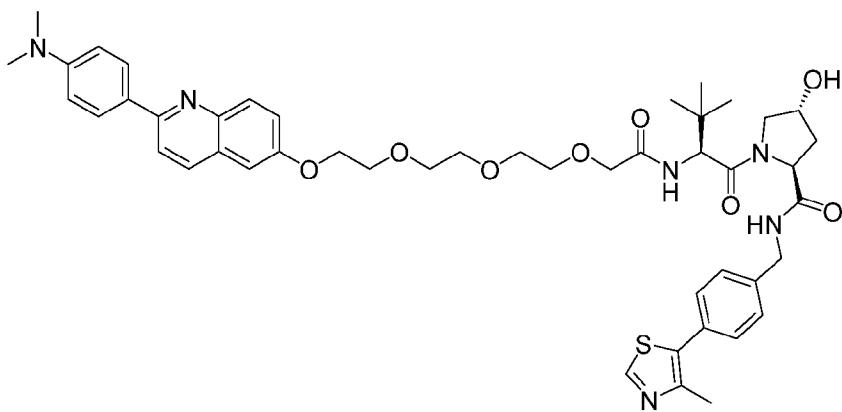
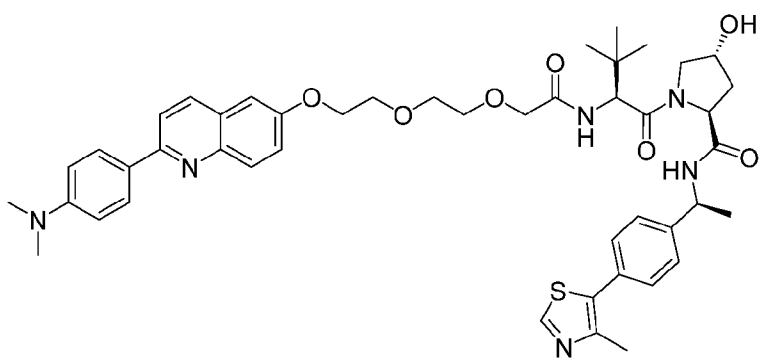
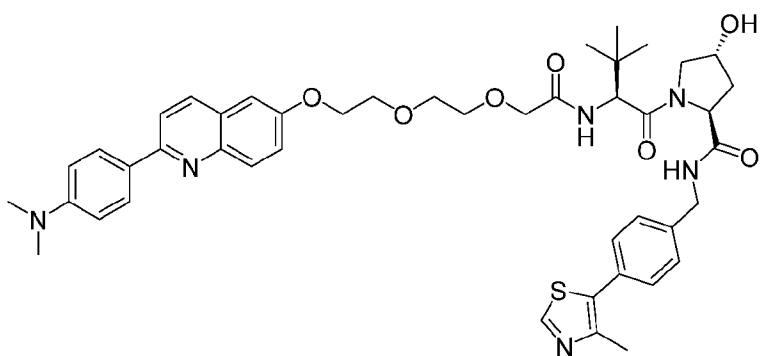


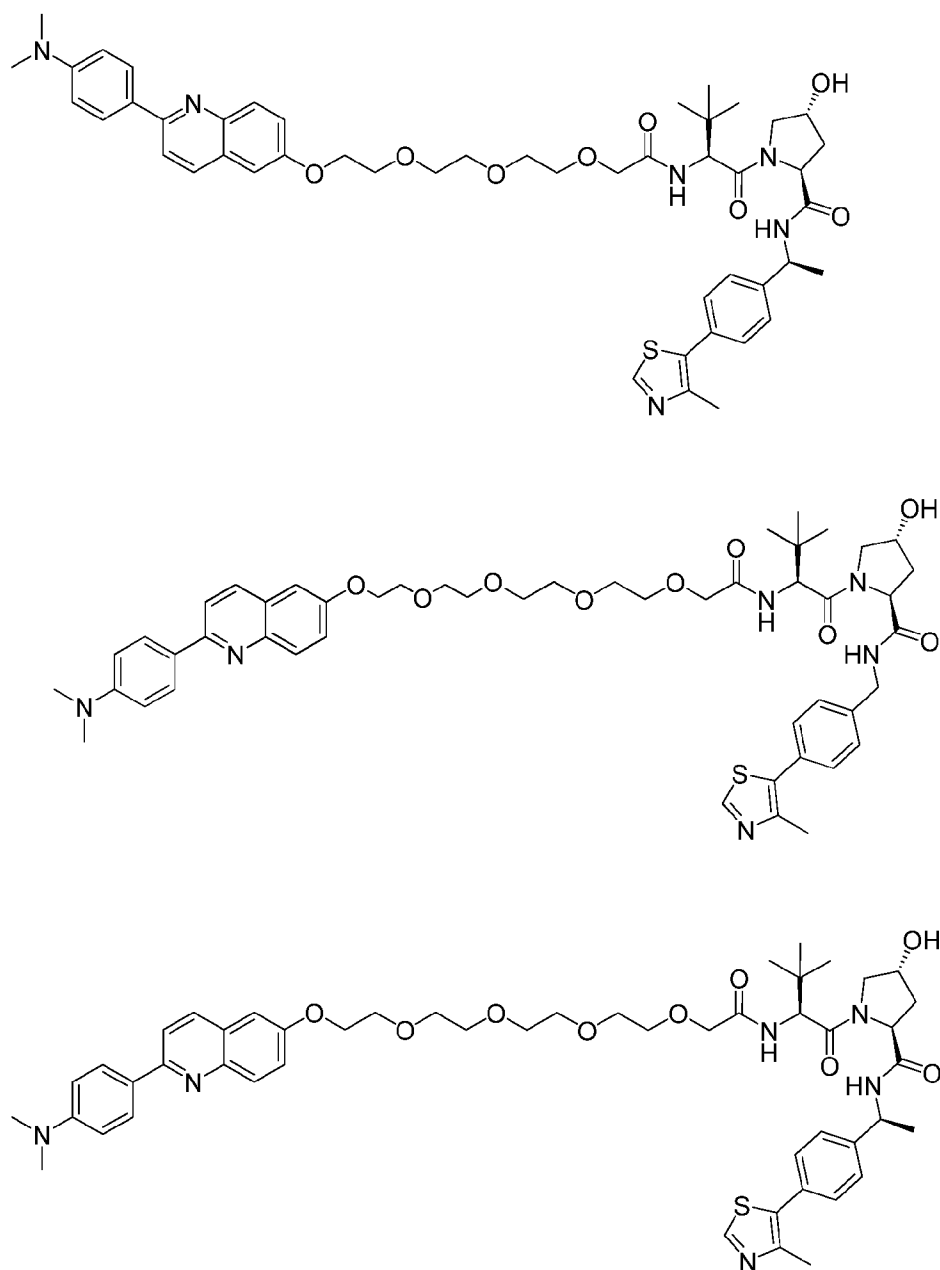


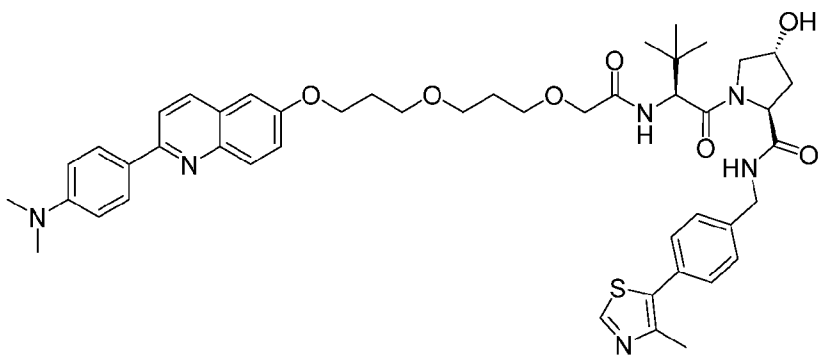
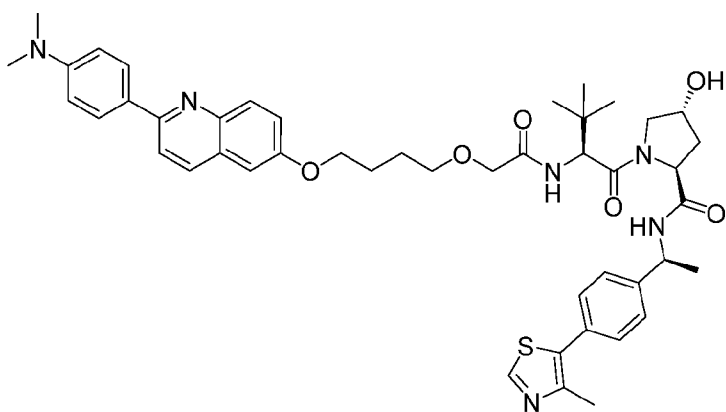
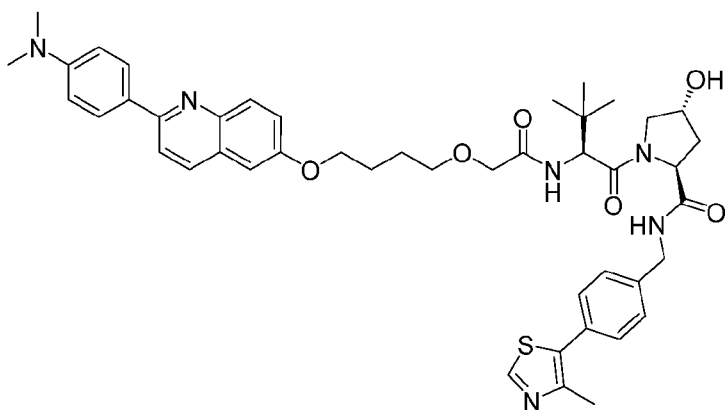




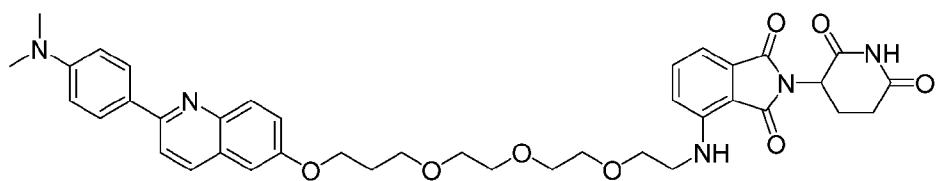
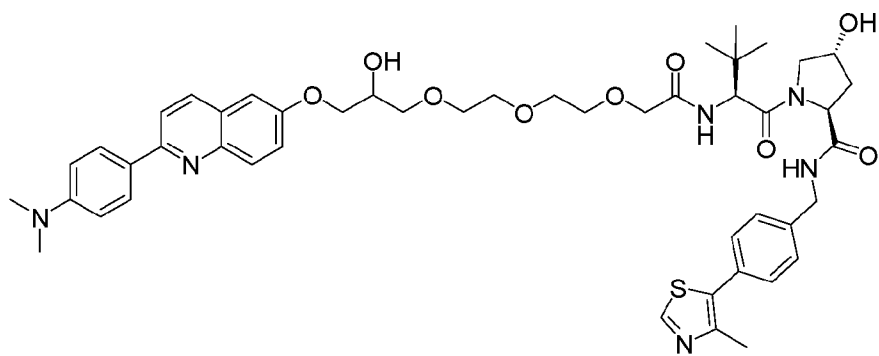
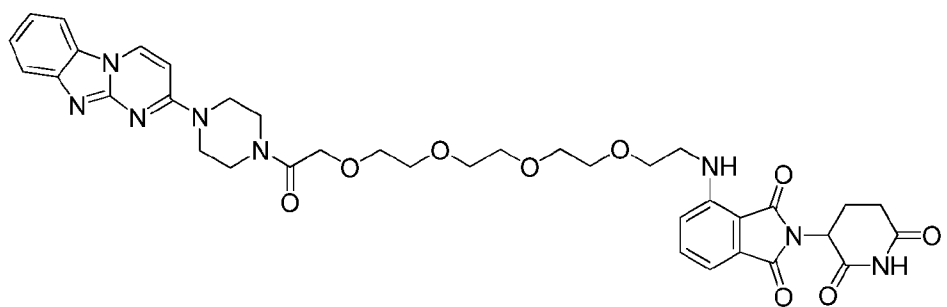
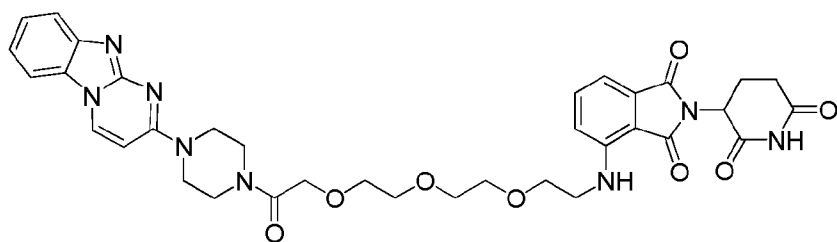
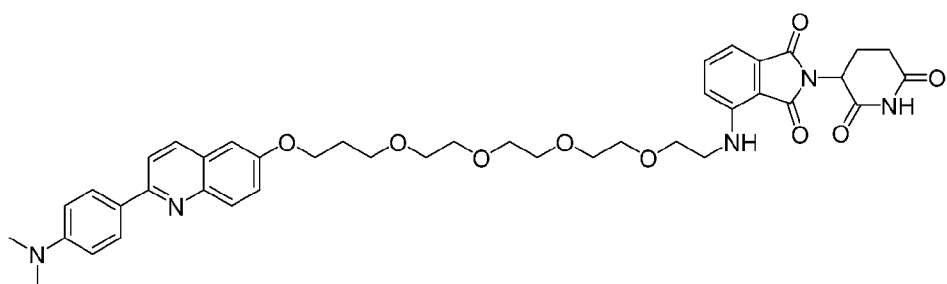


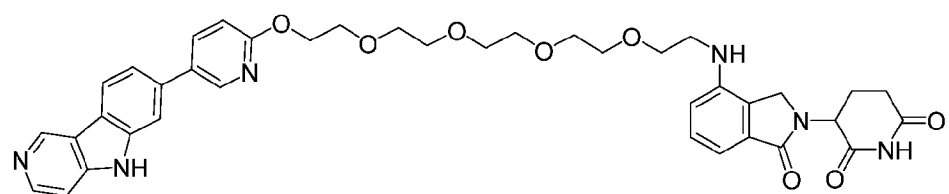
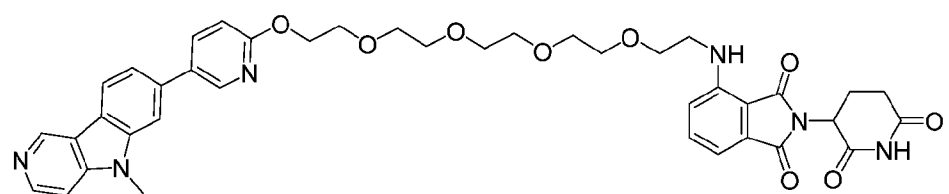
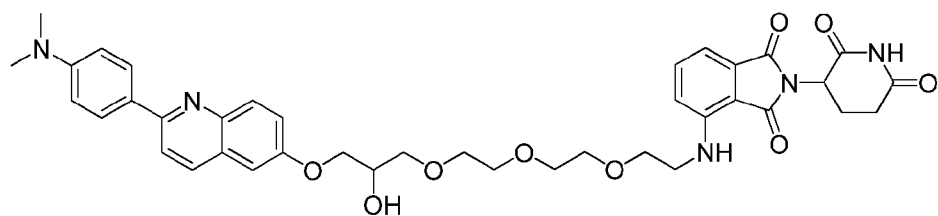
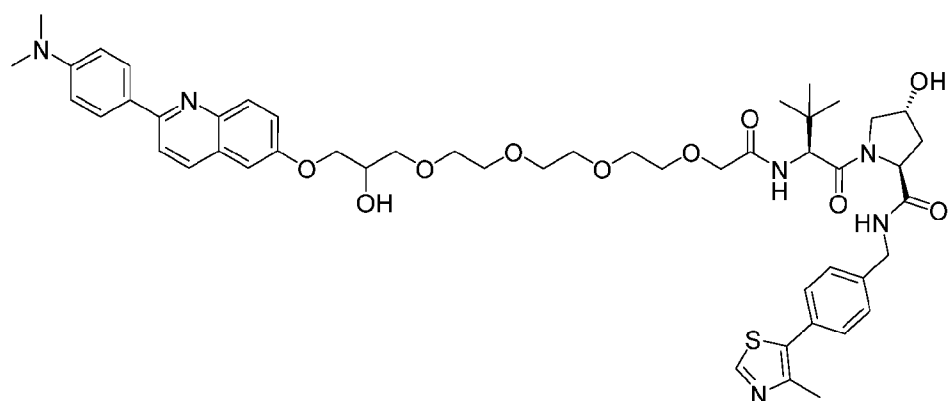
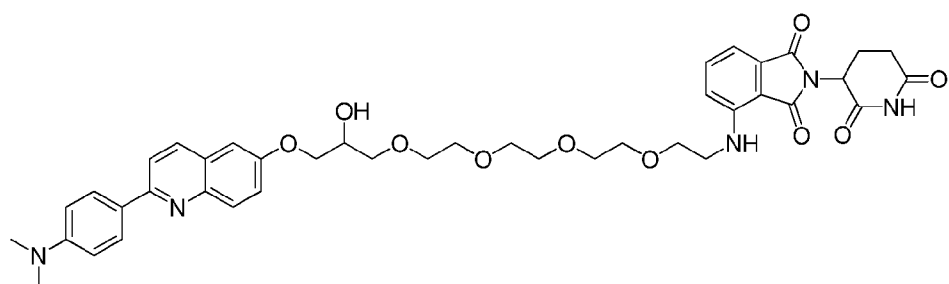




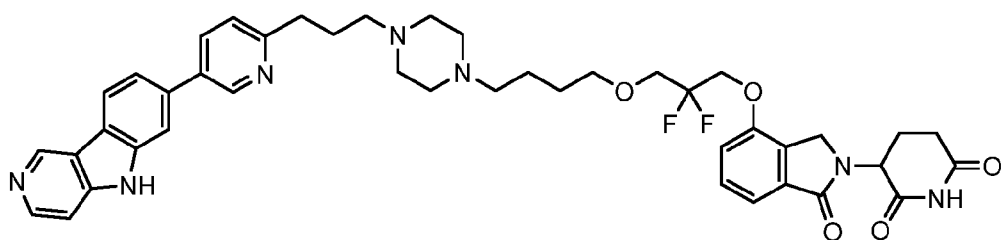
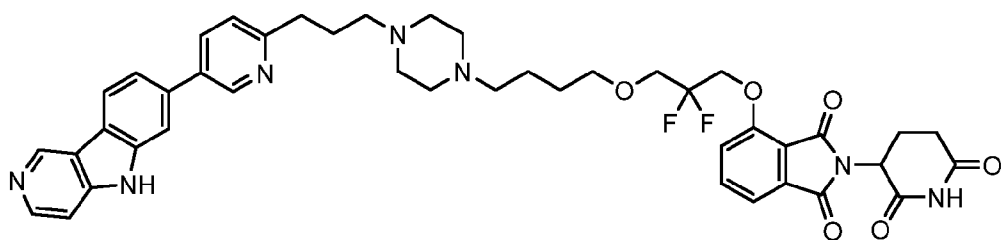
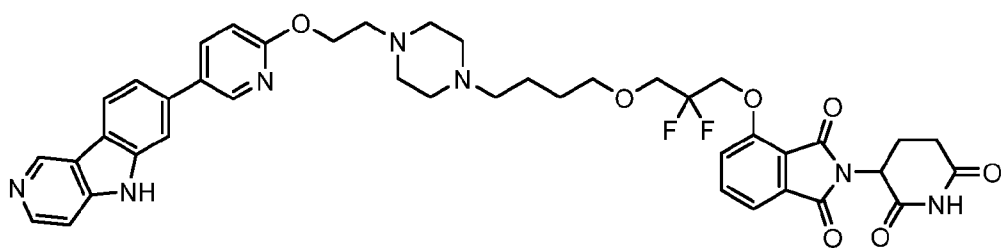
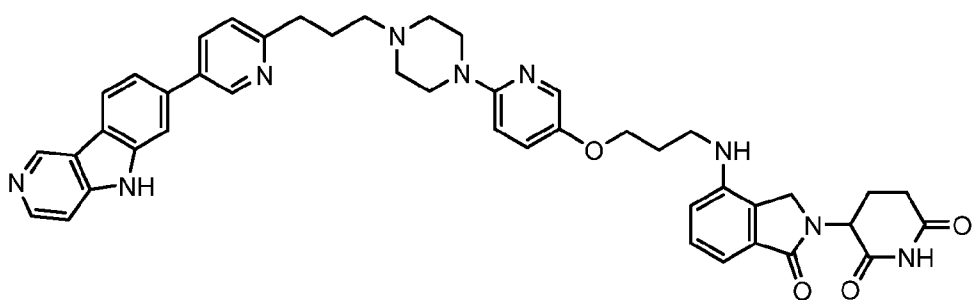
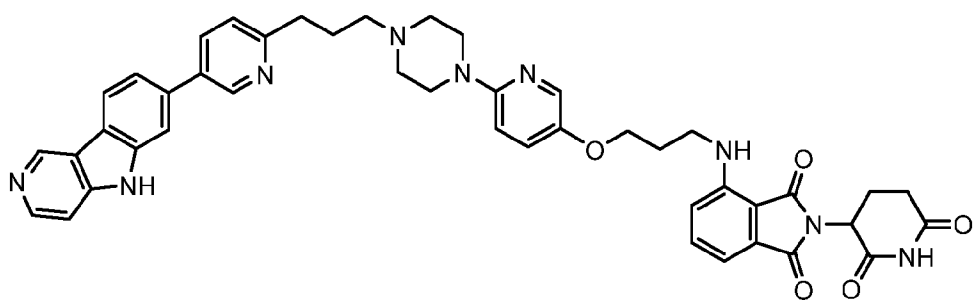


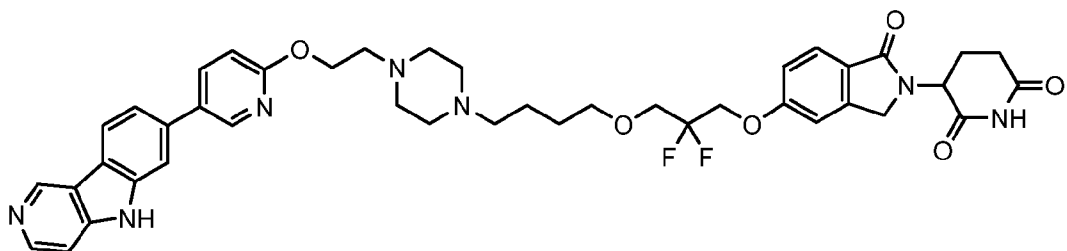
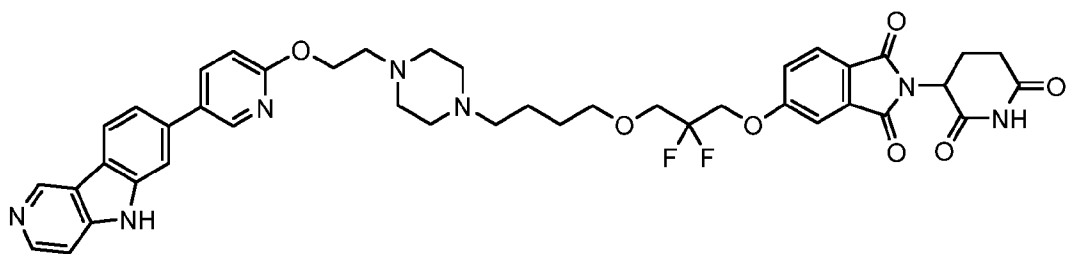
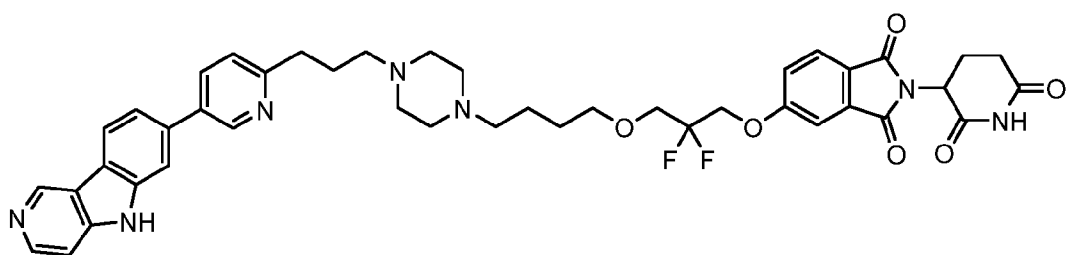
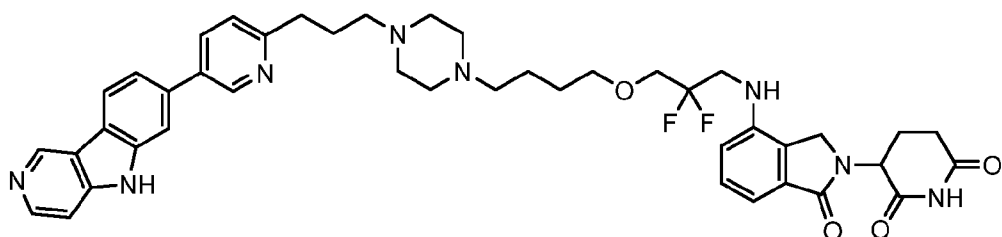
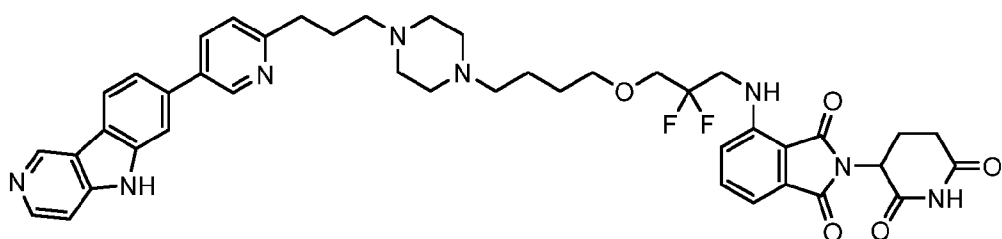


