



(51) International Patent Classification:

A61P 35/00 (2006.01) C07D 471/10 (2006.01)
C07D 239/22 (2006.01) C07D 471/14 (2006.01)
C07D 401/06 (2006.01) C07D 487/14 (2006.01)
C07D 401/12 (2006.01) A61K 31/513 (2006.01)
C07D 401/14 (2006.01)

(21) International Application Number:

PCT/IB2020/058535

(22) International Filing Date:

14 September 2020 (14.09.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/901,161 16 September 2019 (16.09.2019) US
62/905,849 25 September 2019 (25.09.2019) US

(71) Applicant: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35,
4056 Basel (CH).(72) Inventors: **ARISTA, Luca**; Schützenrainweg 6, 4125
Riehen (CH). **BROENNIMANN, Valerie**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **D'ALESSANDRO,**

Pier Luca; Novartis Pharma AG, Postfach, 4002 Basel (CH). **DOUMAMPOUOM-METOUL, Lionel**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **GOUDE, Marie-Line**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **HEBACH, Christina**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **HOLLINGWORTH, Gregory John**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **JEULIN, Ingrid Karen Jennifer**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **KIRMAN, Louise Clare**; 35 Elmwood Road, Swampscott, Massachusetts 01907 (US). **LORBER, MA, Fupeng**; Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **VULPETTI, Anna**; Novartis Pharma AG, Postfach, 4002 Basel (CH). **YAMADA, Ken**; Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, Massachusetts 02139 (US). **ZOLLER, Thomas**; Novartis Pharma AG, Postfach, 4002 Basel (CH).

(74) Agent: **NOVARTIS AG**; Lichtstrasse 35, 4056 Basel (CH).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

(54) Title: BIFUNCTIONAL DEGRADERS AND THEIR METHODS OF USE

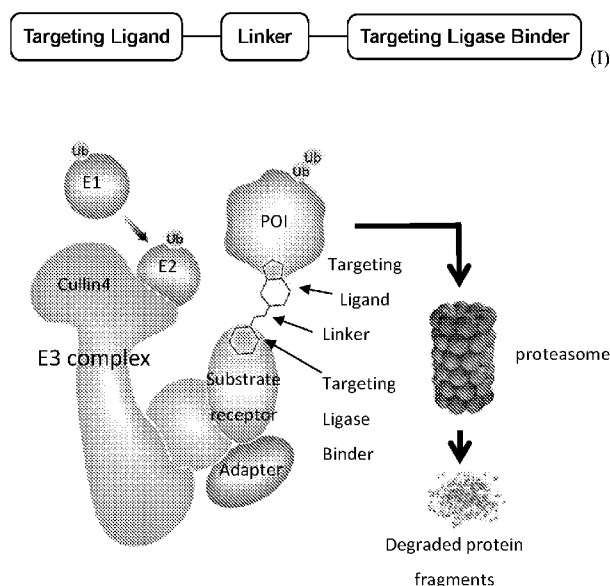


FIG. 1

(57) **Abstract:** Described herein are bifunctional degrader compounds, their various targets, their preparation, pharmaceutical compositions comprising them, and their use in the treatment of conditions, diseases, and disorders mediated by various target proteins.



AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- *with international search report (Art. 21(3))*
- *with sequence listing part of description (Rule 5.2(a))*
- *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

BIFUNCTIONAL DEGRADERS AND THEIR METHODS OF USE

CLAIM OF PRIORITY

This application claims the benefit of priority to U.S. Provisional Application No. 62/901,161 filed September 16, 2019 and U.S. Provisional Application No. 62/905,849 filed September 25, 2019, the disclosure of each of which is incorporated by reference herein in its entirety.

FIELD OF THE DISCLOSURE

Described herein are bifunctional degrader compounds, their various targets, their preparation, pharmaceutical compositions comprising them, and their use in the treatment of conditions, diseases, and disorders mediated by various target proteins.

REFERENCE TO A SEQUENCE LISTING

This application is filed with a Computer Readable Form of a Sequence Listing in accordance with 37 C.F.R. § 1.821(c). The text file submitted by EFS, "PAT058639-US-PSP_14293-889_sequence_listing.txt," was created on September 9, 2019, has a file size of 7 Kbytes, and is hereby incorporated by reference in its entirety.

BACKGROUND

The Ubiquitin-Proteasome Pathway (UPP) is a critical pathway that regulates key regulator proteins and degrades misfolded or abnormal proteins. UPP is central to multiple cellular processes, and if defective or imbalanced, it leads to pathogenesis of a variety of diseases. The covalent attachment of ubiquitin to specific protein substrates is achieved through the action of E3 ubiquitin ligases. These ligases comprise over 500 different proteins and are categorized into multiple classes defined by the structural element of their E3 functional activity.

Cereblon (CRBN) interacts with damaged DNA binding protein 1 and forms an E3 ubiquitin ligase complex with Cullin 4 where it functions as a substrate receptor in which the proteins recognized by CRBN might be ubiquitinated and degraded by proteasomes.

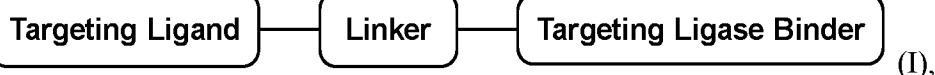
Proteasome-mediated degradation of unneeded or damaged proteins plays a very important role in maintaining regular cellular functions, such as cell survival, proliferation and growth. More

recently, CRBN has been identified as the target of immunomodulatory drugs (IMiDs) like thalidomide and lenalidomide and is associated with teratogenicity and also the cytotoxicity of IMiDs which are widely used to treat multiple myeloma patients. Krönke et al., *Science* 343: 301-305 (2014); Petzold et al., *Nature* 532:127-130 (2016); Bjorklund et al., *Blood Cancer J.* 5, e354 (2015); Lu et al., *Science* 343:305-309 (2014); Gandhi et al., *Br. J. Haematol.* 164: 811-821 (2014).

The principle of induced degradation of protein targets as a potential therapeutic approach has been described by Crews, *J. Med. Chem.* 61(2): 403-404 (2018) and references cited therein. There is a need for selective target protein degraders and the present application addresses the generation of bifunctional degrader molecules that are directed to a variety of protein targets for *in vivo* target validation and as therapeutics.

SUMMARY

In one aspect, the disclosure provides a bifunctional compound of Formula (I):



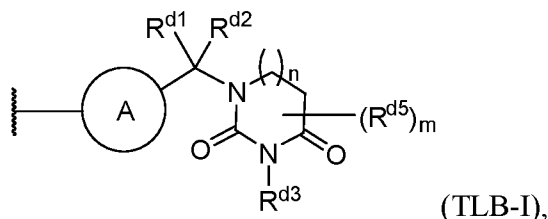
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

the Targeting Ligand is a group that is capable of binding to a Target Protein;

the Linker is a group that covalently links the Targeting Ligand to the Targeting Ligase Binder; and

the Targeting Ligase Binder is a group that is capable of binding to a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase).

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

5 R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

10 each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^p is H or C_{1-6} alkyl;

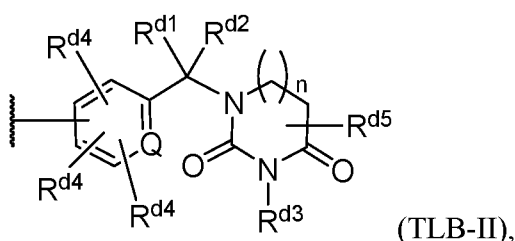
m is 1 or 2; and

15 n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, A is a 5-membered nitrogen-containing heteroaryl. In an embodiment, A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl or pyridonyl. In an embodiment, R^{d4} is hydroxyl or C_{1-6} alkoxy.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

Q is N or CR^{d4};

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

5 R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ heteroalkyl;

10 R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

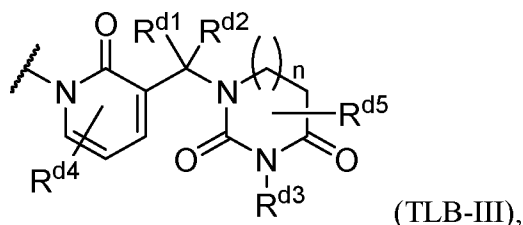
R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is -CH₂OP(O)(OR^p)₂.

15 In an embodiment, R^{d4} is hydroxyl or C₁₋₆ alkoxy.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

20  denotes the point of attachment to the Linker in Formula (I);

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

25 R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

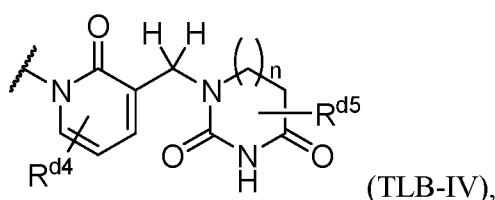
R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

- 5 In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-IV):



- 10 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

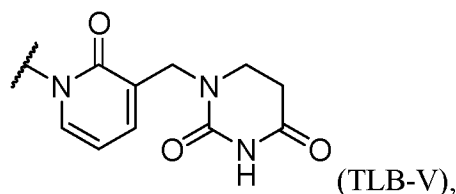
R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

- 15 R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl; and

n is 1 or 2.

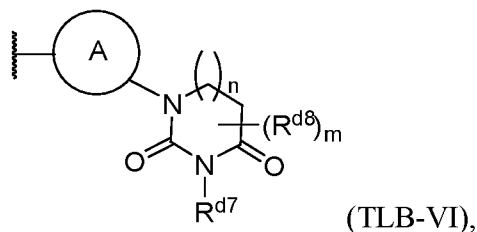
- In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d4} is H or C₁₋₃ alkyl. In an embodiment, R^{d4} is H. In an embodiment, R^{d5} is H or C₁₋₃ alkyl. In an embodiment, R^{d5} is H.
- 20

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-V):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VI):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

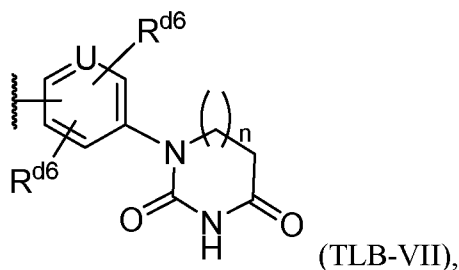
┌ denotes the point of attachment to the Linker in Formula (I);

- 5 Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;
- each R^{d6} is independently selected from the group consisting of H, hydroxyl, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;
- R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$,
 10 $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;
- R^p is H or C_{1-6} alkyl;
- each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;
- or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;
- 15 or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;
- m is 1 or 2; and
- n is 1 or 2.

In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is
 20 a nitrogen-containing 6-membered heteroaryl. In an embodiment, ring A is pyridyl.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d7} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d7} is H. In an embodiment, R^{d8} is H. In an embodiment, R^{d7} and R^{d8} are both H. In an embodiment, R^{d6} is H. In an embodiment, R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy. In an embodiment, R^{d6} is selected
 25 from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^{d7} , and R^{d8} are each H.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

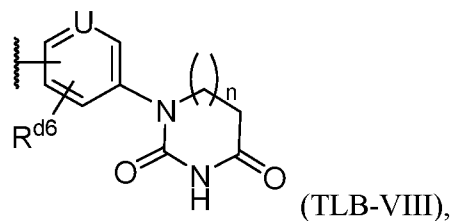
5 U is $-\text{CR}^{\text{d6}}$ or N;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

10 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, each R^{d6} is independently selected from the group consisting of H, halogen, C_{1-3} alkyl, and C_{1-3} alkoxy. In an embodiment, each R^{d6} is H. In an embodiment, one of R^{d6} is H. In an embodiment, one of R^{d6} is not H.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VIII):



15 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

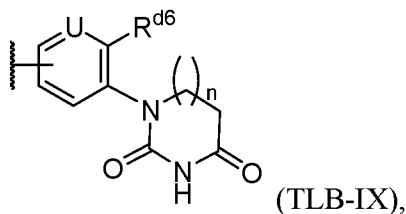
denotes the point of attachment to the Linker in Formula (I);

U is $-\text{CR}^{\text{d6}}$ or N;

R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

20 n is 1 or 2.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-IX):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

5 U is independently $-\text{CR}^{\text{d6}}$ or N;

R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

10 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, U is N. In an embodiment, U is $-\text{CR}^{\text{d6}}$. In an embodiment, each R^{d6} is independently selected from the group consisting of H, methyl, halogen, methoxy, and methoxymethyl. In an embodiment, R^{d6} is H. In an embodiment, R^{d6} is methyl. In an embodiment, R^{d6} is halogen. In an embodiment, R^{d6} is methoxy.

In an embodiment, the Linker has Formula (L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

20 L^1 is selected from the group consisting of a bond, O, NR' , $\text{C}(\text{O})$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})\text{-C}_{1-6}$ alkylene, $^*\text{C}(\text{O})\text{-C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand in Formula (I);

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

25 L^2 is selected from the group consisting of a bond, O, NR' , $\text{C}(\text{O})$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $^*\text{C}(\text{O})\text{NR}'\text{-C}_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$\text{X}^1\text{-L}^2\text{-X}^2$ form a spiroheterocyclyl;

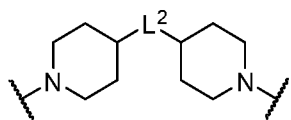
L^3 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $C(O)$, $S(O)_2$, O , NR' , $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in (L-I);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond; and

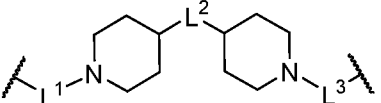
5 R' is hydrogen or C_{1-6} alkyl.

In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl.

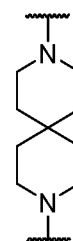
10 In an embodiment, one of X^1 and X^2 is a bond, and the other is a heterocyclyl. In an embodiment, X^1 and X^2 are each independently selected from piperidinyl and piperazinyl. In an embodiment, X^1 and X^2 are both piperidinyl. In an embodiment, $-X^1-L^2-X^2-$ is:

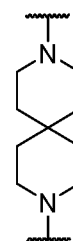


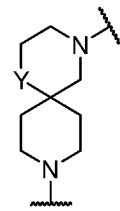
. In an embodiment, the Linker is a compound having the following

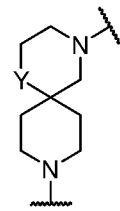
formula: , or a pharmaceutically acceptable salt, hydrate, solvate,

15 prodrug, stereoisomer, or tautomer thereof.



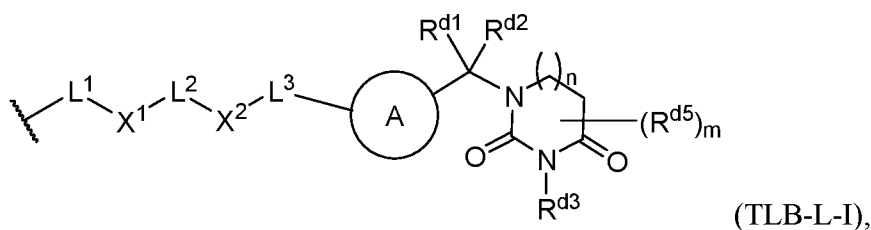
In an embodiment, $-X^1-L^2-X^2-$ forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^a , wherein each R^a is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl.



In an embodiment, $-X^1-L^2-X^2-$ forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^b , wherein Y is selected from CH_2 , oxygen, and nitrogen; and each R^b is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl.

In an embodiment, X^1 and X^2 are each a bond. In an embodiment, L^3 is independently selected from the group consisting of $-C(O)-$, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; and L^1 is $-C(O)-$, C_{1-8} alkylene, C_{1-8} heteroalkylene, and $*C_{1-6}$ alkylene- $C(O)$. In an embodiment, L^3 is selected from the group consisting of $-C(O)-$, $-O-C_{1-6}$ alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^3 is $-C(O)-$ or C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^3 is a bond or $-O-$; and L^1 is $-C(O)-$ or C_{1-8} heteroalkylene. In an embodiment, L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^2 is $-C(O)-$, $-NR'-$, or C_{1-6} alkylene. In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^2 is C_{1-6} alkylene. In an embodiment, L^2 is selected from the group consisting of $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-$ C_{1-6} alkylene. In an embodiment, Y is CH_2 , $CH(C_{1-3}$ alkyl), $C(C_{1-3}$ alkyl) $_2$, oxygen, NH, or $N(C_{1-3}$ alkyl).

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and

*C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

5 L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and *C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

10 L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O), -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (TLB-L-I);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

15 Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0-4 occurrences of R^{d4};

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

20 each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

25 or two R^{d5} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

R^p is H or C₁₋₆ alkyl;

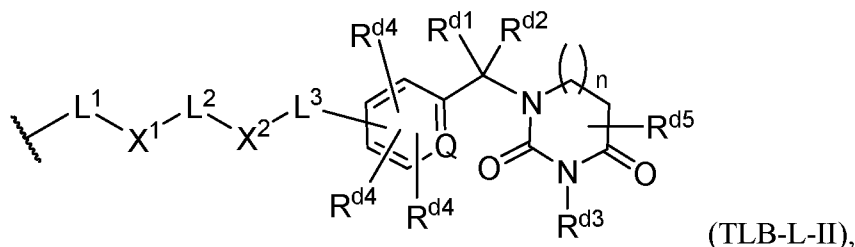
m is 1 or 2; and

n is 1 or 2.

30 In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, ring A is a 5-membered nitrogen-containing

heteroaryl. In an embodiment, ring A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl. In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is -CH₂OP(O)(OR^p)₂.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L¹ is selected from the group consisting of a bond, -O-, -NR'-, -C(O), C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)-C₁₋₆ alkylene, *C(O)-C₁₋₆ heteroalkylene, *C₁₋₆ alkylene-C(O), and *C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and *C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O), -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (TLB-L-II);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

Q is N or CR^{d4};

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC(O)}R^p$, $-\text{CH}_2\text{OP(O)}\text{OHOR}^p$, $-\text{CH}_2\text{OP(O)}(R^p)_2$, and $-\text{CH}_2\text{OP(O)}(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

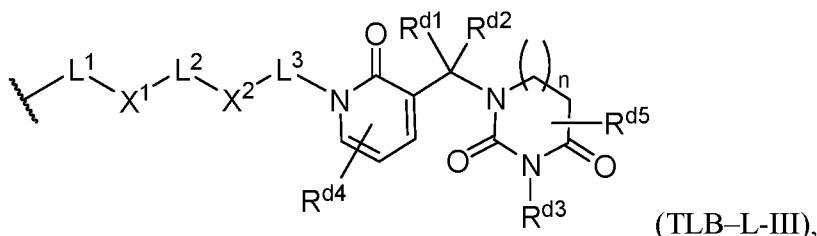
5 R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

10 In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP(O)}(\text{OR}^p)_2$.

In another embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

15 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C(O)}-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C(O)}-\text{C}_{1-6}$ alkylene, $^*\text{C(O)}-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- C(O) , and $^*\text{C}_{1-6}$ heteroalkylene- C(O) , wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

20 X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C(O)}-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

25 $^*\text{C(O)}\text{NR}'-\text{C}_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or $X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-\text{C(O)}-$, $-\text{S(O)}_2-$, $-\text{O}-$, $^*\text{C(O)}-\text{C}_{1-9}$ alkylene, $^*\text{C(O)}-\text{C}_{1-6}$ alkylene- O ,

and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

5 R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

10 R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

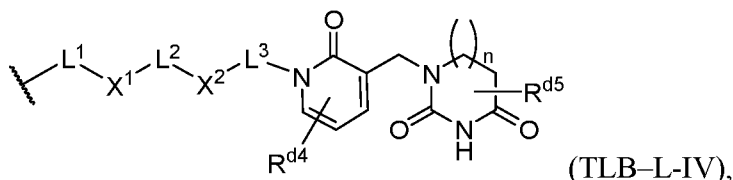
R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

15 In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$.

In another embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

┌— denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the

25 Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or $X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene-O, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-IV);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

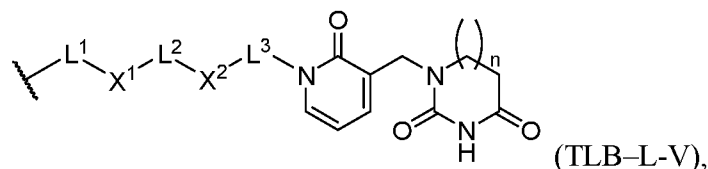
R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2.

In another embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-V):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

- 5 L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-V);

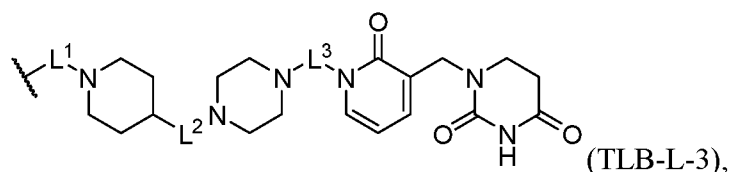
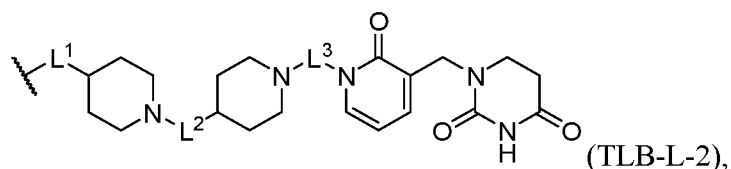
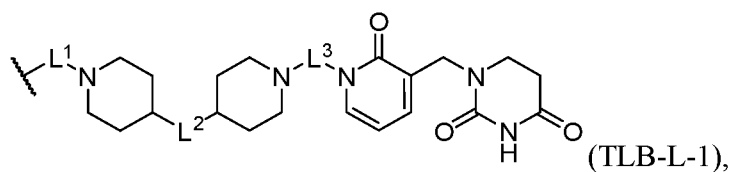
wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

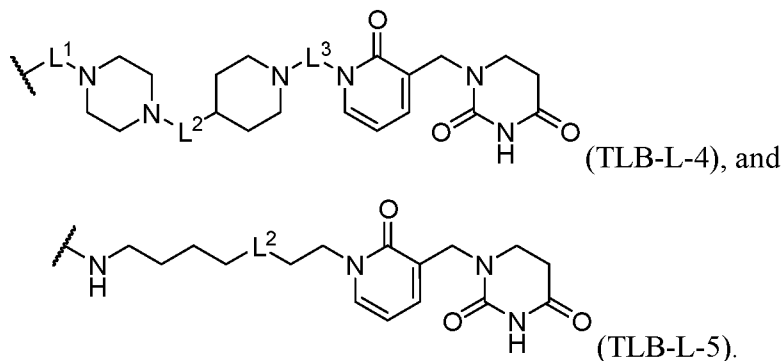
- 10 R' is hydrogen or C_{1-6} alkyl; and

n is 1 or 2.

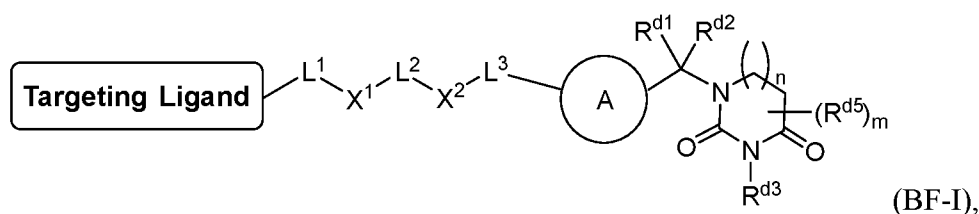
In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl. In an embodiment, one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

In another embodiment, the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:





In another aspect, the compound has the Formula (BF-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene;

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-I);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

5 R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

10 each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^p is H or C_{1-6} alkyl;

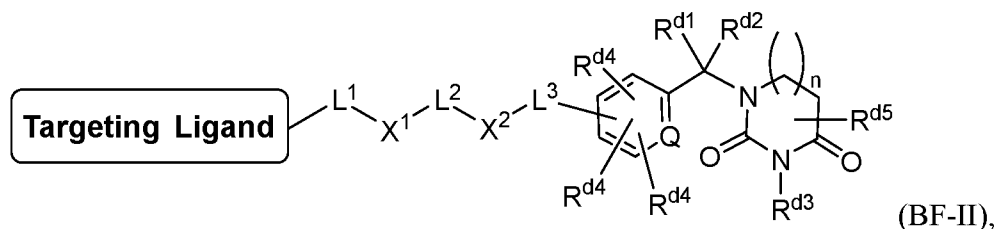
m is 1 or 2; and

15 n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, ring A is a 5-membered nitrogen-containing heteroaryl. In an embodiment, ring A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl.

20 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H.

In another embodiment, the compound has the Formula (BF-II):



25 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and

*C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

5 L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and *C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

10 L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O)-, -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (BF-II);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

Q is N or CR^{d4};

15 R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

20 each R^{d4} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

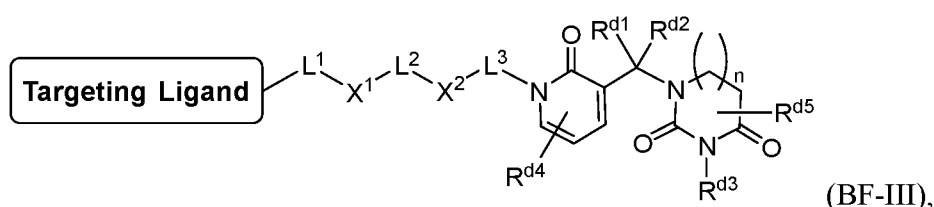
R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

25 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is -CH₂OP(O)(OR^p)₂. In an embodiment, R^{d3} is H.

In another embodiment, the compound has the Formula (BF-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and
 5 $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of
 10 L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O ,
 15 and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;
 20

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

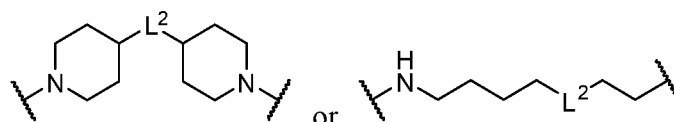
R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

25 R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

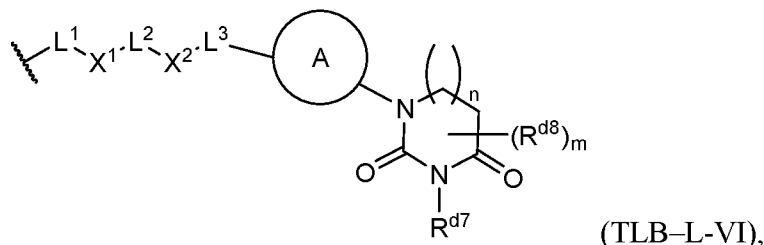
R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H. In an embodiment, $-X^1-L^2-X^2-$ is:
 30


 In an embodiment, L^1 is $-O-$ or C_{1-6} alkylene. In an embodiment, R^{d1} and R^{d2} are both methyl. In an embodiment, R^{d1} and R^{d2} are both H. In an embodiment, R^{d4} is H or C_{1-3} alkyl. In an embodiment, R^{d5} is H or C_{1-3} alkyl.

In another embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-VI):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:


 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-VI);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

5 R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

10 or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

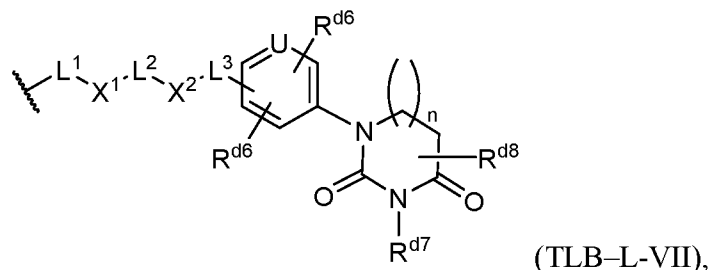
or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d3} is H.