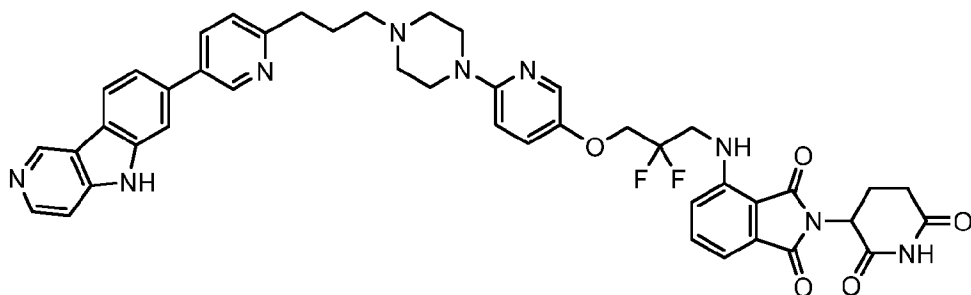
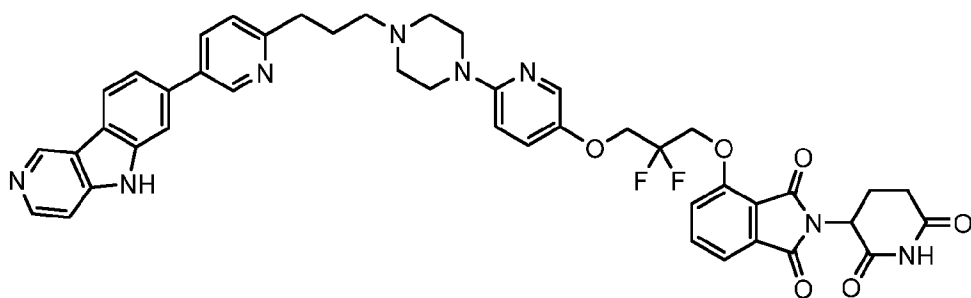
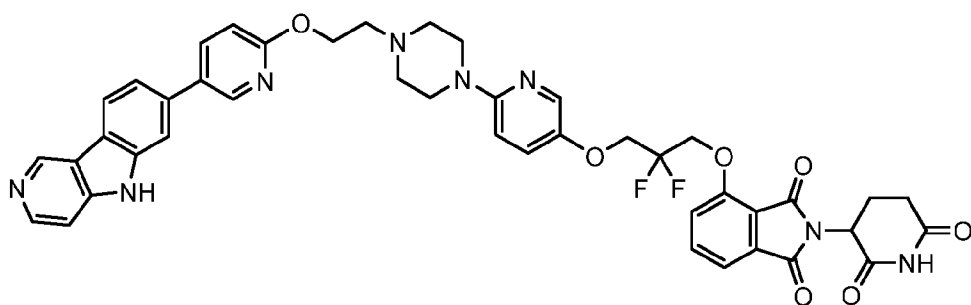
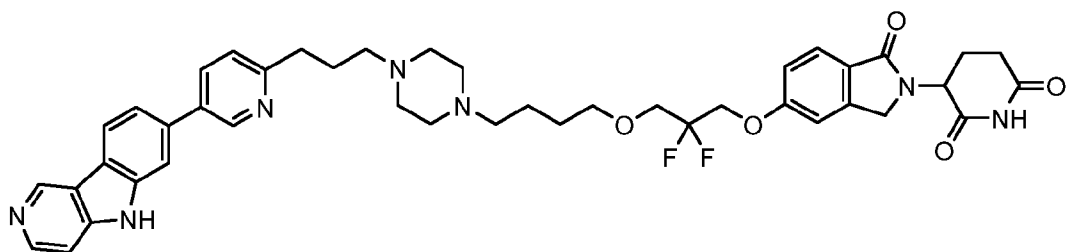


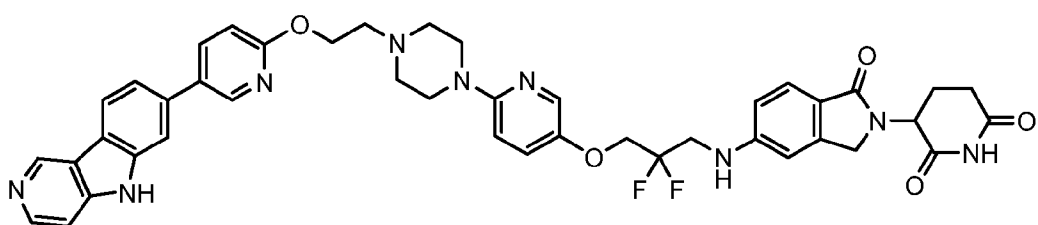
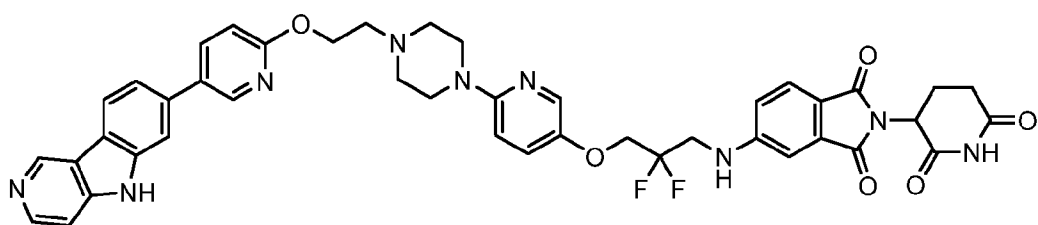
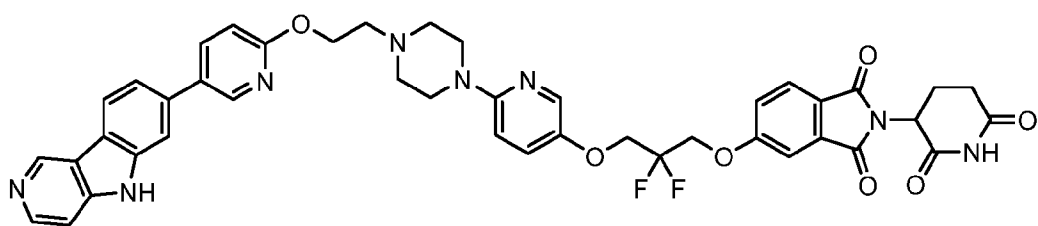
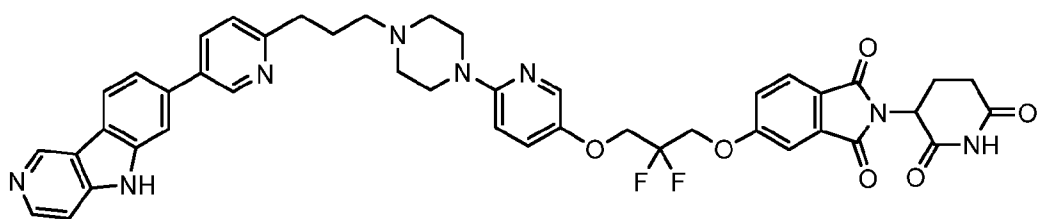
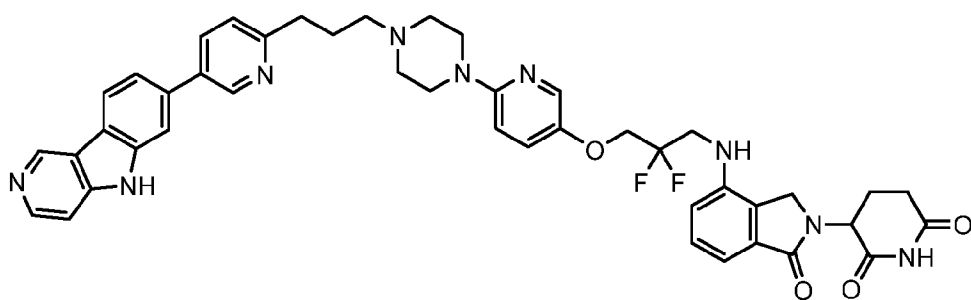


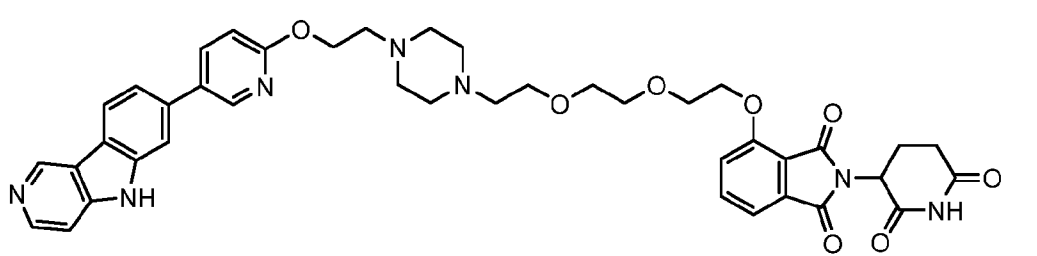
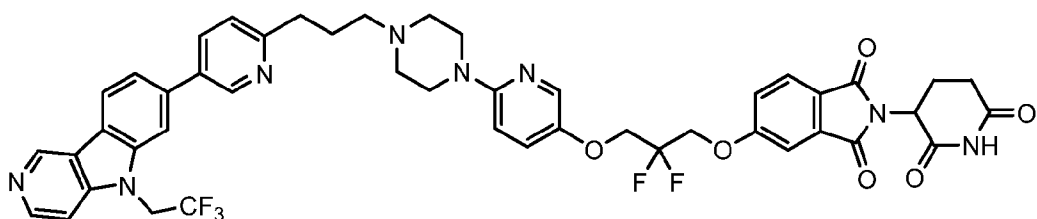
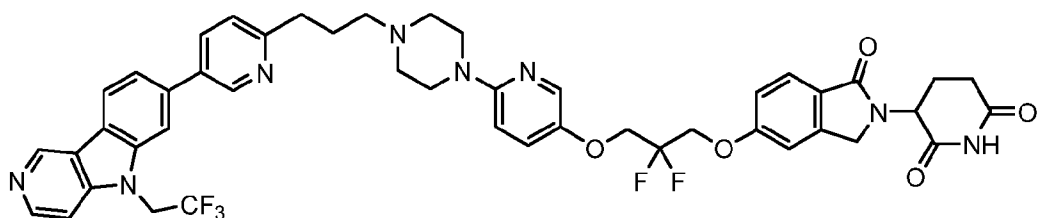
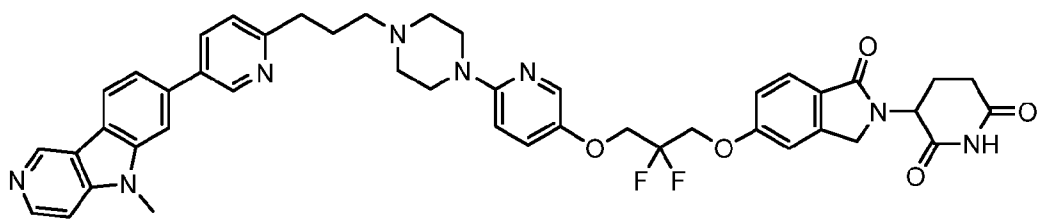
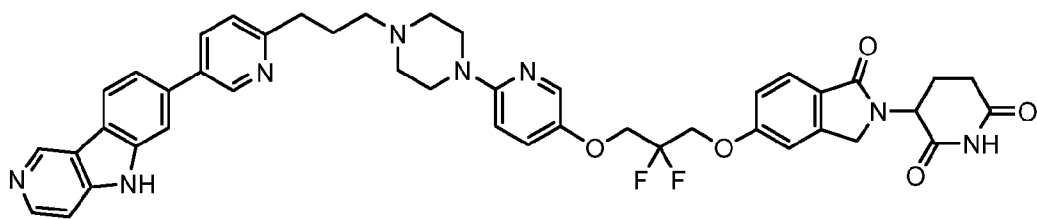
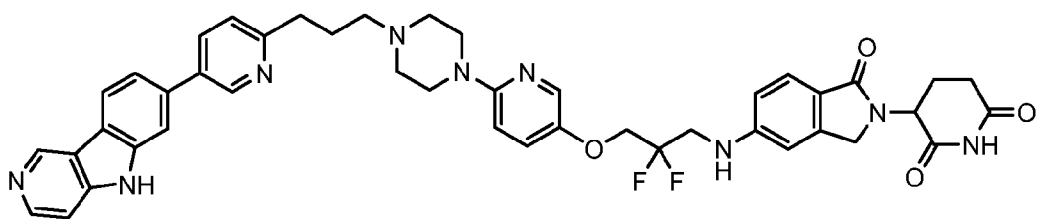


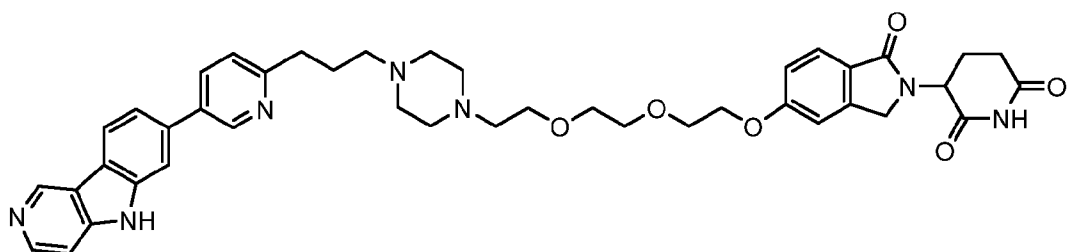
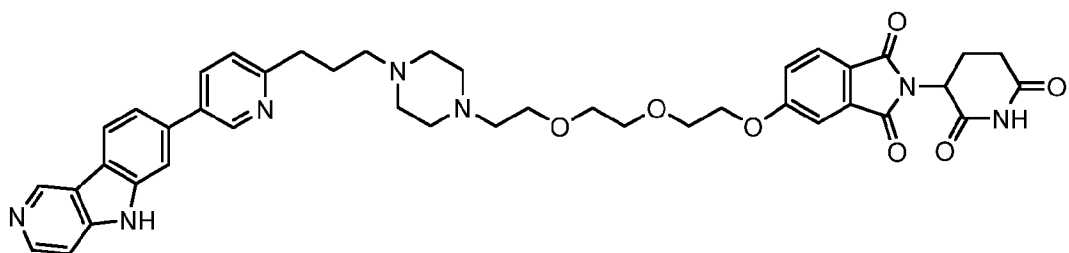
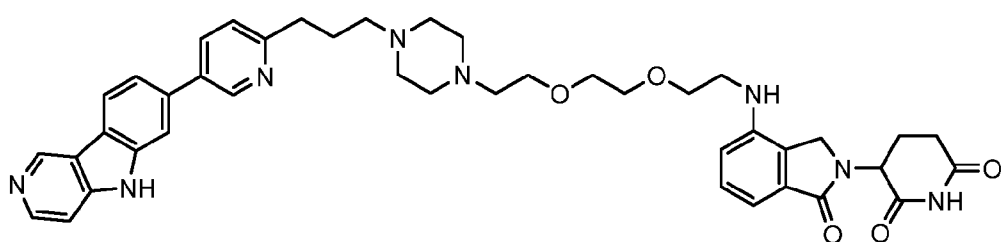
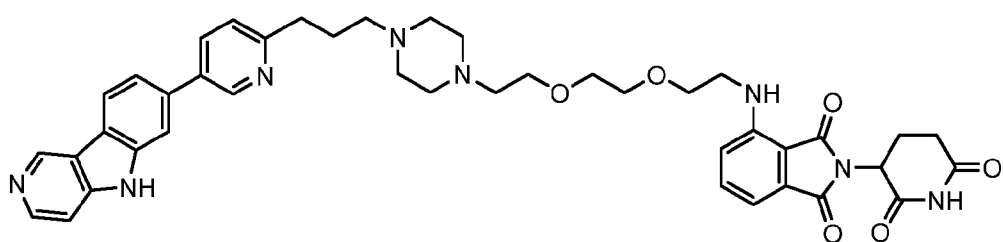
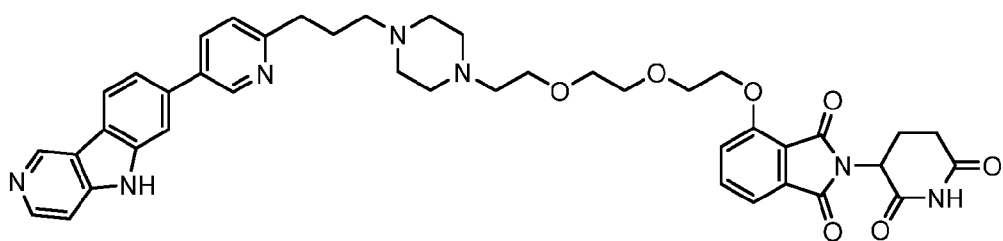


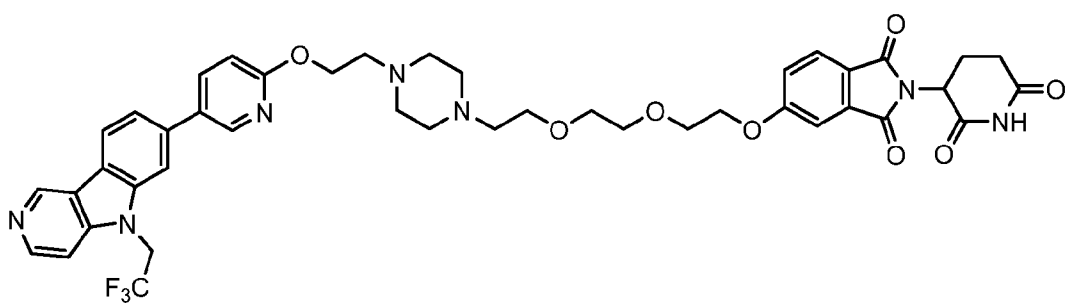
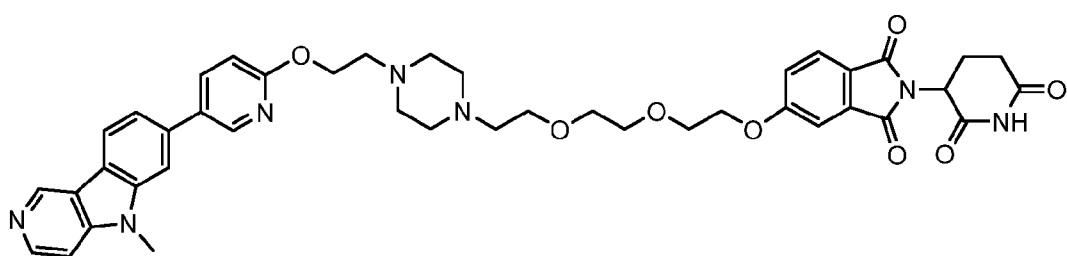
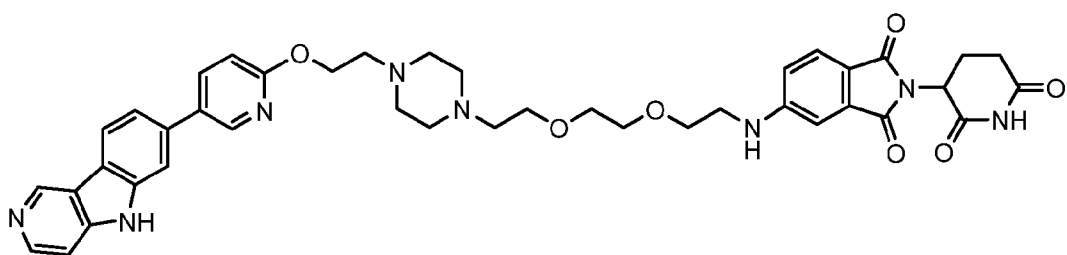
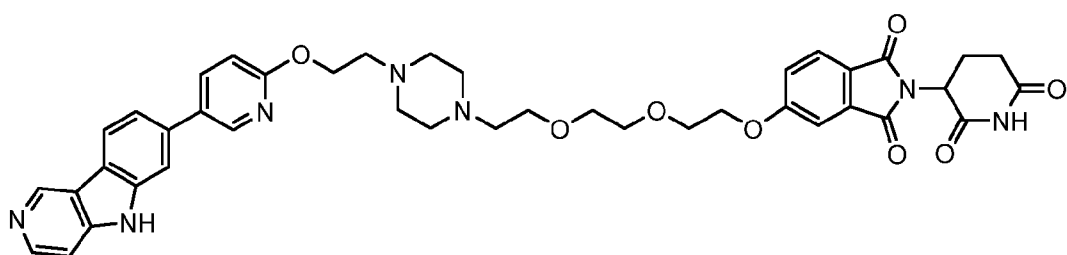
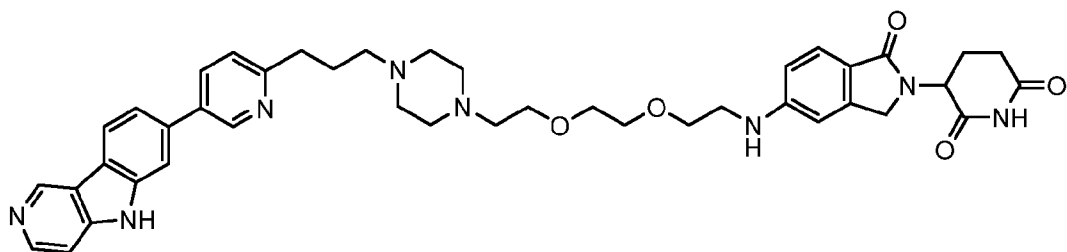


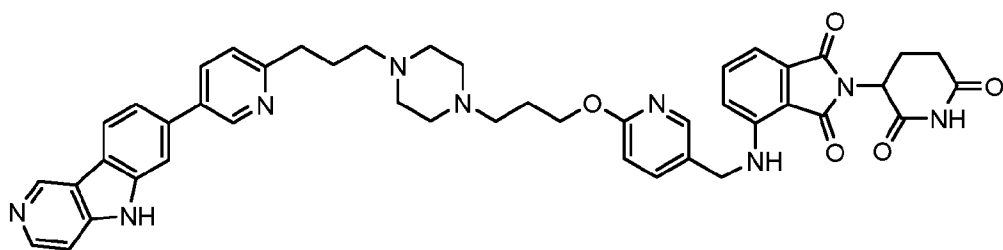
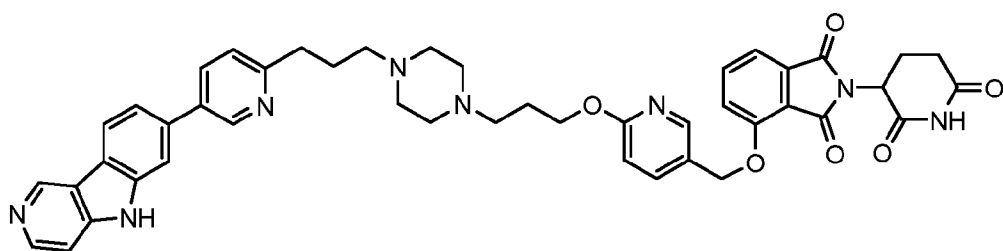
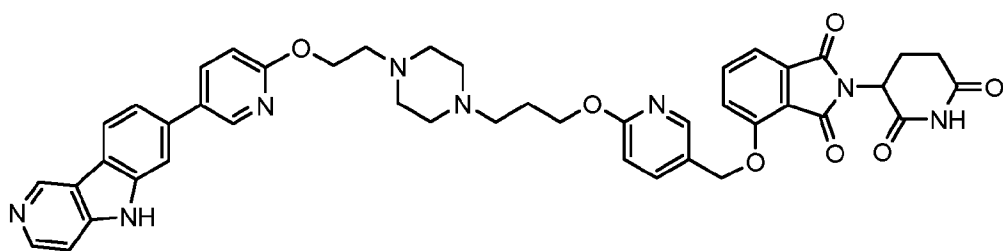
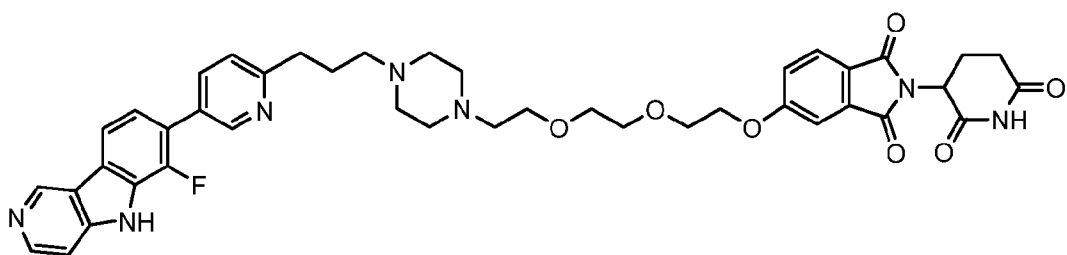
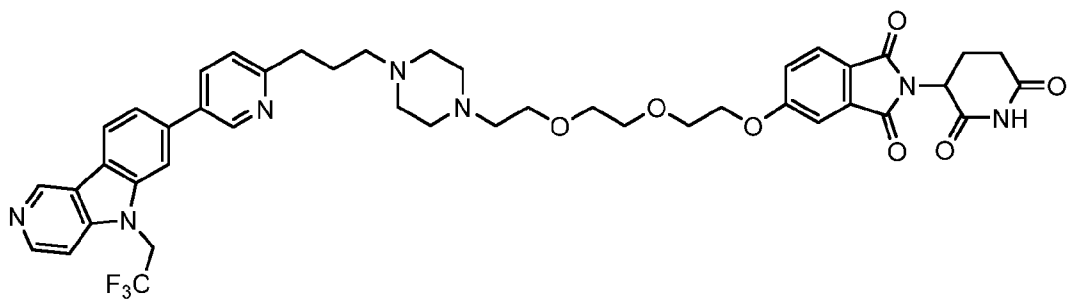


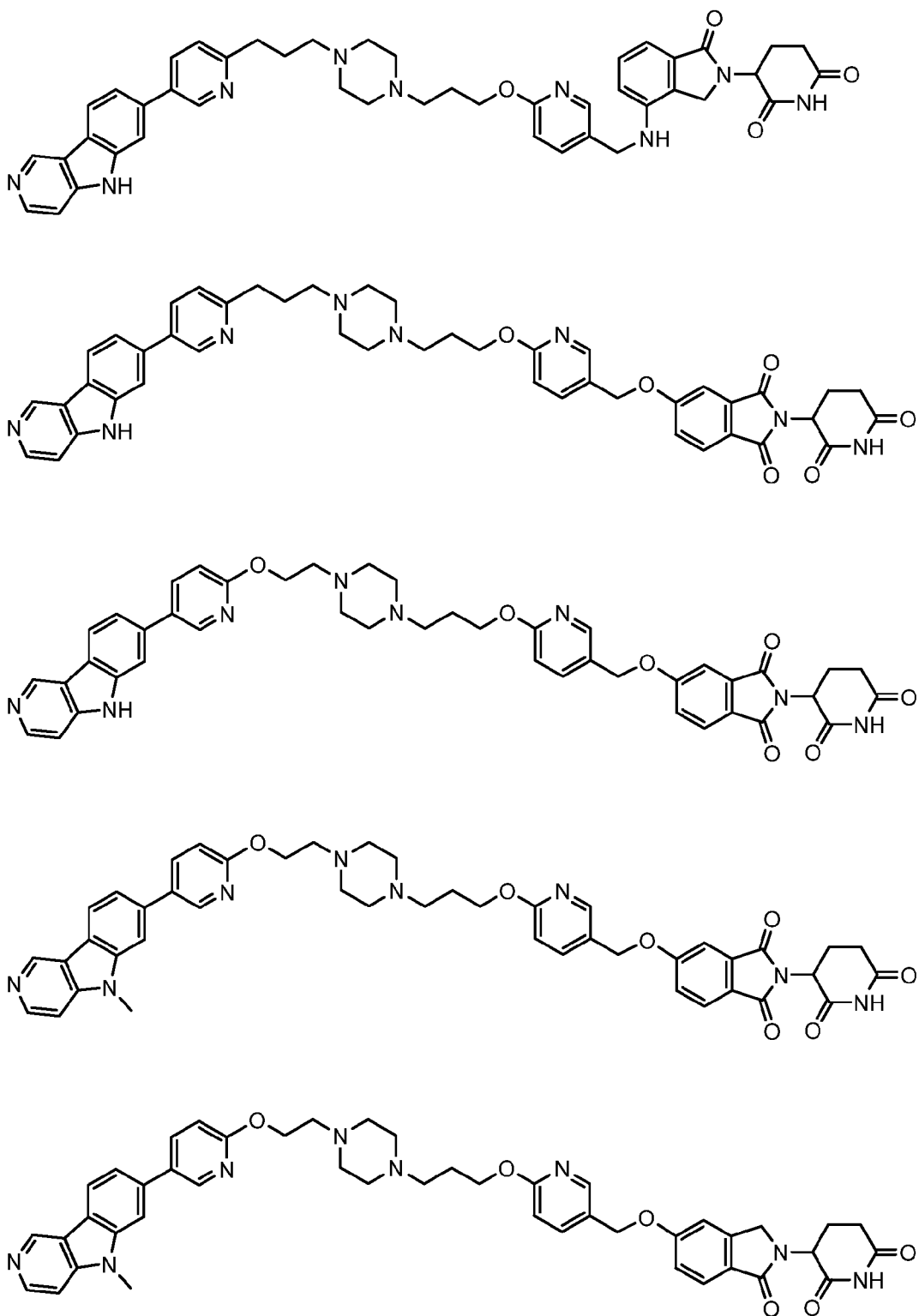


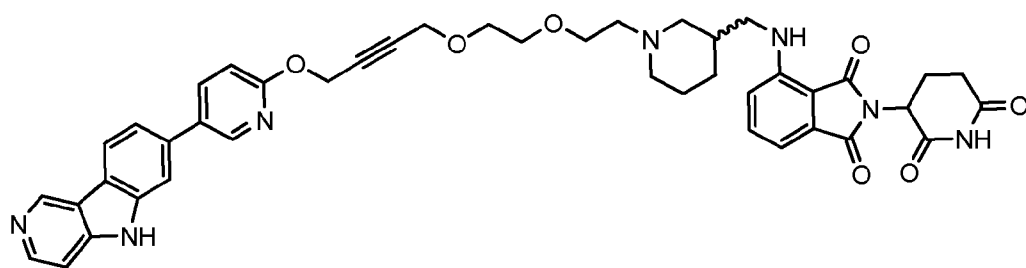
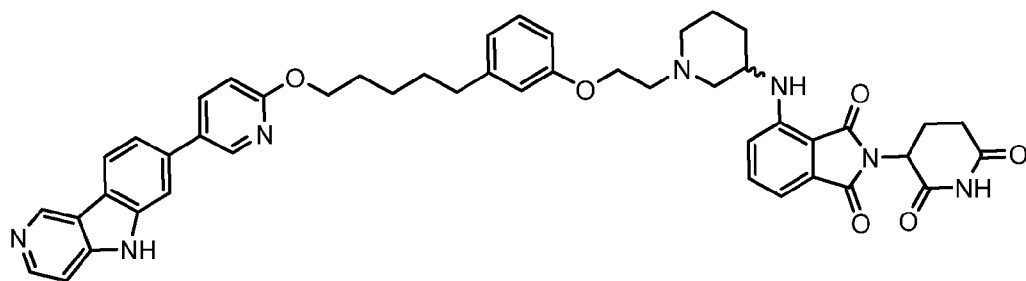
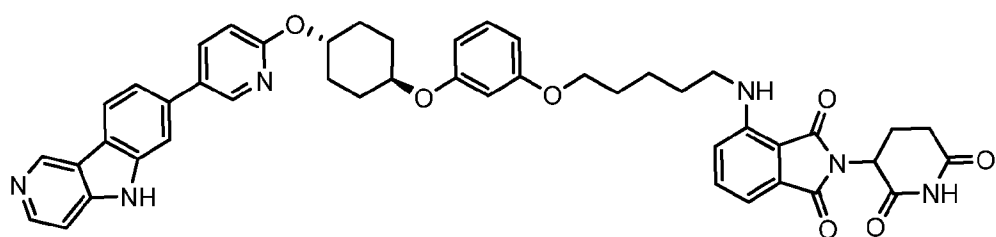
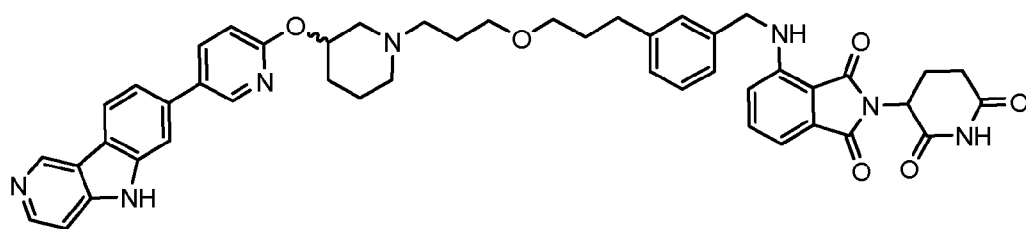
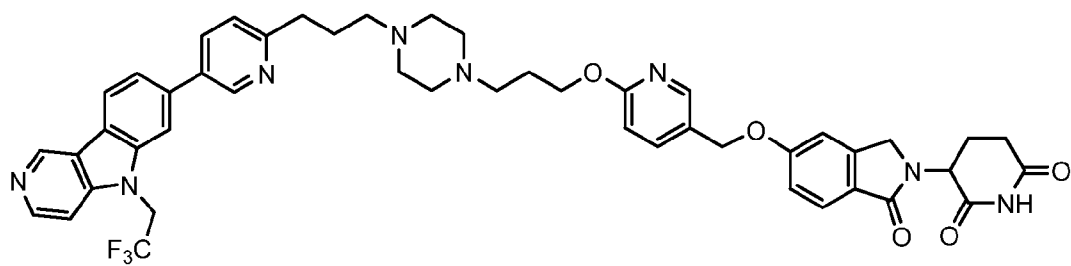


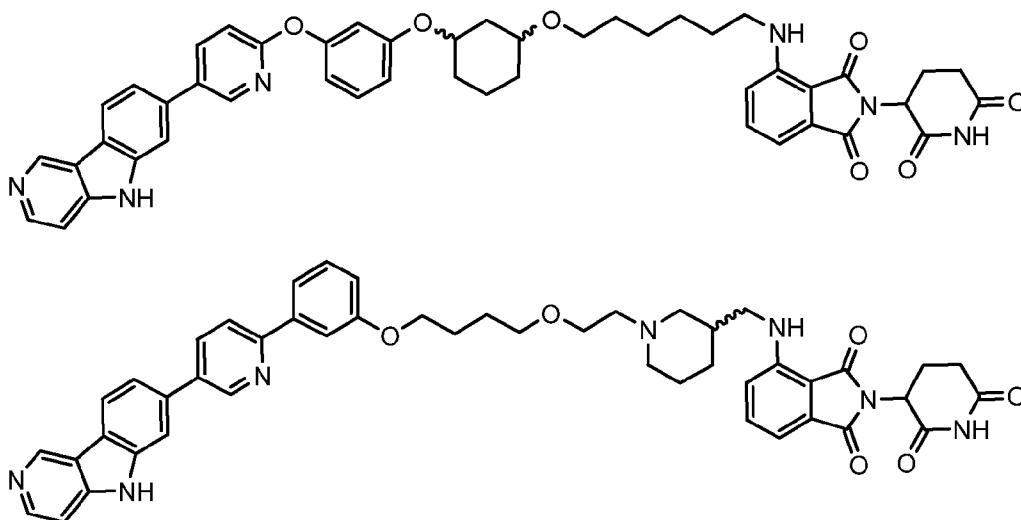












**[00120]** The present description includes, where applicable, the compositions comprising the pharmaceutically acceptable salts, in particular, acid or base addition salts of compounds of the present disclosure.

**[00121]** The term "pharmaceutically acceptable salt" is used throughout the specification to describe, where applicable, a salt form of one or more of the compounds described herein which are presented to increase the solubility of the compound in the gastric juices of the patient's gastrointestinal tract in order to promote dissolution and the bioavailability of the compounds. Pharmaceutically acceptable salts include those derived from pharmaceutically acceptable inorganic or organic bases and acids, where applicable. Suitable salts include those derived from alkali metals such as potassium and sodium, alkaline earth metals such as calcium, magnesium and ammonium salts, among numerous other acids and bases well known in the pharmaceutical art. Sodium and potassium salts are particularly preferred as neutralization salts of the phosphates according to the present disclosure.

**[00122]** The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds useful in this disclosure are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3 naphthoate)]salts, among numerous others.

**[00123]** Pharmaceutically acceptable base addition salts may also be used to produce pharmaceutically acceptable salt forms of the compounds or derivatives according to the present disclosure. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the present compounds that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (eg., potassium and sodium) and alkaline earth metal cations (eg, calcium, zinc and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines, among others.

**Compositions:**

**[00124]** In another aspect, the description provides compositions comprising compounds as described herein, including salts thereof, and a pharmaceutically acceptable carrier. In certain embodiments, the compositions are therapeutic or pharmaceutical compositions comprising an effective amount of a compound as described herein and a pharmaceutically acceptable carrier.

**[00125]** The amount of compound in a pharmaceutical composition of the instant disclosure that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host and disease treated, the particular mode of administration. Generally, an amount between 0.1 mg/kg and 1000 mg/kg body weight/day of active ingredients is administered dependent upon potency of the agent. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compounds that exhibit large therapeutic indices are preferred. While compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects. The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the present disclosure, the

therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC<sub>50</sub> (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

**[00126]** The compositions of the present disclosure may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers and may also be administered in controlled-release formulations. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

**[00127]** In any of the aspects or embodiments described herein, the PTM, ULM or both have an affinity (IC<sub>50</sub>) for their respective target protein of less than about 500  $\mu$ M, 450  $\mu$ M, 400  $\mu$ M, 350  $\mu$ M, 300  $\mu$ M, 250  $\mu$ M, 200  $\mu$ M, 150  $\mu$ M, 100  $\mu$ M, 50  $\mu$ M, 10  $\mu$ M, 0.10  $\mu$ M, 0.01  $\mu$ M, 0.001  $\mu$ M, 0.1 nM, 0.01 nM, 0.001 nM or less. The determination of the IC<sub>50</sub> can be performed using methods well known to those of skill in the art in view of the present disclosure.

**[00128]** In any of the aspects or embodiments, the compounds as described herein effectuate the ubiquitination of a target protein at sufficient levels or amounts to effectuate or induce degradation of the target protein.

**[00129]** The active compound is included in the pharmaceutically acceptable carrier or diluent in an amount sufficient to deliver to a patient a therapeutically effective amount for the desired indication, without causing serious toxic effects in the patient treated. A preferred dose of the active compound for all of the herein-mentioned conditions is in the range from about 10 ng/kg to 300 mg/kg, preferably 0.1 to 100 mg/kg per day, more generally 0.5 to about 25 mg per kilogram body weight of the recipient/patient per day. A typical topical dosage will range from 0.01-5% wt/wt in a suitable carrier.

**[00130]** The compound is conveniently administered in any suitable unit dosage form, including but not limited to one containing less than 1mg, 1 mg to 3000 mg, preferably 5 to 500 mg of active ingredient per unit dosage form. An oral dosage of about 25-250 mg is often convenient.

**[00131]** The active ingredient is preferably administered to achieve peak plasma concentrations of the active compound of about 0.00001-30 mM, preferably about 0.1-30  $\mu$ M. This may be achieved, for example, by the intravenous injection of a solution or formulation of the active ingredient, optionally in saline, or an aqueous medium or administered as a bolus of the active ingredient. Oral administration is also appropriate to generate effective plasma concentrations of active agent.

**[00132]** The concentration of active compound in the drug composition will depend on absorption, distribution, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

**[00133]** If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

**[00134]** In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art.

**[00135]** Liposomal suspensions may also be pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearyl phosphatidyl ethanolamine, stearyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound is then introduced

into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

### **Modes of Administration**

**[00136]** In any of the aspects or embodiments described herein, the therapeutic compositions comprising compounds described herein can be in any suitable dosage form configured to be delivered by any suitable route. For example, the compounds can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, including transdermally, in liquid, cream, gel, or solid form, rectally, nasally, buccally, vaginally or via an implanted reservoir or by aerosol form.

**[00137]** The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

**[00138]** The compounds as described herein may be administered in single or divided doses by the oral, parenteral or topical routes. Administration of the active compound may range from continuous (intravenous drip) to several oral administrations per day (for example, Q.I.D.) and may include oral, topical, parenteral, intramuscular, intravenous, sub-cutaneous, transdermal (which may include a penetration enhancement agent), buccal, sublingual and suppository administration, among other routes of administration. Enteric coated oral tablets may also be used to enhance bioavailability of the compounds from an oral route of administration. The most effective dosage form will depend upon the pharmacokinetics of the particular agent chosen as well as the severity of disease in the patient.

**[00139]** Administration of compounds as sprays, mists, or aerosols for intra-nasal, intra-tracheal or pulmonary administration may also be used. Compounds as described herein may be administered in immediate release, intermediate release or sustained or controlled release forms. Sustained or controlled release forms are preferably administered orally, but also in suppository and transdermal or other topical forms. Intramuscular injections in liposomal form may also be used to control or sustain the release of compound at an injection site.

**[00140]** Sterile injectable forms of the compositions as described herein may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-

acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

**[00141]** The pharmaceutical compositions as described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound or its prodrug derivative can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials are included as part of the composition.

**[00142]** The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a dispersing agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or enteric agents.

**[00143]** The active compound or pharmaceutically acceptable salt thereof can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain,

in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

**[00144]** Alternatively, the pharmaceutical compositions as described herein may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient, which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

**[00145]** The pharmaceutical compositions of the disclosure may also be administered topically. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-acceptable transdermal patches may also be used. For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. In certain preferred aspects of the disclosure, the compounds may be coated onto a stent which is to be surgically implanted into a patient in order to inhibit or reduce the likelihood of occlusion occurring in the stent in the patient.

**[00146]** Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

**[00147]** For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

**[00148]** The pharmaceutical compositions of this disclosure may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl

alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

**[00149]** Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

**[00150]** It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease or condition being treated.

**[00151]** A patient or subject in need of therapy using compounds as described herein can be treated by administering to the patient (subject) an effective amount of the compound including pharmaceutically acceptable salts, solvates or polymorphs, thereof optionally in a pharmaceutically acceptable carrier or diluent, either alone, or in combination with other known agents.

#### **Co-administration**

**[00152]** Disease states or conditions which may be treated using compounds or compositions according to the present description include, but not limited to, for example, cancer (e.g., prostate cancer), and Kennedy's disease. In certain embodiments, the therapeutic or pharmaceutical compositions comprise an effective amount of an additional biologically or bioactive agent, e.g., an agent effective for the treatment of cancer, that is co-administered.

**[00153]** The term "co-administration" or "combination therapy" shall mean that at least two compounds or compositions are administered to the patient at the same time, such that effective amounts or concentrations of each of the two or more compounds may be found in the patient at a given point in time. Although compounds according to the present disclosure may be co-administered to a patient at the same time, the term embraces both administration of two or more agents at the same time or at different times, provided that effective concentrations of all co-administered compounds or compositions are found in the subject at a given time. In certain

preferred aspects of the present disclosure, one or more of the present compounds described above, are co-administered in combination with at least one additional bioactive agent, especially including an anticancer agent. In particularly preferred aspects of the disclosure, the co-administration of compounds results in synergistic therapeutic, including anticancer therapy.

**[00154]** In another aspect, the description provides a composition comprising an effective amount of two or more of the PROTAC compounds as described herein, and a pharmaceutically acceptable carrier. In certain embodiments, the composition further comprises an effective or synergistic amount of another bioactive agent that is not a PROTAC compound.

**[00155]** Pharmaceutical compositions comprising combinations of an effective amount of at least one bifunctional compound according to the present disclosure, and one or more of the compounds otherwise described herein, all in effective amounts, in combination with a pharmaceutically effective amount of a carrier, additive or excipient, represents a further aspect of the present disclosure.

**[00156]** The term “bioactive agent” is used to describe an agent, other than the PROTAC compounds described herein, which is used in combination with the present compounds as an agent with biological activity to assist in effecting an intended therapy, inhibition and/or prevention/prophylaxis for which the present compounds are used. Preferred bioactive agents for use herein include those agents which assist in effecting an intended therapy, for example, P-gp inhibitors or agents that have pharmacological activity similar to that for which the present compounds are used or administered and include for example, anti-neurodegenerative agents.

**[00157]** The term “P-gp” is used to describe “permeability glycoprotein” or P-glycoprotein (ABCB1) which was discovered in 1976 in rodent cells. The presence of “endogenous or physiological” P-gp is a potential problem to achieving targeted exposure with therapeutic agents. P-gp is expressed at barrier tissue to sanctuary sites (e.g., blood-brain barrier) and at secretory/absorptive tissues (e.g., gastrointestinal tract) (Cordon-Cardo et al., 1989, 1990). The protein acts as a cellular defender and influences the overall pharmacokinetic profile of numerous drugs by actively pumping them out of the intracellular environment (effluxing) thereby reducing drug penetration of the barrier tissues. In particular, P-gp efflux reduces drug permeability across the gastrointestinal tract membranes and may lead to reduced systemic exposure of the drug. P-gp efflux also reduces drug access across the blood-brain barrier. P-gp inhibitors could indirectly contribute to efficacy by increasing PROTAC exposure, particularly CNS exposure

**[00158]** The term “additional anti-neurodegenerative agent” is used to describe an anti-neurodegenerative agent, which may be combined with PROTAC compounds according to the present description to treat neurodegenerative diseases.

**[00159]** In certain embodiments, the PROTAC(s) are used along with P-gp inhibitors.

**[00160]** In certain additional embodiments, the P-gp inhibitors are selected from the group consisting of, but not limited to, Amiodarone, Azithromycin, Captopril, Clarithromycin, Cyclosporine, Piperine, Quercetin, Quinidine, Quinine, Reserpine, Ritonavir, Tariquidar, Elacridar and Verapamil.

### **Methods of Treatment**

**[00161]** In another aspect, the disclosure provides methods of modulating protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a PROTAC compound as described herein or a composition comprising an effective amount of the same to a subject, wherein the compound or composition comprising the same is effective in modulating protein ubiquitination and degradation of the protein in the subject. In certain embodiments, the protein is Tau protein.

**[00162]** In certain embodiments, the description provides a method for regulating protein activity of Tau protein by degenerating Tau aggregates in a patient in need comprising administering to said patient an amount of a compound as described herein to a patient.

**[00163]** In still additional embodiments, the description provides a method of treating a disease state or condition in a patient wherein dysregulated protein activity (Tau aggregation and accumulation) is responsible for said disease state or condition, said method comprising administering to said patient an effective amount of a compound as described herein to said patient in order to regulate said protein activity in said patient. In certain embodiments, the protein is Tau.