In another embodiment, the Targeting Ligase Binder–Linker has Formula (TLB–L–VII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

20  denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'$, $-\text{C}(\text{O})-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})-C_{1-6}$ alkylene, $^*\text{C}(\text{O})-C_{1-6}$ heteroalkylene, $^*C_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*C_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

25 X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

- 5 L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-VII);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

- 10 R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

- R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$,
15 $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

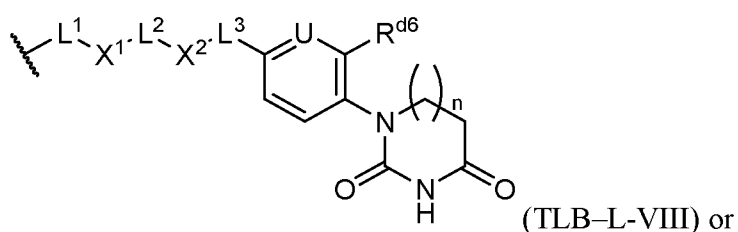
R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

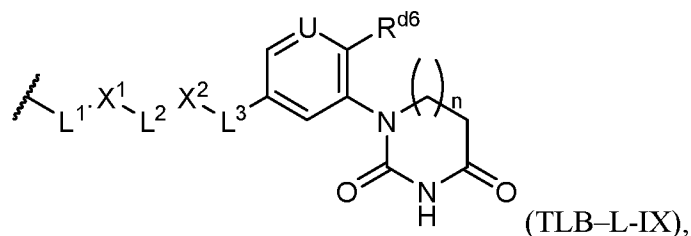
R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

- 20 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H. In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl. In an embodiment, one of X^1 and
25 X^2 is a bond, and the other is a heterocyclyl.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-VIII or TLB-L-IX):

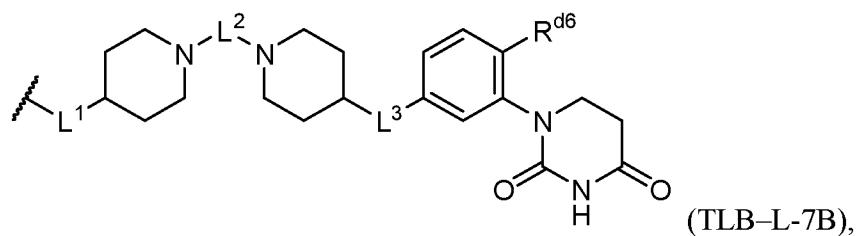
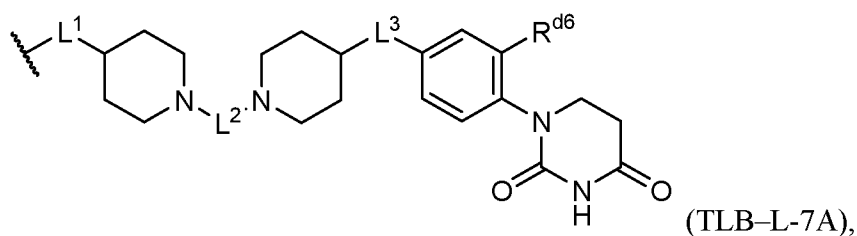
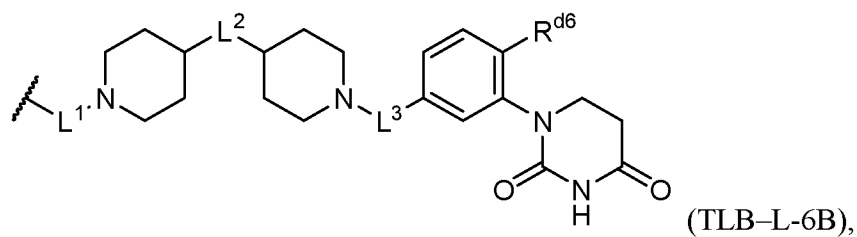
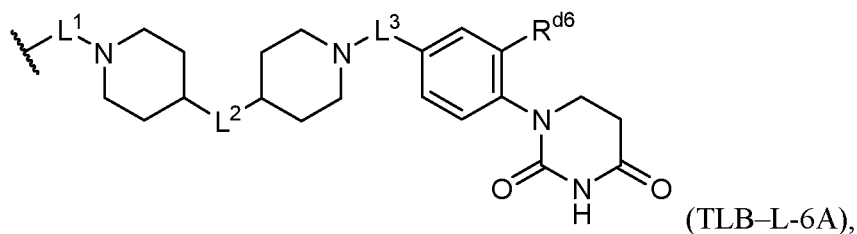




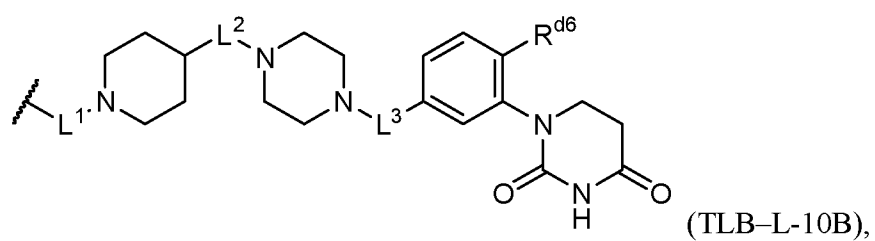
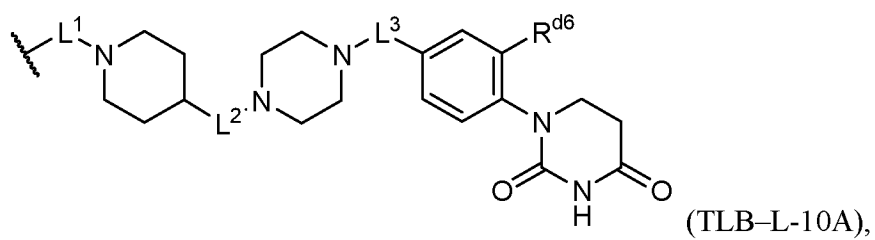
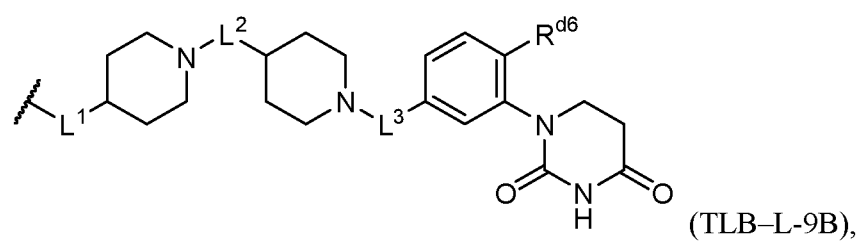
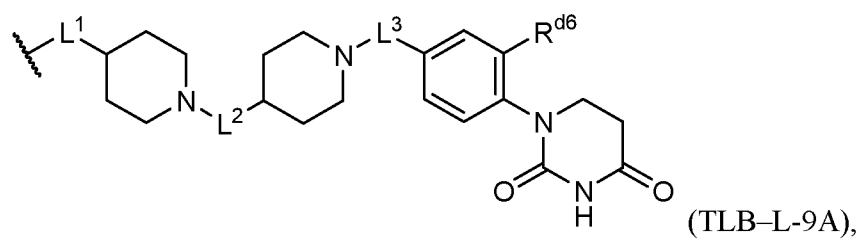
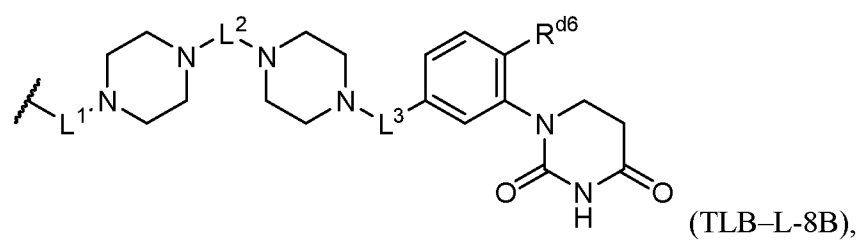
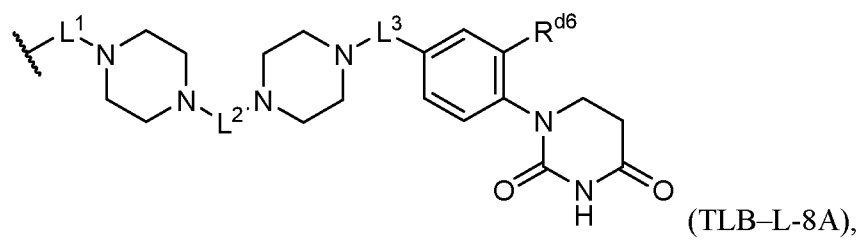
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the point of attachment to the Targeting Ligand is through L¹.

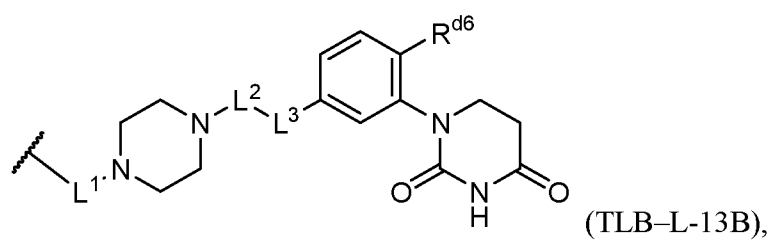
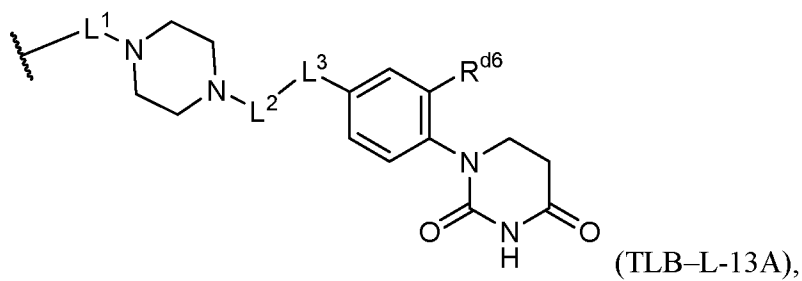
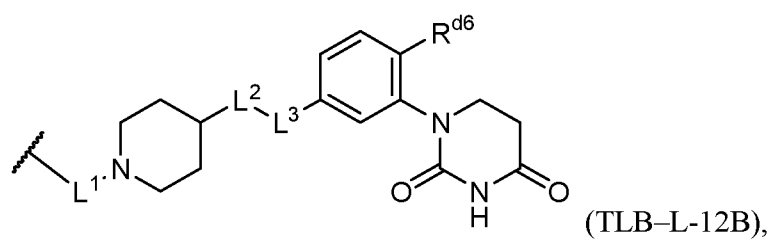
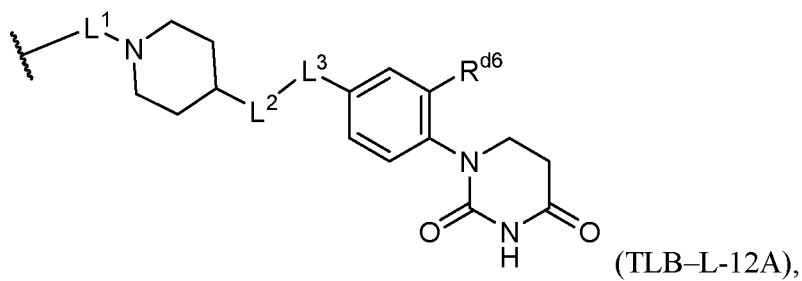
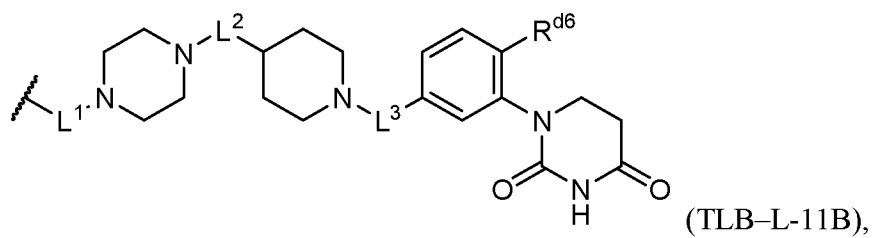
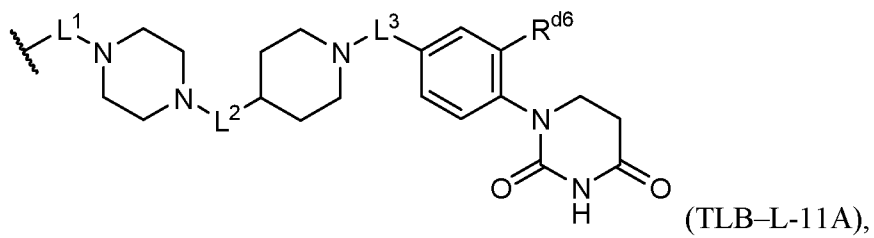
In an embodiment, n is 1. In an embodiment, n is 2.

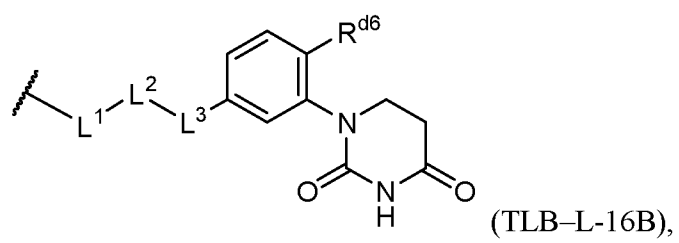
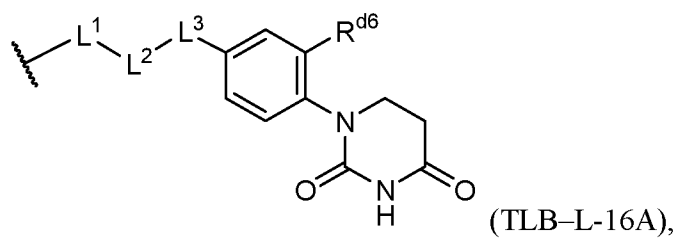
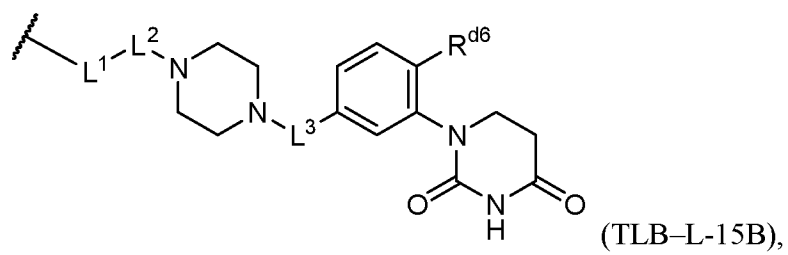
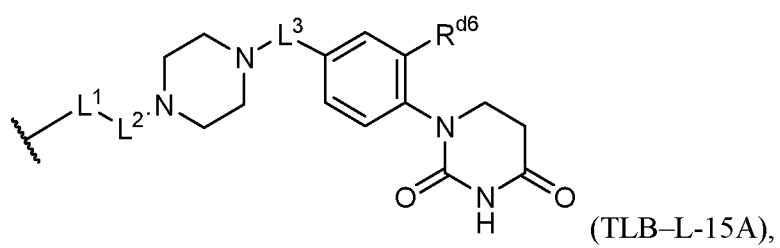
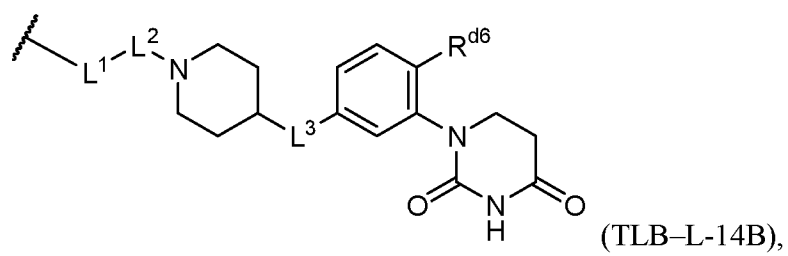
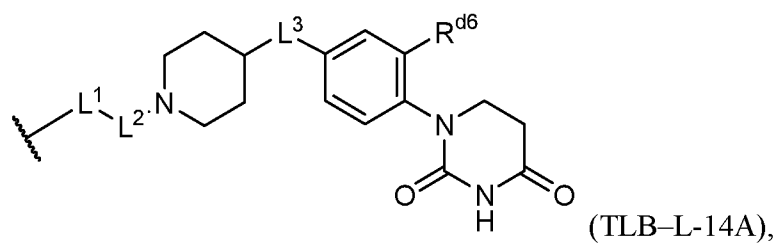
5 In another embodiment, the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:

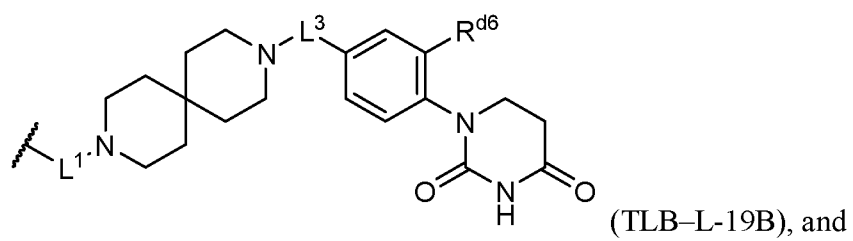
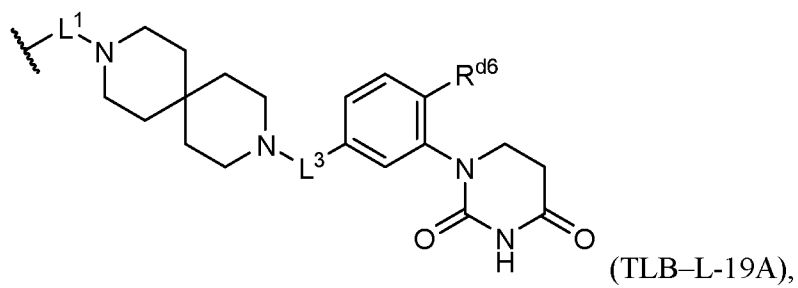
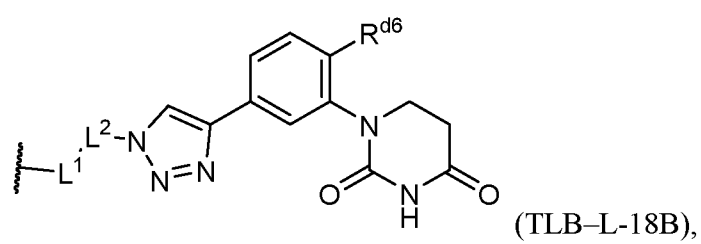
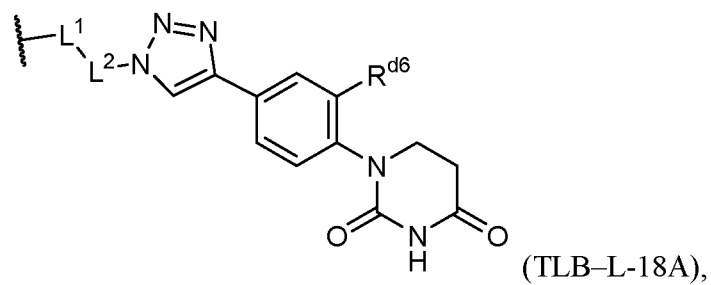
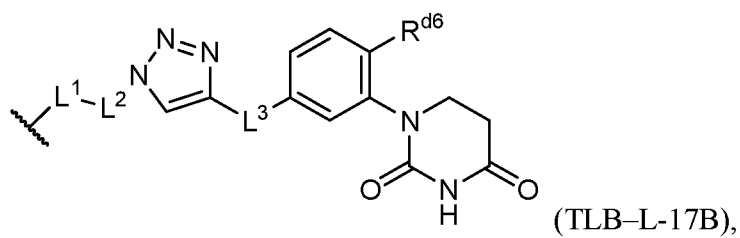
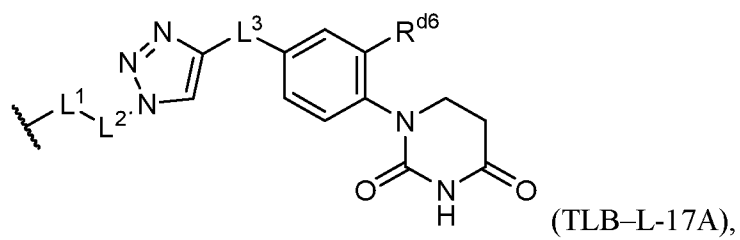


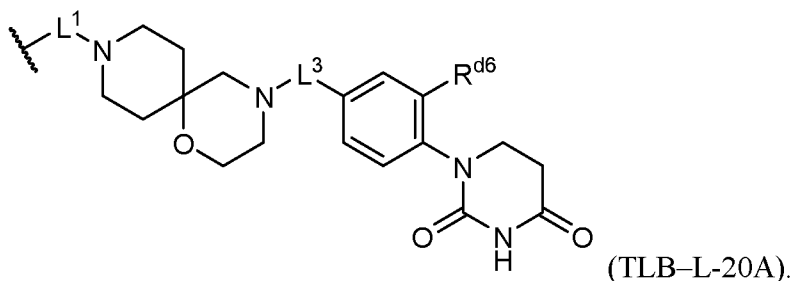
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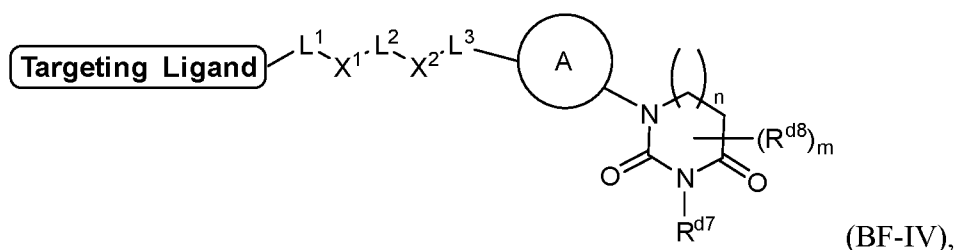








In another embodiment, the compound has the Formula (BF-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,
 5 wherein:

L¹ is selected from the group consisting of a bond, -O-, -NR', -C(O)-, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)-C₁₋₆ alkylene, *C(O)-C₁₋₆ heteroalkylene, *C₁₋₆ alkylene-C(O), and *C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

10 X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L² is selected from the group consisting of a bond, -O-, -NR', -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and

*C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

15 X¹-L²-X² form a spiroheterocyclyl;

L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O)-, -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (BF-IV);

20 wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0-4 occurrences of R^{d6};

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

5 R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

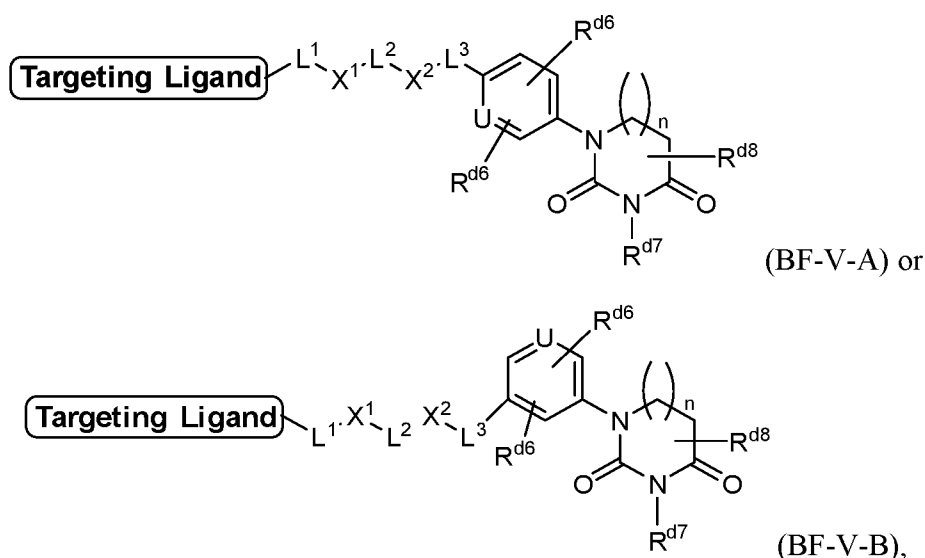
or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

10 m is 1 or 2; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In another embodiment, the compound has the Formula (BF-V-A or BF-V-B):



15 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

20

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

- 5 L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene-O, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-V-A or BF-V-B);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

- 10 R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

- R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

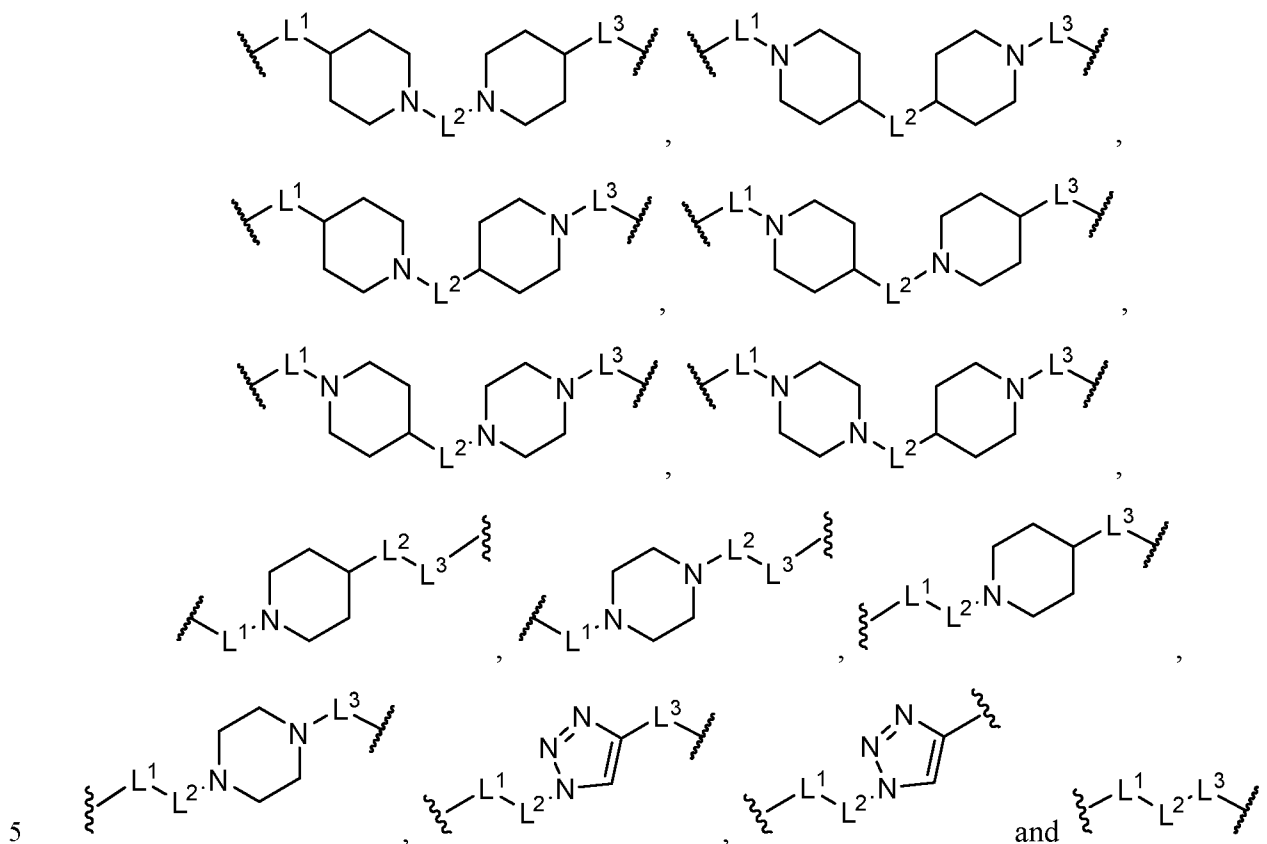
R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

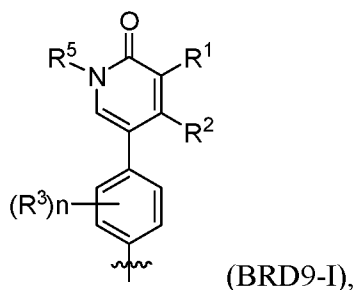
- 20 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d7} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d7} is H. In an embodiment, U is $-CR^{d6}$. In an embodiment, R^{d8} is H. In an embodiment, R^{d7} and R^{d8} are each independently H. In an embodiment, R^{d6} is H. In an embodiment, R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy. In an embodiment, R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^{d7} , and R^{d8} are each H.

In another embodiment, $L^1-X^1-L^2-X^2-L^3$ is selected from the group consisting of:



In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

In another embodiment, the Targeting is a BRD9 targeting ligand of Formula (BRD9-I):



10 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

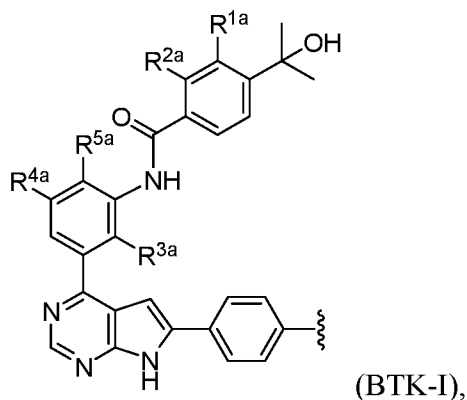
R^1 and R^2 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 together with the atoms to which they are attached form an aryl or heteroaryl;

15 R^3 are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, and halogen;

R^5 is selected from the group consisting of hydrogen and C_{1-3} alkyl;

n is 0, 1, or 2.

In another embodiment, the Targeting Ligand is a BTK targeting ligand of Formula (BTK-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo; and

R^{5a} is H or halo.

Another embodiment is a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

Another embodiment is a pharmaceutical combination comprising a compound described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more additional therapeutic agent(s).

Another embodiment is a method for inducing degradation of a Target Protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another embodiment is a method of inhibiting, reducing, or eliminating the activity of a Target Protein, the method comprising administering to the subject a compound described herein,

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In an embodiment, inhibiting, reducing, or eliminating the activity of a Target Protein comprises recruiting a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase) with the Targeting Ligase Binder, *e.g.*, a Targeting Ligase Binder described herein, of the bifunctional compound, *e.g.*, a bifunctional compound described herein, forming a ternary complex of the Target Protein, bifunctional compound, and the ligase, to thereby inhibit, reduce or eliminate the activity of the Target Protein.