**[00164]** The terms “treat”, “treating”, and “treatment”, etc., as used herein, refer to any action providing a benefit to a patient for which the present compounds may be administered, including the treatment of any disease state or condition which is modulated through the protein to which the present compounds bind. Disease states or conditions, including neurological and neurodegenerative diseases, which may be treated using compounds according to the present disclosure are set forth hereinabove.

**[00165]** In another aspect, the disclosure provides methods of modulating Tau protein ubiquitination and degradation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of a compound as described herein to a subject, wherein the compound or composition comprising the same is effective in modulating Tau protein ubiquitination and degradation of the protein in the subject.

**[00166]** In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to Tau accumulation or aggregation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same to a subject in need thereof, wherein the compound or composition comprising the same is effective in treating or ameliorating a symptom of a disease related to Tau aggregation in the subject.

**[00167]** In certain embodiments, the disease or disorder is a neurological disorder including but not limited to Absence of the Septum Pellucidum, Acquired Epileptiform Aphasia, Acute Disseminated Encephalomyelitis, ADHD, Adie's Pupil, Adie's Syndrome, Adreno-leukodystrophy, Agenesis of the Corpus Callosum, Agnosia, Aicardi Syndrome, AIDS-Neurological Complications, Alexander Disease, Alpers' Disease, Alternating Hemiplegia, Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Anencephaly, Aneurysm, Angelman Syndrome, Angiomatosis, Anoxia, Aphasia, Apraxia, Arachnoid Cysts, Arachnoiditis, Arnold-Chiari Malformation, Arteriovenous Malformation, Asperger Syndrome, Ataxia, Ataxia, Telangiectasia, Ataxias and Cerebellar/Spinocerebellar Degeneration, Attention Deficit-Hyperactivity Disorder, Autism, Autonomic Dysfunction, Back Pain, Barth Syndrome Batten Disease, Becker's Myotonia, Behcet's Disease, Bell's Palsy, Benign Essential Blepharospasm, Benign Focal Amyotrophy, Benign Intracranial Hypertension, Bernhardt-Roth Syndrome, Binswanger's Disease, Blepharospasm, Bloch-Sulzberger Syndrome, Brachial Plexus Birth Injuries, Brachial Plexus Injuries, Bradbury-Eggleston Syndrome, Brain and Spinal Tumors, Brain Aneurysm, Brain Injury, Brown-Sequard Syndrome, Bulbospinal Muscular Atrophy, Canavan Disease, Carpal Tunnel Syndrome Causalgia, Cavernomas, Cavernous Angioma, Cavernous Malformation, Central Cervical Cord Syndrome, Central Cord Syndrome, Central Pain Syndrome, Cephalic Disorders, Cerebellar Degeneration, Cerebellar Hypoplasia, Cerebral Aneurysm, Cerebral Arteriosclerosis, Cerebral Atrophy, Cerebral Beriberi, Cerebral Gigantism, Cerebral Hypoxia, Cerebral Palsy, Cerebro-Oculo-Facio-Skeletal Syndrome, Charcot-Marie-Tooth Disease, Chiari Malformation, Chorea, Choreoacanthocytosis,

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Chronic Orthostatic Intolerance, Chronic Pain Cockayne Syndrome Type II, Coffin Lowry Syndrome, COFS, Colpocephaly, Coma and Persistent Vegetative State, Complex Regional Pain Syndrome, Congenital Facial Diplegia, Congenital Myasthenia, Congenital Myopathy, Congenital Vascular Cavernous, Malformations, Corticobasal Degeneration, Cranial Arteritis, Craniosynostosis, Creutzfeldt-Jakob Disease, Cumulative Trauma Disorders, Cushing's Syndrome, Cytomegalic Inclusion Body Disease, Cytomegalovirus Infection, Dancing Eyes-Dancing Feet Syndrome, Dandy-Walker Syndrome, Dawson Disease, De Morsier's Syndrome, Deep Brain Stimulation for Parkinson's Disease, Dejerine-Klumpke Palsy, Dementia, Dementia—Multi-Infarct, Dementia—Semantic, Dementia—Subcortical, Dementia With Lewy Bodies, Dentate Cerebellar Ataxia, Dentatorubral Atrophy, Dermatomyositis, Developmental Dyspraxia, Devic's Syndrome, Diabetic Neuropathy, Diffuse Sclerosis, Dysautonomia, Dysgraphia, Dyslexia, Dysphagia, Dyspraxia, Dyssynergia Cerebellaris, Myoclonica, Dyssynergia Cerebellaris Progressiva, Dystonias, Early Infantile Epileptic, Encephalopathy, Empty Sella Syndrome, Encephalitis Lethargica, Encephaloceles, Encephalopathy, Encephalotrigeminal Angiomatosis, Epilepsy, Erb-Duchenne and Dejerine-Klumpke Palsies, Erb's Palsy, Fabry's Disease, Fahr's Syndrome, Fainting, Familial Dysautonomia, Familial Hemangioma, Familial Idiopathic Basal Ganglia, Calcification, Familial Periodic Paralysis, Familial Spastic Paralysis, Febrile Seizures, Fisher Syndrome, Floppy Infant Syndrome, Friedreich's Ataxia, Frontotemporal, Dementia, Gaucher's Disease, Gerstmann's Syndrome, Gerstmann-Straussler-Scheinker, Disease, Giant Cell Arteritis, Giant Cell Inclusion Disease, Globoid Cell Leukodystrophy, Glossopharyngeal Neuralgia, Guillain-Barre Syndrome, Hallervorden-Spatz Disease, Head Injury, Headache, Hemicrania Continua, Hemifacial Spasm, Hemiplegia Alterans, Hereditary Neuropathies, Hereditary Spastic Paraplegia, Heredopathia Atactica Polyneuritiformis, Herpes Zoster, Herpes Zoster Oticus, Hirayama Syndrome, Holmes-Adie syndrome, Holoprosencephaly, HTLV-1 Associated, Myelopathy, Huntington's Disease, Hydranencephaly, Hydrocephalus, Hydrocephalus—Normal Pressure, Hydromyelia, Hyperactivity, Hypercortisolism, Hypersomnia, Hypertonia, Hypotonia,—Infantile, Hypoxia, Immune-Mediated Encephalomyelitis, Inclusion Body Myositis, Incontinentia Pigmenti, Infantile Hypotonia, Infantile Neuroaxonal Dystrophy, Infantile Phytanic Acid Storage Disease, Infantile Refsum Disease, Infantile Spasms, Inflammatory Myopathy, Iniencephaly, Intestinal Lipodystrophy, Intracranial Cysts, Intracranial Hypertension, Isaac's Syndrome, Joubert Syndrome, Kearns-Sayre Syndrome, Kennedy's Disease, Kinsbourne syndrome, Kleine-Levin Syndrome, Klippel-Feil Syndrome,

Klippel-Trenaunay Syndrome (KTS), Klüver-Bucy Syndrome, Korsakoff's Amnesic Syndrome, Krabbe Disease, Kugelberg-Welander Disease, Kuru, Lambert-Eaton Myasthenic Syndrome, Landau-Kleffner Syndrome, Lateral Femoral, Cutaneous Nerve Entrapment, Lateral Medullary Syndrome, Learning Disabilities, Leigh's Disease, Lennox-Gastaut Syndrome, Lesch-Nyhan Syndrome, Leukodystrophy, Levine-Critchley Syndrome, Lewy Body Dementia, Lipid Storage Diseases, Lissencephaly, Locked-In Syndrome, Lou Gehrig's Disease, Lupus—Neurological, Sequelae, Lyme Disease—Neurological Complications, Machado-Joseph Disease, Macrencephaly, Mania, Megalencephaly, Melkersson-Rosenthal Syndrome, Meningitis, Meningitis and Encephalitis, Menkes Disease, Meralgia Paresthetica, Metachromatic, Leukodystrophy, Microcephaly, Migraine, Miller Fisher Syndrome, Mini-Stroke, Mitochondrial Myopathies, Mobius Syndrome, Monomelic Amyotrophy, Motor Neuron Diseases, Moyamoya Disease, Mucopolysaccharidoses, Mucopolysaccharidoses, Multifocal Motor Neuropathy, Multi-Infarct Dementia, Multiple Sclerosis, Multiple System Atrophy, Multiple System Atrophy with Orthostatic Hypotension, Muscular Dystrophy, Myasthenia—Congenital, Myasthenia Gravis, Myelinoclastic Diffuse Sclerosis, Myoclonic Encephalopathy of Infants, Myoclonus, Myopathy, Myopathy—Congenital, Myopathy-Thyrotoxic, Myotonia, Myotonia Congenita, Narcolepsy, Neuroacanthocytosis, Neurodegeneration with Brain Iron Accumulation, Neurofibromatosis, Neuroleptic Malignant Syndrome, Neurological Complications of AIDS, Neurological Complications Of Lyme Disease, Neurological Consequences of Cytomegalovirus Infection, Neurological Manifestations of Pompe Disease, Neurological Sequelae Of Lupus, Neuromyelitis Optica, Neuromyotonia, Neuronal Ceroid, Lipofuscinosis, Neuronal Migration Disorders, Neuropathy—Hereditary, Neurosarcoidosis, Neurotoxicity, Nevus Cavernosus, Niemann-Pick Disease, Normal Pressure Hydrocephalus, Occipital Neuralgia, Obesity, Occult Spinal Dysraphism Sequence, Ohtahara Syndrome, Olivopontocerebellar Atrophy, Opsoclonus Myoclonus, Orthostatic Hypotension, O'Sullivan-McLeod Syndrome, Overuse Syndrome, Pain—Chronic, Paine, Pantothenate Kinase-Associated Neurodegeneration, Paraneoplastic Syndromes, Paresthesia, Parkinson's Disease, Paroxysmal Choreoathetosis, Paroxysmal Hemicrania, Parry-Romberg, Pelizaeus-Merzbacher Disease, Pena Shokeir II Syndrome, Perineural Cysts, Periodic Paralysis, Peripheral Neuropathy, Periventricular Leukomalacia, Persistent Vegetative State, Pervasive Developmental Disorders, Phytanic Acid Storage Disease, Pick's Disease, Pinched Nerve, Piriformis Syndrome, Pituitary Tumors, Polymyositis, Pompe Disease, Porencephaly, Postherpetic Neuralgia, Postinfectious Encephalomyelitis, Post-Polio Syndrome, Postural Hypotension,

Postural Orthostatic, Tachycardia Syndrome, Postural Tachycardia Syndrome, Primary Dentatum Atrophy, Primary Lateral Sclerosis, Primary Progressive Aphasia, Prion Diseases, Progressive Hemifacial Atrophy, Progressive Locomotor Ataxia, Progressive Multifocal, Leukoencephalopathy, Progressive Sclerosing Poliodystrophy, Progressive Supranuclear, Palsy, Prosopagnosia, Pseudotumor Cerebri, Ramsay Hunt Syndrome I (formerly known as), Ramsay Hunt Syndrome II (formerly known as), Rasmussen's Encephalitis, Reflex Sympathetic Dystrophy Syndrome, Refsum Disease, Refsum Disease—Infantile, Repetitive Motion Disorders, Repetitive Stress Injuries, Restless Legs Syndrome, Retrovirus-Associated Myelopathy, Rett Syndrome, Reye's Syndrome, Riley-Day Syndrome, Sacral Nerve Root Cysts, Saint Vitus Dance, Salivary Gland Disease, Sandhoff Disease, Schilder's Disease, Schizencephaly, Seitelberger Disease, Seizure Disorder, Semantic Dementia, Septo-Optic Dysplasia, Shaken Baby Syndrome, Shingles Shy-Drager Syndrome, Sjogren's Syndrome, Sleep Apnea, Sleeping Sickness, Sotos Syndrome, Spasticity, Spina Bifida, Spinal Cord Infarction, Spinal Cord Injury, Spinal Cord Tumors, Spinal Muscular Atrophy, Spinocerebellar Atrophy, Spinocerebellar, Degeneration, Steele-Richardson-Olszewski Syndrome, Stiff-Person Syndrome, Striatonigral Degeneration, Stroke, Sturge-Weber Syndrome, Subacute Sclerosing Panencephalitis, Subcortical Arteriosclerotic Encephalopathy, SUNCT Headache Swallowing Disorders, Sydenham Chorea, Syncope, Syphilitic Spinal Sclerosis, Syringohydromyelia, Syringomyelia, Systemic Lupus Erythematosus, Tabes Dorsalis Tardive Dyskinesia, Tarlov Cysts, Tay-Sachs Disease, Temporal Arteritis, Tethered Spinal Cord Syndrome, Thomsen's Myotonia, Thoracic Outlet Syndrome, Thyrotoxic Myopathy, Tic Douloureux, Todd's Paralysis, Tourette Syndrome, Transient Ischemic Attack, Transmissible Spongiform Encephalopathies, Transverse Myelitis, Traumatic Brain Injury, Tremor, Trigeminal Neuralgia, Tropical Spastic Paraparesis, Tuberous Sclerosis, Vascular Erectile Tumor, Vasculitis including Temporal Arteritis, Von Economo's Disease, Von Hippel-Lindau Disease (VHL), Von Recklinghausen's Disease, Wallenberg's Syndrome, Werdnig-Hoffman Disease, Wernicke-Korsakoff Syndrome, West Syndrome, Whiplash, Whipple's Disease, Williams Syndrome, Wilson's Disease, X-Linked Spinal and Bulbar Muscular Atrophy, or Zellweger Syndrome.

**[00168]** In certain embodiments, the disease or disorder is at least one of Huntington's disease, muscular dystrophy, Parkinson's disease, Alzheimer's disease, Batten disease, Injuries to the spinal cord and brain, Seizure disorders, epilepsy, brain tumors, meningitis, autoimmune diseases such as multiple sclerosis, Neurofibromatosis, Depression, Amyotrophic Lateral Sclerosis, Arteriovenous

Malformation, Brain Aneurysm, Dural Arteriovenous Fistulae, Headache, Memory Disorders, Peripheral Neuropathy, Post-Herpetic Neuralgia, Spinal Cord Tumor and Stroke.

**[00169]** In certain embodiments, the disease or disorder is Alzheimer's disease.

**[00170]** In another aspect, the disclosure provides methods of treating or ameliorating a symptom of a disease related to Tau accumulation or aggregation in a subject, e.g., a cell, a tissue, mammal, or human patient, the method comprising administering an effective amount of a compound as described herein or a composition comprising an effective amount of the same and an effective or synergistic amount of another bioactive agent to a subject in need thereof, wherein the composition comprising the same is effective in treating or ameliorating a symptom of a disease related to Tau accumulation or aggregation in the subject by Tau degradation/inhibition.

**[00171]** In certain embodiments, the disease to be treated is Neurological disorder. In a preferred embodiment, the subject is a human.

**[00172]** In certain additional embodiments, the additional bioactive agent is an anti-neurodegenerative agent.

**[00173]** In alternative aspects, the present disclosure relates to a method for treating a disease state by degrading a protein or polypeptide through which a disease state or condition is modulated comprising administering to said patient or subject an effective amount of at least one compound as described hereinabove, optionally in combination with an additional bioactive agent. The method according to the present disclosure may be used to treat a large number of neurological disease states or conditions, by virtue of the administration of effective amounts of at least one compound described herein.

**[00174]** In another aspect, the disclosure provides methods for identifying the effects of the degradation of proteins of interest in a biological system using compounds according to the present disclosure.

### **Kits**

**[00175]** In another aspect, the description provides kits comprising compounds or compositions as described herein. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present disclosure. In addition, the kits of the present disclosure may preferably contain instructions, which describe a suitable use. Such kits can be conveniently used, e.g., in clinical settings, to treat patients with Neurological disorders.

### **Examples**

**[00176]** The PROTAC compounds of the instant invention are effective in Tau degradation. Exemplary compounds are presented in Table 1 with in vitro data of some selected examples in Table 2 showing degradation of tau protein. In vivo studies showing degradation of tau protein are illustrated in Figure 1.

#### **General Methods of Chemical Synthesis**

**[00177]** The synthesis of the claimed chimeric compounds can be carried out according to the general synthetic procedures known in literature. Synthetic routes shown in the schemes in the present disclosure are described as one of the methods that can be used to obtain the desired compounds. Other methods can also be used for those skilled in the art of synthesis. The ULM and PTM described in schemes only represent one of many ULMs and PTMs in this application.

#### **LC-MS method for purity analysis (quality control)**

**[00178]** LCMS Method:

Instrumentations: Agilent infinity 1260 LC; Agilent 6230 TOF mass spectrometer

The analysis is conducted on a Poroshell 120 EC C18 column (50mm x 3.0mm internal diameter 2.7µm packing diameter) at 45°C.

The solvents employed are:

A = 0.1% v/v solution of formic acid in water.

B = 0.1% v/v solution of formic acid in acetonitrile.

The gradient employed are as follows:

| <b>Time<br/>(minutes)</b> | <b>Flow Rate<br/>(mL/min)</b> | <b>% A</b> | <b>% B</b> |
|---------------------------|-------------------------------|------------|------------|
| 0                         | 1                             | 95         | 5          |
| 0.5                       | 1                             | 95         | 5          |
| 3.0                       | 1                             | 1          | 99         |
| 4.0                       | 1                             | 1          | 99         |
| 4.1                       | 1                             | 95         | 5          |
| 4.5                       | 1                             | 95         | 5          |

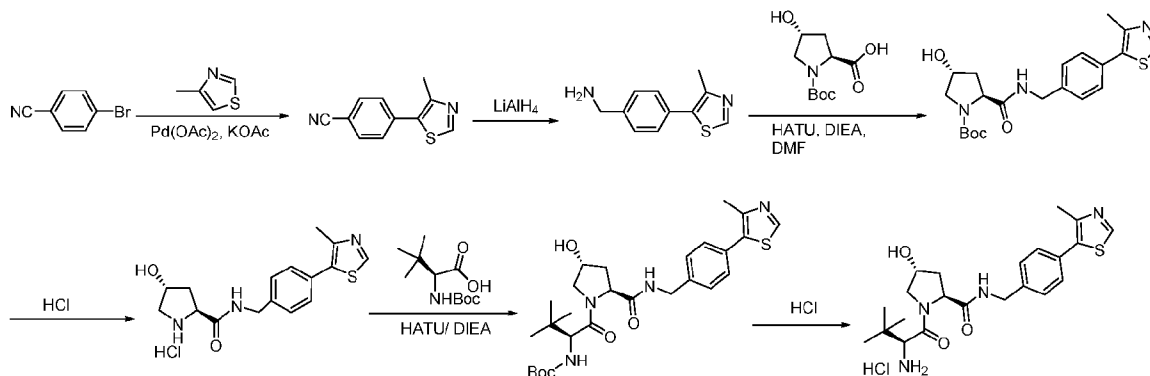
The UV detection is an averaged signal from wavelength of 210nm to 350nm and mass spectra are recorded on a mass spectrometer using positive mode electrospray ionization.

**[00179]** **Abbreviations:**

ACN: acetonitrile  
Boc<sub>2</sub>O: di-tert-butyl dicarbonate  
DCM: dichloromethane.  
DIPEA: *N,N*-diisopropylethylamine  
DMA: *N,N*-dimethylacetamide  
DMF: *N,N*-dimethylformamide  
EA: ethyl acetate  
HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate  
HPLC: high-performance liquid chromatography  
LC-MS: liquid chromatography-mass spectrometry  
Min: minutes  
MTBE: methyl tert-butyl ether  
PE: petroleum ether  
RT: room temperature  
SPB: sodium perborate  
tBu: tert-butyl  
TBACl: tetra-butyl ammonium chloride  
TFA: trifluoroacetic acid  
THF: tetrahydrofuran  
TLC: thin layer chromatography  
TMS: trimethylsilyl  
t<sub>R</sub>: retention time  
TsCl: p-toluene sulfonyl chloride

**[00180] Intermediates of ubiquitin E3 ligase targeting moiety (ULM) and protein targeting moiety (PTM)**

**[00181] Intermediate 1: (2*S*, 4*R*)-1-[(2*S*)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-*N*-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride (ULM-1)**



#### Step 1: Preparation of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile

**[00182]** To a stirred solution of 4-bromobenzonitrile (20 g, 109.88 mmol) in DMA (250 mL) under a nitrogen atmosphere was added 4-methyl-1,3-thiazole (21.88 g, 220.67 mmol), palladium (II) acetate (743 mg, 3.31 mmol) and potassium acetate (21.66 g, 220.71 mmol) at rt. The resulting mixture was heated to 150 °C and stirred at this temperature for 5 h, at which time LC-MS indicated completion of the reaction. The mixture was cooled to rt, diluted with 1 L of water and extracted with ethyl acetate (300 mL x 3). The organic layers were combined, washed with brine (200 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel column chromatography (eluent: ethyl acetate/petroleum ether, v: v = 1:5) to give the titled compound (yield: 91%) as a white solid.

#### Step 2: Preparation of of [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine

**[00183]** To a stirred solution of 4-(4-methyl-1,3-thiazol-5-yl)benzonitrile (35 g, 174.77 mmol) in tetrahydrofuran (1000 mL) was added LiAlH<sub>4</sub> (20 g, 526.32 mmol) in portions at 0°C in 10 min under a nitrogen atmosphere. The resulting mixture was then stirred at 60 °C for 3h, at which time LC-MS indicated completion of reaction. The mixture was cooled to 0°C, then quenched by the addition of water (20 mL, added slowly), aq. solution of NaOH (15%, 20 mL) and water (60 mL). The resulting mixture was then extracted with ethyl acetate (300 mL x 2). The organic layers were combined, washed with brine (100 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel column chromatography (eluent: dichloromethane/methanol (v:v = 10:1)) to give the titled compound (yield: 56%) as a yellow oil.

#### Step 3: Preparation of tert-butyl (2S,4R)-4-hydroxy-2-([(4-(4-methyl-1,3-thiazol-5-yl)phenyl)methyl]carbamoyl)pyrrolidine-1-carboxylate

**[00184]** To a stirred solution of (2S,4R)-1-[(tert-butoxy)carbonyl]-4-hydroxypyrrolidine-2-carboxylic acid (2.7 g, 11.68 mmol) in N,N-dimethylformamide (20 mL) was added DIPEA (2.52 g, 19.50 mmol), HATU (4.47 g, 11.76 mmol) and [4-(4-methyl-1,3-thiazol-5-yl)phenyl]methanamine (2 g, 9.79 mmol) at rt. The resulting mixture was stirred at rt overnight, at which time LC-MS indicated completion of reaction. The reaction mixture was diluted with 20 mL of water and extracted with ethyl acetate (50 mL x 3). The organic layers were combined, washed with brine (50 mL), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel column chromatography (eluent: dichloromethane/methanol (v:v = 20:1)) to give the titled compound (yield: 56%) as a yellow solid.

Step 4: Preparation of (2S,4R)-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride

**[00185]** To 1L round bottom flask containing tert-butyl (2S,4R)-4-hydroxy-2-([4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl)carbamoylpyrrolidine-1-carboxylate (45 g, 107.78 mmol) in dioxane was added hydrogen chloride in dioxane (4N, 300 mL). The resulting solution was stirred for 2h at rt. The solids were collected by filtration to give the titled product (yield: 98%) as a yellow solid.

Step 5: Preparation of tert-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-([4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl)carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate

**[00186]** To a stirred solution of (2S)-2-[[[(tert-butoxy)carbonyl]amino]-3,3-dimethylbutanoic acid (15.7 g, 68.0 mmol) in N,N-dimethylformamide (500 mL) was added DIPEA (29.2 g, 225.9 mmol), HATU (25.9 g, 68.1 mmol) and (2S,4R)-4-hydroxy-N-{[4-(4-methyl-1,3-thiazol-5-yl)-phenyl]methyl} pyrrolidine-2-carboxamide hydrochloride (20.0 g, 56.5 mmol) at rt.

**[00187]** The resulting solution was stirred at rt for 16h, LC-MS indicated formation of the desired product. The reaction mixture was diluted by water (200 mL) and extracted with ethyl acetate (200 mL x 3). The organic layers were combined, washed with saturated aqueous solution of sodium chloride (50 mL x 2), dried over anhydrous sodium sulfate and then concentrated under reduced pressure to give a crude residue, which was purified by flash silica gel chromatography (eluent: ethyl acetate/petroleum ether (v:v = 2:1)) to give the title compound (yield: 51%) as a yellow solid.

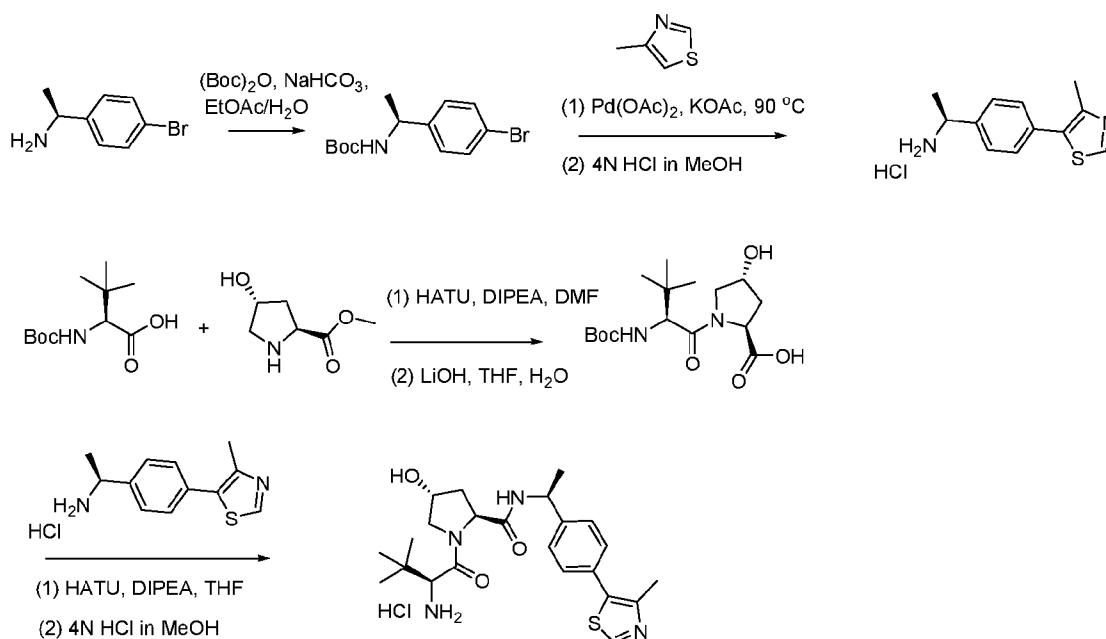
Step 6: Synthesis of (2S, 4R)-1-[(2S)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[[4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl]pyrrolidine-2-carboxamide hydrochloride (**ULM-1**)

**[00188]** To a stirred solution of *tert*-butyl *N*-[(2*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-([4-(4-methyl-1,3-thiazol-5-yl)phenyl]methyl)carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (12 g, 22.61 mmol) in dioxane (20 mL) was added a solution of hydrogen chloride in dioxane (4*N*, 80 mL) at rt. The resulting solution was stirred at rt for 2 h, at which time LC-MS indicated completion of reaction. Precipitated solids were collected by filtration to give the titled product (yield: 48%) as a yellow solid.

**[00189]** d: 48%) as a yellow solid.

<sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 9.84-9.82 (s, 1H), 7.58-7.54 (m, 4H), 4.71-4.41 (m, 4H), 4.13-4.08 (m, 1H), 3.86-3.71 (m, 2H), 3.36 (s, 1H), 2.60-2.58 (s, 3H), 2.35-2.07 (m, 2H), 1.19-1.12(m, 9H). LC-MS (ES<sup>+</sup>): *m/z* 431.11 [MH<sup>+</sup>], *t<sub>R</sub>* = 0.73 min.

**Intermediate 2: (2*S*,4*R*)-1-[(*S*)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-*N*-[(*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl]-pyrrolidine-2-carboxamide hydrochloride (ULM-2)**



**Step 1: Preparation of (*S*)-*tert*-butyl 1-(4-bromophenyl)-ethyl carbamate**

**[00190]** To a mixture of (*S*)-1-(4-bromophenyl)ethanamine (3.98 g, 19.9 mmol) and NaHCO<sub>3</sub> (1.24 g, 14.8 mmol) in H<sub>2</sub>O (10 mL) and ethyl acetate (10 mL) was added (Boc)<sub>2</sub>O (5.20 g, 23.8 mmol) at 5°C. The reaction was continued to react for 2 h. TLC showed reaction was complete. The reaction mixture was filtered. The solid was collected and suspended in a mixture of hexane (10 mL) and H<sub>2</sub>O (10 mL) for 0.5 h. The mixture was filtered and the solid was collected and dried in oven at 50°C to afford the title compound as white solid (5.9 g, 98.7%).

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.28 (d, *J* = 7.2 Hz, 3H), 1.36 (s, 9H), 4.55-4.60 (m, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.39 (br, 1H), 7.49 (d, *J* = 8.4 Hz, 2H).

Step 2: Preparation of (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride

**[00191]** A mixture of (*S*)-*tert*-butyl 1-(4-bromophenyl)-ethyl carbamate (4.0 g, 13.3 mmol), 4-methylthiazole (2.64 g, 26.6 mmol), palladium (II) acetate (29.6 mg, 0.13 mmol) and potassium acetate (2.61 g, 26.6 mmol) in DMF (10 mL) was stirred at 90°C under N<sub>2</sub> for 18 h. After cooling to ambient temperature, the reaction mixture was filtered. To the filtrate was added H<sub>2</sub>O (50 mL) and the resulting mixture was stirred at ambient temperature for 4 h. The reaction mixture was filtered. The solid was collected by filtration and dried in oven at 50°C to afford (*S*)-*tert*-butyl 1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamate (3.48 g, 82.3%) as gray solid.

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.33 (d, *J* = 7.2 Hz, 3H), 1.38 (s, 9H), 2.46 (s, 3H), 4.64-4.68 (m, 1H), 7.23 (br d, 0.5H), 7.39 (d, *J* = 8 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.50 (br d, 0.5H), 8.99 (s, 1H); LC-MS [*M*+1]<sup>+</sup>: 319.5

**[00192]** This solid material (1.9 g, 6.0 mmol) was dissolved in 4N hydrochloride in methanol (5 mL, 20 mmol, prepared from acetyl chloride and methanol) and the mixture was stirred at ambient temperature for 3h then concentrated and triturated with ether. The mixture was filtered and the solid was collected and dried in oven at 60°C to afford (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride (1.3 g, 85%) as a light green solid.

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.56 (d, *J* = 6.8 Hz, 3H), 2.48 (s, 3H), 4.41-4.47 (m, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz), 8.75 (s, 3H), 9.17 (s, 1H); LC-MS [*M*+1]<sup>+</sup>: 219.2

Step 3: Preparation of (2*S*, 4*R*)-1-[(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxylic acid

**[00193]** HATU (2.15 g, 5.7 mmol) was added to a solution of (*S*)-2-(*tert*-butoxycarbonyl)amino-3,3-dimethylbutanoic acid (1.25 g, 5.4 mol), (2*S*,4*R*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (0.98 g, 5.4 mmol) and DIPEA (2.43 g, 18.9 mmol) in DMF (10 mL) at 0°C under nitrogen. The mixture was stirred at ambient temperature for 18 h. TLC showed the reaction complete. The reaction mixture was quenched with water (30 mL) and extracted with ethyl acetate (15 mL X 4). The combined organic layer was washed with the 5% citric acid (10 mL x 2), saturated NaHCO<sub>3</sub> solution (10 mL x 2), brine (10 mL x 2) and dried over Na<sub>2</sub>SO<sub>4</sub>. The organic solution was filtered and concentrated to afford (2*S*, 4*R*)-methyl 1-[(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxylate as pale yellow oil (1.93 g, 100% yield). This crude product (1.93 g) and lithium hydroxide hydrate (2.2 g, 54

mmol) were taken into THF (20 mL) and H<sub>2</sub>O (10 mL). The resulting mixture was stirred at ambient temperature for 18 h. THF was removed by concentration. The residue was diluted with ice-water (10 mL) and slowly adjusted to pH 2-3 with 3N HCl. The resulting suspension was filtered, washed with H<sub>2</sub>O (6 mL × 2). The solid was collected by filtration and dried in oven at 50°C to afford the title compound as a white solid (1.4 g, 75% for two steps).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 6.50 (d, *J* = 9.6 Hz, 1H), 5.19 (br s, 1H), 4.32 (br s, 1H), 4.25 (t, *J* = 8.4 Hz, 1H), 4.16 (d, *J* = 9.2 Hz, 1H), 3.57-3.66 (m, 2H), 2.08-2.13 (m, 1H), 1.85-1.91 (m, 1H), 1.38 (s, 9H), 0.94 (s, 9H).

Step 4: Preparation of (2*S*,4*R*)-1-[(*S*)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-N-[(*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl]-pyrrolidine-2-carboxamide hydrochloride (**ULM-2**)

**[00194]** HATU (1.6 g, 4.2 mmol) was added to a stirred solution containing (2*S*, 4*R*)-1-[(*S*)-2-[(*tert*-butoxycarbonyl)amino]-3,3-dimethylbutanoyl]-4-hydroxypyrrolidine-2-carboxylic acid (1.21 g, 3.5 mmol), (*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethanamine hydrochloride (0.9 g, 3.5 mmol), and DIPEA (1.36 g, 10.5 mmol) in anhydrous THF (15 mL) at 0°C. The resulting mixture was allowed to warm up to ambient temperature and continued to stir for 2 h. TLC showed reaction completed. THF was removed by concentration. To the residue was added water (15 mL) and the resulting mixture was stirred for 4 h. The resulting mixture was filtered. The solid was collected and dried in oven at 50°C to give a white solid. This solid was taken into methanol (10 mL) and activated carbon (150 mg) was added. The resulting mixture was heated at 80°C and stirred for 1h. The mixture was filtered while it was hot. Water (5 mL) was added to the filtrate at 80°C. The resulting mixture was cooled to ambient temperature and continued to stir for 18 h. The suspension was filtered. The solid was collected and dried in oven at 50°C to afford *tert*-butyl-[(*S*)-1-[(2*S*,4*R*)-4-hydroxy]-2-[(*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)-ethylcarbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl-carbamate (1.41 g, 74.2%) as a white solid.

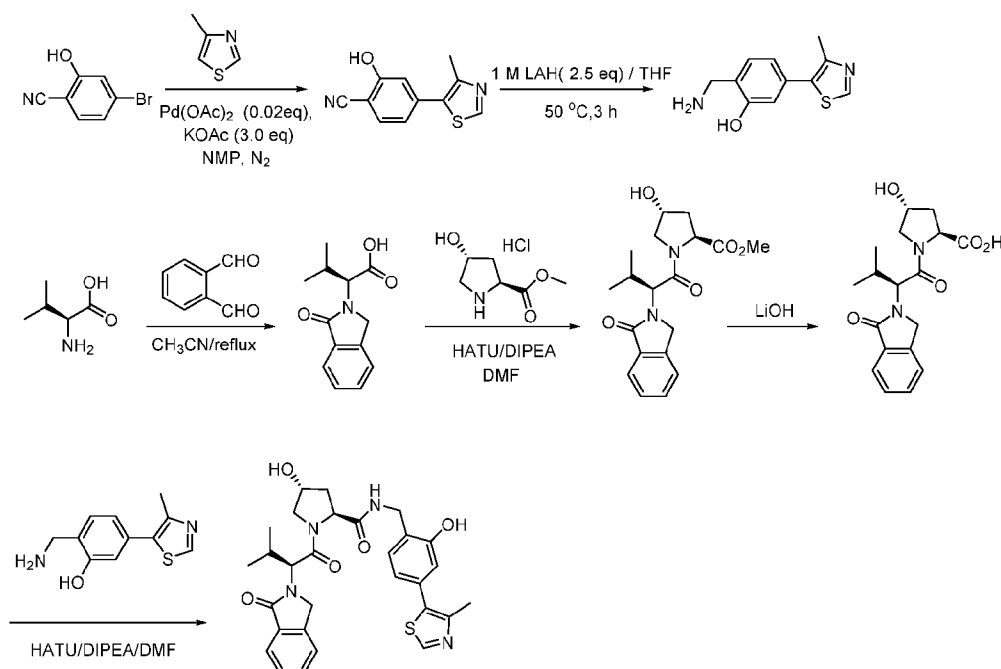
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.05 (s, 9H), 1.42 (s, 9H), 1.47 (d, *J* = 7.2 Hz, 3H), 2.04-2.10 (m, 1H), 2.53 (s, 3H), 2.58-2.64 (m, 1H), 3.23 (s, 1H), 3.58 (dd, *J* = 11.2 Hz, 3.2 Hz, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 9.2 Hz, 1H), 4.51 (br, 1H), 4.79 (t, *J* = 8.0 Hz, 1H), 5.04-5.11 (m, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 7.36-7.42 (m, 4H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.68 (s, 1H).

**[00195]** This solid (1.04 g, 1.9 mmol) was dissolved in 4N hydrogen chloride in methanol (3.0 mL) and the mixture was stirred at ambient temperature for 3 h. TLC showed reaction complete. The reaction mixture was concentrated to remove all volatiles under reduced pressure to give a light yellow solid. The solid was added to TBME (5 mL) and the resulting mixture was stirred at

ambient temperature for 4 h. The reaction mixture was filtered and the solid was collected and dried in oven at 50°C to afford the title compound (0.92 g, 100%).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>): δ 1.03 (s, 9H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.72-1.79 (m, 1H), 2.09-2.14 (m, 1H), 2.49 (s, 3H), 3.48-3.52 (m, 1H), 3.75-3.79 (m, 1H), 3.88-3.90 (m, 1H), 4.31 (br, 1H), 4.56 (t, *J* = 8.4 Hz, 1H), 4.89-4.95 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 8.20 (br, 3H), 8.67 (d, *J* = 7.6 Hz, 1H), 9.22 (s, 1H); <sup>13</sup>C NMR (400 MHz, DMSO-d<sub>6</sub>): δ 170.7, 167.1, 153.0, 146.5, 145.7, 132.5, 129.4, 129.3, 126.9, 69.4, 59.3, 58.5, 56.9, 48.3, 38.4, 34.8, 26.6, 23.0, 15.7; LC-MS [*M*+1]<sup>+</sup>: 445.6

**Intermediate 3: (2*S*,4*R*)-4-hydroxy-*N*-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide (ULM-3)**



**Step 1: Preparation of 2-hydroxy-4-(4-methylthiazol-5-yl) benzonitrile**

**[00196]** A mixture of 4-bromo-2-hydroxybenzonitrile (15 g, 76 mmol), 4-methylthiazole (14 mL, 152 mmol), KOAc (14.9 g, 152 mmol) and Pd(OAc)<sub>2</sub> (0.34g, 1.52 mmol) in dry NMP (125 mL) was stirred at 110 °C for 6 hours under nitrogen atmosphere. TLC showed the reaction was complete. The mixture was first cooled to room temperature, then partitioned between EtOAc and water. The combined organic fraction was filtered and the filtrate was washed with water, brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was dissolved in toluene (100 mL) and re-evaporated to afford the crude product. The crude product was treated with cold MeOH (80

mL). The resulting precipitate was collected by filtration, washed with MeOH (20 mL), and dried under vacuum to afford the title compound as a light yellow solid (10.5 g, 64 %).

LC/MS: 217.2 [M+1]<sup>+</sup>.

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 2.49(s, 3H), 7.07(dd, J=8.0, 1.6Hz, 1H), 7.13(d, J=1.6Hz, 1H), 7.70(d, J=8.0 Hz, 1H), 9.07(s, 1H), 11.34 (s, 1H).

Step 2: Preparation of 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol

**[00197]** To a solution of 2-hydroxy-4-(4-methylthiazol-5-yl)benzonitrile (2.9 g, 13.41 mmol) in dry THF (150 mL), was added LiAlH<sub>4</sub> (1.5 g, 40.23 mmol) in portions at 0 °C. The resulting mixture was stirred at 50 °C for 3h under nitrogen atmosphere. TLC showed the reaction was complete. The mixture was cooled in ice-water bath then Na<sub>2</sub>SO<sub>4</sub>·10H<sub>2</sub>O (5 g) was added carefully and stirred at this temperature for 1h. The mixture was filtered and the filter cake was washed with 10% MeOH in DCM for four times. The combined filtrates were concentrated to afford the crude 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol as a light yellow solid (2.0 g, 68%). It was used in next step without further purification.

LCMS: 221.2[M+H]<sup>+</sup>.

<sup>1</sup>HNMR (400MHz, DMSO-d<sub>6</sub>): δ 2.43 (s, 3H), 3.54 (br, 2H), 6.11 (d, J=7.2Hz, 1H), 6.40 (d, J=11.6Hz, 1H), 6.83 (d, J=7.6Hz, 1H), 8.81 (s, 1H).

Step 3: Preparation of (S)-3-methyl-2-(1-oxoisindolin-2-yl) butanoic acid

**[00198]** L-Valine (4.37 g, 37.3 mmol) was added to a solution of phthalic dicarboxaldehyde (5.0 g, 37.3 mmol) in acetonitrile (350 mL). The resulting mixture was refluxed for 5 h. The reaction mixture was filtered whilst hot and the filtrate was cooled to room temperature slowly. The resulting precipitate was filtered and dried to afford (S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoic acid as a white solid (6.45 g, 74 %).

<sup>1</sup>HNMR (400 MHz, DMSO-d<sub>6</sub>): δ 0.85(d, J=6.8Hz, 3H), 1.0(d, J=6.8Hz, 3H), 2.25-2.34(m, 1H), 4.51(d, J=4.4Hz, 1H), 4.54(d, J=3.6Hz, 1H), 4.64(d, J=18.0Hz, 1H), 7.48-7.54(m, 1H), 7.63 (d, J=3.6 Hz, 2H), 7.72(d, J=7.6Hz, 1H), 13.01(br, 1H).

Step 4: Preparation of (2S,4R)-methyl 4-hydroxy-1-((S)- 3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxylate

**[00199]** To a solution containing 4-hydroxy-L-proline methyl ester hydrochloride (1.0 g, 5.52 mmol), (S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoic acid (1.16 g, 4.97 mmol), and DIPEA (2.58 g, 20 mmol) in dry DMF (15 mL) was added HATU (3.8 g, 10 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 2 h. The mixture was partitioned between EtOAc and

water. The organic phase was washed with water, brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by silica gel chromatography using 30-50% EtOAc in hexane as eluent to afford the title compound as a light yellow solid (1.21g, 67.6%).

LCMS: 361.3[M+1]<sup>+</sup>.

Step 5: Preparation of (2S,4R)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxylic acid

**[00200]** A mixture containing (2S,4R)-methyl 4-hydroxy-1-((S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxylate (1.2 g, 3.33 mmol), LiOH·H<sub>2</sub>O (559 mg, 13.32 mmol) in THF (20 mL) and H<sub>2</sub>O (10 mL) was stirred at room temperature for 2 h. TLC showed the reaction was complete. The reaction mixture was acidified with 1N HCl to pH 1-2, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to afford the title compound as a light yellow solid (1.05 g, 91% yield).

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): δ 0.91 (d, J=6.4Hz, 3H), 1.05 (d, J=6.8Hz, 3 H), 2.30 (dd, J=8.4,2.8 Hz, 2H), 2.44-2.50 (m, 1H), 3.75 (dd, J=11.2, 3.2 Hz, 1H), 4.42 (d, J=17.6Hz, 1H), 4.50-4.55 (m, 2H), 4.66 (t, J=8.4Hz, 1H), 4.75 (d, J=17.6Hz, 1H), 4.83 (d, J=11.2Hz, 1H), 7.42-7.45 (m, 2H), 7.51-7.56 (m, 1H), 7.78 (d, J=7.6 Hz, 1H).

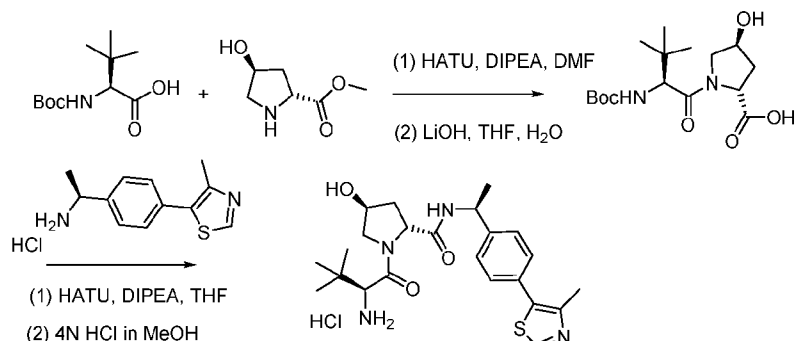
Step 6: Preparation of (2S,4R)-4-hydroxy-N-(2-hydroxy-4-(4-methylthiazol-5-yl)benzyl)-1-((S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxamide

**[00201]** To a solution containing (2S,4R)-4-hydroxy-1-((S)-3-methyl-2-(1-oxoisindolin-2-yl)butanoyl)pyrrolidine-2-carboxylic acid (1.0 g, 2.89 mmol), 2-(aminomethyl)-5-(4-methylthiazol-5-yl)phenol (954 mg, 4.33 mmol), and DIPEA (1.5 g, 11.55 mmol) in DMF (20 mL) was added HATU (2.2 g, 5.77 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 1h. TLC showed the reaction was complete. The mixture was partitioned between EtOAc and water. The organic phase was washed with water, brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by silica gel column chromatography using 2-5% MeOH in DCM to afford the title compound as a light yellow solid (650 mg, 43% yield).

LCMS: 549.2[M+H]<sup>+</sup>

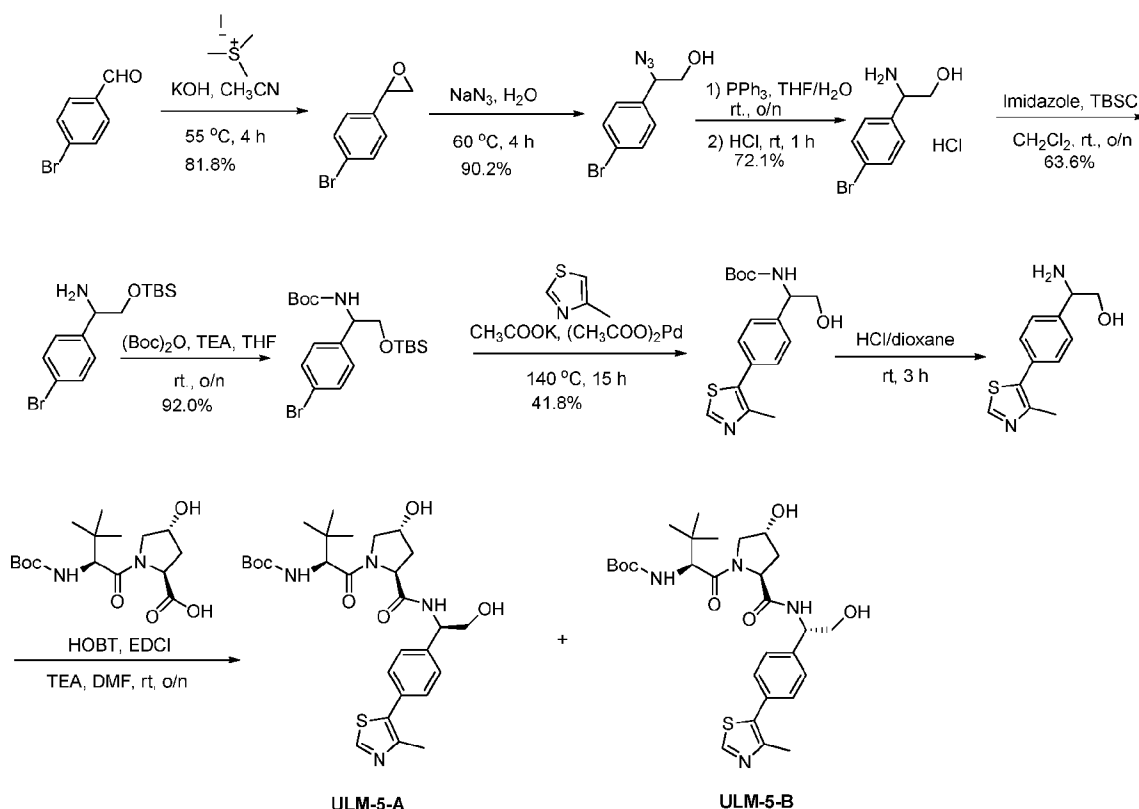
<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): δ 0.80 (d, J=6.8Hz, 3H), 0.88 (d, J=6.8Hz, 3 H), 1.96-2.01 (m, 1H), 2.34-2.40 (m, 1H), 2.47-2.53 (m, 4H), 3.61 (dd, J=11.6, 3.6 Hz, 1H), 4.29-4.37 (m, 2H), 4.38-4.41 (m, 1H), 4.47-4.50 (m, 2H), 4.64-4.69 (m, 2H), 4.72 (s, 1H), 6.90 (dd, J=8.0, 2.0 Hz, 1H), 7.01 (d, J=2.0Hz, 1H), 7.14 (d, J=8.0Hz, 1H), 7.39-7.44 (m, 2H), 7.51-7.54 (m, 1H), 7.76 (d, J=7.6Hz, 1H), 8.03 (t, J=6.4Hz, 1H), 8.66 (s, 1H), 9.27 (br, 1H).