In an embodiment, the Target Protein is selected from **Table 1**:

Table 1. Exemplary Target Proteins	
Target Code	Target Name
a5b1	Integrin a5b1
AAK1	Adaptor protein complex 2-associated protein kinase 1
ABL1	Abelson Tyrosine-Protein Kinase 1 including T314I
ACAT2	Acetyl-CoA Acetyltransferase 2
ADAR	adenosine deaminase RNA specific
ADORA2A	adenosine A2a receptor
AHR	Aryl hydrocarbon receptor
Akt	Protein Kinase B
ALK	ALK receptor tyrosine kinase
AR	Androgen hormone receptor including
ARAF	A-Raf proto-oncogene, serine/threonine kinase
ASC	Apoptosis-Associated Speck-Like
ATP4	ATP Synthase Subunit 4
AURKA	Aurora Kinase A
AURKB	Aurora Kinase B
BACH1	BTB and CNC homology 1
BACH2	BTB and CNC homology 2
BCL 2	BCL2 apoptosis regulator
BCL11A	BAF Chromatin Remodeling Complex Subunit BCL11A
BCL2L1	BCL2 like 1
BCR-ABL	BCR-ABL protein

BKV JCV	Human Polyomaviruses - capsid
BLK	B-lymphoid tyrosine kinase
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BRD2	Bromodomain containing protein 2
BRD3	Bromodomain containing protein 3
BRD4	Bromodomain containing protein 4
BRD5	Bromodomain containing protein 5
BRD7	Bromodomain containing protein 7
BRD8	Bromodomain containing protein 8
BRD9	Bromodomain containing protein 9
BRDT	bromodomain testis associated protein
BTK	Bruton's tyrosine kinase
BTK mutant	various Bruton's tyrosine kinase mutations
BTKC481S	mutant Bruton's tyrosine kinase
BTLA	B and T lymphocyte associated
CCR7	C-C motif chemokine receptor 7
CD274	CD274 molecule
CD47	CD47 molecule
CDK12	Cyclin Dependent Kinase 12
CDK13	Cyclin Dependent Kinase 13
CDK17	Cyclin Dependent Kinase 17
CDK2	Cyclin Dependent Kinase 2
CDK4	Cyclin Dependent Kinase 4
CDK5	Cyclin Dependent Kinase 5
CDK6	Cyclin Dependent Kinase 6
CDK7	Cyclin Dependent Kinase 7
CDK9	Cyclin Dependent Kinase 9
CDPK1	Calcium Dependent Protein Kinase 1
CDPK4	Calcium Dependent Protein Kinase 4
CDX2	caudal type homeobox 2

CEBPA	CCAAT enhancer binding protein alpha
cGAS	Cyclic GMP-AMP Synthase ATI
c-Met	Met tyrosine-protein kinase or hepatocyte growth factor receptor (HGFR)
CRABP-I/II	Cellular retinoic acid-binding protein 1/2
CREBBP	CREB binding protein
CSF1	colony stimulating factor 1
CSK	C-terminal Src kinase
CTLA4	cytotoxic T-lymphocyte associated protein 4
CTNNB1	catenin beta 1
DAPK1	Death-associated protein kinase 1
DDX58	DEXD/H-Box Helicase 58
DHFR	Dihydrofolate reductase
DHODH	Dihydroorotate dehydrogenase
DNMT3A	DNA methyltransferase 3 alpha, WT and variant R882H,C, or P
DOT1L	DOT1L like histone lysine methyltransferase
DXR	1-deoxy-D-xylulose 5-phosphate reductoisomerase
EBF1	EBF transcription factor 1
EGFR	Epidermal growth factor receptor
EGFR L858R	Epidermal growth factor receptor L859→R mutation
EGFR Δ Exon 19	Epidermal growth factor receptor exon 19 deletion
ENTPD2	ectonucleoside triphosphate diphosphohydrolase 2
EP300	E1A binding protein p300
EPAS1	Endothelial PAS domain protein 1
ER	Estrogen receptor
ER	Estrogen receptor mutant including ESR Y573S/C/N; ESR D538G
ERRα	Estrogen-related receptor alpha
ERα	Estrogen receptor alpha
ESR1	estrogen receptor 1
Fak	Focal adhesion kinase

FARS2	alpha subunit of the cytosolic phenylalanyl-tRNA synthetase (Pf PheRS)
FER	FER Tyrosine Kinase
FES	FES Tyrosine Kinase
FKBP12	Peptidyl-prolyl cis-trans isomerase FKBP12
FLI1	Fli-1 proto-oncogene, ETS transcription factor
FLT3	Receptor-type tyrosine-protein kinase FLT3
FOXA1	forkhead box A1
GAK	Cyclin G-associated kinase
GATA3	GATA binding protein 3
GATA6	GATA binding protein 6
GSK3	Serine/threonine protein kinase 3
HAVCR2	hepatitis A virus cellular receptor 2
HBV	Hepatitis B virus - capsid
HCMV	cytomegalovirus - capsid
HCV	Hepatitis C virus- - capsid
HDAC1	Histone Deacetylase 1
HDAC10	Histone Deacetylase 10
HDAC11	Histone Deacetylase 11
HDAC2	Histone Deacetylase 2
HDAC3	Histone Deacetylase 3
HDAC4	Histone Deacetylase 4
HDAC5	Histone Deacetylase 5
HDAC6	Histone Deacetylase 6
HDAC7	Histone Deacetylase 7
HDAC8	Histone Deacetylase 8
HDAC9	Histone Deacetylase 9
HER2	Human epidermal growth factor receptor 2
HHV 6A and 6B	Human herpesvirus 6A and 6B - capsid
HHV 7	Human herpesvirus 7 - capsid
HHV-8	Kaposi's sarcoma-associated herpesvirus - capsid

HIF1A	hypoxia inducible factor 1 subunit alpha
HIV	Human immunodeficiency virus -- capsid
HNF1A	HNF1 homeobox A
HNF1B	HNF1 homeobox B
HNF4A	hepatocyte nuclear factor 4 alpha
HRV	Rhinovirus and enteroviruses, including polioviruses, Coxsackie A viruses (CA), Coxsackie B viruses (CB), and echoviruses
HSD17b13	hydroxysteroid 17-beta dehydrogenase 13
HSV1	Herpes simplex viruses 1 - capsid
HSV1	Herpes simplex viruses 2 - capsid
HTT	Huntingtin
ICOS	Inducible T cell costimulator
IDH1	Isocitrate dehydrogenase (NADP(+)) 1, including R132H/S/G/L/I
IDH2	Isocitrate dehydrogenase (NADP(+)) 2, including R132H/S/G/L/I
IKZF1	Ikaros transcription factors
IKZF3	Aiolos transcription factors
IL15	interleukin 15
IL27	interleukin 27
IRAK1	Interleukin-1 receptor-associated kinase 1
IRAK1/4	Interleukin-1 receptor-associated kinase 4
IRF4	interferon regulatory factor 4
ITK	Interleukin-2-inducible T-cell kinase
JAK1	Janus kinase 1
JAK2	Janus kinase 2
JAK2	Janus kinase 2, WT abd variant V617F
KARS1	Lysyl-tRNA-Synthetase
KLF5	Kruppel like factor 5
KLRK1	killer cell lectin like receptor K1
KRAS	K-Ras P21 Protein
KRAS	KRAS proto-oncogene, GTPase, WT and variants G12V, C, D or G13D

KRAS G12V/C/D	mutant K-Ras P21 Protein
KRAS G13D	mutant K-Ras P21 Protein
LAG3	lymphocyte activating 3
LATS1	Large Tumor Suppressor Kinase 1
LATS2	Large Tumor Suppressor Kinase 2
LCAT	Lecithin-Cholesterol Acyltransferase
LCK	Protein tyrosine kinase Lck
LIMK2	Leucine-rich repeat kinase 2
LMO2	LIM domain only 2
M1 and M17 aminopeptidases	M1 and M17 aminopeptidases
MAP2K1	mitogen-activated protein kinase kinase 1
MAP2K2	mitogen-activated protein kinase kinase 2
MAPK1	mitogen-activated protein kinase 1
MAPK3	mitogen-activated protein kinase 3
MARK2	Microtubule Affinity Regulating Kinase 2
MAX	MYC associated factor X
MCL1	MCL1 apoptosis regulator, BCL2 family member
MetAP-2	Methionyl Aminopeptidase 2
MICA	MHC class I polypeptide-related sequence A
MICB	MHC class I polypeptide-related sequence B
MITF	melanocyte inducing transcription factor
MLKL	Mixed lineage kinase domain-like protein
MLL	KMT2A (MLL) lysine methyltransferase 2A
MPL	MPL proto-oncogene, thrombopoietin receptor, WT and variant W515S, L or A
MRK	MO15-related protein kinase
MUC1	mucin 1, cell surface associated
MYB	MYB proto-oncogene, transcription factor
MYBL2	MYB proto-oncogene like 2

MYC	MYC proto-oncogene, bHLH transcription factor
MYCN	MYCN proto-oncogene, bHLH transcription factor
MyD88	Myeloid Differentiation Primary Response 88
MYOC	Myocilin
NFE2L2	nuclear factor, erythroid 2 like 2
NPM1	nucleophosmin 1, WT and variant NPM1c (AML frameshift mut)
Nr2E3	Photoreceptor-Specific Nuclear Receptor
NRAS	NRAS proto-oncogene, GTPase, WT and variants Q61R, K, or L
Nrl	Neural Retina Leucine Zipper
NT5E	5'-nucleotidase ecto
NTRK	SLIT and NTRK 3 [neurotrophic receptor tyrosine kinase 3]
p16INK4a	CDKN2A (P16INK4A) cyclin dependent kinase inhibitor 2A
p21CIP/WAF1	Zinc finger protein Gfi-1?
p38	Mitogen-activated protein (MAP) kinase (MAPK11)
PARS2	cytoplasmic prolyl-tRNA (transfer RNA) synthetase (PfcPRS)
PAX8	paired box 8
PDCD1	programmed cell death 1
PDE4	Phosphodiesterase 4
PI3K34	Phosphatidylinositol 3-kinase 34
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha WT and variants H1047R or E545K
PIK3CB	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta
PIK3CD	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta
PKA	cAMP dependent protein kinase
PKG	Protein kinase G
Plasmepsin IX	Plasmepsin IX
Plasmepsin X	Plasmepsin X
PNPLA2	Patatin like phospholipase domain containing 2
PNPLA3	Patatin like phospholipase domain containing 2
POU2AF1	POU class 2 homeobox associating factor 1

PPP1R12B	Protein phosphatase 1 regulatory subunit 12B
PRKAA1	Protein Kinase AMP-Activated Catalytic Subunit Alpha 1
PRMT5	Protein arginine methyltransferase 5
PRS	Prolyl-tRNA-Synthetase
PSD-95	Post synaptic density protein 95, a membrane associated guanylate kinase
PTK2	Protein Tyrosine Kinase 2
PTK2B	Protein Tyrosine Kinase 2 beta
PTPN11	protein tyrosine phosphatase non-receptor type 11
PTPN2	protein tyrosine phosphatase non-receptor type 2
PTPN6	protein tyrosine phosphatase non-receptor type 6
PTPRB	Protein Tyrosine Phosphatase Receptor Type B
RAC1	Rac family small GTPase 1, WT and variant P29S
RAET1E	retinoic acid early transcript 1E
RAET1G	retinoic acid early transcript 1G
RAET1L	retinoic acid early transcript 1L
RAF1	Raf-1 proto-oncogene, serine/threonine kinase
RAR	Retinoic acid receptor
RET	ret proto-oncogene
RHOA	ras homolog family member A
RHOB	ras homolog family member B
RIPK2	Receptor Interacting Serine/Threonine Kinase 2
ROCK 1	Rho Associated Coiled-Coil Containing Protein Kinase 1
RSV	Human respiratory syncytial virus - capsid
RUNX1	RUNX family transcription factor 1
SARM1	Sterile Alpha And TIR Motif-Containing Protein 1
SHOC2	SHOC2 leucine rich repeat scaffold protein
Sirt 1	Sirtuin 1
Sirt 2	Sirtuin 2, an NAD-dependent deacetylase
Sirt 3	Sirtuin 3
Smad3	SMAD Family Member 3

SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
SMARCA4	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SNAIL1	Snail Family Transcriptional Repressor 1
SNCA	Alpha synuclein
SOX10	SRY-box transcription factor 10
SPI1	Spi-1 proto-oncogene
SPTLC1	Serine palmitoyltransferase 1
STAT1	Signal transducer and activator of transcription 1
STAT2	Signal transducer and activator of transcription 2
STAT3	Signal transducer and activator of transcription 3
STAT4	Signal transducer and activator of transcription 4
STAT5	Signal transducer and activator of transcription 5
STAT6	Signal transducer and activator of transcription 6
STK17A	Death-Associated Protein Kinase-Related 1
STK17B	Death-Associated Protein Kinase-Related 2
TACC3	Transforming Acidic Coiled-Coil Containing Protein 3
TANK	TRAF Family Member Associated NFkB Activator
Tau	Tau protein
TBK1	TANK binding kinase 1
TCF7L2	transcription factor 7 like 2
TDP43	TAR DNA-binding protein 43
TEAD1	TEA domain transcription factor 1
TEAD2	TEA domain transcription factor 2
TEAD3	TEA domain transcription factor 3
TEAD4	TEA domain transcription factor 4
TEC	Tec non-receptor protein-tyrosine kinase
TFAP2A	Transcription factor AP-2 alpha
TFAP2C	Transcription factor AP-2 gamma

TGFB1	Transforming growth factor beta 1
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TLR7	Toll like receptor 7
TMEM173/STING1	Stimulator of interferon response cGAMP interactor 1
TNFRSF18	TNF receptor superfamily member 18
TNNI3K	TNNI3 Interacting Kinase
TP63	tumor protein p63
TRIM24	Tripartite Motif Containing 24; transcriptional intermediary factor 1 α
TYK2	Tyrosine Kinase 2
ULBP1	UL16 binding protein 1
ULBP2	UL16 binding protein 2
ULBP3	UL16 binding protein 3
ULK1	Unc-51 Like Autophagy Activating Kinase 1
VHL	Von Hippel-Lindau Tumor Suppressor
VZV	Varicella-zoster virus - capsid
WEE1	WEE1 G2 Checkpoint Kinase
WRN	WRN RecQ like helicase
WWTR1	WW domain containing transcription regulator 1
XIAP	X-linked inhibitor of apoptosis
X-Protein	Hepatitis B X-protein.
ZFP64	ZFP64 zinc finger protein.

In an embodiment, the Target Protein is a fusion target protein. In an embodiment, the fusion target protein is selected from **Table 2**:

Table 2. Exemplary Fusion Target Proteins

NCBI symbol	NCBI gene ID	Gene Name (extended from NCBI)	Example fusion partners (NCBI symbol)
RUNX1	861	RUNX family transcription factor 1	ETV6, MECOM, RUNX1T1
ABL1	25	ABL proto-oncogene 1	BCR, NUP214, EML1, ETV6
TCF3	6929	transcription factor 3	PBX1, TFPT, ZNF384, HLF
ZNF384	171017	zinc finger protein 384	EWSR1, TAF15, TCF3, EP300, CREBBP
CRLF2	64109	cytokine receptor like factor 2	P2RY8

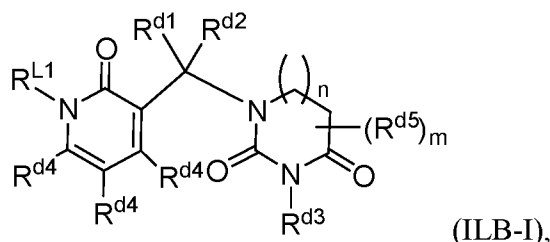
MEF2D	4209	myocyte enhancer factor 2D	BCL9, SS18, FOXJ2, CSF1R, DAZAP1
PAX5	5079	paired box 5	ELN, ETV6, AUTS2, POM121, JAK2, FOXP1, NCOR1
TRBC1	28639	T cell receptor beta constant 1	TAL1, TAL2, LYL1, OLIG2, LMO1, LMO2, TLX1, TLX3, MYC, and MYB
TRAC	28755	T cell receptor alpha constant	TAL1, TAL2, LYL1, OLIG2, LMO1, LMO2, TLX1, TLX3, MYC, and MYB
KMT2A	4297	lysine methyltransferase 2A	AFF1, MLLT3, MLLT1, MLLT10, MLLT4, ELL, AFDN, MLLT6, AFF4
FLI1	2313	Fli-1 proto-oncogene	EWSR1
ERG	2078	ETS transcription factor ERG	TMPRSS2, EWSR1, SLC45A3, FUS, ETV6
ETV1	2115	ETS variant transcription factor 1	TMPRSS2, EWSR1, SLC45A3, ACSL3, FOXP1
ETV4	2118	ETS variant transcription factor 4	TMPRSS2, EWSR1, KLK2, CANT1, DDX5
ETV5	2119	ETS variant transcription factor 5	TMPRSS2, SLC45A3
PML	5371	promyelocytic leukemia	RARA
NUP98	4928	nucleoporin 98	NSD1, HOXA9, PRRX1, HOXA11, HOXA13, HOXC11, HOXC13
CBFA2T3	863	CBFA2/RUNX1 partner transcriptional co-repressor 3	GLIS2
CBFB	865	core-binding factor, beta subunit	MYH11
KAT6A	7994	lysine acetyltransferase 6A	CREBBP, EP300, NCOA2
FGFR3	2261	fibroblast growth factor receptor 3	TACC3, BAIAP2L1
FGFR2	2263	fibroblast growth factor receptor 2	BICC1, KLK2, CIT, CCAR2
FGFR1	2260	fibroblast growth factor receptor 1	FN1, TACC1
RET	5979	ret proto-oncogene	CCDC6, ERC1, NCOA4, KIF5B, TRIM33, CUX1, CLIP1, RUFY3
ALK	238	anaplastic lymphoma receptor tyrosine kinase	EML4, KIF5B, RANBP2, TFG, PRKAR1A, TPM3, NPM1
NTRK3	4916	neurotrophic tyrosine kinase, receptor, type 3	ETV6, BTBD1, AML4, TFG, LYN, RBPMS
NTRK2	4915	neurotrophic receptor tyrosine kinase 2	QKI, NACC2, VCL, AGBL4, PAN3, AFAP1, DAB2IP
NTRK1	4914	neurotrophic receptor tyrosine kinase 1	CD74, MPRIP, TPM3, TFG, TPR
ROS1	6098	ROS proto-oncogene 1, receptor tyrosine kinase	CD74, EZR, TPM3, SDC4, LRIG3, FIG, CCDC6, GOPC
RSPO3	84870	R-spondin 3	PTPRK
RSPO2	340419	R-spondin 2	EIFE3
SMYD3	64754	SET and MYND domain containing 3	KIF26B
MAML3	55534	mastermind like transcriptional coactivator 3	UBTF, PAX3, BCOR, TCF4

MAML2	84441	mastermind like transcriptional coactivator 2	CRTC1
TFE3	7030	transcription factor binding to IGHM enhancer 3	SFPQ, PRCC, ASPSCR1, NONO, CLTC
TFEB	7942	transcription factor EB	MALAT1
EGFR	1956	epidermal growth factor receptor	SEPT14
BRAF	673	B-Raf proto-oncogene, serine/threonine kinase	KIAA1549, PAPSS1, TRIM24, TAX1BP1, CDC27, SND1
SS18	6760	SS18 subunit of BAF chromatin remodeling complex	SSX1, SSX2, SSX4
PAX3	5077	paired box 3	FOXO1, MLLT7, NCOA1
PAX7	5081	paired box 7	FOXO1
EWSR1	2130	EWS RNA binding protein 1	DDIT3, CREB3L1, CREB3L2, CREB1, PBX1, ATF1, NR4A3
FUS	2521	FUS RNA binding protein	ERG, CREB3L2, DDIT3
CIC	23152	capicua transcriptional repressor	DUX4, DUX4L10, FOXO4
FOSB	2354	FosB proto-oncogene, AP-1 transcription factor	ZFP36, SERPINE1
VGLL2	245806	vestigial like family member 2	CITED2, NCOA2
VAV1	7409	vav guanine nucleotide exchange factor 1	GSS, MYO1F
STAT6	6778	signal transducer and activator of transcription 6	NAB2
HMGA2	8091	high mobility group AT-hook 2	LPP
PDGFRB	5159	platelet derived growth factor receptor beta	ETV6
BRD4	23476	bromodomain containing 4	NUTM1
PAX8	7849	paired box 8	PPARG

Another embodiment is a method of treating a Target Protein-mediated disorder, disease, or condition in a patient comprising administering to the patient any of the compounds described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. In an embodiment, the disorder is selected from a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder. In an embodiment, the disorder is a proliferative disorder. In an embodiment, the proliferative disorder is cancer.

Another embodiment is a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

Another embodiment is a compound of Formula (ILB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,
wherein:

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆
haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$,
 $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆
haloalkyl, C₁₋₆ alkoxy; C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆
haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

R^{L1} is selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆
hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, C₃₋₆ heteroalkyl, C₂₋₆ haloalkyl, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$,
 $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{1-3}\text{O}(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}_{3-7}$ carbocyclyl, $-(\text{CH}_2)_{0-3}$
heterocyclyl, C₆ aryl, and heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and
heteroaryl is substituted with 0-2 occurrences of $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -
heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆
heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C₁₋₄ alkyl, or C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl;

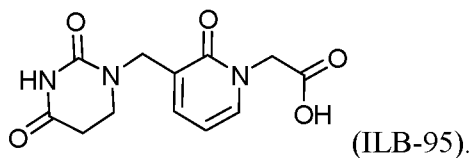
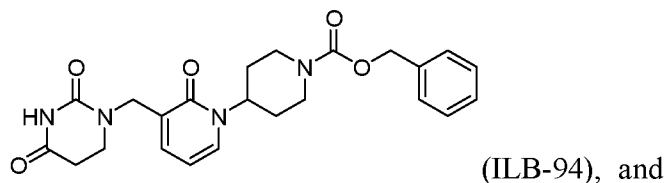
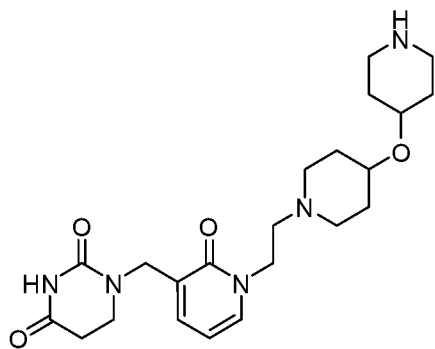
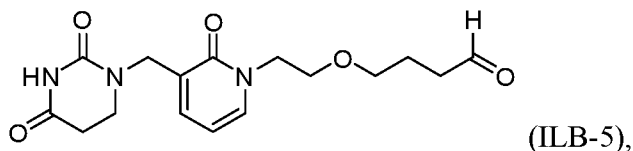
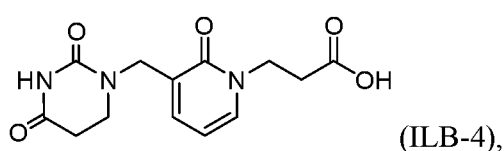
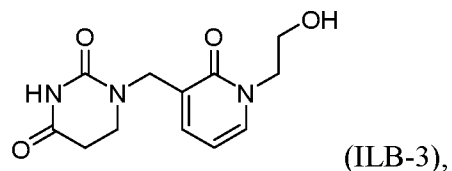
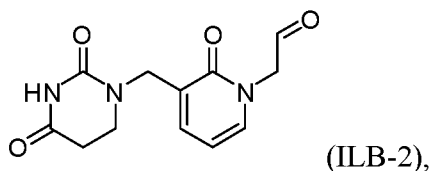
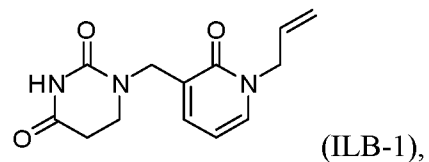
m is 1 or 2; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d3} is H.

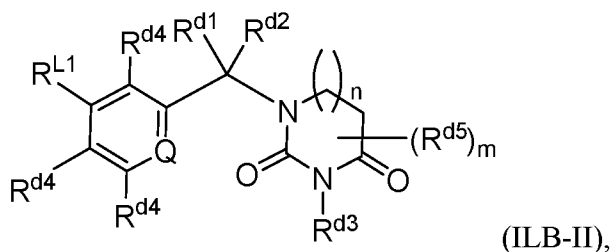
In an embodiment, the compound or a pharmaceutically acceptable salt, hydrate, solvate,

prodrug, stereoisomer, or tautomer thereof, is selected from:



Another embodiment is a compound of Formula

(ILB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

Q is N or CR^{d4},

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2(\text{O})(\text{CH}_2)_2\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

5 each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

10 or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L1} is selected from the group consisting of C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{3-6} heteroalkyl, C_{2-6} haloalkyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}_{3-7}$ carbocyclyl, $-(\text{CH}_2)_{0-3}$ heterocyclyl, C_6 aryl, and heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and heteroaryl is substituted with
15 0-2 occurrences of $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, or C_{1-6} heteroalkyl;

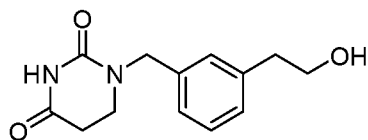
R^p is H or C_{1-6} alkyl;

20 m is 1 or 2; and

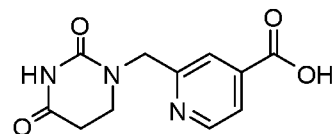
n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d3} is H.

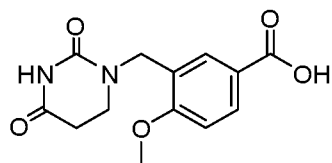
Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate,
25 solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



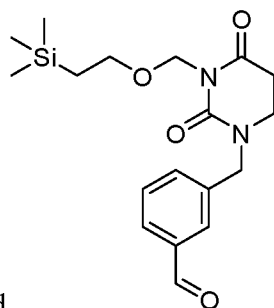
(ILB-7),



(ILB-8),

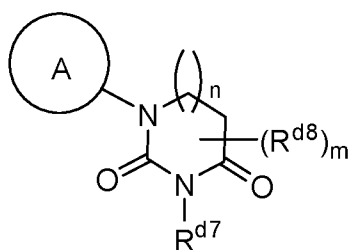


(ILB-9), and



(ILB-10).

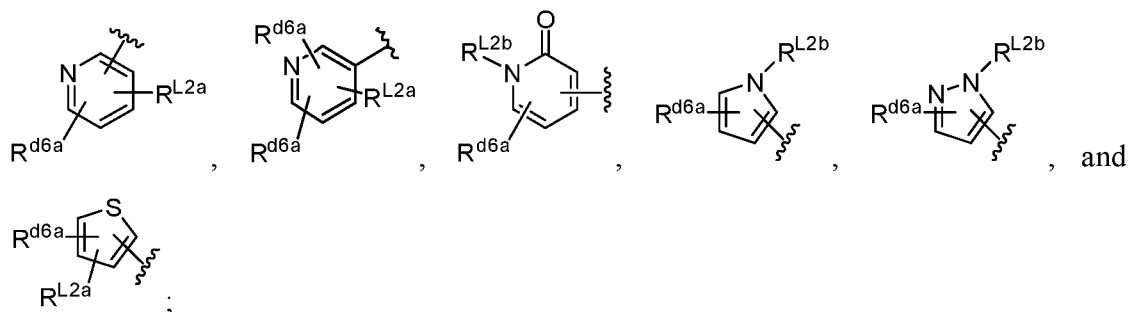
Another embodiment is a compound of Formula (ILB-III):



(ILB-III),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

Ring A is selected from the group consisting of: ,



denotes the point of attachment to the base molecule of (ILB-III);

each R^{d6} is independently selected from the group consisting of H, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

each R^{d6a} is independently selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

R^{d7} is H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L2} is selected from the group consisting of, hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{4-8} heteroalkyl, C_{2-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^c$, $-\text{O}-C_{2-6}$ alkenyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})$ -heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{N}(\text{R}^c)_2$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl wherein the heterocyclyl may optionally be substituted with halogen;

R^{L2a} is selected from the group consisting of H, hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{1-8} heteroalkyl, C_{1-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^c$, $-\text{O}-C_{2-6}$ alkenyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})$ -heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{N}(\text{R}^c)_2$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6}

alkoxyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl, wherein the heterocyclyl may optionally be substituted with halogen;

R^{L2b} is selected from the group consisting of H, polyethylene glycol (PEG), C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, C₂₋₆ hydroxyalkyl,
 5 -(CH₂)₂₋₆NHR^c, -(CH₂)₂₋₆NR^cR^d, C₂₋₈ heteroalkyl, C₂₋₆ haloalkyl, -(CH₂)₁₋₃C(O)OH, -(CH₂)₁₋₃C(O)H, -(CH₂)₀₋₃ heterocyclyl, -C(O)-(CH₂)₀₋₃ heterocyclyl, -C₃₋₆ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, -(CH₂)₀₋₃C(O)H,
 10 -(CH₂)₂₋₆NHR^c, heterocyclyl, -O-heterocyclyl, -O-carbocyclyl, -C(O)-heterocyclyl, -C(O)-carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C₁₋₄ alkyl, C₁₋₆ heteroalkyl, and -C(O)OC₁₋₆ alkyl;

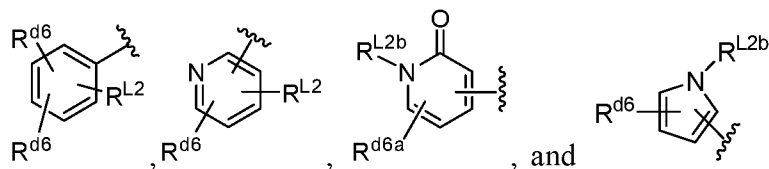
R^d is H or C₁₋₄ alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0-2 occurrences of -O-heterocyclyl,

15 R^p is H or C₁₋₆ alkyl;

m is 1 or 2; and

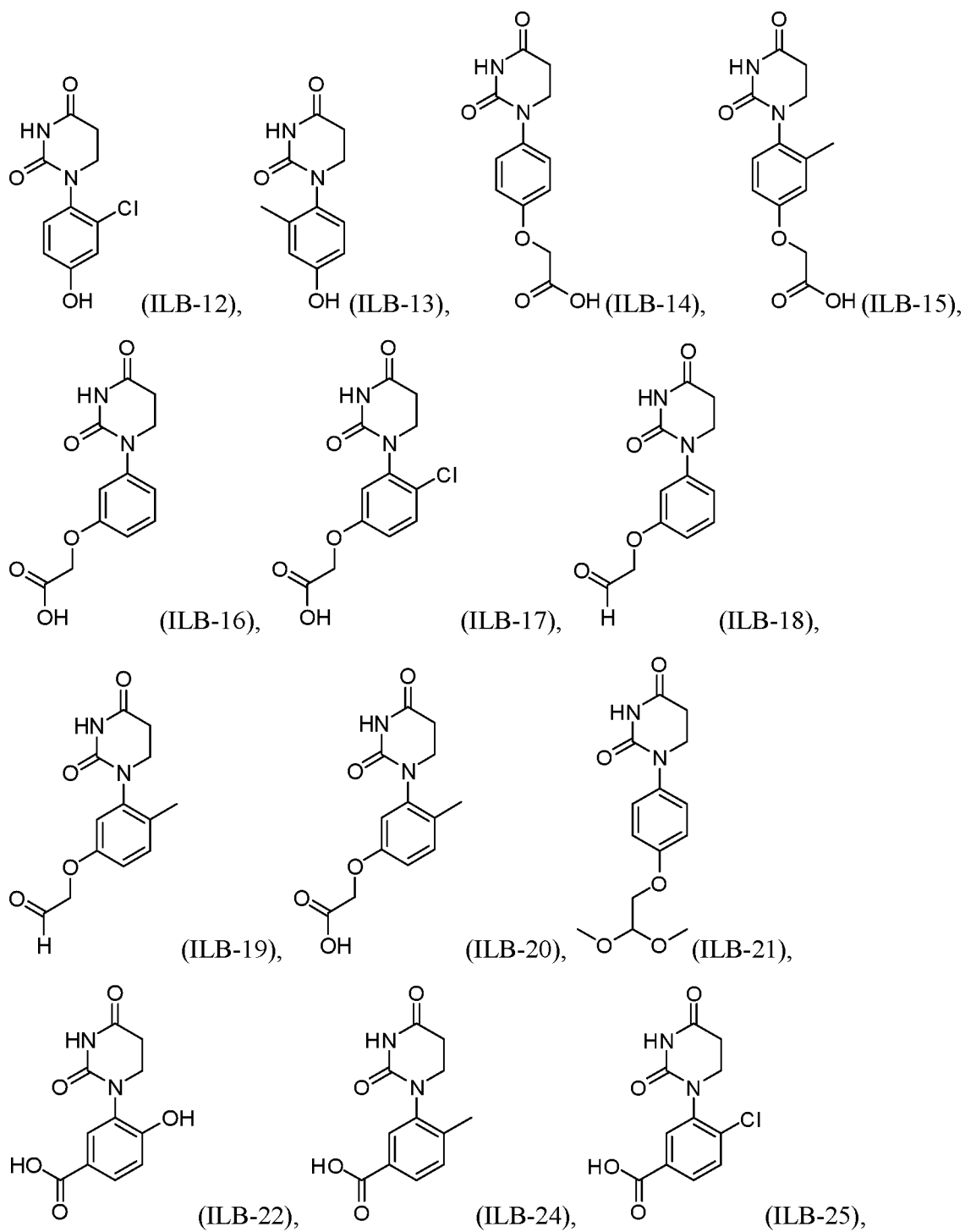
n is 1 or 2.