**Intermediate 4: (2*R*,4*S*)-1-[(*S*)-2-amino-3,3-dimethylbutanoyl]-4-hydroxy-*N*-[(*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl]-pyrrolidine-2-carboxamide hydrochloride (ULM-4)**



**[00202]** This compound was synthesized using the same method as described in the preparation of **ULM-2** using (2*R*,4*S*)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride. <sup>1</sup>HNMR (400 MHz, CD<sub>3</sub>OD): δ 1.14 (s, 9H), 1.55 (d, *J* = 6.8 Hz, 3H), 2.00-2.05 (m, 1H), 2.51-2.58 (m, 1H), 2.65 (s, 3H), 3.77-3.81 (m, 1H), 3.88-3.92 (m, 1H), 4.06 (br, 1H), 4.41-4.46 (m, 1H), 4.56-4.60 (m, 1H), 5.07-5.12 (m, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 10.02 (s, 1H). LC-MS [M+H]<sup>+</sup>: 445.3

**Intermediate 5 and Intermediate 6: *tert*-butyl-*N*-[(2*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[*(1R)*]-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (ULM-5-A) and *tert*-butyl *N*-[(2*S*)-1-[(2*S*,4*R*)-4-hydroxy-2-[[*(1S)*]-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (ULM-5-B)**



#### Step 1: The synthesis of 2-(4-bromophenyl)oxirane

**[00203]** A mixture of 4-bromobenzaldehyde (2.52 g, 13.6 mmol), trimethylsulfonium iodide (2.87 g, 14.1 mmol), water (0.65 mL, 36.1 mmol) and potassium hydroxide (1.56 g, 27.7 mmol) in acetonitrile (20 mL) was warmed to 55 °C for 4 hours. The resulting solution was partitioned between water and diethyl ether, and the organic layer was washed with water, diluted hydrochloric acid, and brine, and dried over sodium sulfate. Crude product of 2-(4-bromophenyl)oxirane (2.20 g, 81.8% yield) was obtained by removal of organic solvent under reduced pressure, which was used for next reaction without purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 2.74 (1H, q, *J* = 2.8 Hz), 3.14 (1H, dd, *J* = 4.0 Hz, 5.2 Hz), 3.82 (1H, dd, *J* = 2.4 Hz, 4.0 Hz), 7.15 (2H, d, *J* = 8.4 Hz), 7.47 (2H, d, *J* = 8.8 Hz).

#### Step 2: The synthesis of 2-azido-2-(4-bromophenyl)ethanol

**[00204]** To a stirred suspension of 2-(4-bromophenyl)oxirane (5.0 g, 25.3 mmol) in distilled water (70 mL) was added the sodium azide (3.28 g, 50.5 mmol), the resulting mixture was stirred at 60 °C for 4 hour and was monitored by TLC. After reaction completion, the mixture was extracted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in*

*vacuo* to give 2-azido-2-(4-bromophenyl)ethanol (5.5 g, 90.2 %) as pale yellow oils. The crude product was used for next step directly.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.94 (1H, s), 3.63-3.66 (2H, m), 4.57 (1H, dd, *J* = 5.2 Hz, 7.6 Hz), 7.15 (2H, d, *J* = 8.4 Hz), 7.46 (2H, d, *J* = 8.4 Hz).

Step 3: The synthesis of 2-amino-2-(4-bromophenyl)ethanol hydrochloride

**[00205]** To a solution of 2-azido-2-(4-bromophenyl)ethanol (2.0 g, 8.30 mmol) in tetrahydrofuran (20.0 mL) and water (5.00 mL) was added triphenylphosphine (4.35 g, 16.6 mmol). The reaction mixture was stirred at room temperature overnight and the solvent was removed *in vacuo*. The residue was dissolved in HCl/ dioxane (4M, 10.0 mL) and stirred at room temperature for 1 h. After being concentrated, the solid was washed with dichloromethane to give 2-amino-2-(4-bromophenyl)ethanol hydrochloride (1.5 g, 72.1 % yield) as white solids.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.70 (2H, s), 4.28 (1H, s), 5.55 (1H, s), 7.47 (2H, d, *J* = 8.4 Hz), 7.63 (2H, d, *J* = 8.4 Hz), 8.61 (3H, s); LC/MS 216.2 [M+H]<sup>+</sup>.

Step 4: The synthesis of 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine

**[00206]** To a solution of 2-amino-2-(4-bromophenyl)ethanol hydrochloride (1.80 g, 7.17 mmol) in dichloromethane (50 mL) was added imidazole (1.95 g, 2.87 mmol) and tert-butyldimethylsilyl chloride (TBSCl) (1.63 g, 10.8 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight and then quenched with water. The aqueous phase was extracted with dichloromethane (30 mL x 3), the combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude compound. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5:1) to give 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine (1.50 g, 63.6%) as white solids.

LC/MS: 330.1 [M+H]<sup>+</sup>;

Step 5: The synthesis of tert-butyl 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethylcarbamate

**[00207]** To a solution of 1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethanamine (1.50 g, 4.56 mmol) in tetrahydrofuran (20 mL) was added triethylamine (0.69 g, 6.84 mmol) and di-tert-butyl dicarbonate (1.49 g, 6.84 mmol). The reaction mixture was stirred at room temperature overnight and then quenched with water. The aqueous phase was extracted with ethyl acetate (50 mL x 3) and washed with brine. The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude compound. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100:1) to give tert-butyl

1-(4-bromophenyl)-2-(tert-butyldimethylsilyloxy)ethylcarbamate (1.80 g, 92.0%) as pale yellow oils.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.01 (6H, d, *J* = 9.6 Hz), 0.86 (9H, s), 1.42 (9H, s), 3.65-3.70 (2H, m), 4.60-4.63 (1H, m), 7.34 (2H, d, *J* = 8.0 Hz), 7.39 (1H, d, *J* = 8.8 Hz), 7.56 (2H, d, *J* = 8.4 Hz).

Step 6: The synthesis of tert-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)-ethylcarbamate

**[00208]** A mixture of *tert*-butyl 1-(4-bromophenyl)-2-(*tert*-butyldimethylsilyloxy)ethylcarbamate (4.0 g, 9.32 mmol), 4-methylthiazole (1.85 g, 18.6 mmol), potassium acetate (1.82 g, 18.6 mmol), palladium (II) acetate (0.11 g, 0.47 mmol) were dissolved in dimethylacetamide and stirred under argon. The mixture was heated to 140 °C and stirred for 15 hours, then diluted with water. The aqueous phase was extracted with ethyl acetate (50 mL x 3) and washed with brine. The combined organic layer was dried over sodium sulfate, filtered and concentrated under vacuum to give crude compound which was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 100:1) to give *tert*-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl) ethylcarbamate (1.30 g, 41.8%) as pale yellow solids.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.38 (9H, s), 2.46 (3H, s), 3.52 (2H, t, *J* = 6.0 Hz), 4.55-4.58 (1H, m), 4.84 (1H, t, *J* = 6.0 Hz), 7.30 (1H, d, *J* = 8.0 Hz), 7.38-7.45 (4H, m), 8.99 (1H, s); LC/MS 335.2 [M+H]<sup>+</sup>; Rt = 1.859 min

Step 7: The synthesis of 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride

**[00209]** The *tert*-butyl 2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamate (300 mg, 0.536 mmol) was dissolved in hydrochloric acid/dioxane (5 mL, 4M). The resulting reaction mixture was stirred at room temperature for 3 h. The solvent was concentrated *in vacuo* to give 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride as white solids, which was used for the next step without further purification.

Step 8: The synthesis of *tert*-butyl

N-[(2S)-1-[(2S,4R)-4-hydroxy-2-[(1R)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**ULM-5-A**) and *tert*-butyl N-[(2S)-1-[(2S,4R)-4-hydroxy-2-[(1S)-2-hydroxy-1-[4-(4-methyl-1,3-thiazol-5-yl)phenyl]ethyl]carbamoyl]pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl]carbamate (**ULM-5-B**)

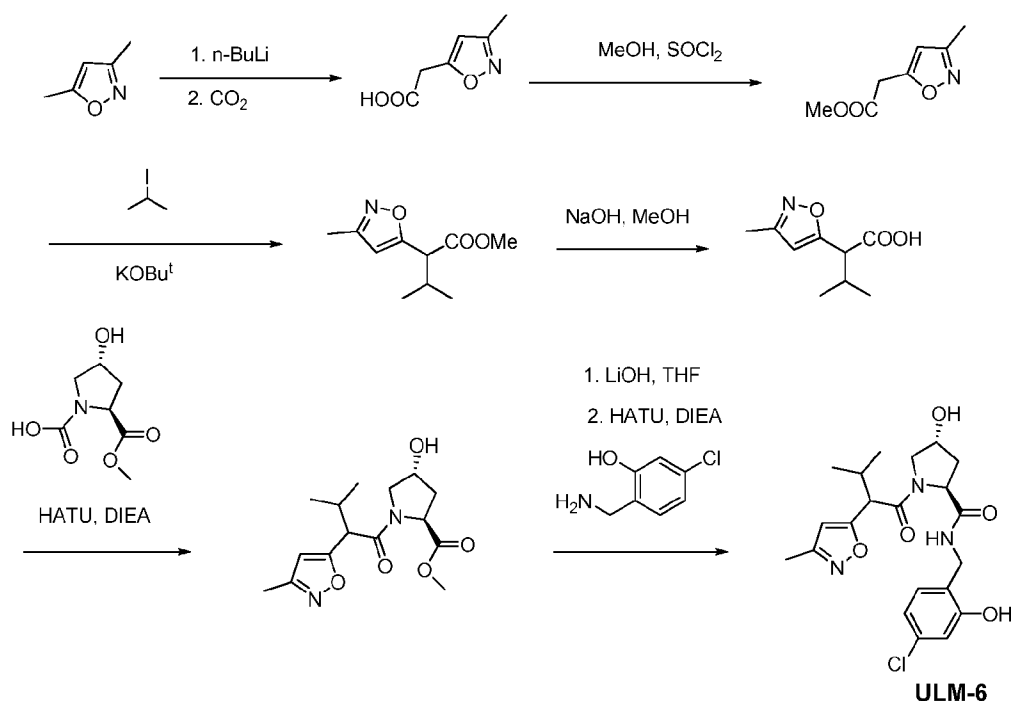
**[00210]** A solution of 2-amino-2-(4-(4-methylthiazol-5-yl)phenyl)ethanol hydrochloride (1000 mg, 3.70 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) (995 mg, 5.19 mmol), 1-hydroxybenzotriazole (HOBT) (695 mg, 5.19 mmol), (2*S*,4*R*)-1-((*S*)-2-(tert-butoxycarbonylamino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylic acid (1273 mg, 3.70 mmol) and triethylamine (747 mg, 7.40 mmol) in *N,N*-dimethylformamide (50 mL) was stirred at room temperature overnight under argon, and then water (80 mL) was added to the mixture. The aqueous layer was extracted with ethyl acetate (50 mL x 5). The combined organic layer was washed with brine (50 mL x 3), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The crude product was purified by preparative TLC (dichloromethyl/methanol = 15:1) to give tert-butyl (*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((*R*)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethylcarbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (700 mg) as pale yellow oils and tert-butyl (*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((*S*)-2-hydroxy-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-ylcarbamate (500 mg) as pale yellow oils.

**[00211] ULM-5-A:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.93 (9H, s), 1.39 (9H, s), 1.77-1.83 (1H, m), 2.01-2.06 (1H, m), 2.46 (3H, s), 3.54-3.60 (4H, m), 4.13-4.19 (1H, m), 4.29-4.36 (1H, m), 4.50 (1H, t, *J* = 8.0 Hz), 4.78 (1H, t, *J* = 5.6 Hz), 4.81-4.88 (1H, m), 5.12-5.16 (1H, m), 6.46 (1H, d, *J* = 9.2 Hz), 7.36-7.46 (4H, m), 8.41 (1H, d, *J* = 8.0 Hz), 8.99 (1H, s); LC/MS 561.2 [M+H]<sup>+</sup>; Rt = 1.897 min

**[00212] ULM-5-B:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.87 (9H, s), 1.38 (9H, s), 1.92-2.06 (2H, m), 2.45 (3H, s), 3.56-3.69 (4H, m), 4.06-4.14 (1H, m), 4.36 (1H, s), 4.56 (1H, t, *J* = 7.6 Hz), 4.76-4.81 (1H, m), 4.87 (1H, t, *J* = 5.6 Hz), 5.146 (1H, d, *J* = 2.8 Hz), 6.47 (1H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.0 Hz), 8.37 (1H, d, *J* = 7.6 Hz), 8.98 (1H, s); LC/MS 561.2 [M+H]<sup>+</sup>; Rt = 1.887 min

**Intermediate7:**

**(2*S*,4*R*)-*N*-[(4-chloro-2-hydroxyphenyl)methyl]-4-hydroxy-1-[3-methyl-2-(3-methyl-1,2-oxazol-5-yl)butanoyl]pyrrolidine-2-carboxamide (ULM-6)**



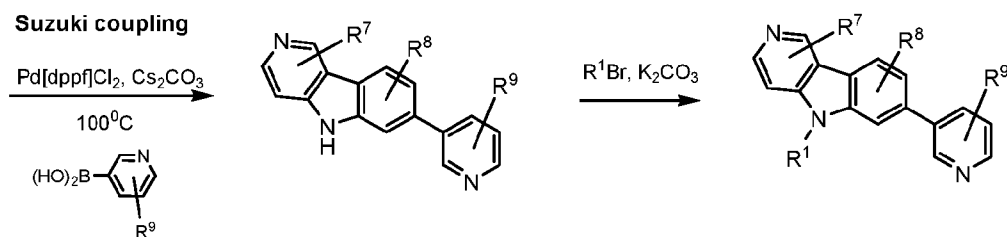
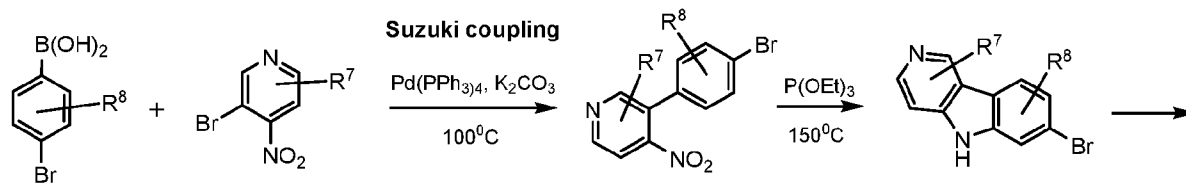
**[00213]** This key intermediate was prepared using the synthetic route above. The required 3-methylisoxazole-5-acetic acid was prepared according to the literature (J. Org. Chem. 66, 6595-6603, 2001). The alkylation with 2-iodopropane has been described in the literature. The desired ULM-6 was prepared using the same synthetic method as described in the preparation of intermediate ULM-3.

**[00214]**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) :  $\delta$  9.33 (s, 0.5H), 9.20 (s, 0.5H), 8.07(t,  $J = 6.4$  Hz, 0.5H), 7.83(t,  $J = 6.0$  Hz, 0.5H), 6.99(dd,  $J = 2.4, 8.0$  Hz, 1H), 6.89-6.90(m, 1H), 6.76-6.78 (m, 1H), 6.02(s, 0.5H), 5.99(s, 0.5H), 5.80-5.83(m, 0.5H), 4.35(q,  $J = 6.4$  Hz, 1.5), 4.16-4.25(m, 2H), 3.72-3.76(m, 0.5H), 3.61(d,  $J = 9.2$  Hz, 1.0H), 3.51-3.55(m, 1.5H), 2.30-2.46(m, 2.5H), 2.26(s, 1.5H), 2.24(s, 1.5H), 1.95-2.05(m, 1H), 1.01(d,  $J = 6.8$  Hz, 1.5H), 0.82-0.87(m, 4.5H); LC-MS 436.1  $[\text{M}+1]^+$ ;  $R_t = 3.57$  min.

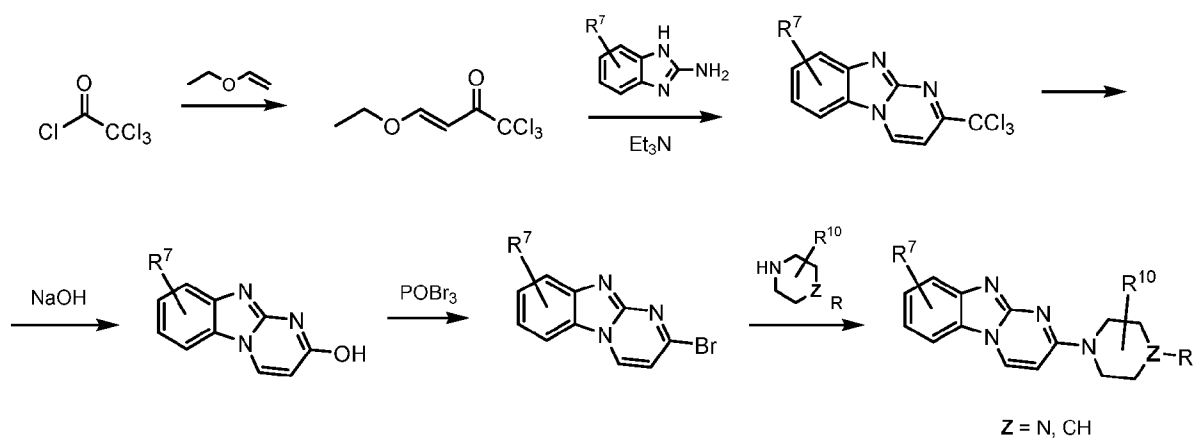
#### PTM Synthesis:

**[00215]** Preferred PTM embodiments of the current invention can be prepared according to the synthetic routes in schemes 1–3 below. These routes can be modified and adapted to the synthesis of the particular PTM embodiment using general methods known to those skilled in the art.

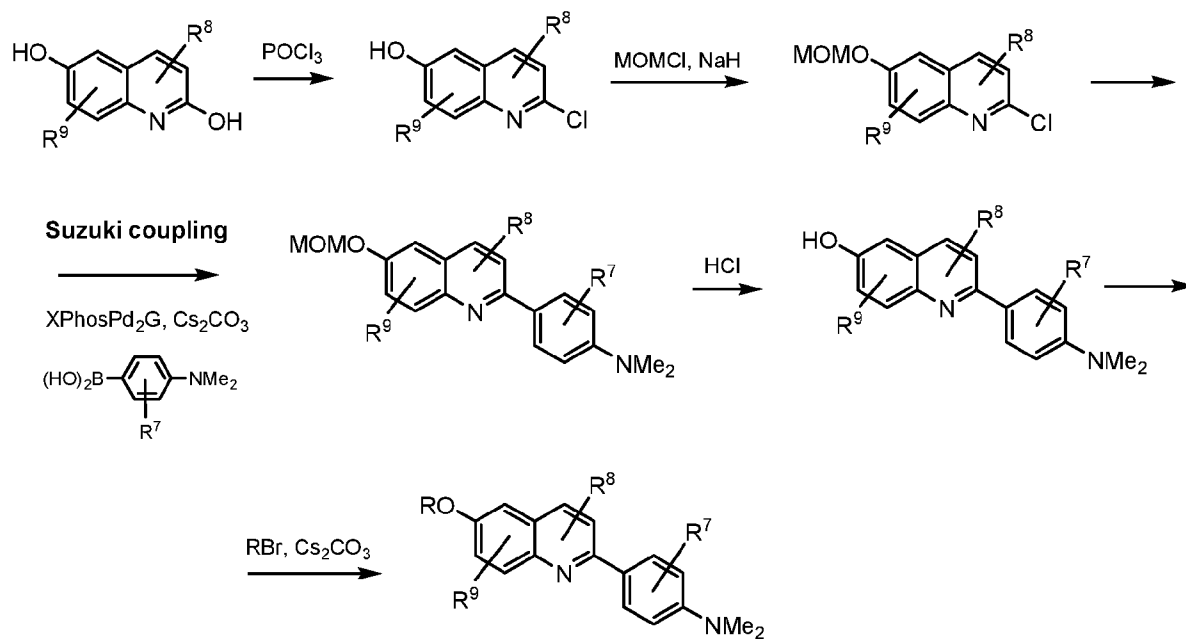
**[00216]**



**Scheme 1**



**Scheme 2**



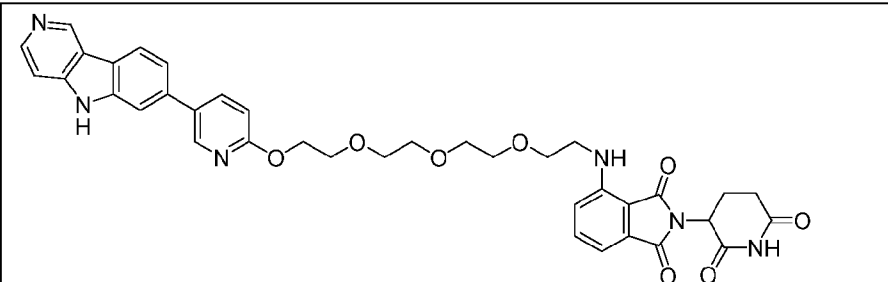
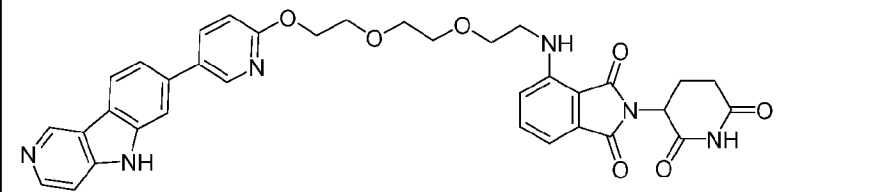
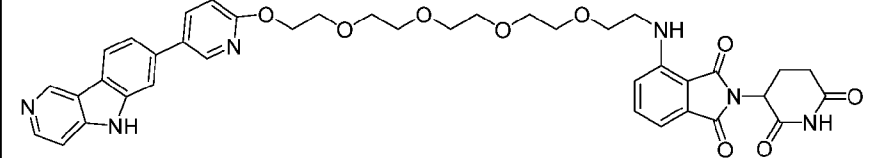
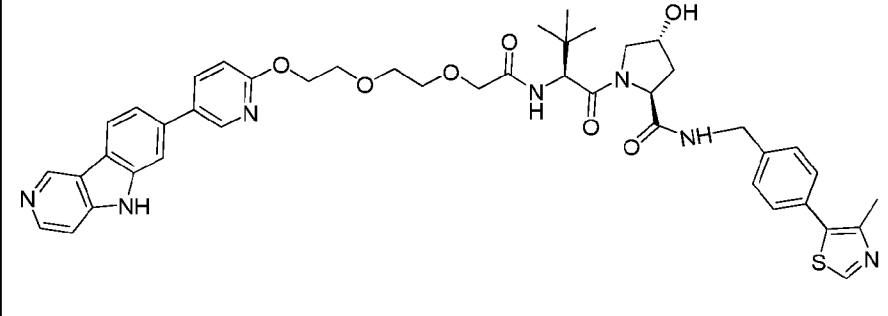
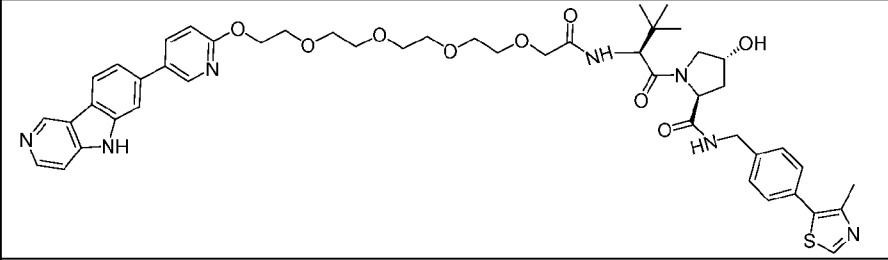
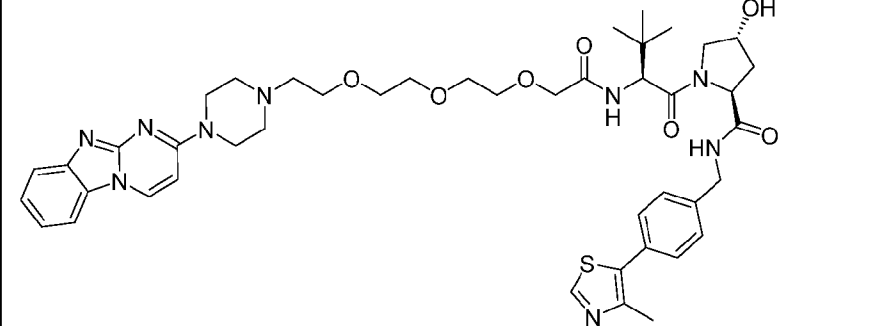
**Scheme 3**