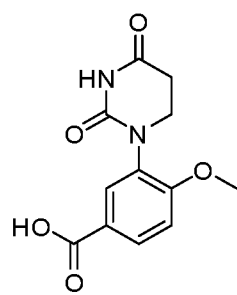
In an embodiment, ring A is selected from the group consisting of:



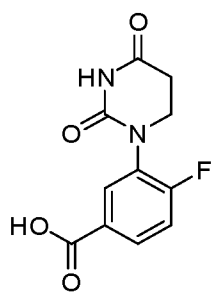
20 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d7} is -CH₂OP(O)(OR^p)₂. In an embodiment, R^{d7} is H.

Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:

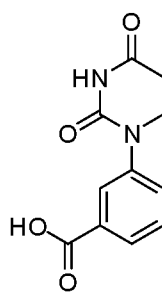




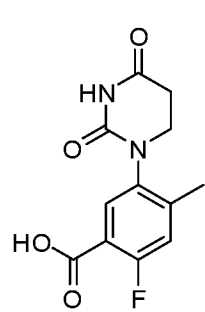
(ILB-26),



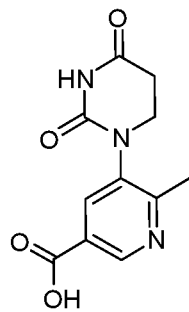
(ILB-27),



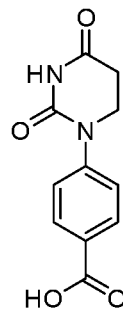
(ILB-28),



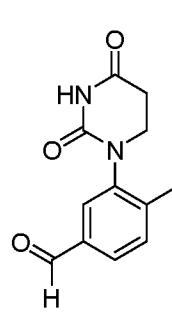
(ILB-29),



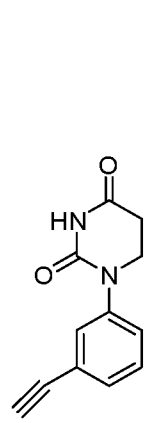
(ILB-30),



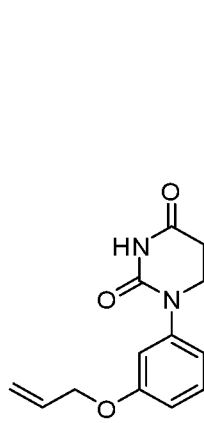
(ILB-31),



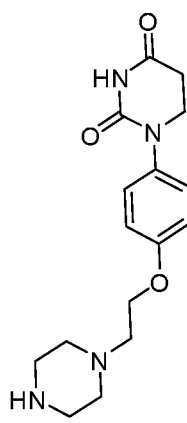
(ILB-32),



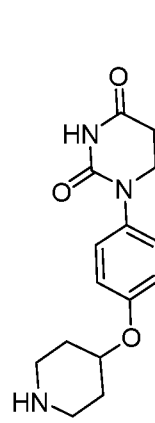
(ILB-33),



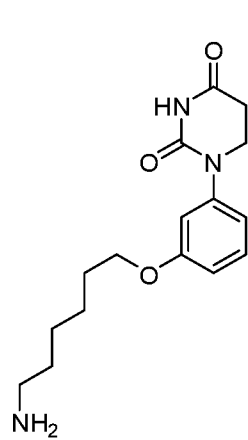
(ILB-34),



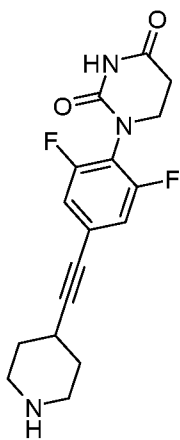
(ILB-35),



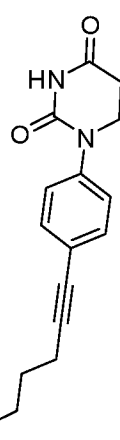
(ILB-36),



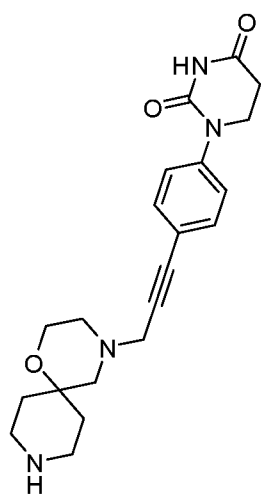
(ILB-37),



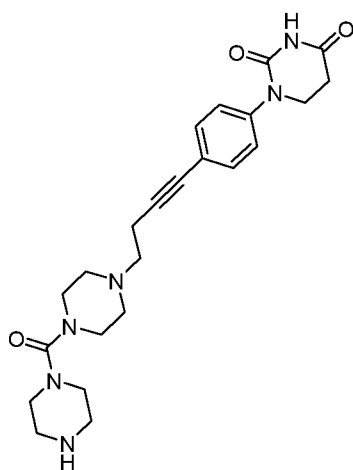
(ILB-38), I



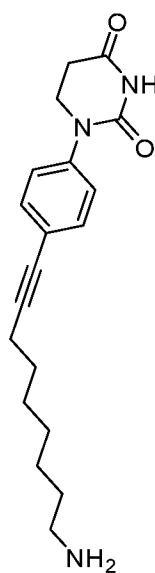
(ILB-39),



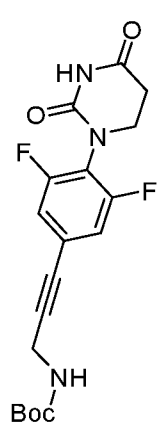
(ILB-40),



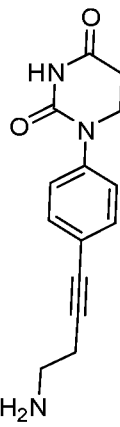
(ILB-41),



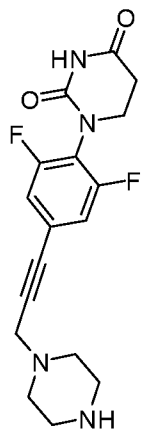
(ILB-42),



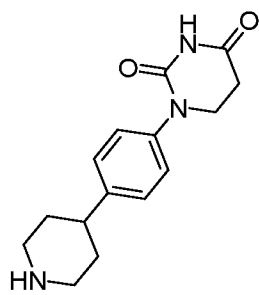
(ILB-43),



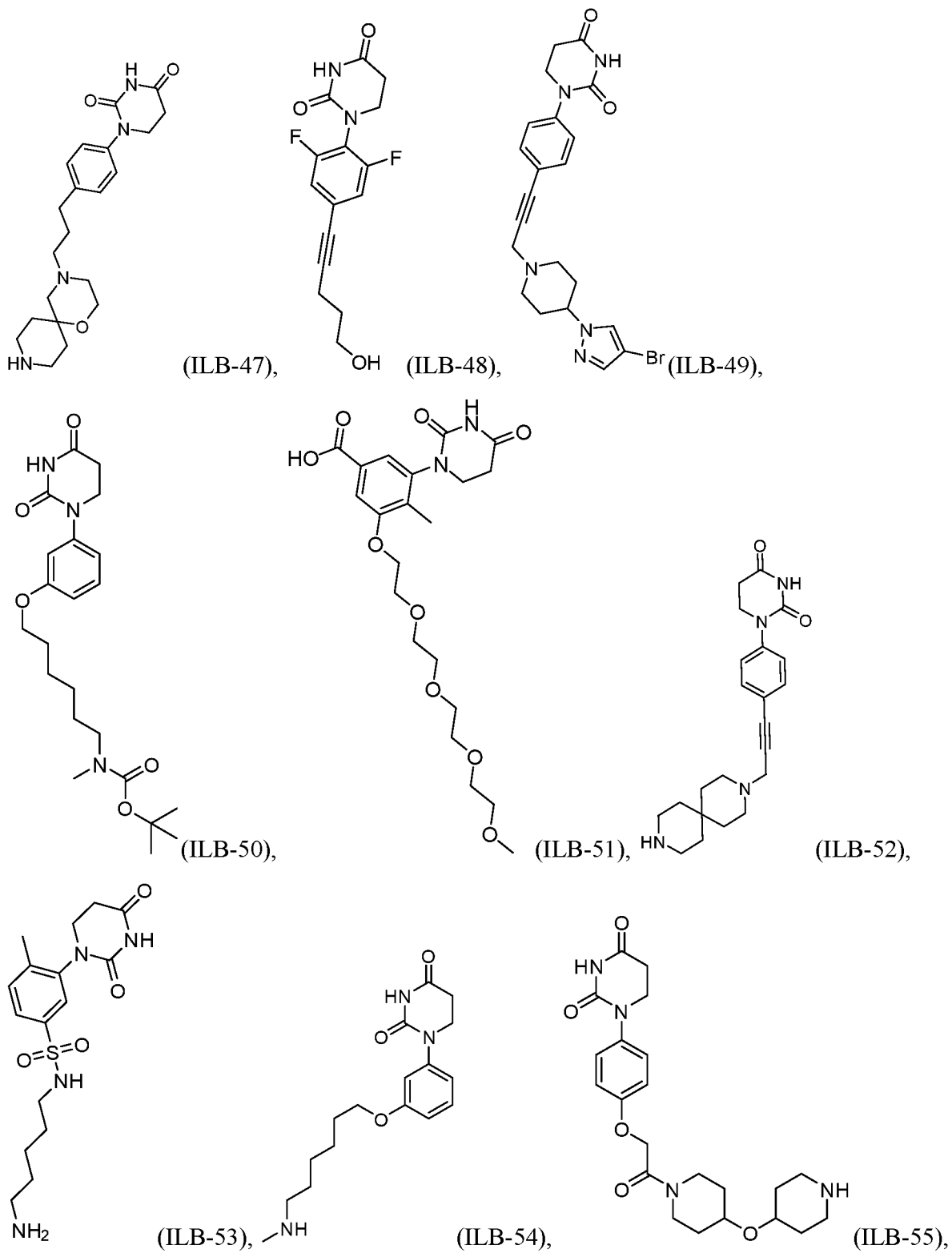
(ILB-44),

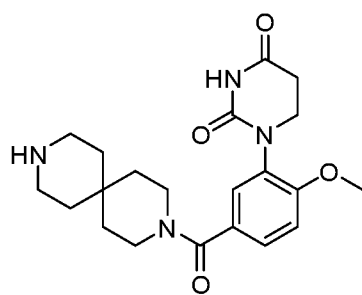


(ILB-45),

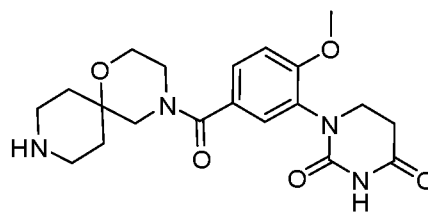


(ILB-46),

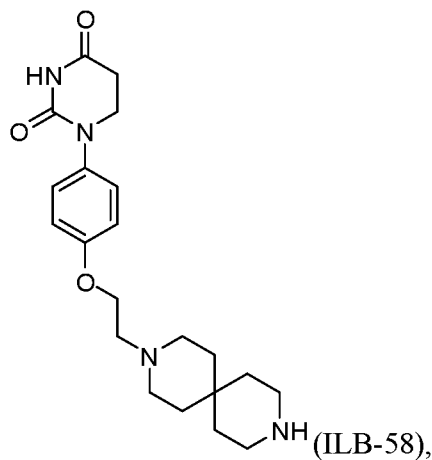




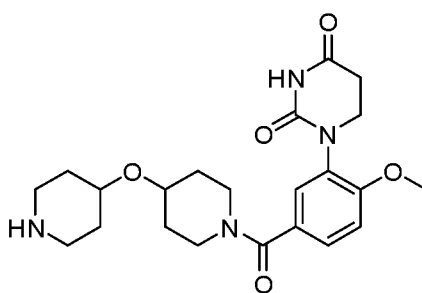
(ILB-56),



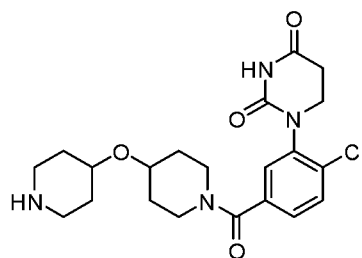
(ILB-57),



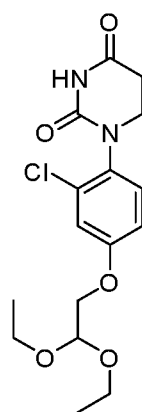
(ILB-58),



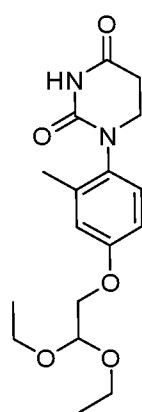
(ILB-59),



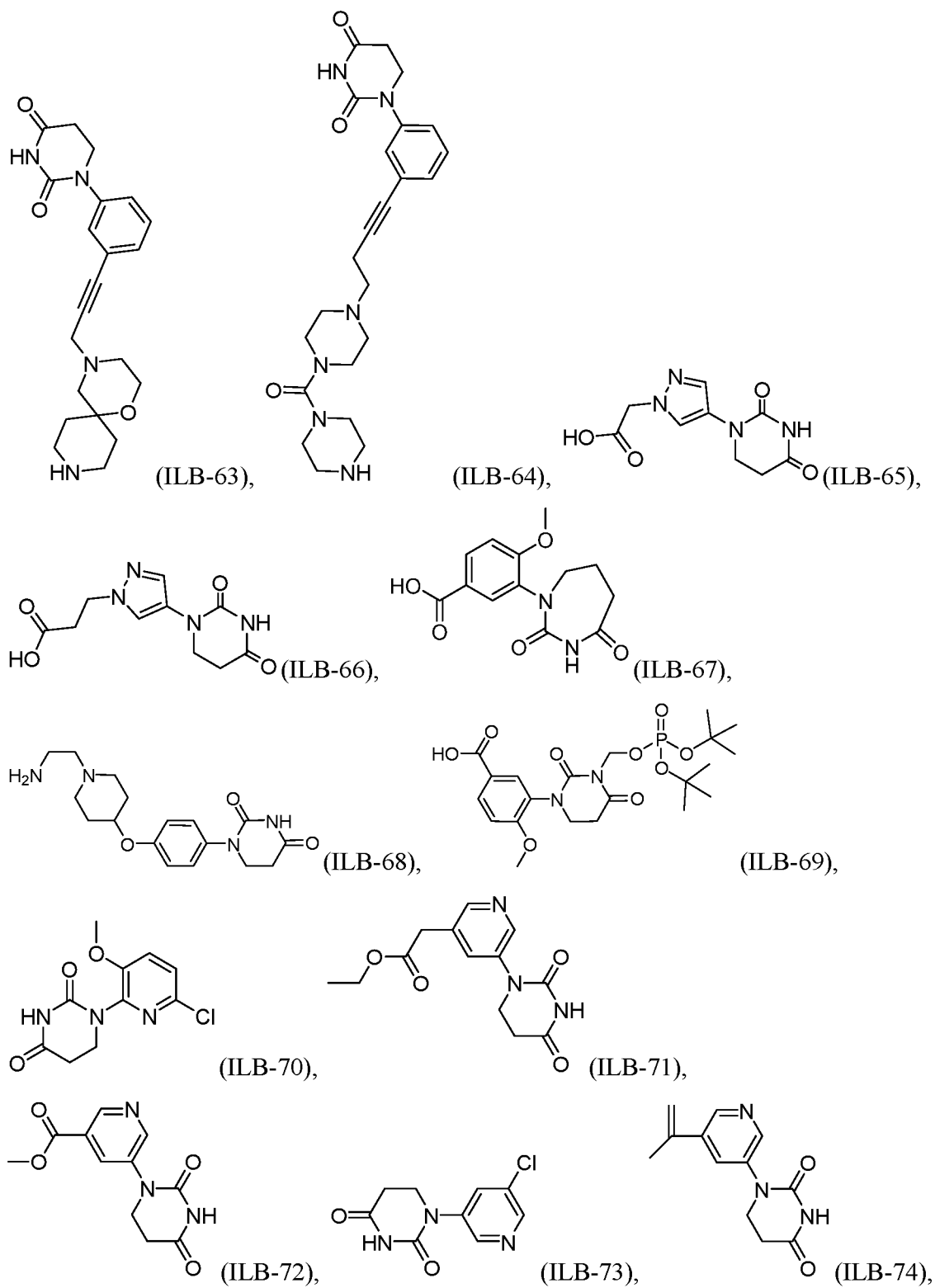
(ILB-60),

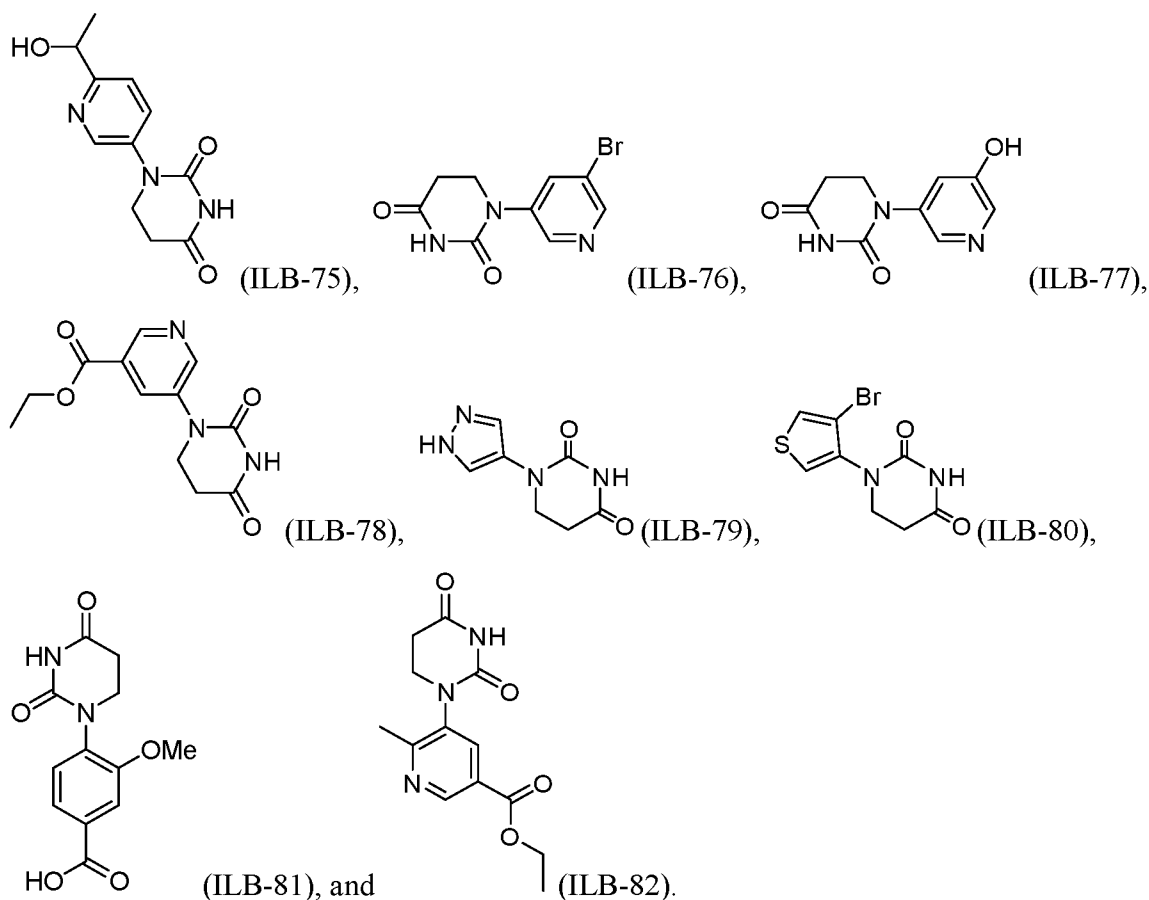


(ILB-61),

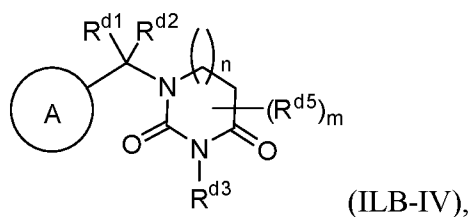


(ILB-62),



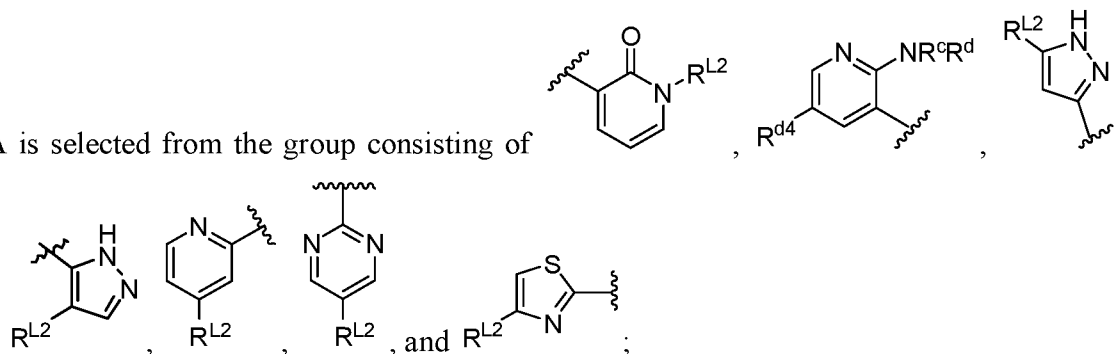


5 Another embodiment is a compound of Formula (ILB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

Ring A is selected from the group consisting of



 denotes the point of attachment to the base molecule of (ILB-IV);

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

R^{d3} is H, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and -OC₁₋₇ heteroalkyl;

each R^{d4a} is independently selected from the group consisting of H, polyethylene glycol (PEG), C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ haloalkyl, and C₂₋₆ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

R^{L2} is selected from the group consisting of hydroxyl, halogen, C₂₋₆ alkyl, C₁₋₃ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-6}NR^cR^d$, $-O-(CH_2)_{2-6}NHR^c$, C₃₋₈ heteroalkyl, C₁₋₆ haloalkyl, $-SO_2-NH-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-3}C(O)OH$, $-O-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{1-3}C(O)H$, $-O-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{0-3}C_{3-7}$ carbocyclyl, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}$ heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl-heteraryl, C₆ aryl, and heteroaryl, wherein the alkynyl, alkoxy, heterocyclyl, heteroalkyl, carbocyclyl, aryl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-C(O)O$ -benzyl, $-(CH_2)_{2-6}NHR^c$, heterocyclyl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C_{1-4} alkyl, C_{1-6} heteroalkyl, and $-C(O)OC_{1-6}$ alkyl;

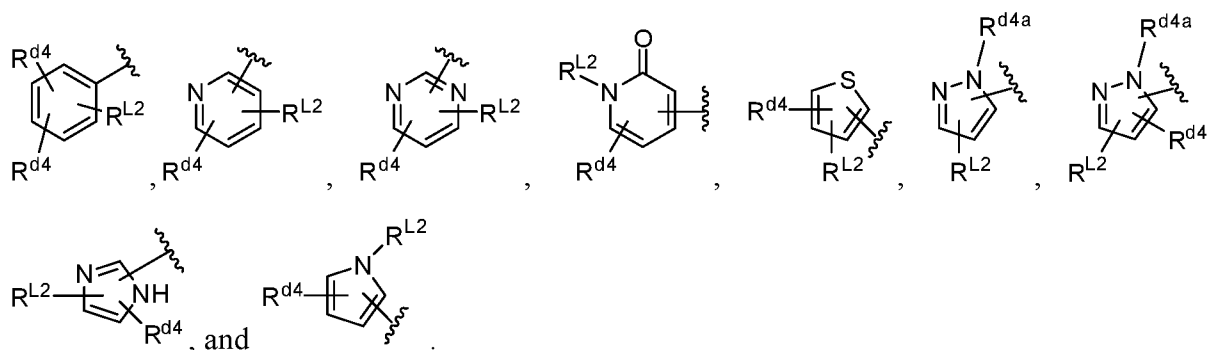
R^d is H or C_{1-4} alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0–2 occurrences of $-O-$ heterocyclyl,

R^p is H or C_{1-6} alkyl;

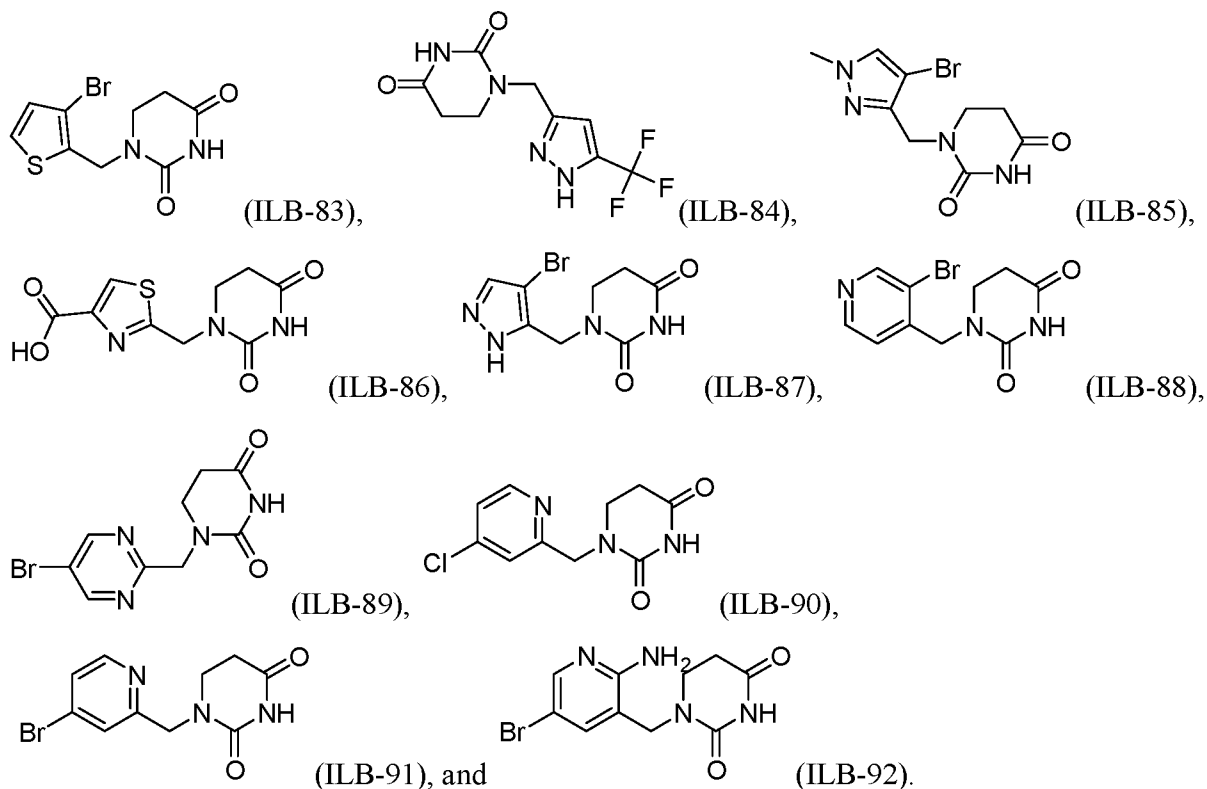
5 m is 1 or 2; and

n is 1 or 2.

In an embodiment, ring A is selected from the group consisting of:

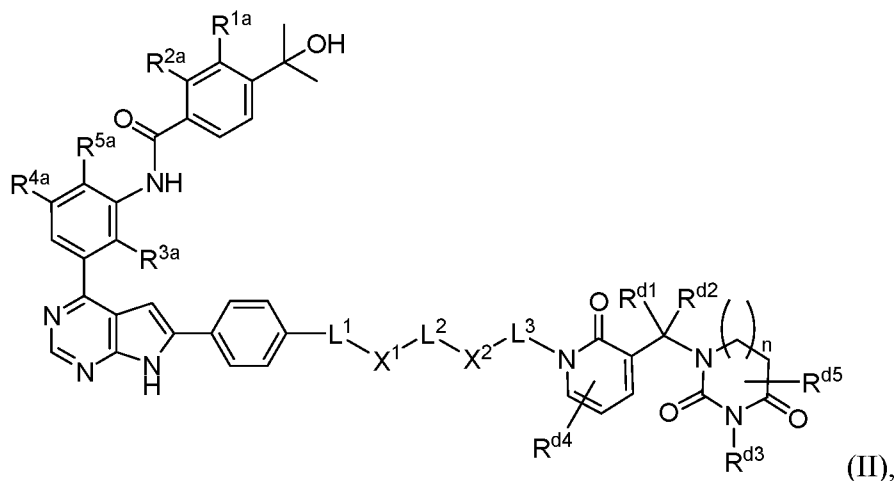


10 Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



15

Another embodiment is a bifunctional compound of Formula (II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,

wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O ,

and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

5 R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

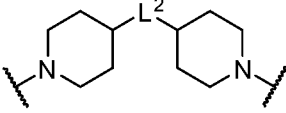
10 R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

R^p is H or C_{1-6} alkyl.

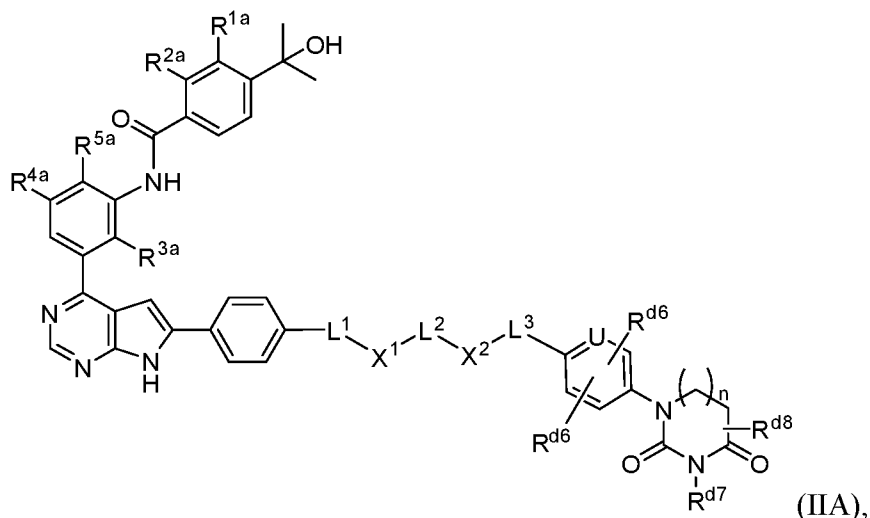
15 In an embodiment, R^{2a} is fluoro. In an embodiment, R^{3a} is C_{1-3} alkyl. In an embodiment, R^{3a} is methyl.

In an embodiment, R^{4a} is fluoro. In an embodiment, L^1 is C_{1-9} alkylene. In an embodiment, $-$

$X^1-L^2-X^2$ is: . In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, R^{d4} is H. In an embodiment, 20 R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H. In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d5} is H or C_{1-3} alkyl.

In an embodiment, R^{d5} is H.

Another embodiment is a bifunctional compound of Formula (IIA):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

5 R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

10 L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

15 L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

20 L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

U is $-CR^{d6}$ or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

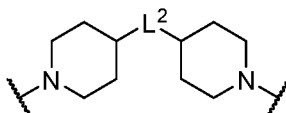
R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

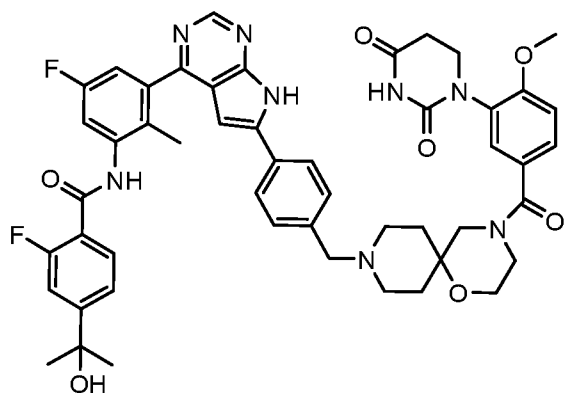
R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

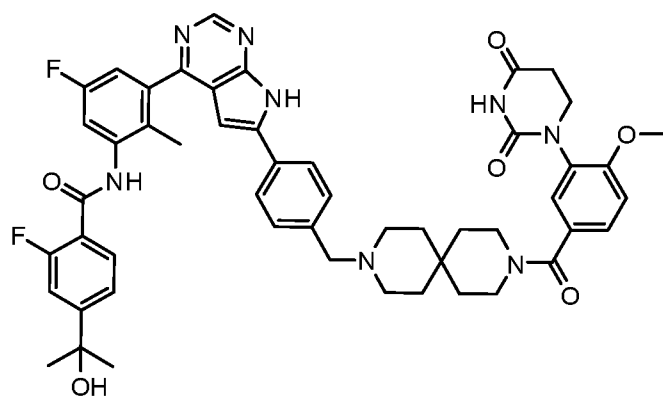
In an embodiment, R^{2a} is fluoro. In an embodiment, R^{3a} is C_{1-3} alkyl. In an embodiment, R^{3a} is methyl. In an embodiment, R^{4a} is fluoro. In an embodiment, L^1 is C_{1-9} alkylene. In an

embodiment, $-X^1-L^2-X^2-$ is: . In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, R^{d4} is H. In an embodiment, R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H. In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d5} is H or C_{1-3} alkyl. In an embodiment, R^{d5} is H.

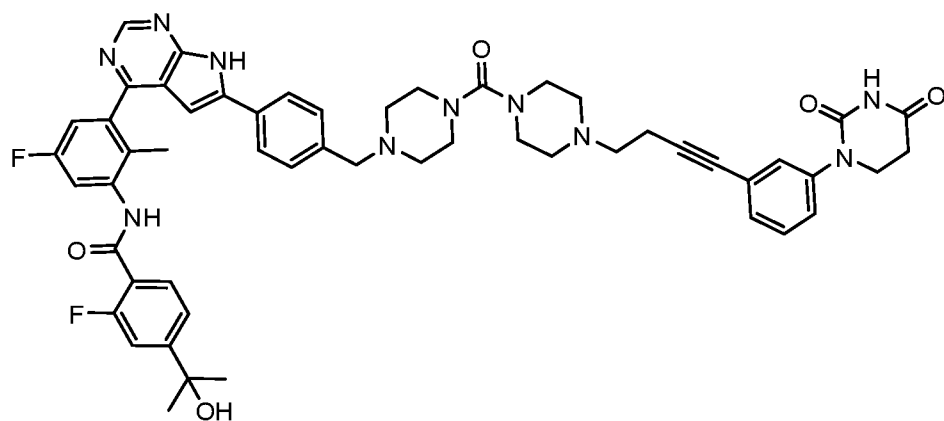
Another embodiment is a bifunctional compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



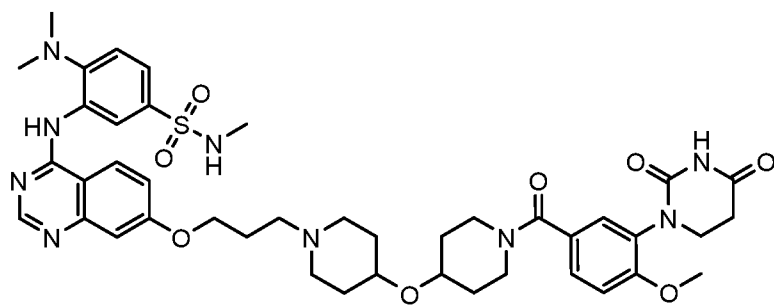
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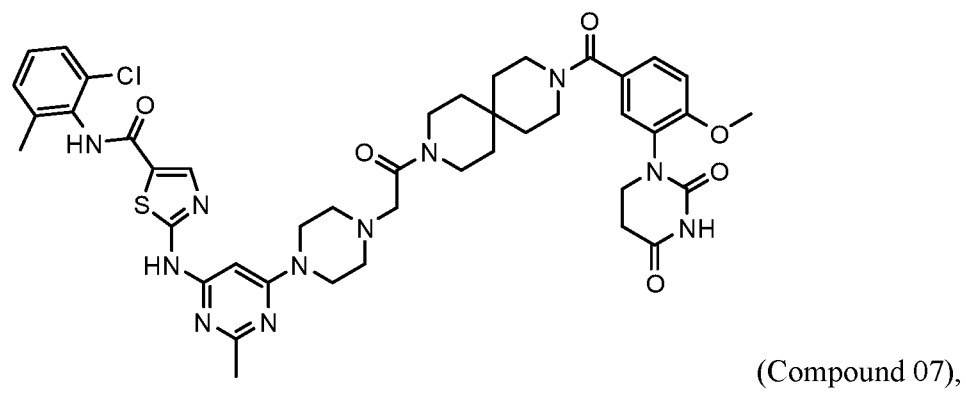
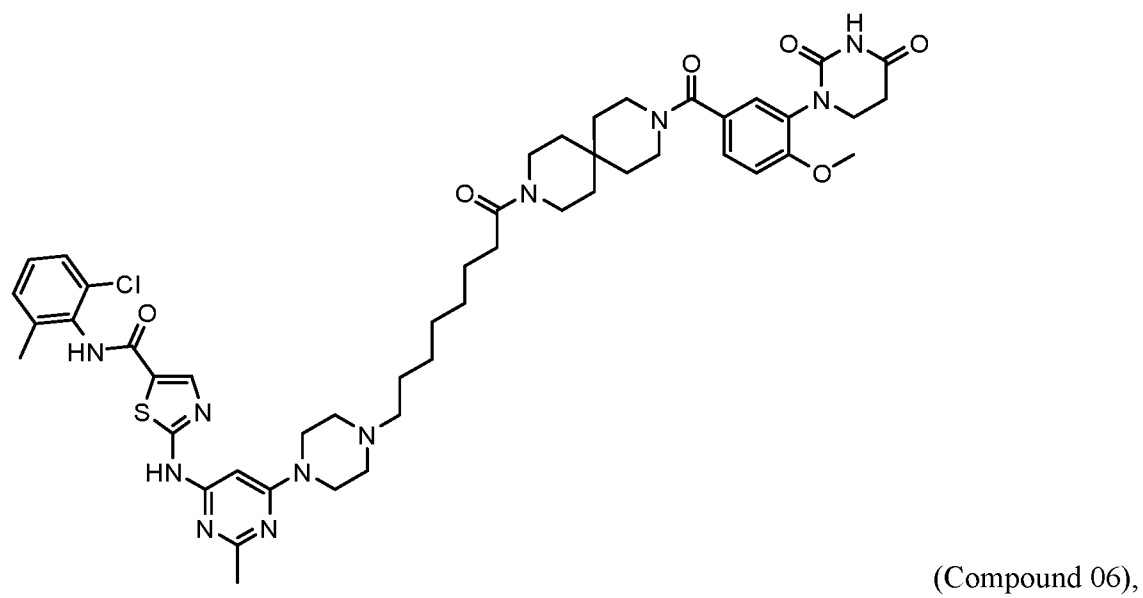
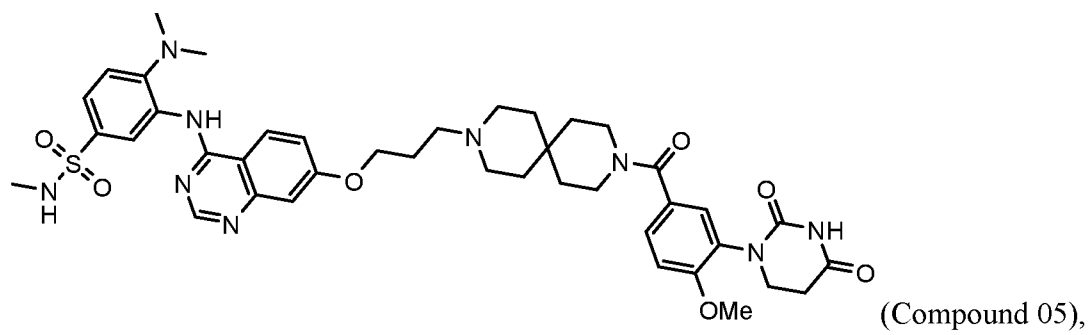
(Compound 02),

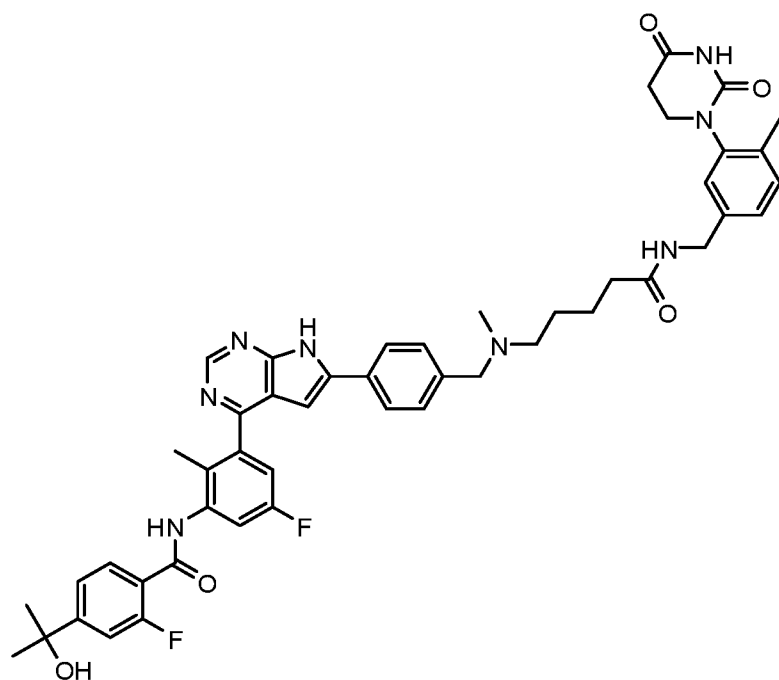


(Compound 03),

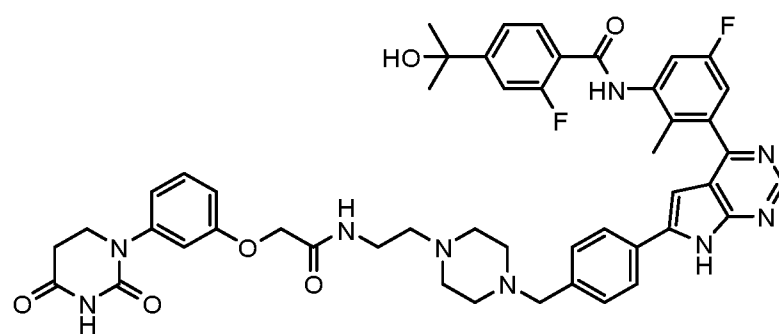


(Compound 04),

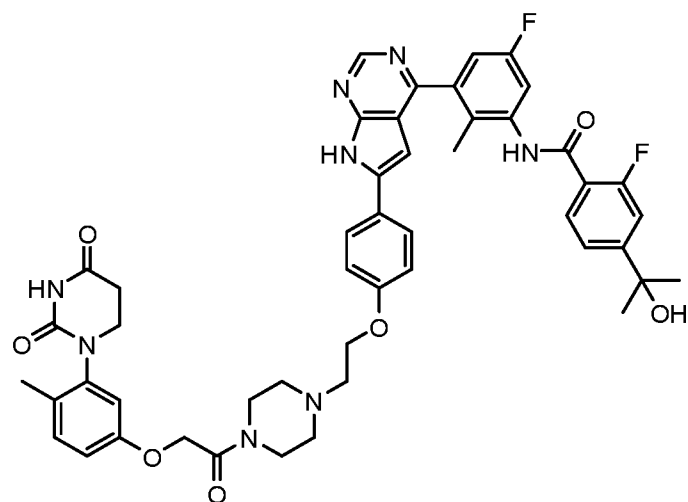




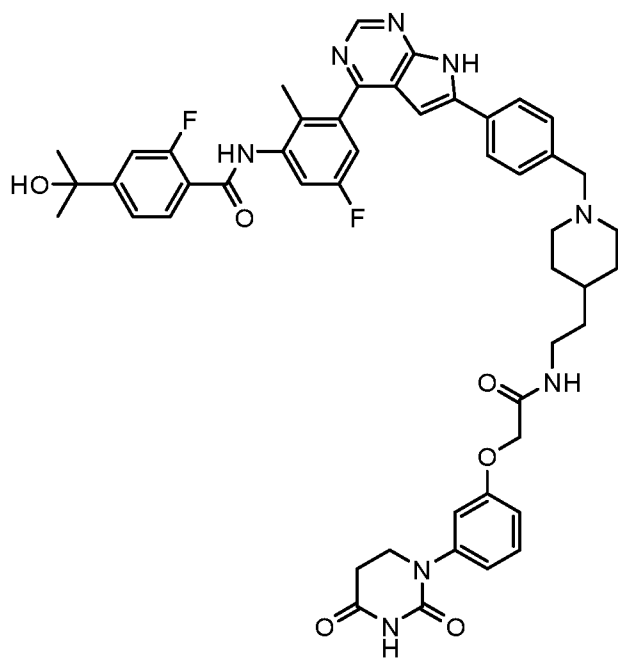
(Compound 08),



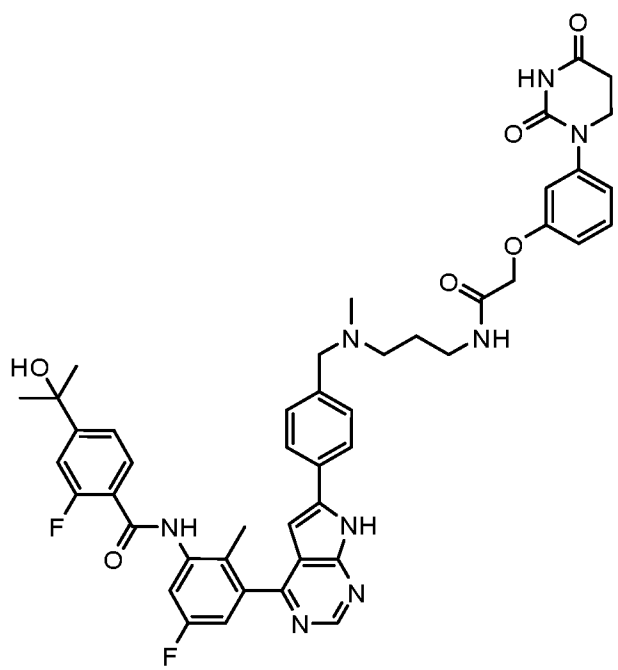
(Compound 09),



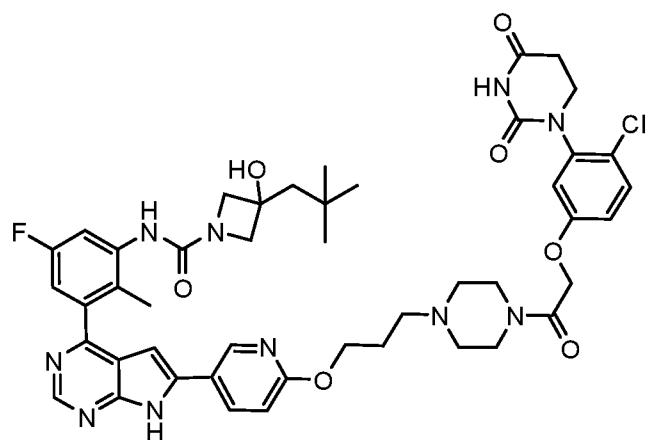
(Compound 10),



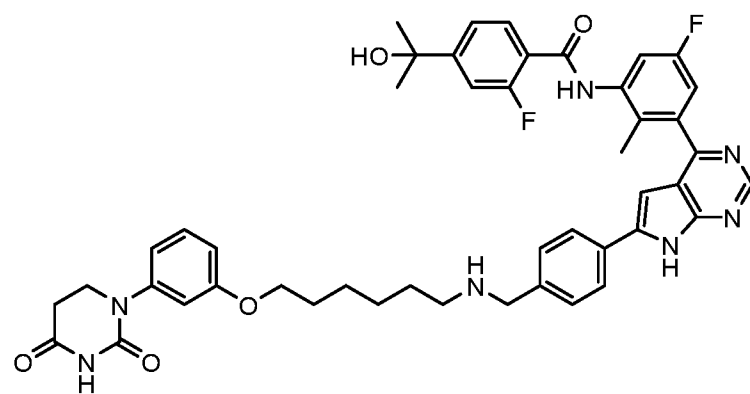
(Compound 11),



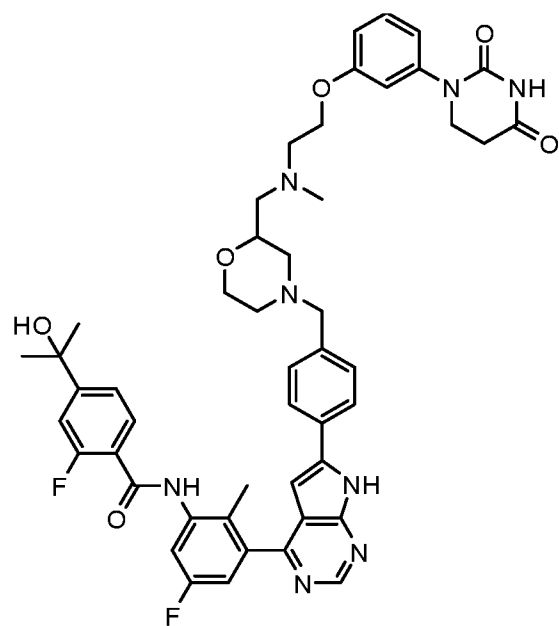
(Compound 12),



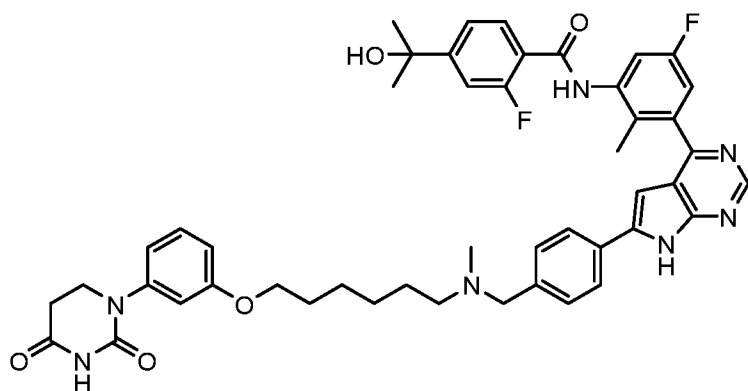
(Compound 13),



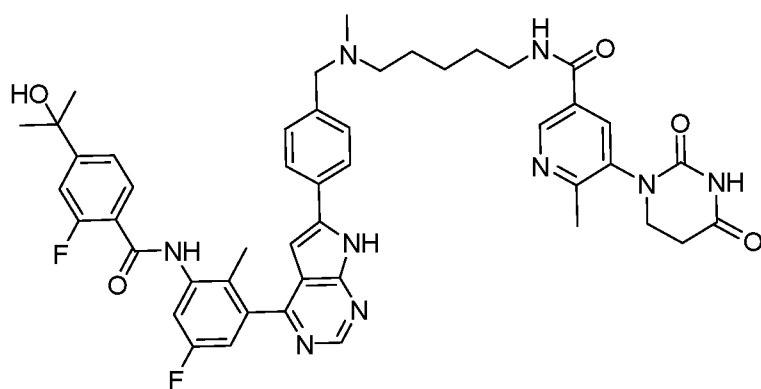
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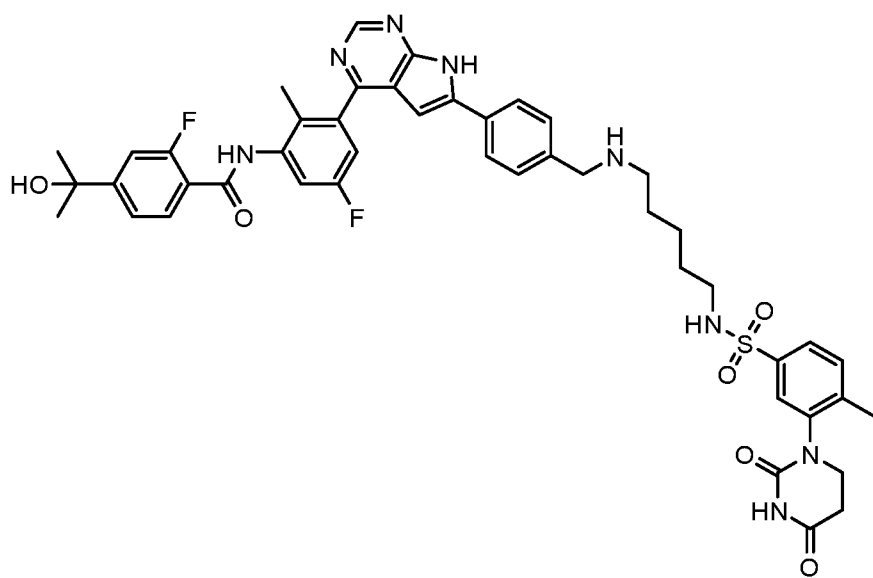
(Compound 15),



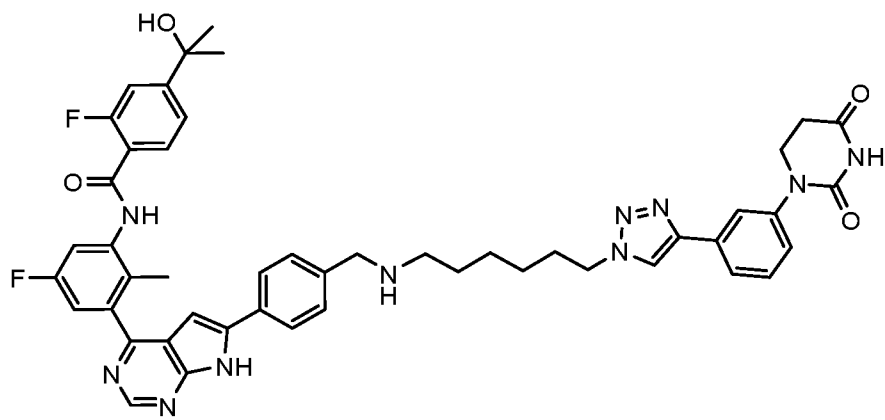
(Compound 16),



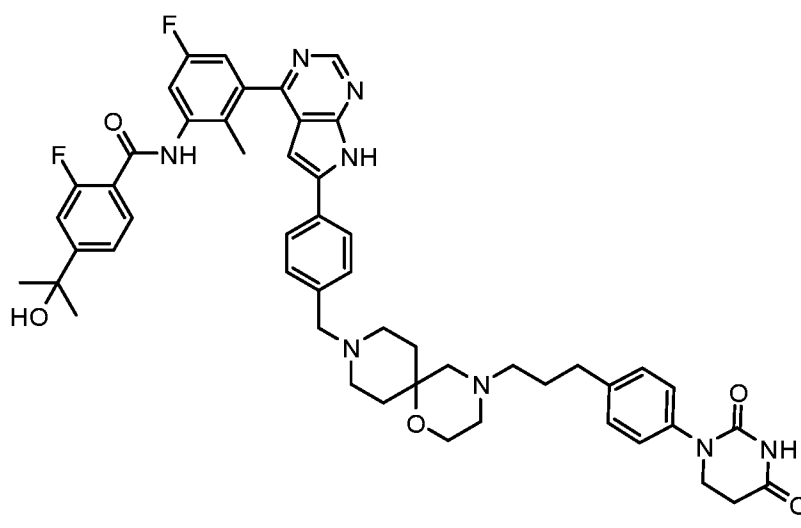
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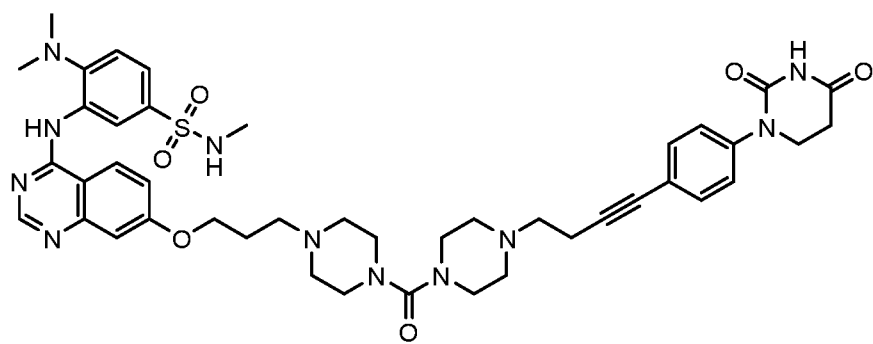
(Compound 18),