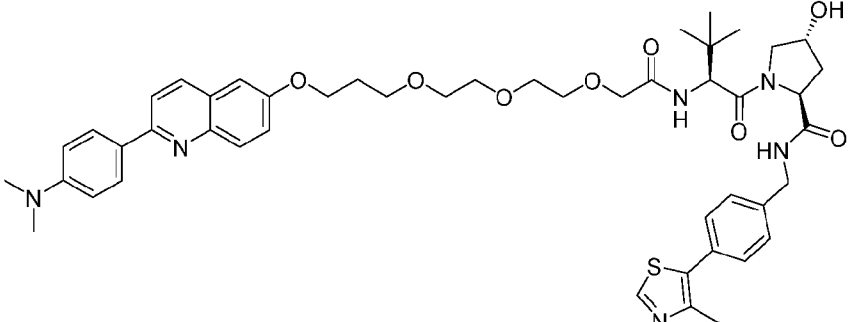
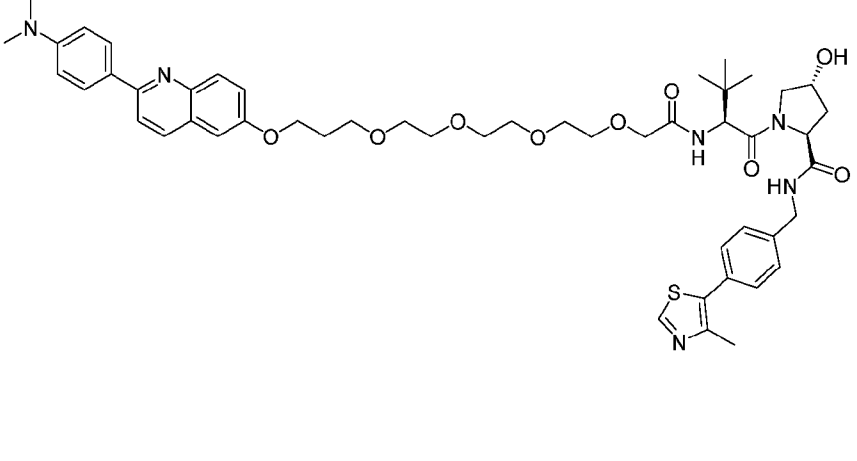
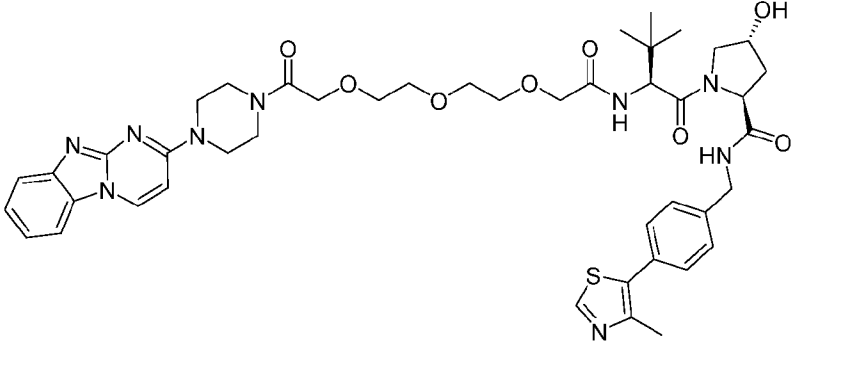
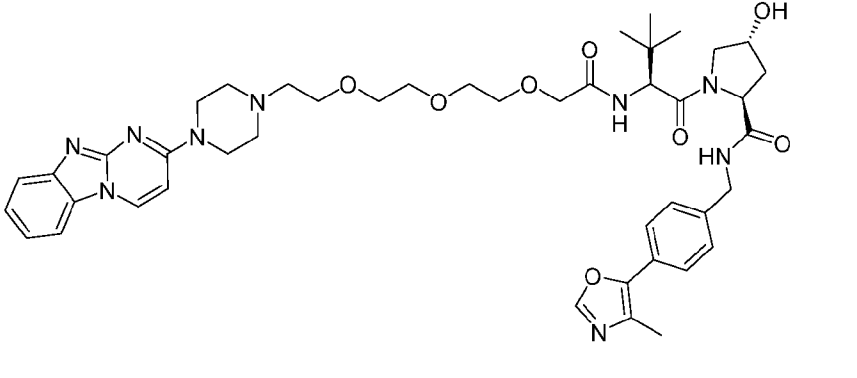
**[00217]** Preferred PROTAC embodiments of the current invention can be prepared from the PTM embodiments of the current invention using the methods of linker and E3 ligase-binding moiety attachment previously described.

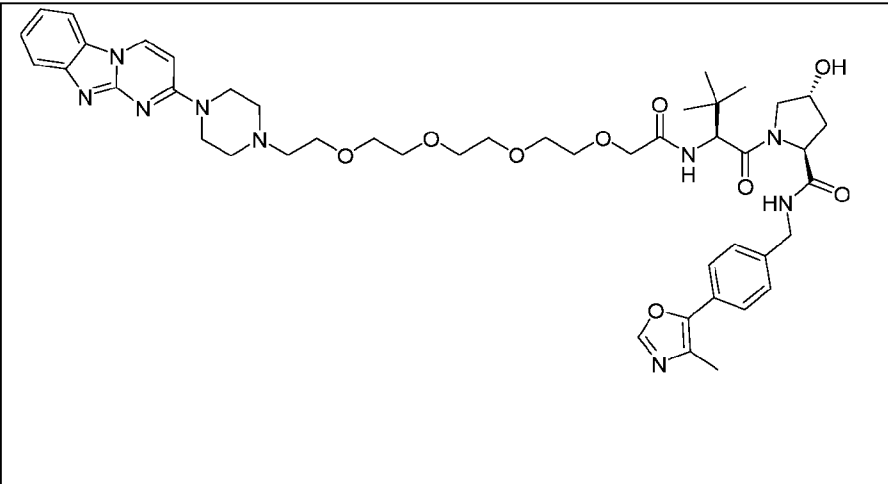
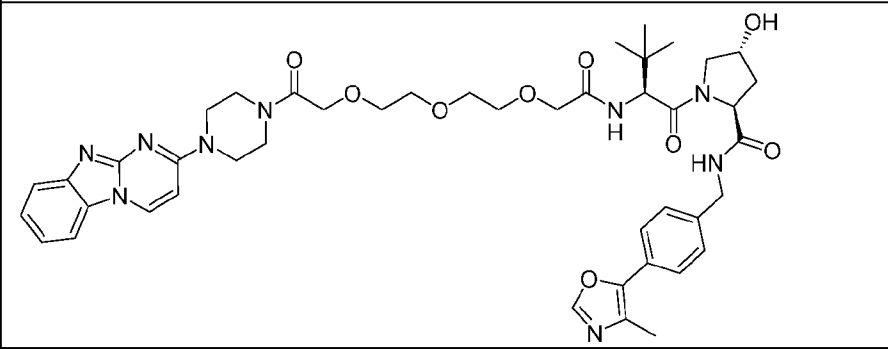
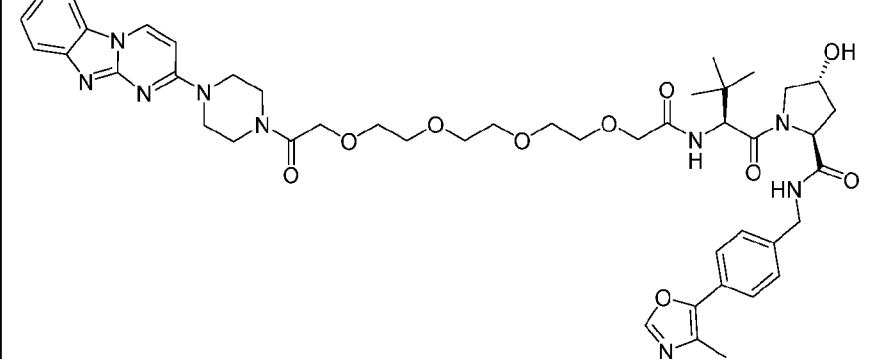
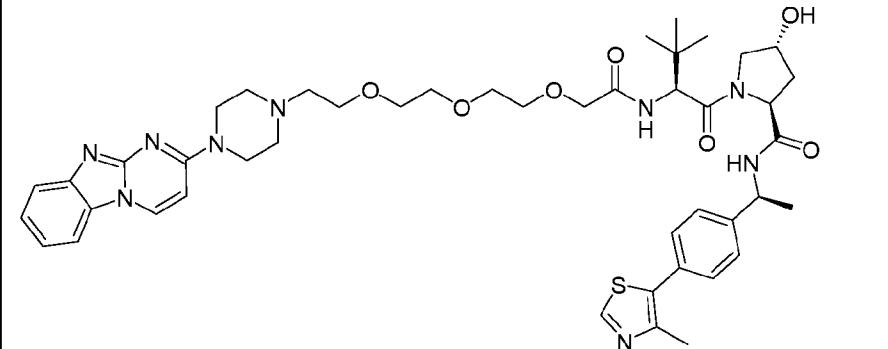
**[00218]** Most preferred PROTAC embodiments of the current invention are represented by the structures in Table 1.

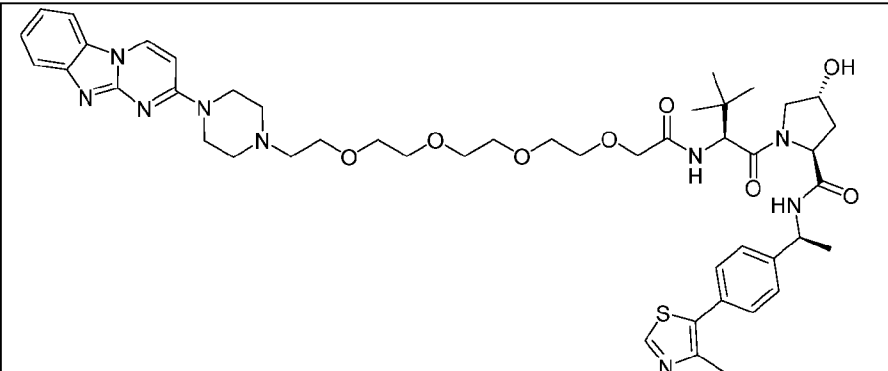
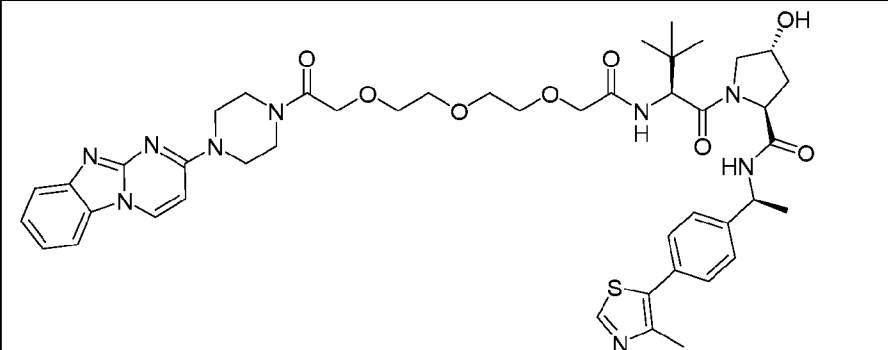
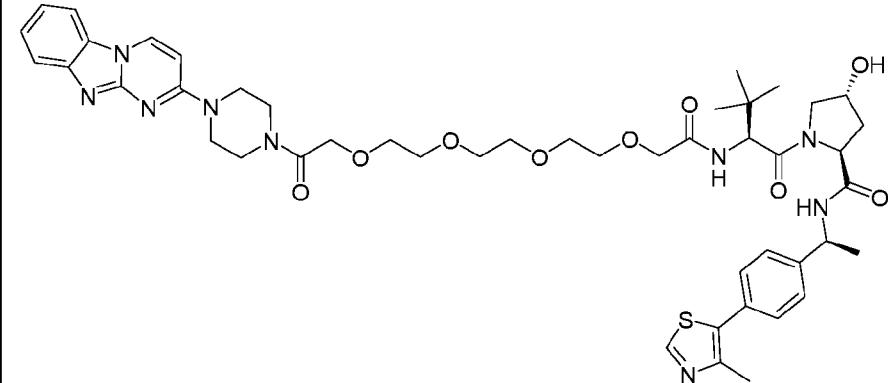
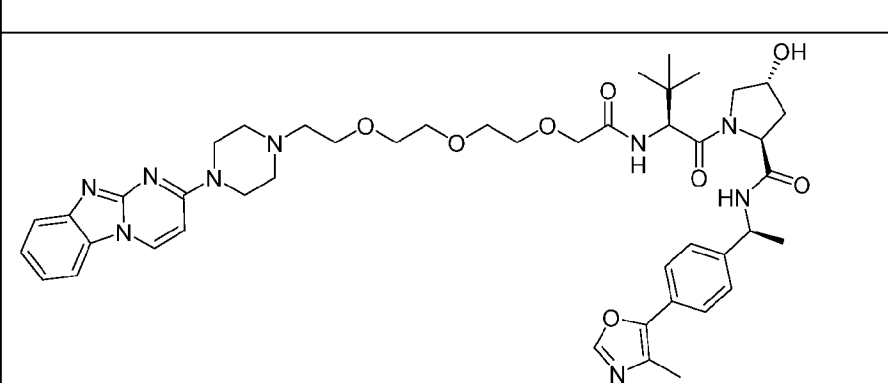
**[00219]** Table 1. **Most preferred PROTAC embodiments of the invention.**

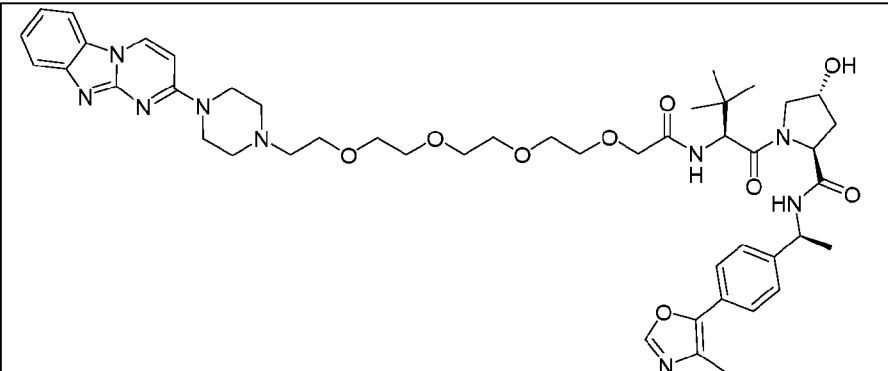
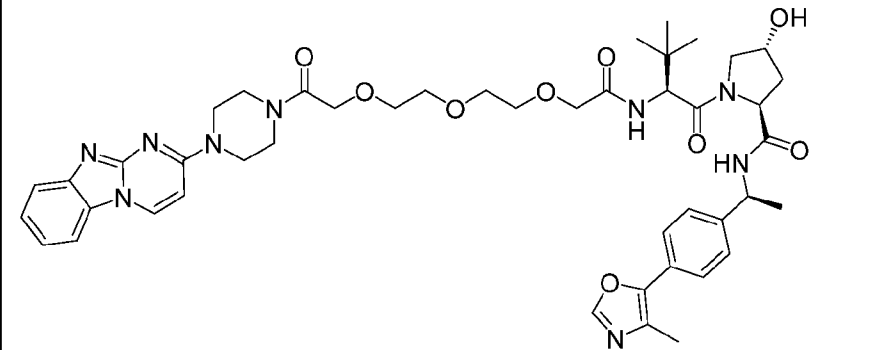
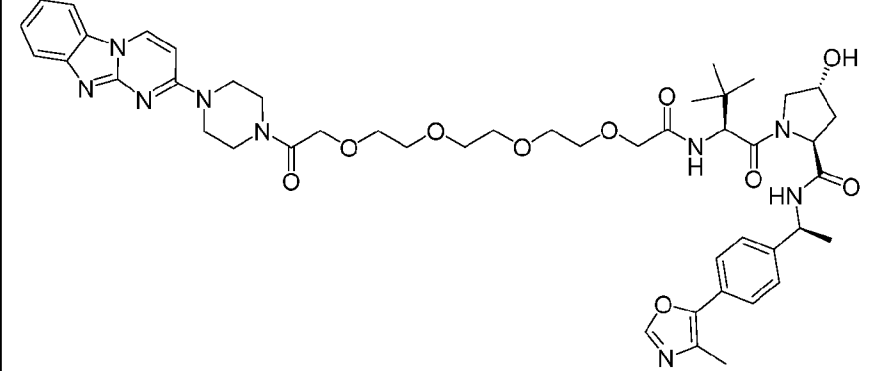
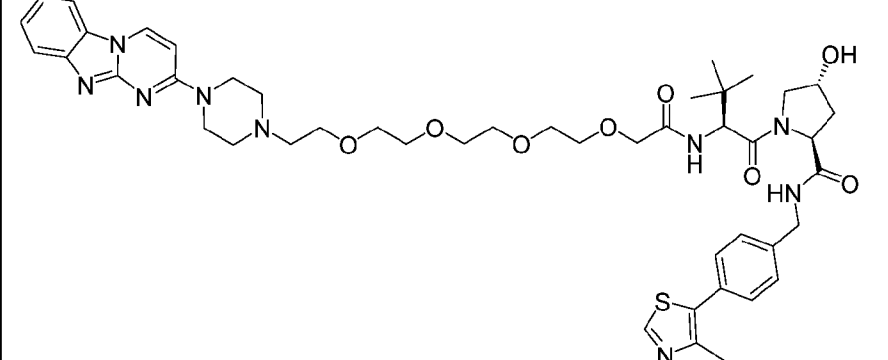
| Example | Structure | (M+H) <sup>+</sup> |
|---------|-----------|--------------------|
| 1       |           | 864.3              |

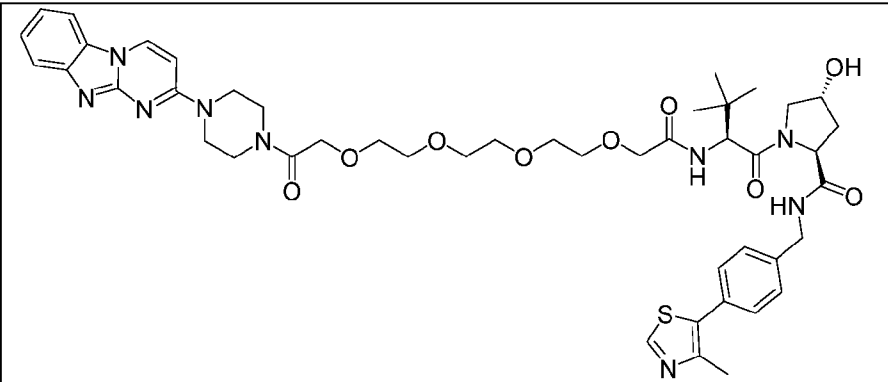
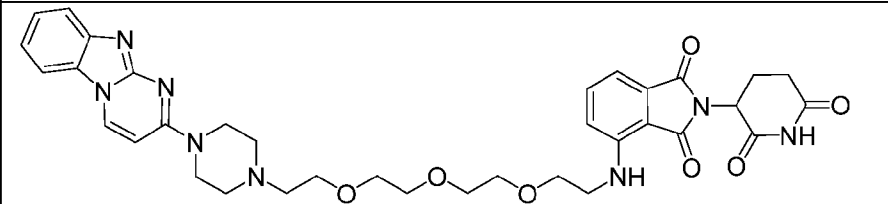
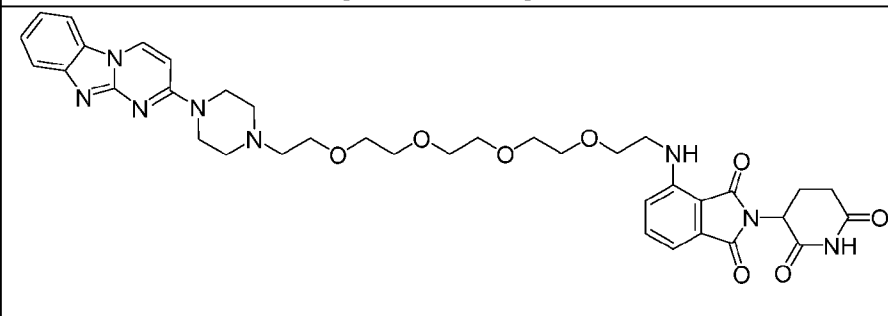
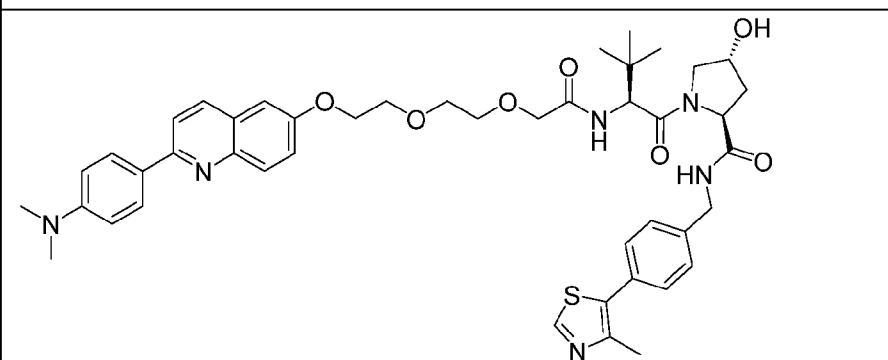
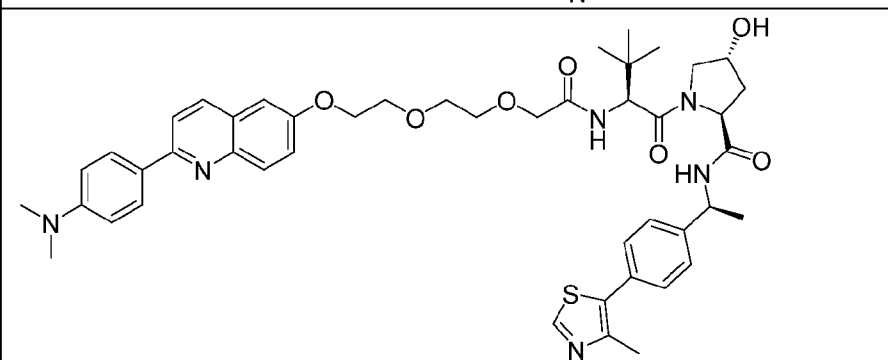
|   |                                                                                      |       |
|---|--------------------------------------------------------------------------------------|-------|
| 2 |    | 693.3 |
| 3 |    | 649.3 |
| 4 |    | 737.4 |
| 5 |   | 820.4 |
| 6 |  | 908.4 |
| 7 |  | 856.5 |