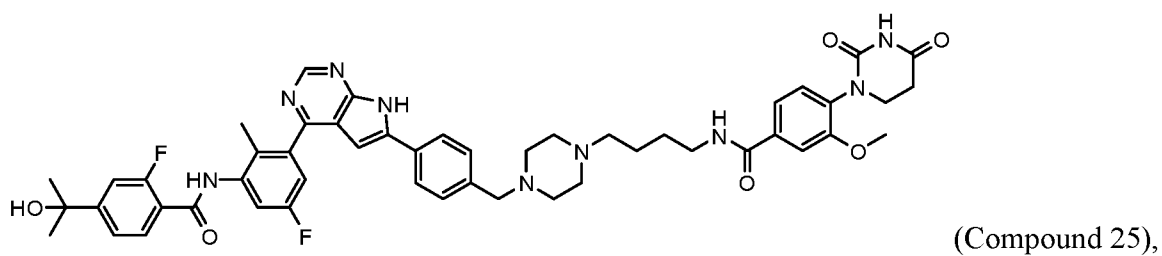
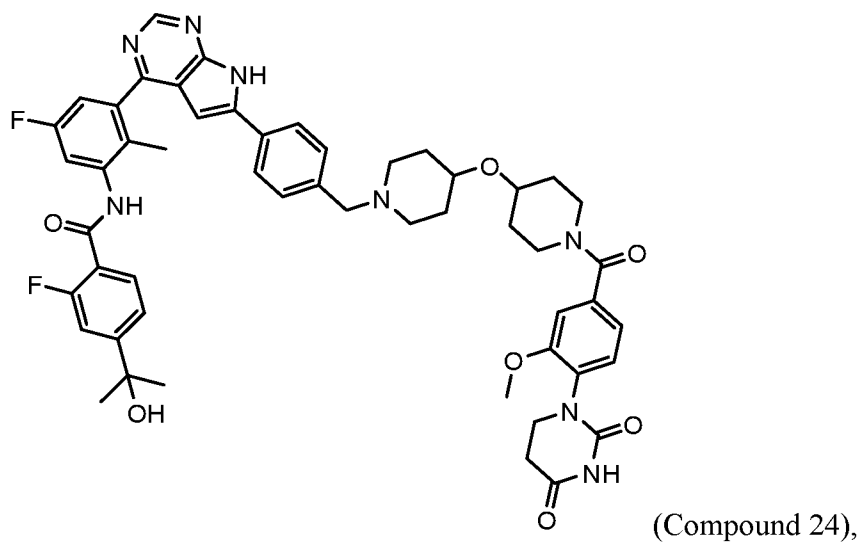
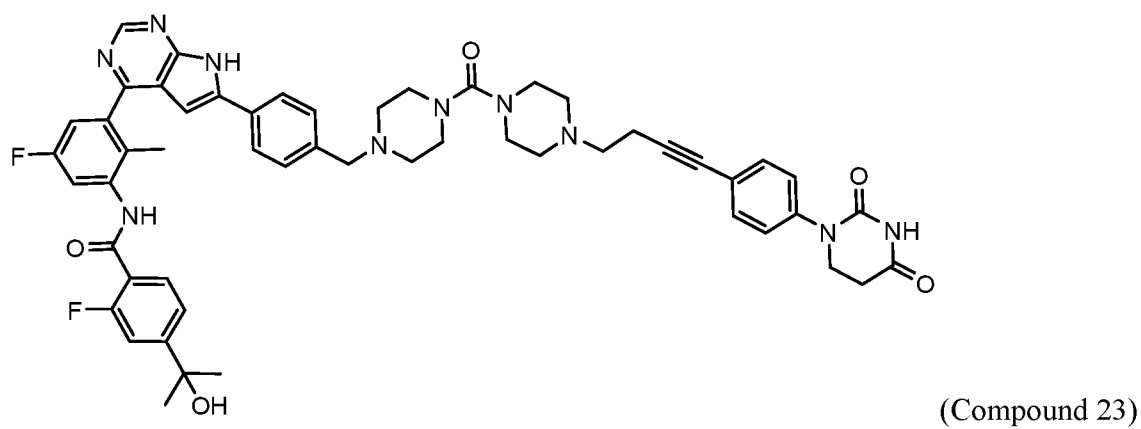
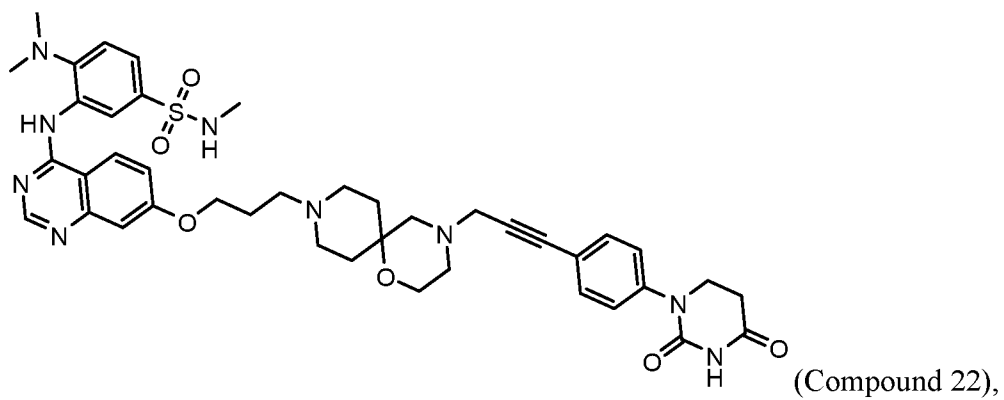
(Compound 19),

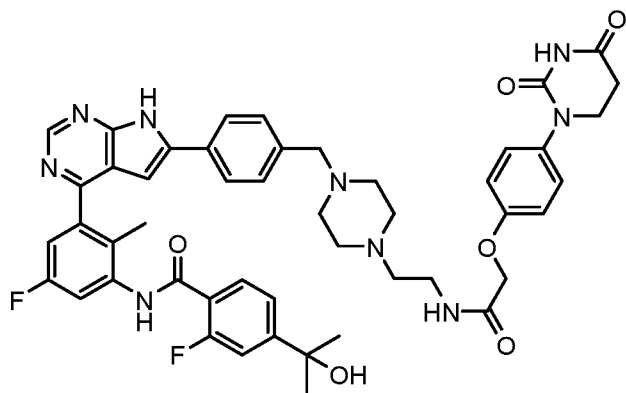


(Compound 20),

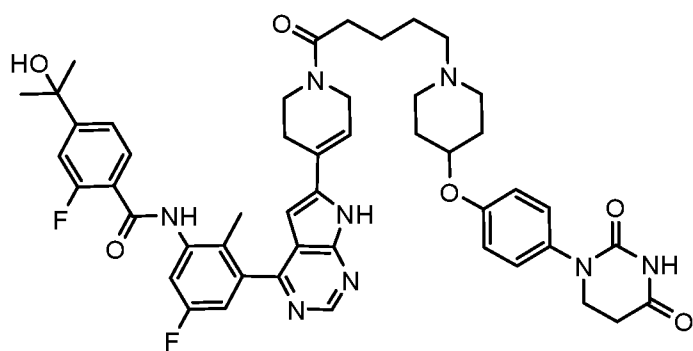


(Compound 21),

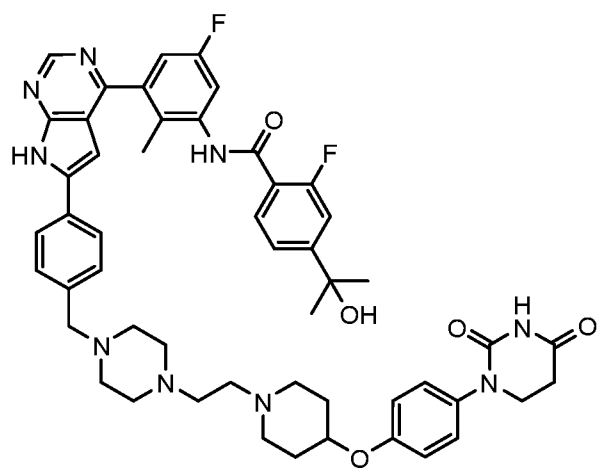




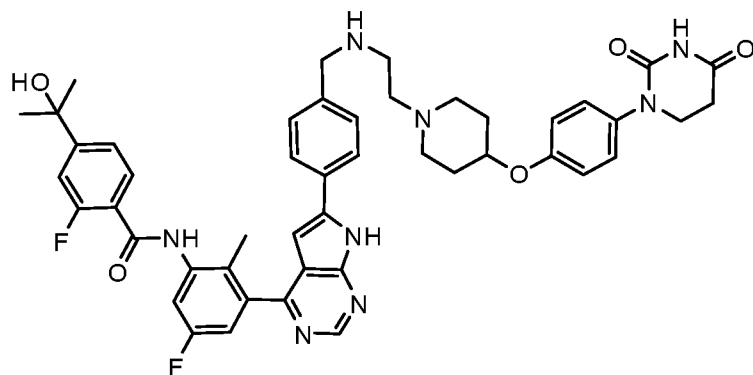
(Compound 26),



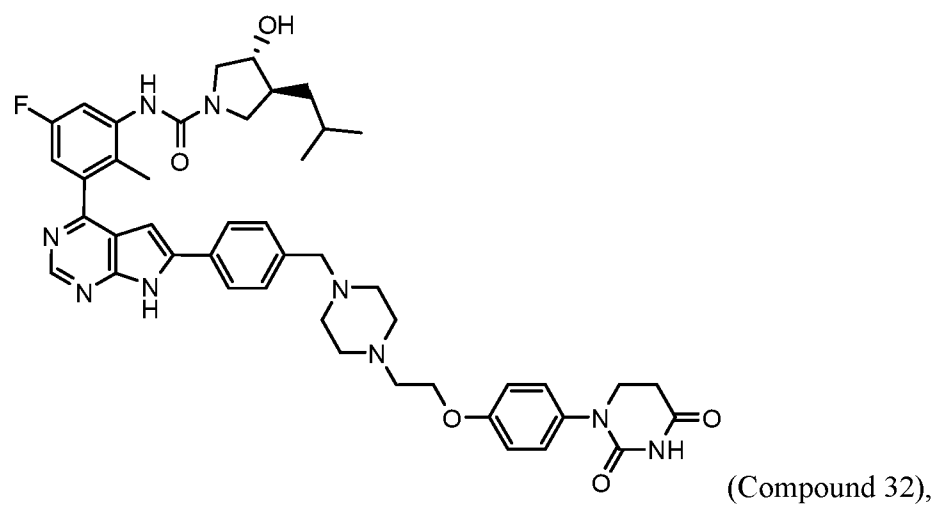
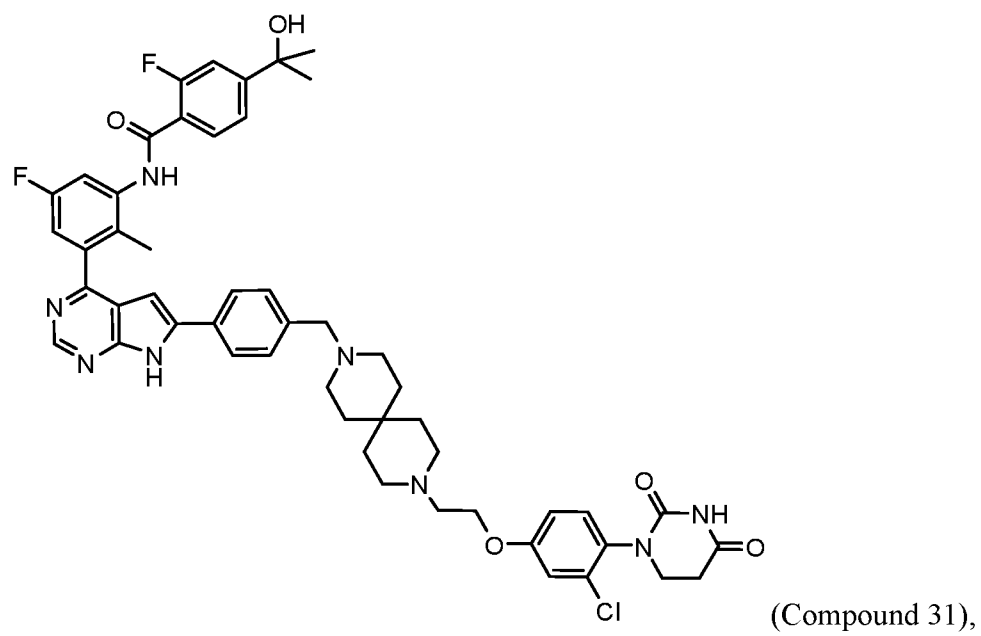
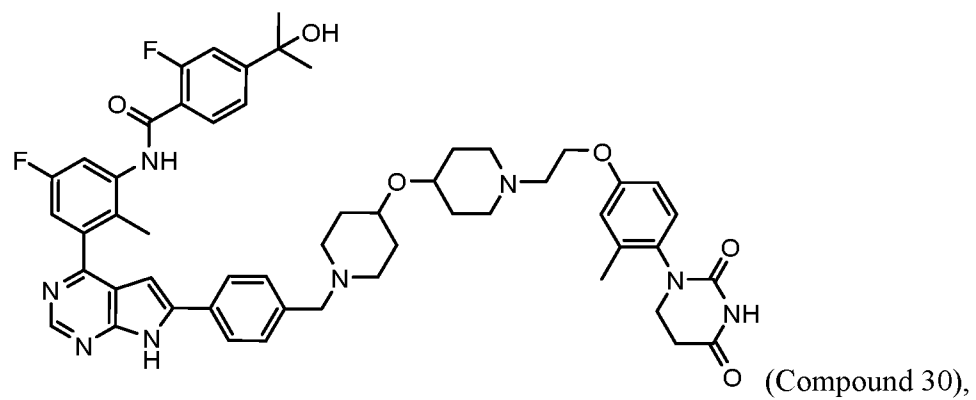
(Compound 27),

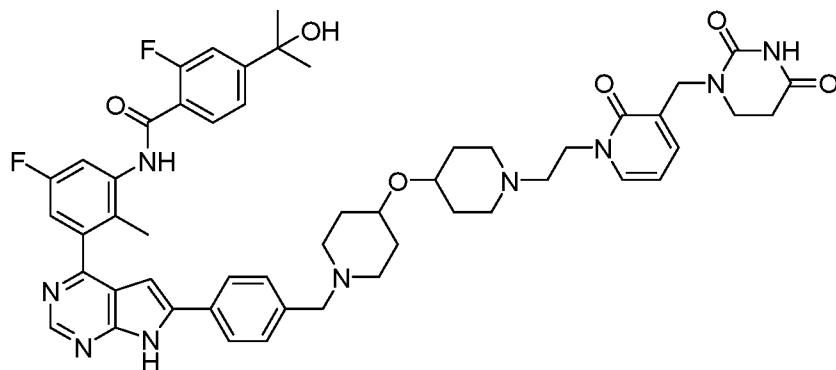


(Compound 28),

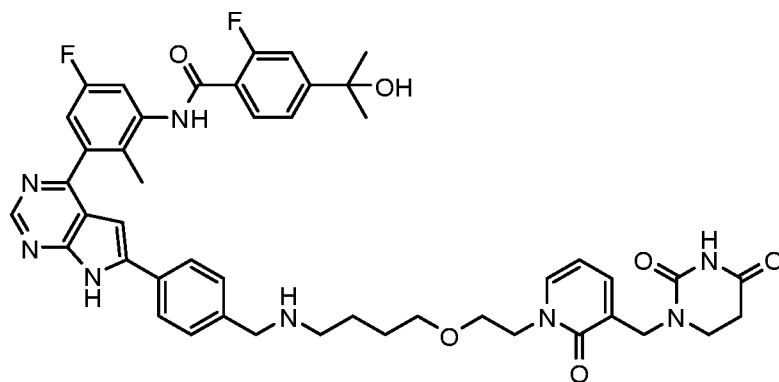


(Compound 29),

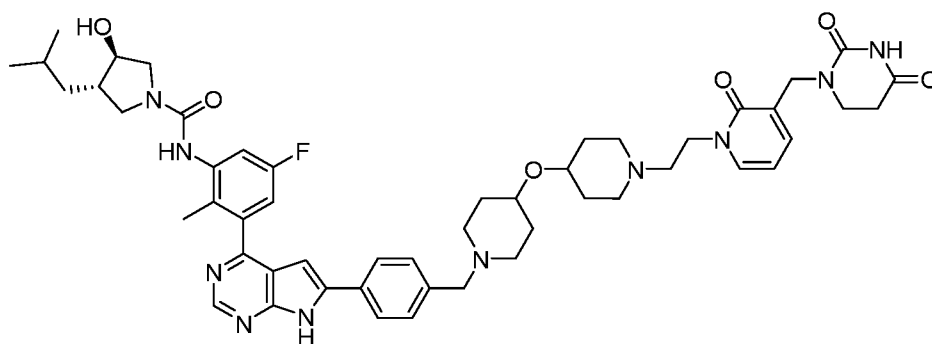




(Compound 33),



(Compound 34), and



(Compound 35).

Another embodiment is a pharmaceutical composition comprising any of the compounds described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

Another embodiment is a pharmaceutical combination comprising any of the compounds described herein, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a therapeutic agent.

Another embodiment is a method of treating a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder in a subject in need thereof, the method comprising

administering to the subject a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof. In an embodiment, the disorder is a proliferative disorder. In an embodiment, the proliferative disorder is cancer.

Another embodiment is the use of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof in the preparation of a medicament for treating a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder in a subject in need thereof. One aspect is se of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof for treating cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 depicts a schematic of a bifunctional compound, such as a compound disclosed herein, which is bound to a protein of interest (POI), and which has recruited the POI to the E3 Ubiquitin ligase binding complex for tagging with Ubiquitin (Ub), marking the POI for degradation by the ligase, followed by translocation to the proteasome and subsequent degradation

FIG. 2 depicts a scheme for *in silico* design of bifunctional degraders. “B” is a hypothetical bifunctional degrader with targeting motifs for the target protein (a) and the E3 ligase substrate receptor (c). Curved arrows on “B” depict conformational degrees of rotation. “A” depicts a target protein. “C” depicts the E3 ligase substrate receptor.

FIG. 3A shows a Hill plot of TNNI3K expression as a function of compound 22 concentration.

FIG 3B shows a bar graph of TNNI3K expression as a function of compound 22 concentration.

FIG, 3C shows a Hill plot of TNNI3K expression as a function of compound 21 concentration.

FIG. 3D shows a bar graph of TNNI3K expression as a function of compound 21 concentration.

FIG. 3E shows volcano plots depicting the identification of degrader-dependent CRBN substrate candidates. HEK293 and TMD8 cells were treated with 1 μ M dasatinib, 1 μ M compound 06, 1 μ M compound 07 or DMSO and protein abundance was analyzed using TMT quantification

mass spectrometry. Significant changes were assessed by limma, log₂ fold changes are shown on the x-axis and p-values on the y-axis. Proteins with kinase annotations in UniProt are shown as squares and kinases with a log₂ fold change ≤ -0.6 and a p-value ≤ 0.01 are labeled with the corresponding gene name.

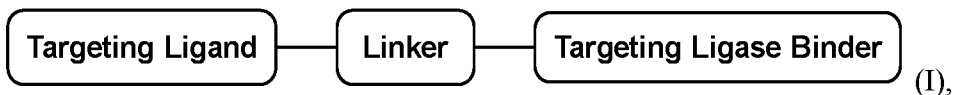
5 FIG. 4A shows a Western blot of TNNI3K expression as a function of compound 22 concentration. β -actin is used as a control.

FIG 4B shows a Western blot of TNNI3K expression as a function of compound 21 concentration. β -actin is used as a control.

10 DETAILED DESCRIPTION

Described herein are compounds or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof that function to recruit targeted proteins to E3 ubiquitin ligase for degradation, methods of preparation thereof, and uses thereof.

15 In one aspect, the disclosure provides are compounds or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which recruit a targeted protein, as a bromodomain-containing protein or a protein kinase, to E3 ubiquitin ligase for degradation. In an embodiment, the compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, is a compound of Formula (I):



20 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

the Targeting Ligand is a group that is capable of binding to a Target Protein;

the Linker is a group that covalently links the Targeting Ligand to the Targeting Ligase Binder;
and

25 the Targeting Ligase Binder is a group that is capable of binding to a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase).

Target Proteins

30 In one aspect, the disclosure provides compounds or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, which recruit a targeted protein, such

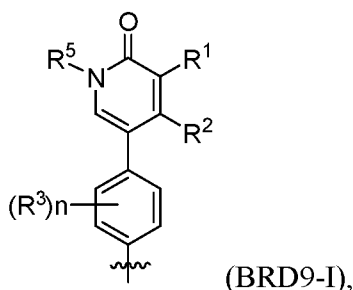
as a bromodomain-containing protein or a protein kinase, to E3 ubiquitin ligase for degradation. In an embodiment, the target protein is selected from **Table 1** or **Table 2**.

Targeting Ligands

The Targeting Ligand is a small molecule moiety that is capable of binding to a target protein or protein of interest (POI). In an embodiment, the target protein or POI is a target protein selected from **Table 1**. In an embodiment, the target protein or POI is a fusion protein. In an embodiment, the target protein or POI is a target protein selected from **Table 2**.

In an embodiment, the Targeting Ligand is a BRD9 targeting ligand of Formula (BRD9-

I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^1 and R^2 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1

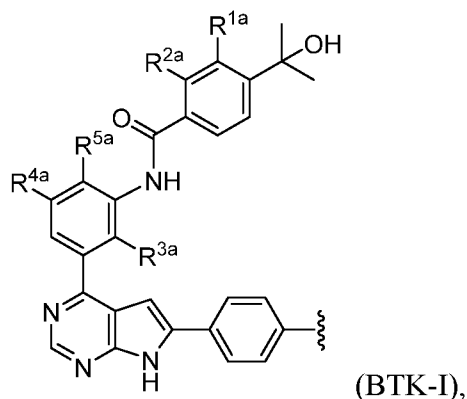
and R^2 together with the atoms to which they are attached form an aryl or heteroaryl;

R^3 are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, and halogen;

R^5 is selected from the group consisting of hydrogen and C_{1-3} alkyl;

n is 0, 1, or 2.

In an embodiment, the Targeting Ligand is a BTK targeting ligand of Formula (BTK-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

5 R^{2a} is halo;

R^{3a} is C₁₋₆ alkyl;

R^{4a} is halo; and

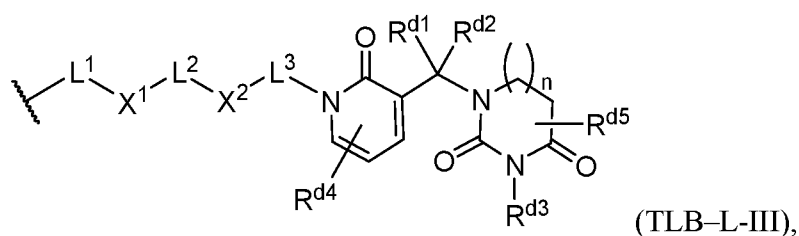
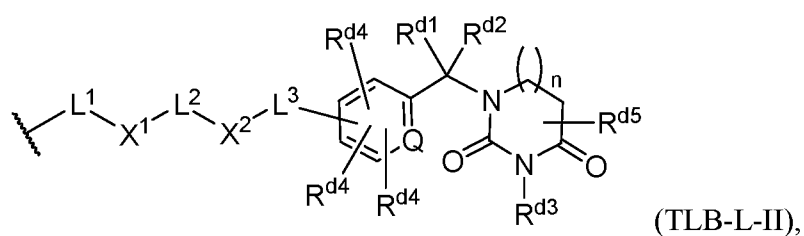
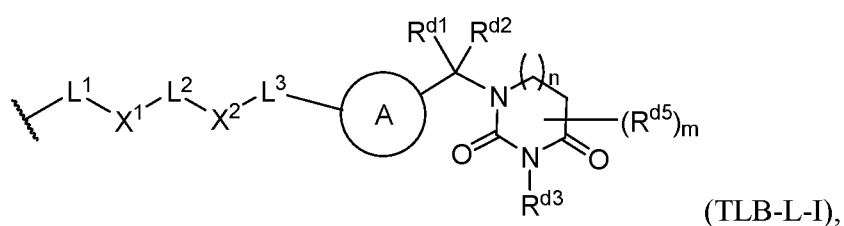
R^{5a} is H or halo.

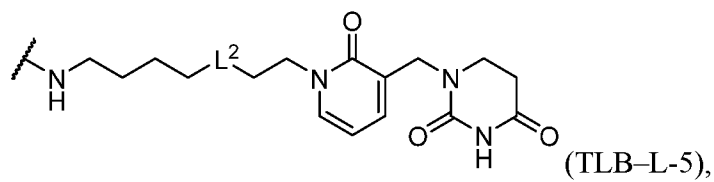
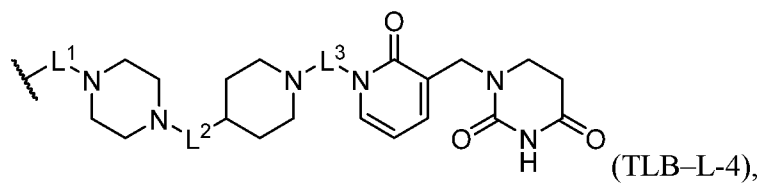
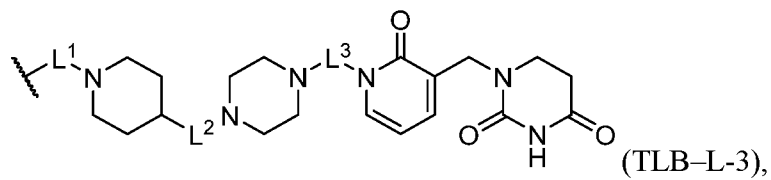
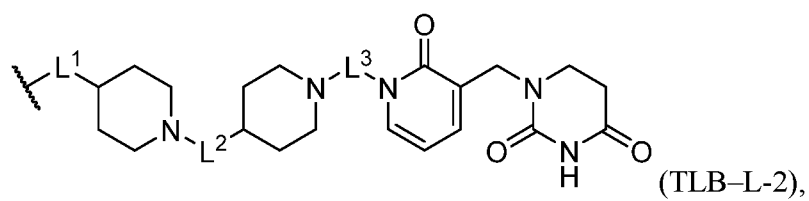
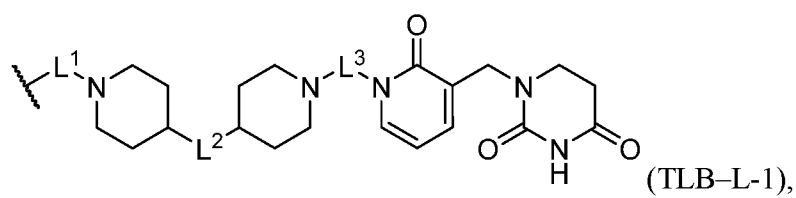
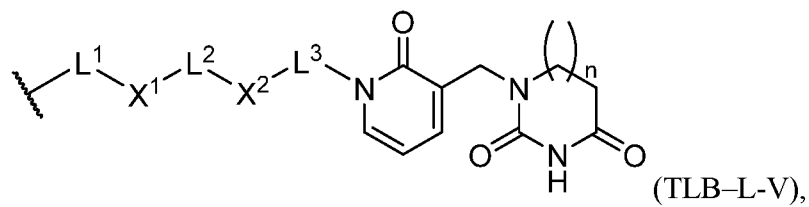
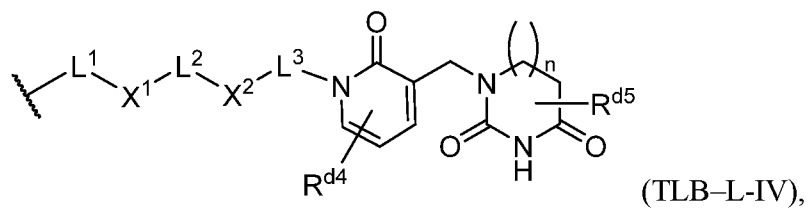
Additional exemplary Targeting Ligands include, but are not limited to, the targeting
10 ligands in **Table 3**:

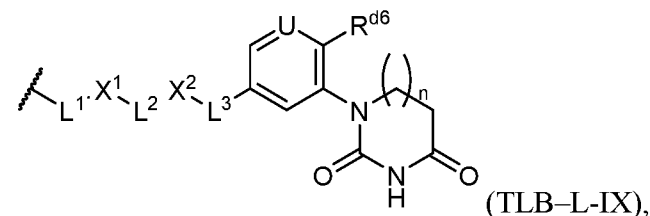
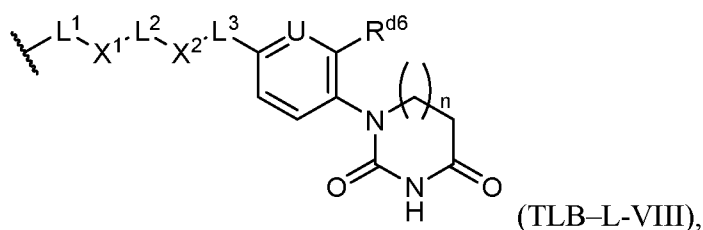
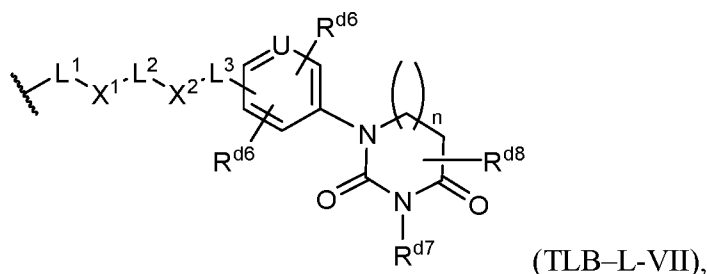
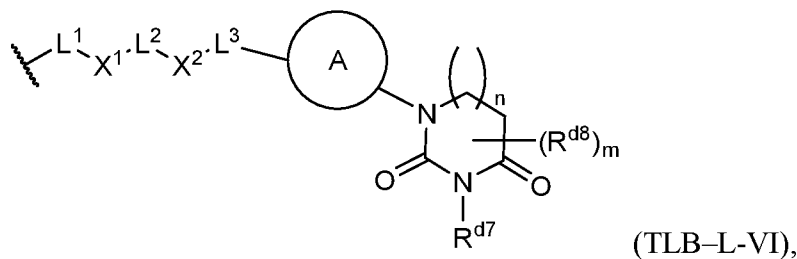
Gene	Targeting Ligand
ALK	ceritinib
AR	7a-methyl-19-nortestosterone
AR	Testosterone
BCR-ABL	dasatinib
BRD4	JQ1
BRD9	BI-7273
BTK	bosutinib
BTK	RN486
CDK9	SNS-032
c-Met	foretinib
EGFR	AC480

EGFR	ARRY-334543
EGFR	afatinib
ER α	4-OHT
EGFR Δ Exon 19	gefitinib
FKBP12	Steel Factor
FLT3	4SC-202
FLT3	Linifanib
FLT3	Quizartinib (AC220)
JAK2	AC430
HDAC4	AR-42
HDAC6	ACY-1215
HDAC6	AR-42
TRIM24	IACS-7e

wherein the Targeting Ligand is attached to the Linker-Targeting Ligase Binder, *e.g.*,



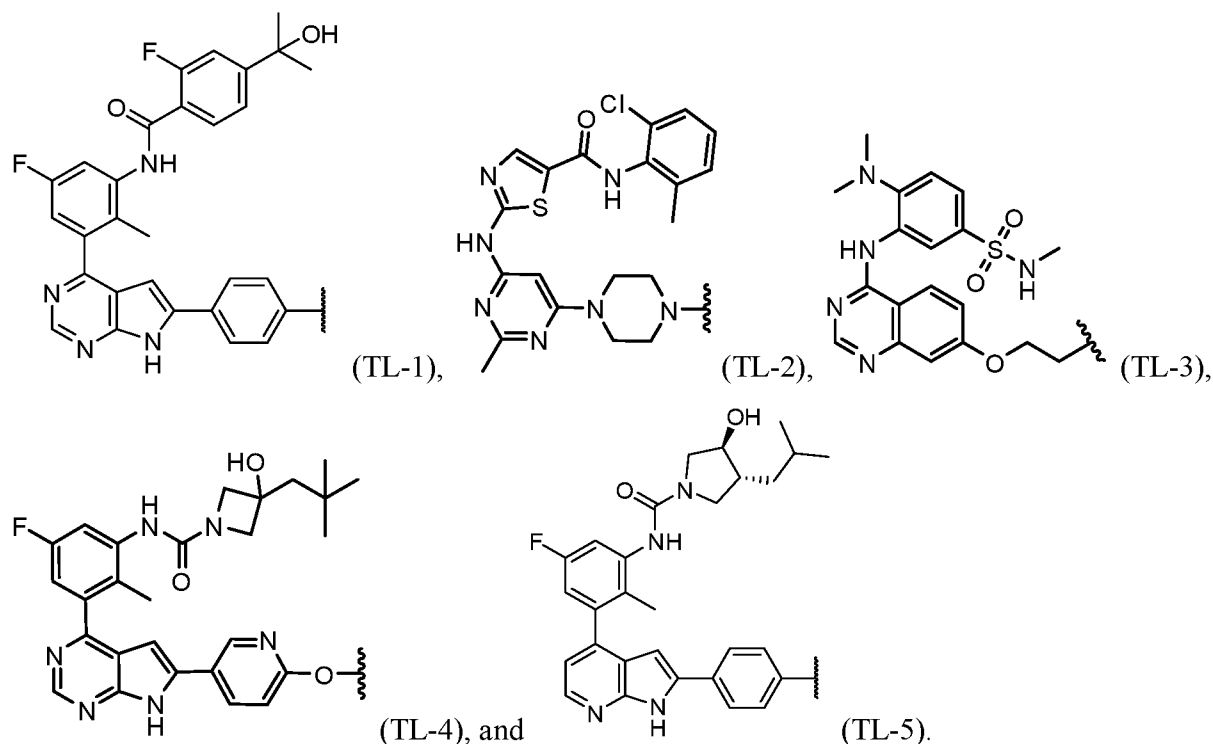




through a modifiable carbon, oxygen, nitrogen or sulfur atom on the Targeting Ligand.

In an embodiment, the Targeting Ligand is a targeting ligand described in Huang et al., “A Chemoproteomic Approach to Query the Degradable Kinome Using a Multi-kinase Degradar,” *Cell Chem. Biol.* 25(1): 88-99 (2018); An and Fu, “Small-molecule PROTACs: An emerging and promising approach for the development of targeted therapy drugs,” *EBioMedicine* 36: 553-562 (2018); Pei et al., “Small molecule PROTACs: an emerging technology for targeted therapy in drug discovery,” *RSC Adv.* 9:16967-16976 (2019); and Zou et al., *Cell Biochem. Funct.* 37: 21-30 (2019), each of which is incorporated by reference herein in its entirety.

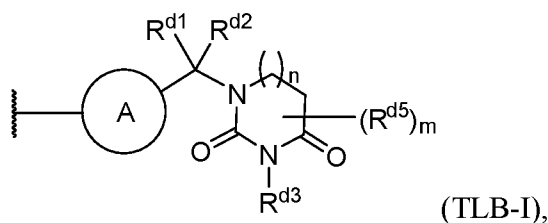
In an embodiment, the Targeting Ligand is selected from the group consisting of:



Targeting Ligase Binder

The Targeting Ligase Binder brings a protein of interest (POI) into close proximity to a ubiquitin ligase for tagging with Ubiquitin (Ub), marking the POI for degradation by the ligase through the linking of the Target Ligase Binder bound to the ubiquitin ligase (*e.g.*, an E3 Ubiquitin ligase binding complex), Linker (L), and a Targeting Ligand (TL) bound to the POI. See *e.g.*, FIG. 1.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Linker in Formula (I);

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

5 each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

10 or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

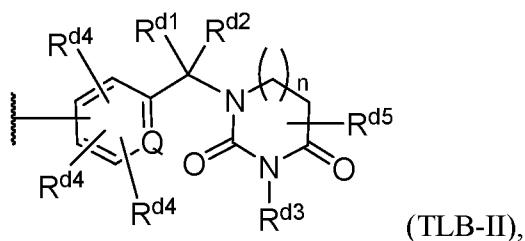
R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, A is a 5-membered nitrogen-containing heteroaryl. In an embodiment, A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl or pyridonyl. In an embodiment, R^{d4} is hydroxyl or C_{1-6} alkoxy.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

25  denotes the point of attachment to the Linker in Formula (I);

Q is N or CR^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

5 each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

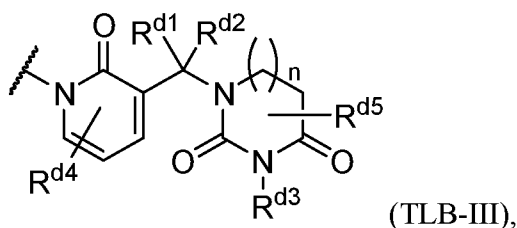
R^p is H or C₁₋₆ alkyl; and

10 n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

In an embodiment, R^{d4} is hydroxyl or C₁₋₆ alkoxy.

In another embodiment, the Targeting Ligase Binder has a Formula (TLB-III):



15

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

20 R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

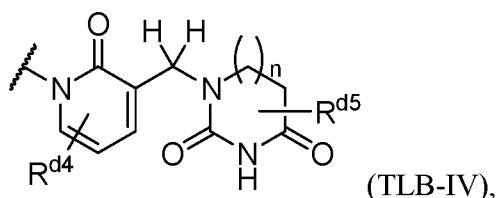
25 R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H.

5 In an embodiment, the Targeting Ligase Binder has a Formula (TLB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

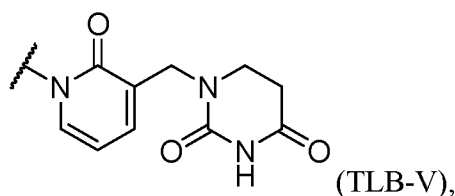
10 R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

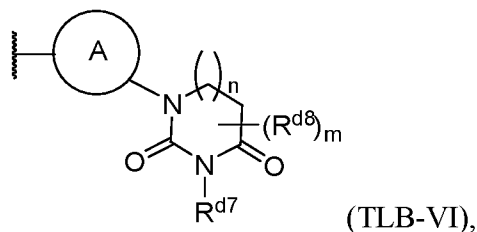
15 In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d4} is H or C_{1-3} alkyl. In an embodiment, R^{d4} is H. In an embodiment, R^{d5} is H or C_{1-3} alkyl. In an embodiment, R^{d5} is H.

In another embodiment, the Targeting Ligase Binder has a Formula (TLB-V):



20 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VI):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Linker in Formula (I);

- 5 Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

- R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$,
10 $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

- 15 or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

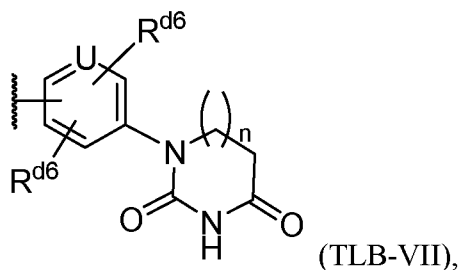
m is 1 or 2; and

n is 1 or 2.

- In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is
20 a nitrogen-containing 6-membered heteroaryl. In an embodiment, ring A is pyridyl.

- In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d7} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d7} is H. In an embodiment, R^{d8} is H. In an embodiment, R^{d7} and R^{d8} are both H. In an embodiment, R^{d6} is H. In an embodiment, R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy. In an embodiment, R^{d6} is selected
25 from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^{d7} , and R^{d8} are each H.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Linker in Formula (I);

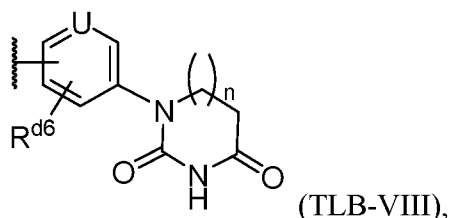
5 U is $-\text{CR}^{\text{d6}}$ or N;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

10 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, each R^{d6} is independently selected from the group consisting of H, halogen, C_{1-3} alkyl, and C_{1-3} alkoxy. In an embodiment, each R^{d6} is H. In an embodiment, one of R^{d6} is H. In an embodiment, one of R^{d6} is not H.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-VIII):



15 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

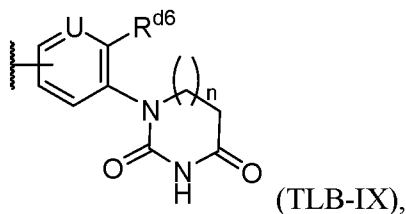
— denotes the point of attachment to the Linker in Formula (I);

U is $-\text{CR}^{\text{d6}}$ or N;

R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

20 n is 1 or 2.

In an embodiment, the Targeting Ligase Binder has a Formula (TLB-IX):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

5 U is independently $-\text{CR}^{\text{d6}}$ or N;

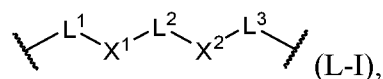
R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, U is N. In an
 10 embodiment, U is $-\text{CR}^{\text{d6}}$. In an embodiment, each R^{d6} is independently selected from the group consisting of H, methyl, halogen, methoxy, and methoxymethyl. In an embodiment, R^{d6} is H. In an embodiment, R^{d6} is methyl. In an embodiment, R^{d6} is halogen. In an embodiment, R^{d6} is methoxy.

15 **Linker**

In an embodiment, the Linker has Formula (L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

20 L^1 is selected from the group consisting of a bond, O, NR' , $\text{C}(\text{O})$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})\text{-C}_{1-6}$ alkylene, $^*\text{C}(\text{O})\text{-C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand in Formula (I);

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl,
 25 heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, O, NR' , $C(O)$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

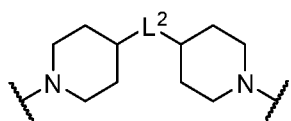
$X^1-L^2-X^2$ form a spiroheterocyclyl;

- 5 L^3 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $C(O)$, $S(O)_2$, O, NR' , $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene-O, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in (L-I);

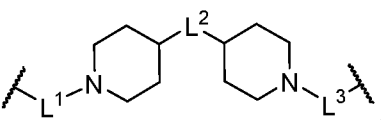
wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond; and

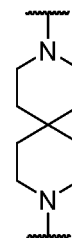
R' is hydrogen or C_{1-6} alkyl.

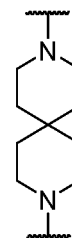
- 10 In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl. In an embodiment, one of X^1 and X^2 is a bond, and the other is a heterocyclyl. In an embodiment, X^1 and X^2 are each independently selected from piperidinyl and piperazinyl. In an embodiment, X^1 and X^2 are both piperidinyl. In an embodiment, $-X^1-L^2-X^2-$ is:

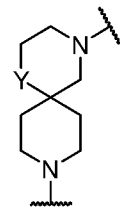


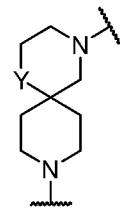
. In an embodiment, the Linker is a compound having the following

formula: , or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.



- 20 In an embodiment, $-X^1-L^2-X^2-$ forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^a , wherein each R^a is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl.



In an embodiment, $-X^1-L^2-X^2-$ forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^b , wherein Y is selected from CH_2 , oxygen, and nitrogen; and each R^b is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl. In an embodiment, X^1 and X^2 are each a bond.

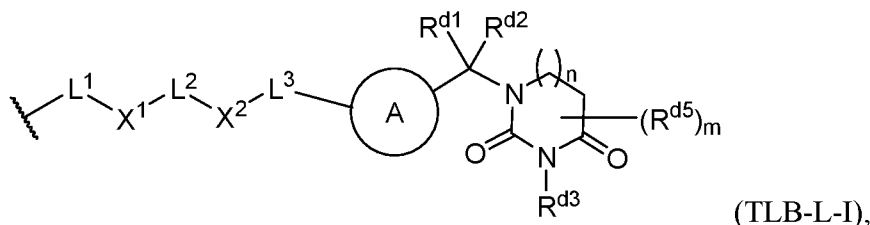
5 In an embodiment, L^3 is independently selected from the group consisting of $-C(O)-$, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; and L^1 is $-C(O)-$, C_{1-8} alkylene, C_{1-8} heteroalkylene, and $*C_{1-6}$ alkylene- $C(O)$. In an embodiment, L^3 is selected from the group consisting of $-C(O)-$, $-O-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^3 is $-C(O)-$ or C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^3 is a bond or $-O-$; and L^1 is $-C(O)-$ or C_{1-8} heteroalkylene. In an embodiment, L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene. In an embodiment, L^2 is $-C(O)-$, $-NR'-$, or C_{1-6} alkylene.

15 In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^2 is C_{1-6} alkylene. In an embodiment, L^2 is selected from the group consisting of $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene.

In an embodiment, Y is CH_2 , $CH(C_{1-3} \text{ alkyl})$, $C(C_{1-3} \text{ alkyl})_2$, oxygen, NH, or $N(C_{1-3} \text{ alkyl})$.

Targeting Ligand-Linkers

20 In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

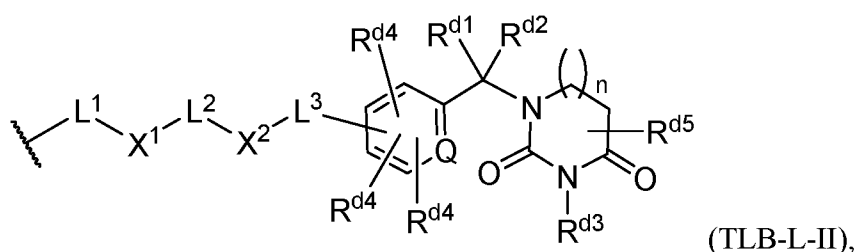
 denotes the point of attachment to the Targeting Ligand in Formula (I);

- L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)-$, and $*C_{1-6}$ heteroalkylene- $C(O)-$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;
- 5 X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;
- L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or
- 10 $X^1-L^2-X^2$ form a spiroheterocyclyl;
- L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- $O-$, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-I);
- 15 wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;
- Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0-4 occurrences of R^{d4} ;
- R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;
- 20 R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;
- each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxyl, and C_{1-6} heteroalkyl;
- each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;
- 25 or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;
- or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;
- R^p is H or C_{1-6} alkyl;
- m is 1 or 2; and
- 30 n is 1 or 2.

In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, ring A is a 5-membered nitrogen-containing heteroaryl. In an embodiment, ring A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl. In an embodiment, n is 1.

In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $^*\text{C}(\text{O})\text{NR}'-\text{C}_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$, $^*\text{C}(\text{O})-\text{C}_{1-9}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene- O , and $^*\text{C}(\text{O})-\text{C}_{1-9}$ heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-II);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Q is N or CR^{d4};

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p,
 5 -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

each R^{d4} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

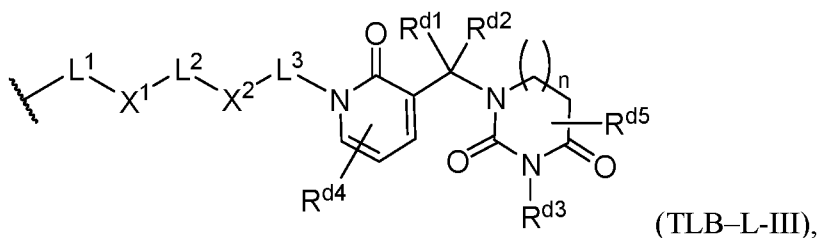
R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

10 R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is -CH₂OP(O)(OR^p)₂.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-III):



15 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

┌ denotes the point of attachment to the Targeting Ligand in Formula (I);

L¹ is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)-C₁₋₆ alkylene, *C(O)-C₁₋₆ heteroalkylene, *C₁₋₆ alkylene-C(O), and
 20 *C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

25 L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and

*C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in

Formula (TLB-L-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

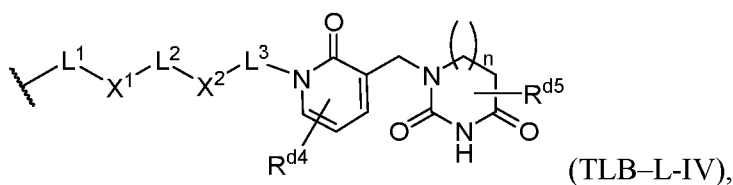
R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

5 $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in

10 Formula (TLB-L-IV);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

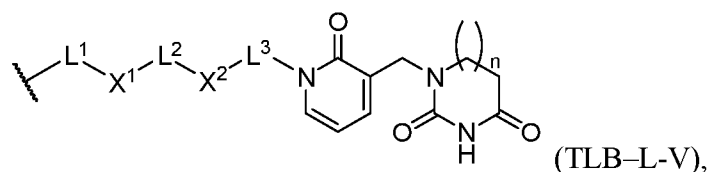
R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

15 R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2.

In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-V):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

25

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-V);

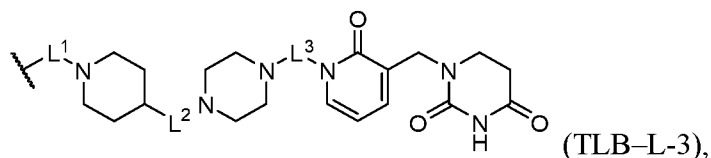
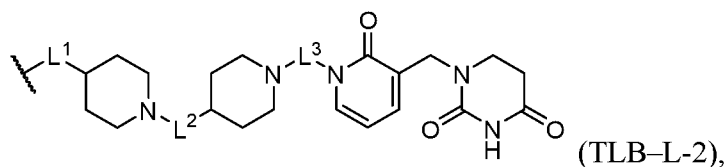
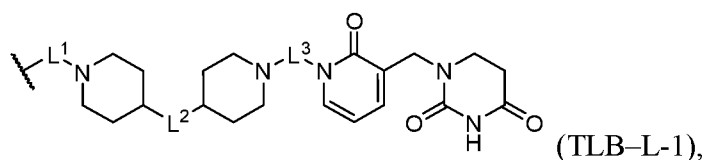
wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

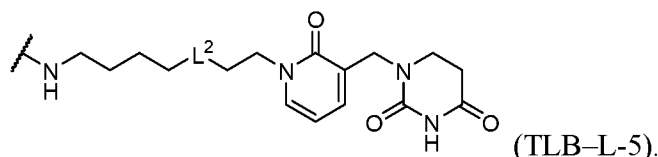
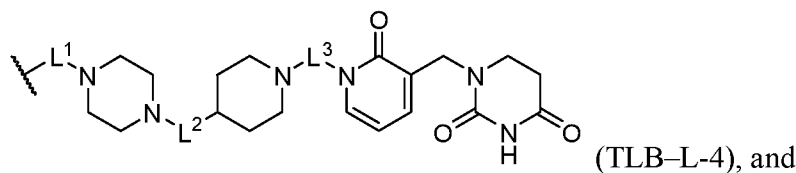
R' is hydrogen or C_{1-6} alkyl; and

n is 1 or 2.

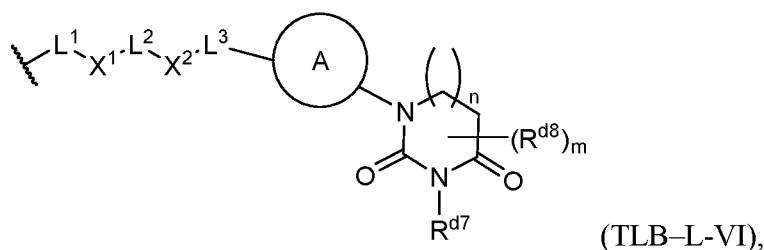
In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl. In an embodiment, one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

In an embodiment, the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:





In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-VI):



- 5 or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Targeting Ligand in Formula (I);

- L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and
10 $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

- L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and
15 $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

- L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O ,
20 and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-VI);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6};

each R^{d6} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d7} is selected from the group consisting of H, –CH₂OC(O)R^p, –CH₂OP(O)OHOR^p, –CH₂OP(O)(R^p)₂, and –CH₂OP(O)(OR^p)₂;

R^p is H or C₁₋₆ alkyl;

each R^{d8} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

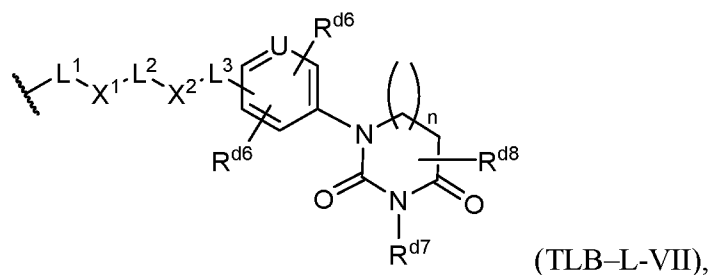
or two R^{d8} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is –CH₂OP(O)(OR^p)₂. In an embodiment, R^{d3} is H.

In an embodiment, the Targeting Ligase Binder–Linker has Formula (TLB–L–VII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Targeting Ligand in Formula (I);

L¹ is selected from the group consisting of a bond, –O–, –NR', –C(O)–, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)–C₁₋₆ alkylene, *C(O)–C₁₋₆ heteroalkylene, *C₁₋₆ alkylene–C(O), and *C₁₋₆ heteroalkylene–C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

5 $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in

10 Formula (TLB-VII);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N ;

each R^{d6} is independently selected from the group consisting of H , oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

15 R^{d7} is selected from the group consisting of H , $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

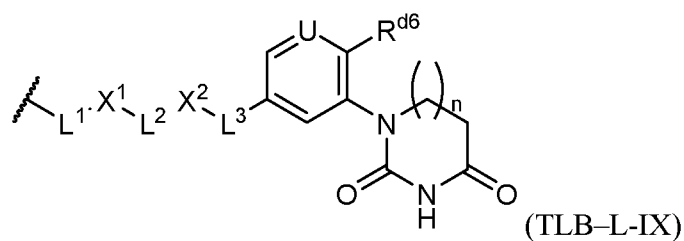
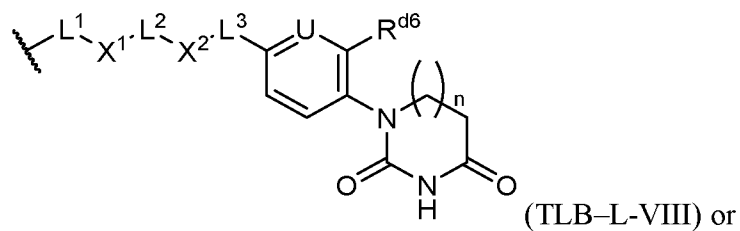
R^{d8} is selected from the group consisting of H , C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

20 R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H . In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, one of X^1 and X^2 is not a bond. In an embodiment, one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl. In an embodiment, one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

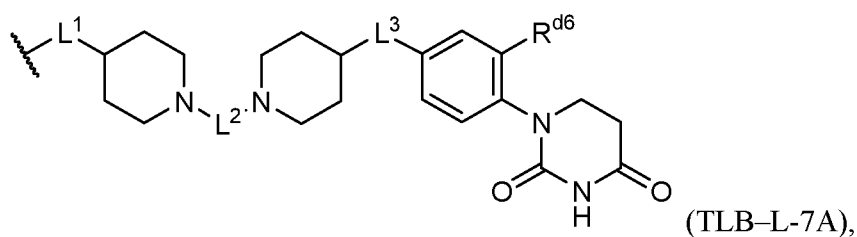
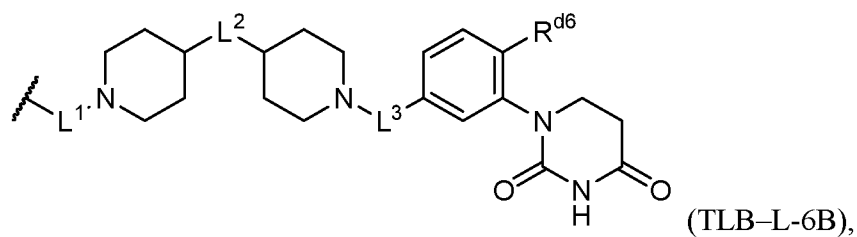
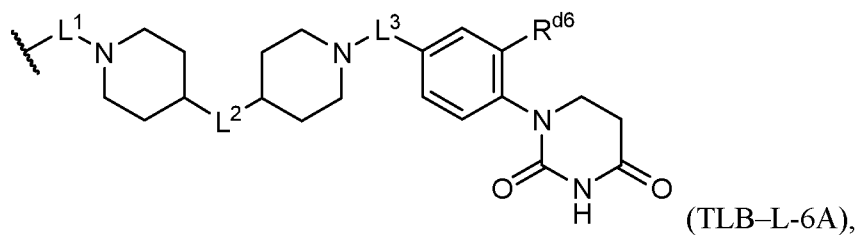
30 In an embodiment, the Targeting Ligase Binder-Linker has Formula (TLB-L-VIII or TLB-L-IX):