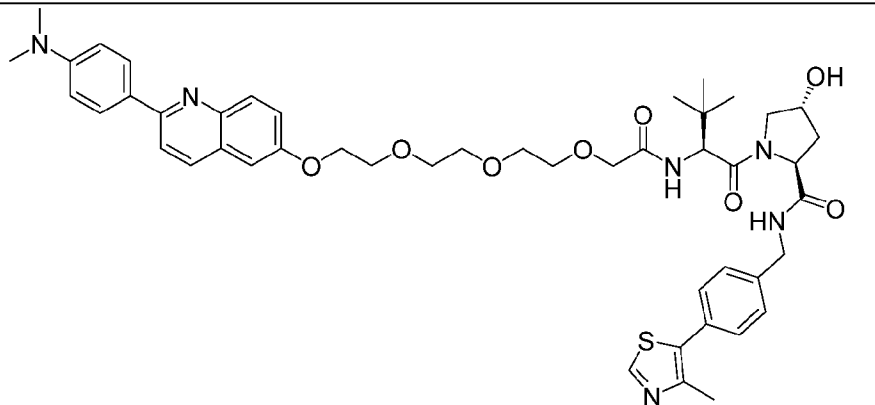
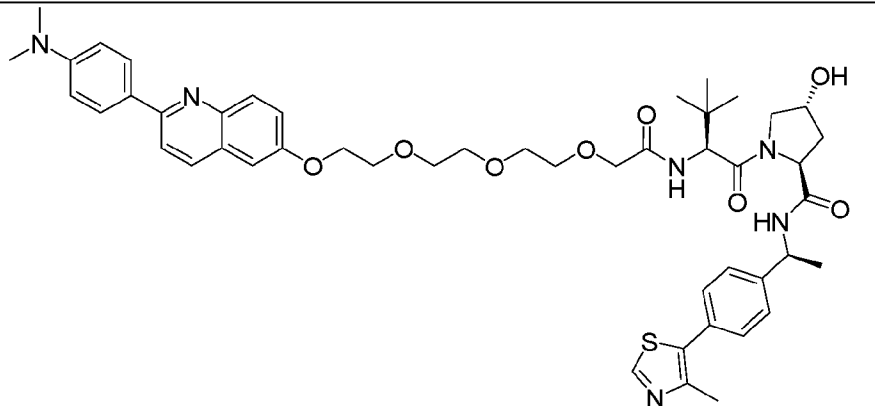
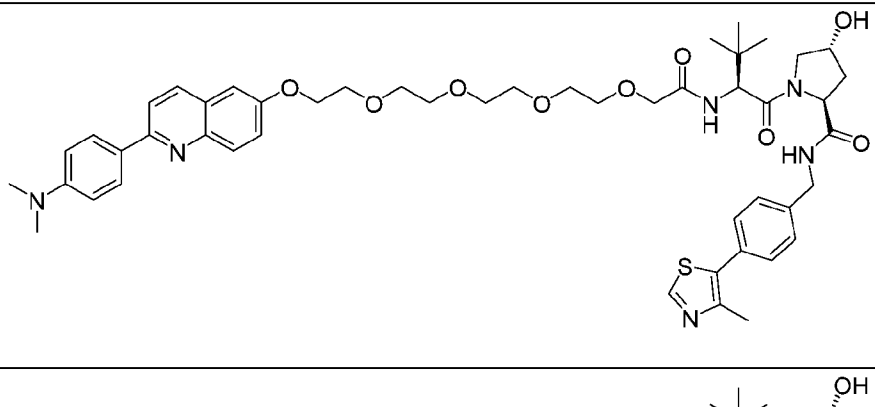
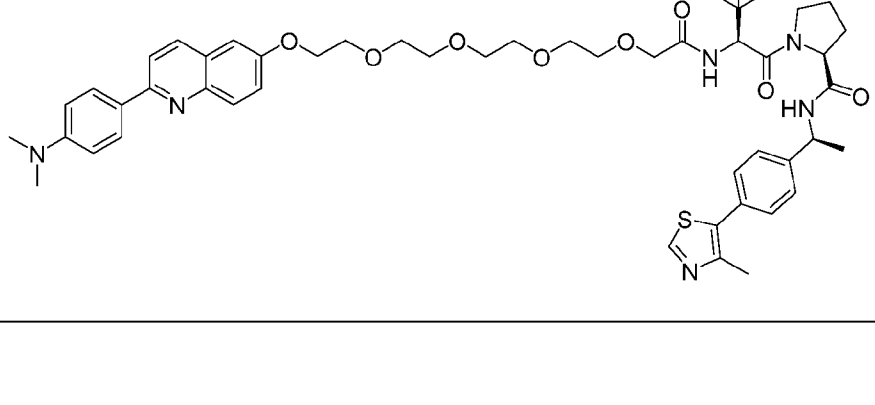
|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 8  |    | 881.6 |
| 9  |   | 925.6 |
| 10 |  | 870.5 |
| 11 |  | 840.6 |

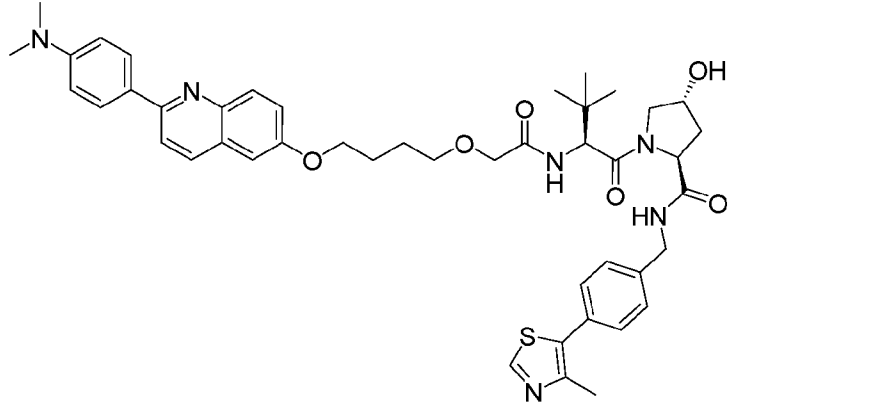
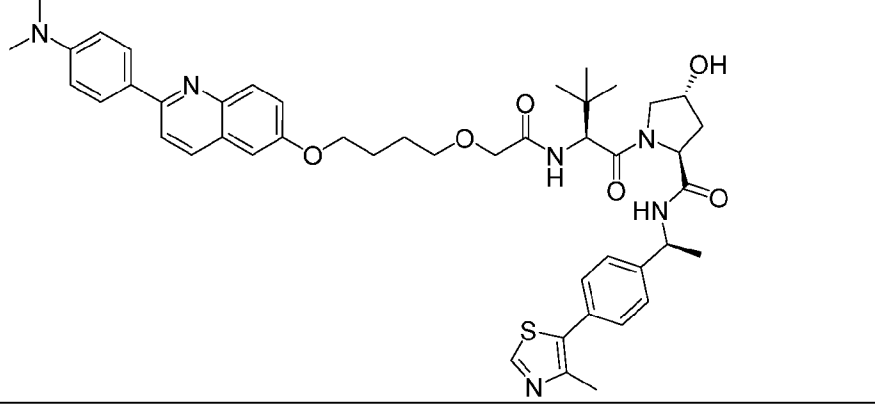
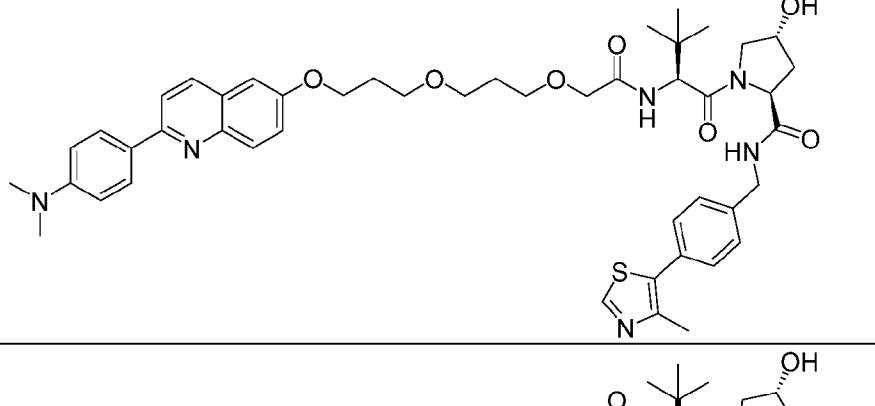
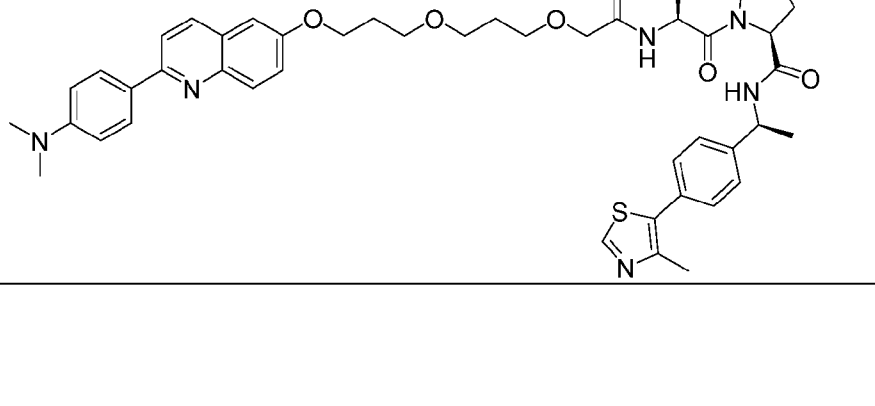
|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 12 |    | 884.4 |
| 13 |   | 854.5 |
| 14 |  | 898.6 |
| 15 |  | 870.6 |

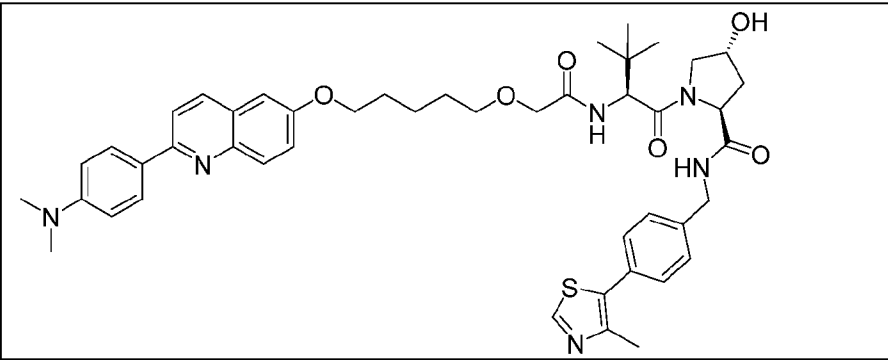
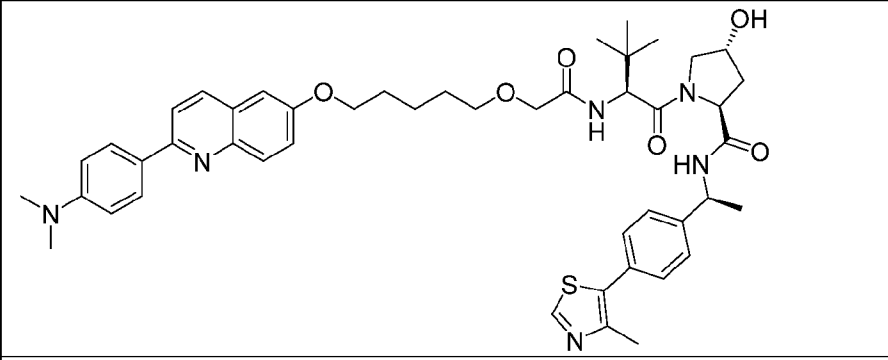
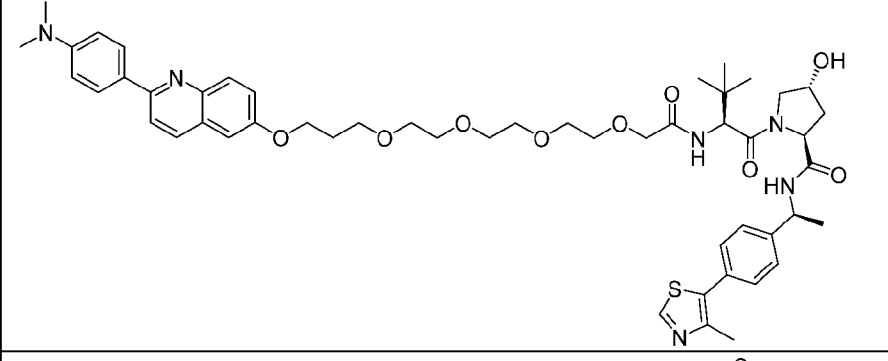
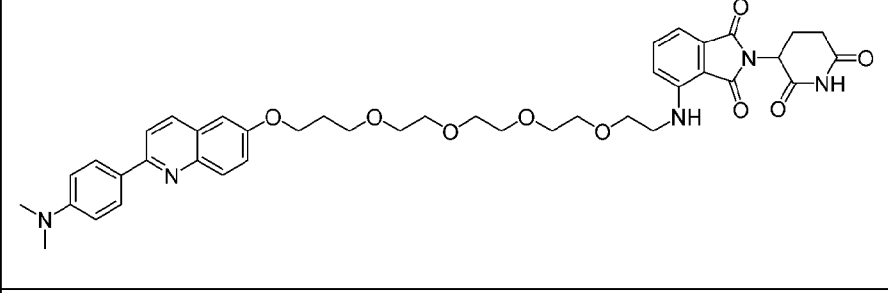
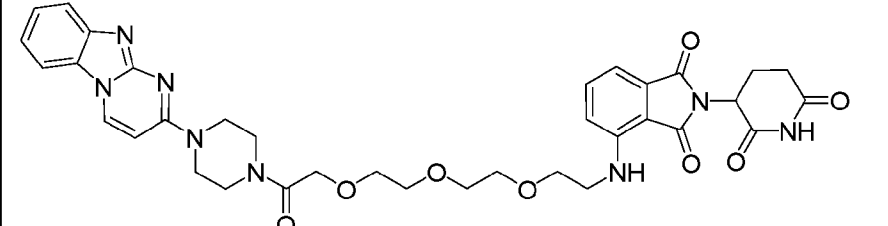
|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 16 |    | 914.6 |
| 17 |   | 884.5 |
| 18 |  | 928.7 |
| 19 |  | 854.6 |

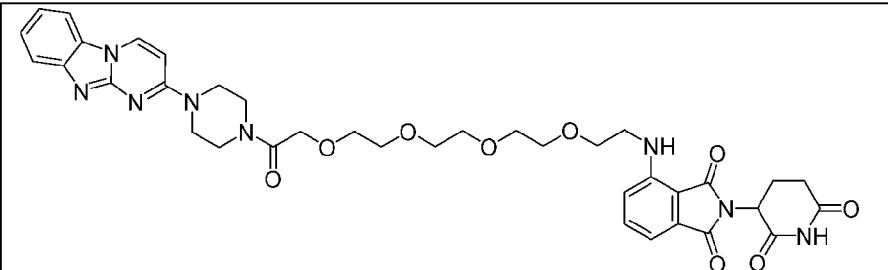
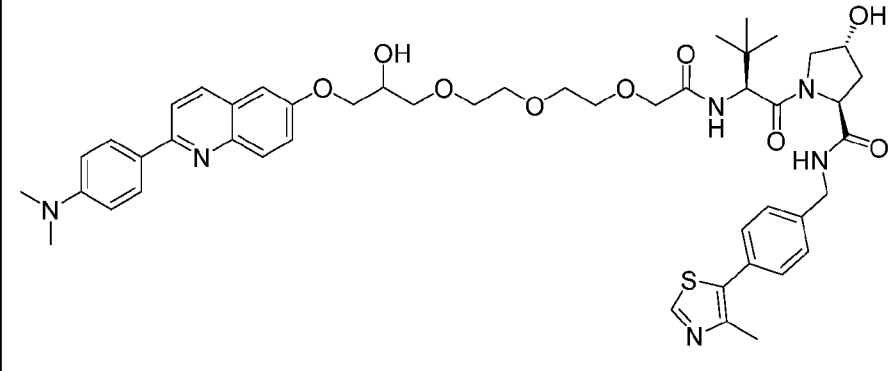
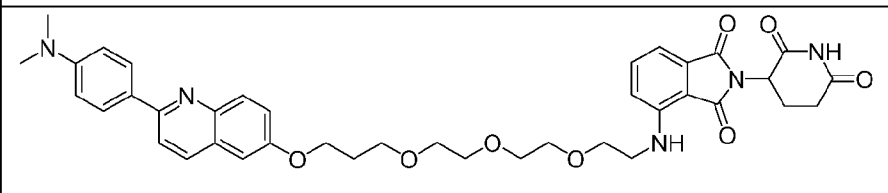
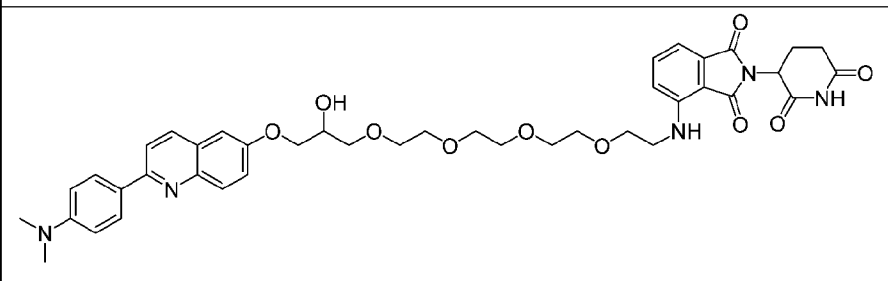
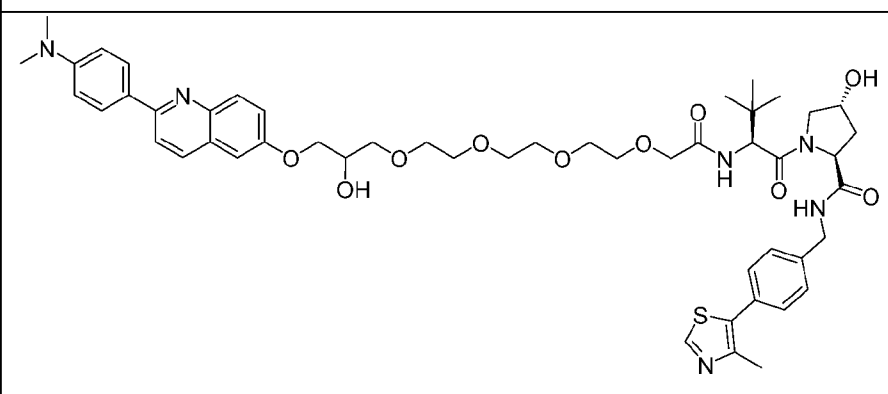
|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 20 |    | 898.6 |
| 21 |   | 868.3 |
| 22 |  | 912.6 |
| 23 |  | 900.6 |

|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 24 |    | 914.6 |
| 25 |    | 685.4 |
| 26 |   | 729.4 |
| 27 |  | 823.7 |
| 28 |  | 837.7 |

|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 29 |    | 867.7 |
| 30 |   | 881.4 |
| 31 |  | 911.4 |
| 32 |  | 925.4 |

|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 33 |    | 807.4 |
| 34 |   | 821.4 |
| 35 |  | 851.4 |
| 36 |  | 865.6 |

|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 37 |    | 821.4 |
| 38 |    | 835.4 |
| 39 |   | 939.4 |
| 40 |  | 754.4 |
| 41 |  | 699.4 |

|    |                                                                                      |       |
|----|--------------------------------------------------------------------------------------|-------|
| 42 |    | 743.7 |
| 43 |    | 897.4 |
| 44 |   | 710.3 |
| 45 |  | 770.3 |
| 46 |  | 941.4 |

|    |  |       |
|----|--|-------|
| 47 |  | 726.3 |
| 48 |  | 751.2 |
| 49 |  | 723.3 |
| 50 |  | 724.3 |

<sup>†</sup>(M-H)<sup>-</sup> (ES-API negative)

### Tau Protein In Vitro Degradation Assay

**[00220]** To determine effect of PROTACs on tau protein degradation SK-N-SH cells were seeded in a 24-well tissue culture-treated plate for at least 18-hours prior to compound addition. Tau PROTACs were evaluated for tau degradation by lysing the cells in RIPA buffer with protease inhibitors following a 72-hour incubation with tau PROTACs. Cell lysates were run on standard SDS-PAGE gels, and tau levels were detected by Western blotting using Tau-13 antibody from Abcam (Cambridge, UK) that binds to all forms of human tau.

**[00221]** Tau protein degradation data for select examples from Table 1 is presented in Table 2 below.

Table 2. **Tau protein degradation data**

| Example | Degradation activity at 1 $\mu$ M <sup>*</sup> | DC <sub>50</sub> , nM |
|---------|------------------------------------------------|-----------------------|
| 1       | B                                              | ND <sup>**</sup>      |
| 2       | A                                              | 28                    |
| 3       | A                                              | ND                    |
| 4       | A                                              | 70                    |

|    |   |     |
|----|---|-----|
| 11 | B | ND  |
| 28 | B | ND  |
| 35 | B | ND  |
| 38 | B | ND  |
| 41 | B | ND  |
| 43 | B | ND  |
| 48 | A | 115 |
| 50 | A | ND  |

\* A: <50% tau protein remaining after 72 hours of incubation; B: >50% tau protein remaining after 72 hours of incubation.

\*\* ND = not determined.

### **Tau Protein In Vivo Degradation**

**[00222]** In the study 21 male B16 wildtype mice, divided into seven groups of three mice, were treated single time via a bilateral intrahippocampal injection with vehicle ECP-1 ([5% EtOH and 5% Cremophore RH40 in pH 7.4 phosphate buffer]; group A; see Figure 1) or **example 4** tau PROTAC ([3 µL of 1 mg/mL solution in ECP-1]; groups B to G; see Figure 1). All animals were sacrificed at certain time points after the test item or vehicle injection as shown in Figure 1, and brain samples were collected. The hippocampus was resected, and levels of total tau were measured with MSD. Results are presented in Figure 1.

## **ABSTRACT**

The present invention relates to bifunctional compounds, which find utility as modulators of tau protein. In particular, the present disclosure is directed to bifunctional compounds, which contain on one end a VHL or cereblon ligand which binds to the E3 ubiquitin ligase and on the other end a moiety which binds tau protein, such that tau protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of tau. The present disclosure exhibits a broad range of pharmacological activities associated with degradation/inhibition of tau protein. Diseases or disorders that result from aggregation or accumulation of tau protein are treated or prevented with compounds and compositions of the present disclosure.

## Electronic Acknowledgement Receipt

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| <b>Application Number:</b>                  | 62415830                                                    |
| <b>International Application Number:</b>    |                                                             |
| <b>Confirmation Number:</b>                 | 6478                                                        |
| <b>Title of Invention:</b>                  | TAU-PROTEIN TARGETING PROTACS AND ASSOCIATED METHODS OF USE |
| <b>First Named Inventor/Applicant Name:</b> | Andrew P. Crew                                              |
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|-----------------|-----------------------------------------------------|-----------------------------|-------------------------------------------|------------------|------------------|
| 1               | Provisional Cover Sheet (SB16)                      | 121US0_ProvisionalCover.pdf | 1486582                                   | no               | 4                |
|                 |                                                     |                             | 9c2f751fd7367c81aac29045135a3b84957f513e  |                  |                  |
| Warnings:       |                                                     |                             |                                           |                  |                  |
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| 2               | Application Data Sheet                              | 121US0_ADS.pdf              | 1845383                                   | no               | 9                |
|                 |                                                     |                             | fc953124e5da28e0e09987074560bd9317ff3cd   |                  |                  |
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| 3               | Drawings-only black and white line drawings         | 121US0_Drawing.pdf          | 58233                                     | no               | 1                |
|                 |                                                     |                             | f5acada85d678c2cd7403199e5606d2873fa4998  |                  |                  |
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| 4               | Claims                                              | 121US0_Claims_asFiled.pdf   | 814214                                    | no               | 61               |
|                 |                                                     |                             | 0fc6e68c4714bf7b83bd376141292308f36309ff  |                  |                  |
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| 5               |                                                     | 121US0_Spec_Abstr.pdf       | 1437322                                   | yes              | 129              |
|                 |                                                     |                             | 100476a91316c855311294a290e0fc991a848830b |                  |                  |
|                 | Multipart Description/PDF files in .zip description |                             |                                           |                  |                  |
|                 | Document Description                                |                             | Start                                     | End              |                  |
|                 | Specification                                       |                             | 1                                         | 128              |                  |
|                 | Abstract                                            |                             | 129                                       | 129              |                  |
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| 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Fee Worksheet (SB06) | fee-info.pdf | <div>31501</div> <div>e4c5dc85993fedd5a33ccf13c85166e88a1b06b3</div> | no | 2 |
| <b>Warnings:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                      |              |                                                                      |    |   |
| <b>Information:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                      |              |                                                                      |    |   |
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