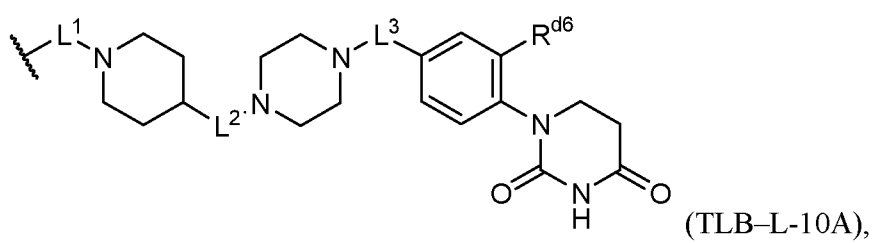
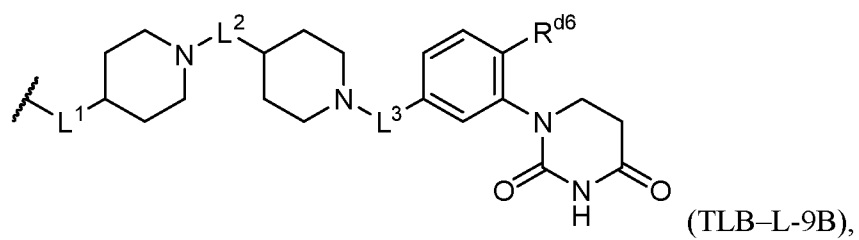
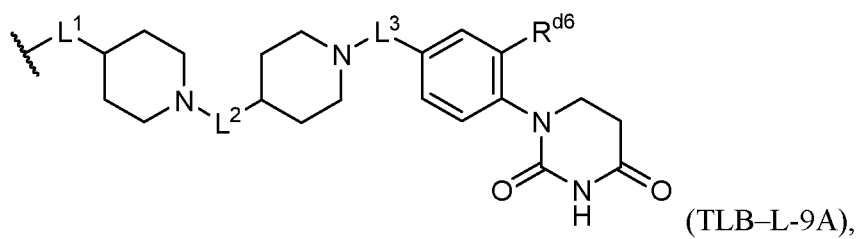
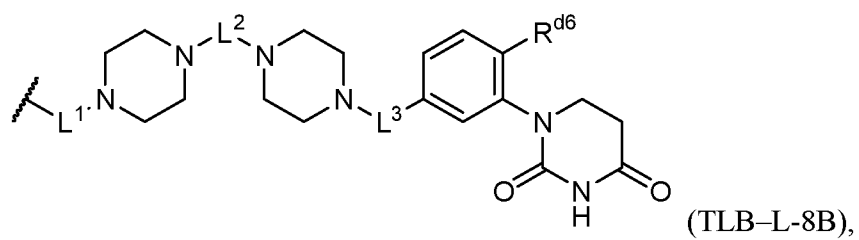
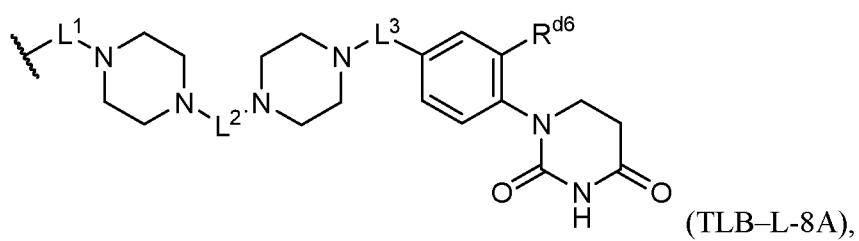
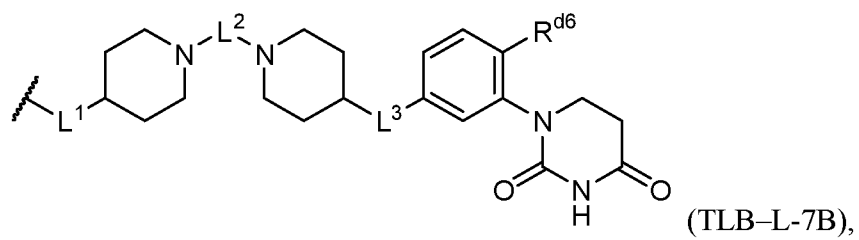


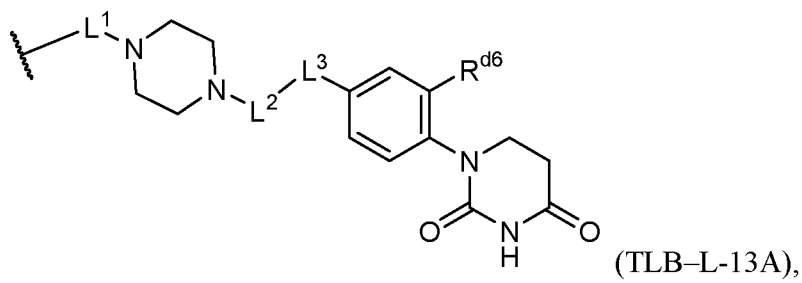
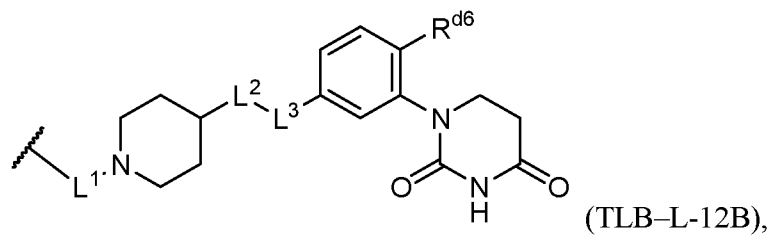
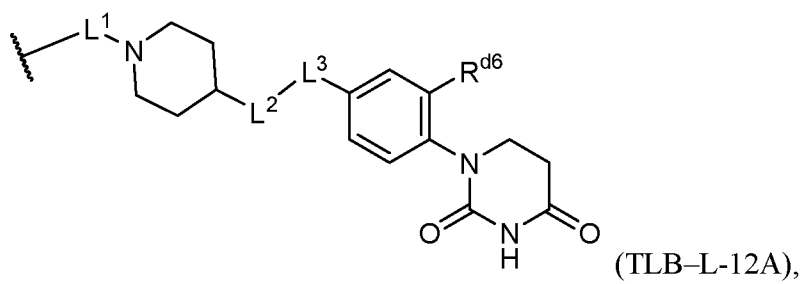
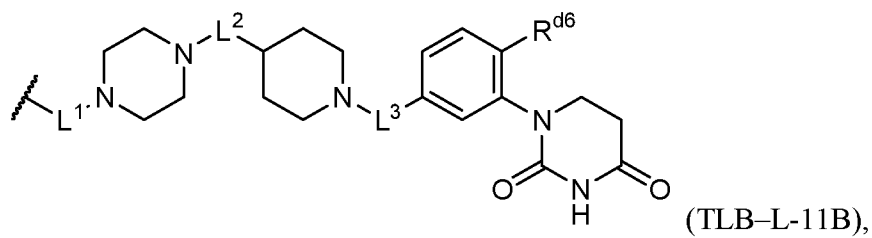
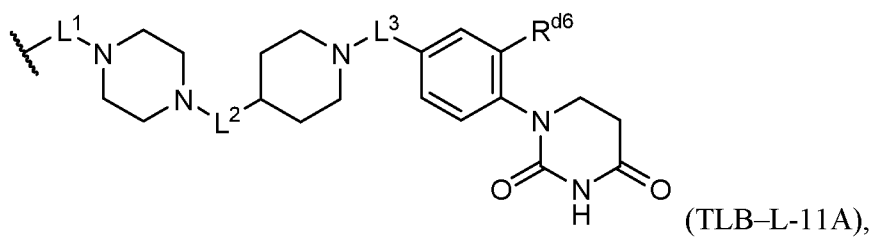
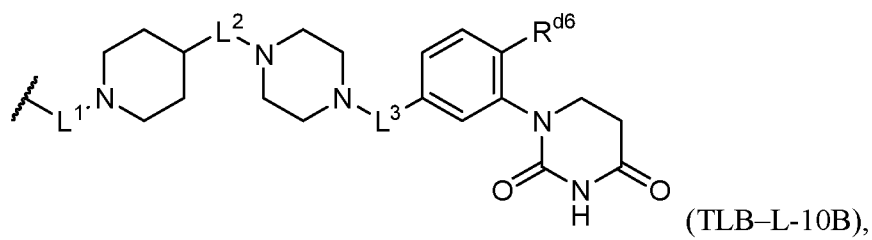
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the point of attachment to the Targeting Ligand is through L^1 .

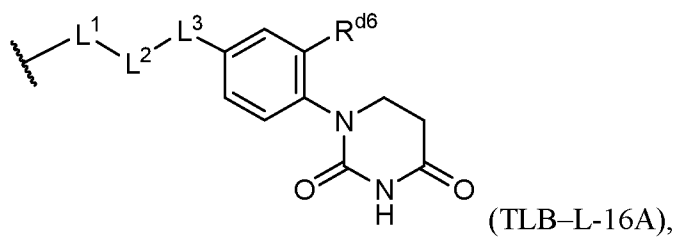
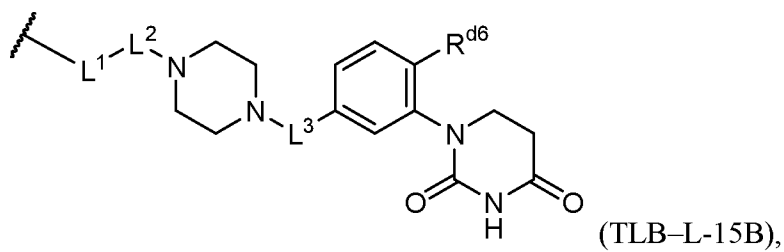
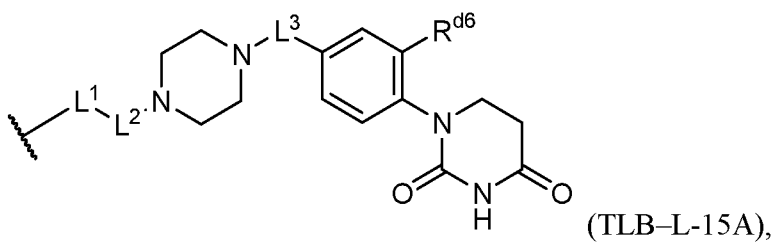
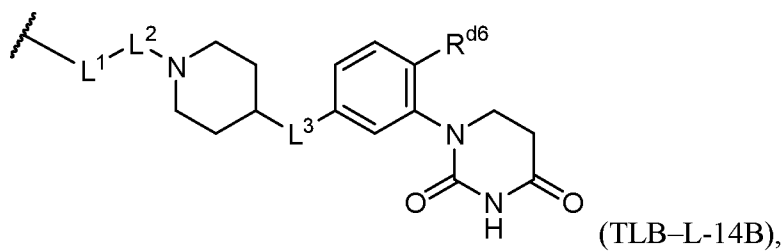
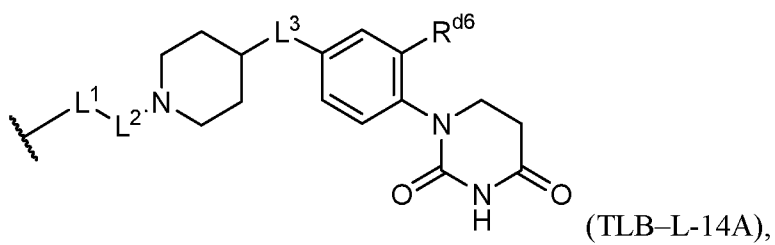
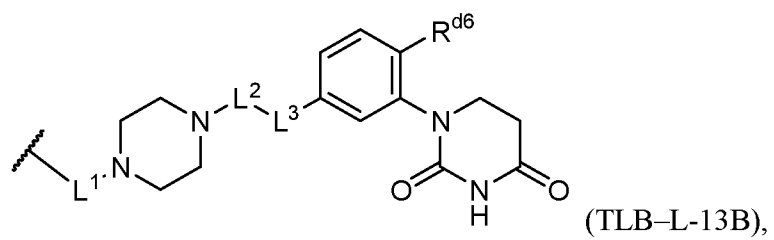
5 In an embodiment, n is 1. In an embodiment, n is 2.

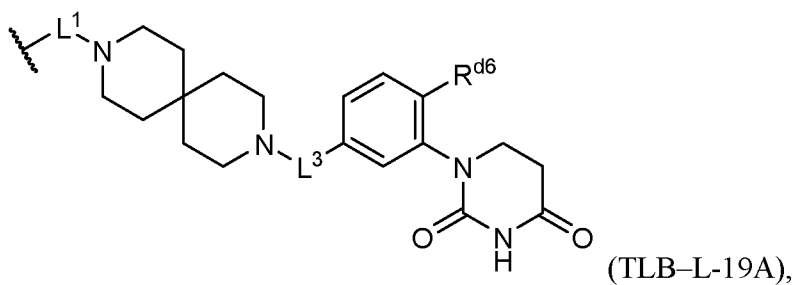
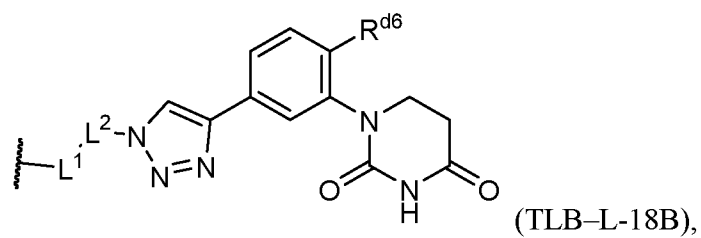
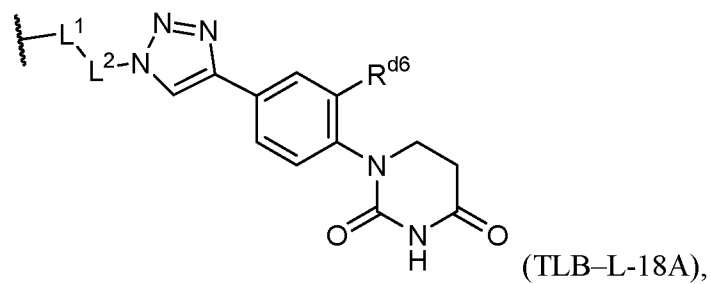
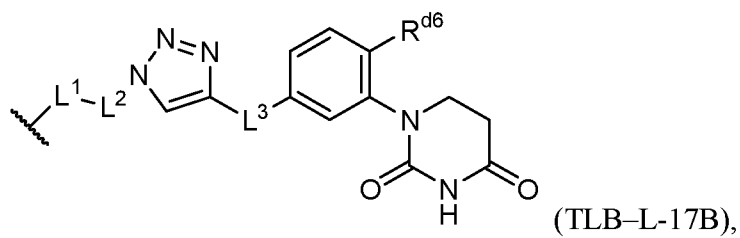
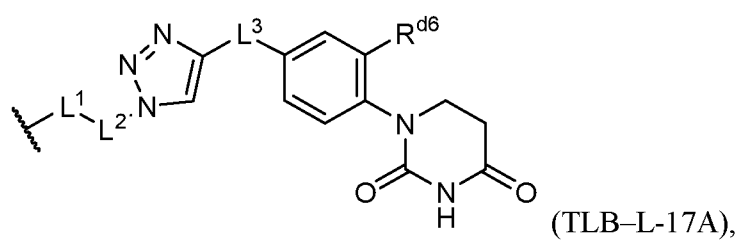
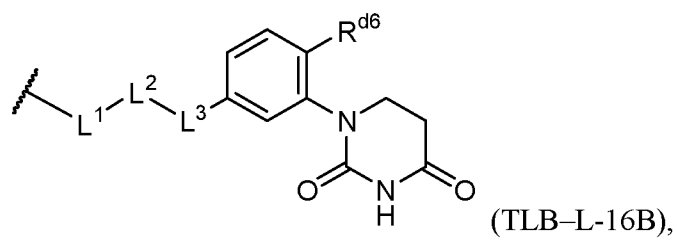
In an embodiment, the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:

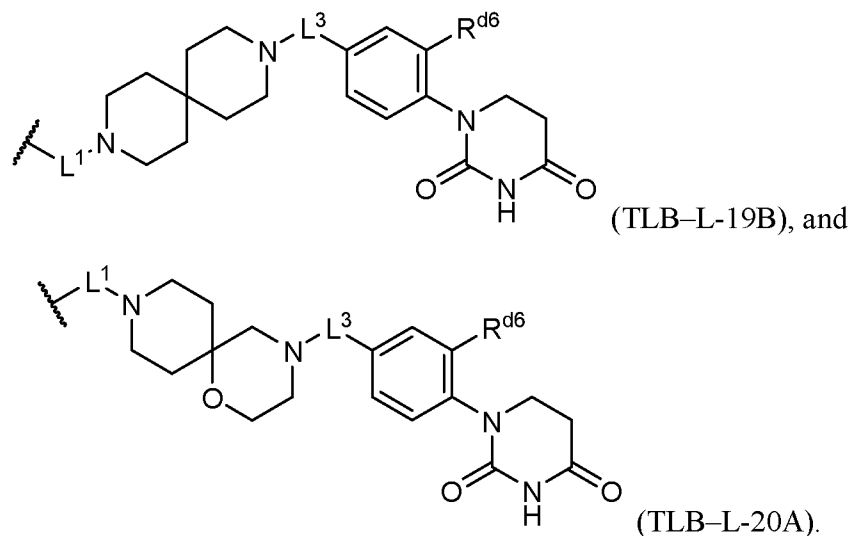






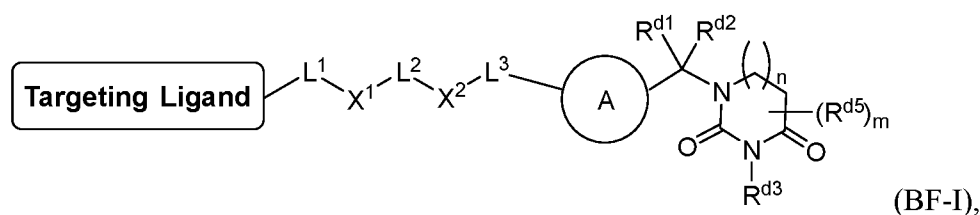






Compound Formulas

In another aspect, the disclosure provides a compound of Formula (BF-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene;

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O ,

and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-I);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with
 5 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

10 each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

15 or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

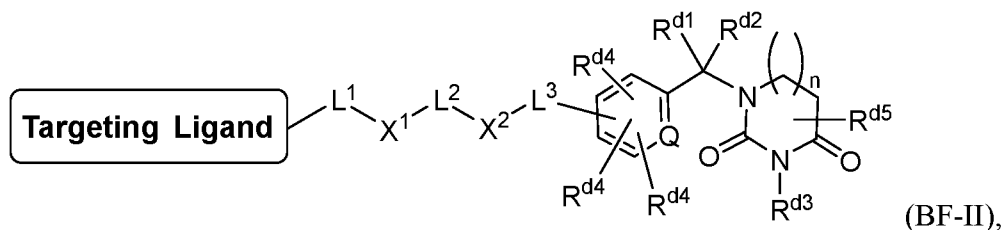
R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl. In an embodiment, ring A is a 5-membered heteroaryl. In an embodiment, ring A is a 5-membered nitrogen-containing heteroaryl. In an embodiment, ring A is a 6-membered heteroaryl. In an embodiment, ring A is a 6-membered nitrogen-containing heteroaryl. In an embodiment, ring A is pyridyl. In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an
 25 embodiment, n R^{d3} is H.

In another aspect, the disclosure provides a compound of Formula (BF-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and
 5 $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of
 10 L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O ,
 15 and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-II);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Q is N or CR^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;
 20

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxyl, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

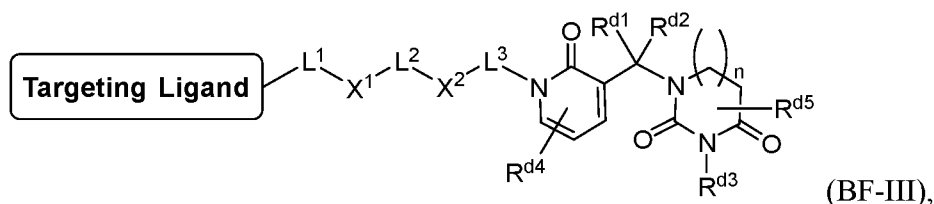
25 R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, n is 1. In another aspect, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H.
 30

In another aspect, the disclosure provides a compound of Formula (BF-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

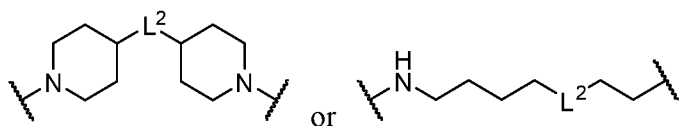
R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

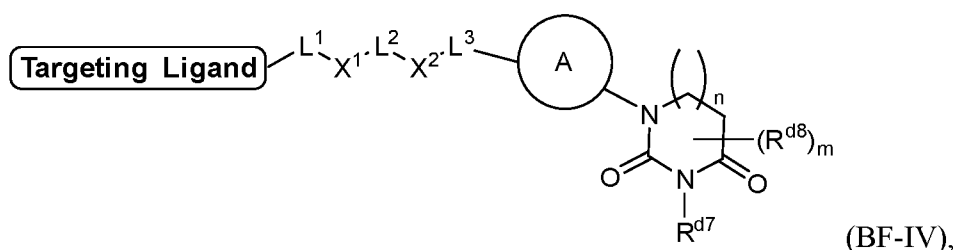
n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$. In an embodiment, R^{d3} is H. In an embodiment, $-\text{X}^1-\text{L}^2-\text{X}^2-$ is:



5 In an embodiment, L^1 is $-\text{O}-$ or C_{1-6} alkylene. In an embodiment, R^{d1} and R^{d2} are both methyl. In an embodiment, R^{d1} and R^{d2} are both H. In another aspect, R^{d4} is H or C_{1-3} alkyl. In an embodiment, R^{d5} is H or C_{1-3} alkyl.

In another aspect, the disclosure provides a compound of Formula (BF-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,
10 wherein:

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'$, $-\text{C}(\text{O})-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

15 X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'$, $-\text{C}(\text{O})-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$^*\text{C}(\text{O})\text{NR}'-\text{C}_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

20 $\text{X}^1-\text{L}^2-\text{X}^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$, $^*\text{C}(\text{O})-\text{C}_{1-9}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene- O , and $^*\text{C}(\text{O})-\text{C}_{1-9}$ heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (BF-IV);

25 wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6};

each R^{d6} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d7} is selected from the group consisting of H, –CH₂OC(O)R^p, –CH₂OP(O)OHOR^p, –CH₂OP(O)(R^p)₂, and –CH₂OP(O)(OR^p)₂;

R^p is H or C₁₋₆ alkyl;

each R^{d8} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

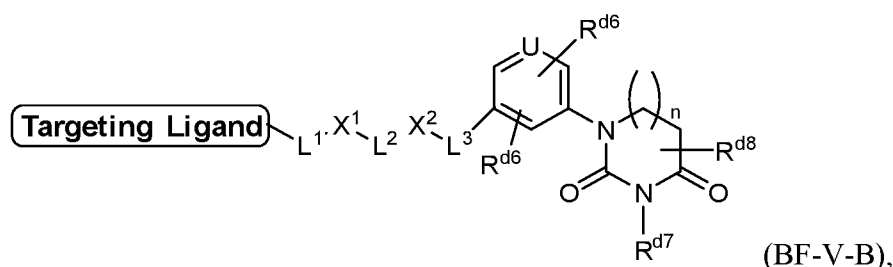
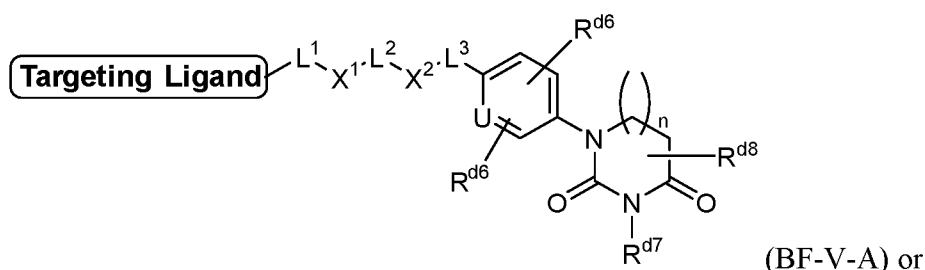
or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

In an embodiment, the compound has the Formula (BF-V-A) or (BF-V-B):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L¹ is selected from the group consisting of a bond, –O–, –NR', –C(O)–, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)–C₁₋₆ alkylene, *C(O)–C₁₋₆ heteroalkylene, *C₁₋₆ alkylene–C(O), and

*C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

5 L² is selected from the group consisting of a bond, -O-, -NR', -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and

*C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

10 L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O)-, -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (BF-V-A or BF-V-B);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

15 U is -CR^{d6} or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxyl, C₁₋₆ alkoxyalkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d7} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

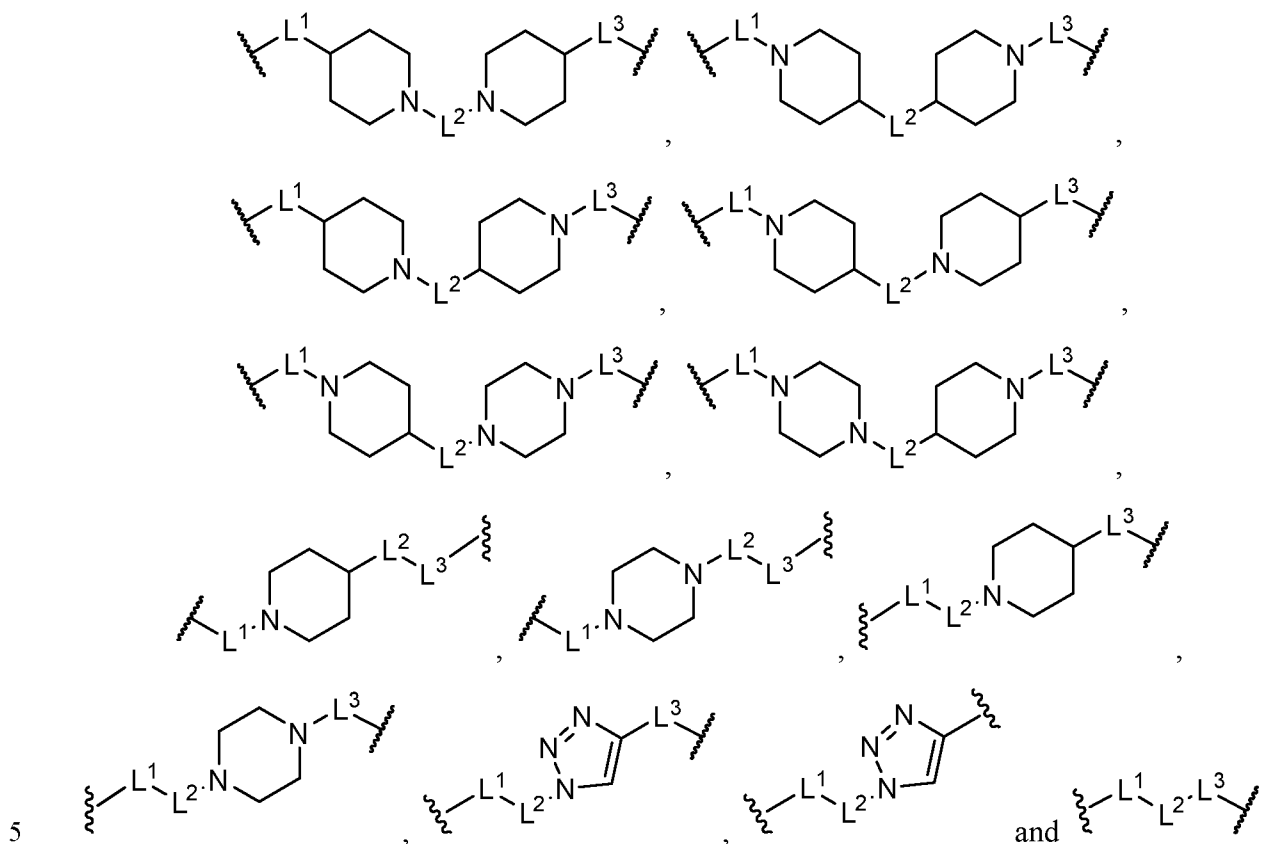
20 R^{d8} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

25 In an embodiment, n is 1. In another aspect, n is 2. In another aspect, R^{d7} is -CH₂OP(O)(OR^p)₂. In another aspect, R^{d7} is H. In another aspect, U is -CR^{d6}. In another aspect, R^{d8} is H. In another aspect, R^{d7} and R^{d8} are each independently H. In another aspect, R^{d6} is H. In another aspect, R^{d6} is selected from the group consisting of H, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxyl. In another aspect, R^{d6} is selected from the group consisting of H, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxyl; and R^{d7}, and R^{d8} are each H.

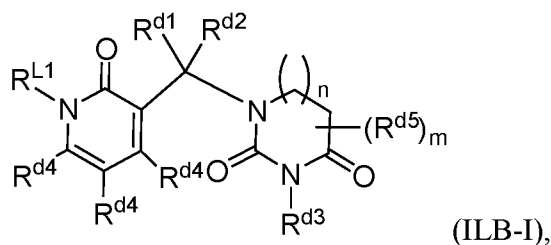
30 In an embodiment, L¹-X¹-L²-X²-L³ is selected from the group consisting of:



In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

Intermediates

10 Another embodiment is a compound of Formula (ILB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

15 R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

5 each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

10 R^{L1} is selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, C_{3-6} heteroalkyl, C_{2-6} haloalkyl, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{1-3}O(CH_2)_{1-3}C(O)H$, $-(CH_2)_{0-3}C_{3-7}$ carbocyclyl, $-(CH_2)_{0-3}$ heterocyclyl, C_6 aryl, and heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and heteroaryl is substituted with 0–2 occurrences of $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, or C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

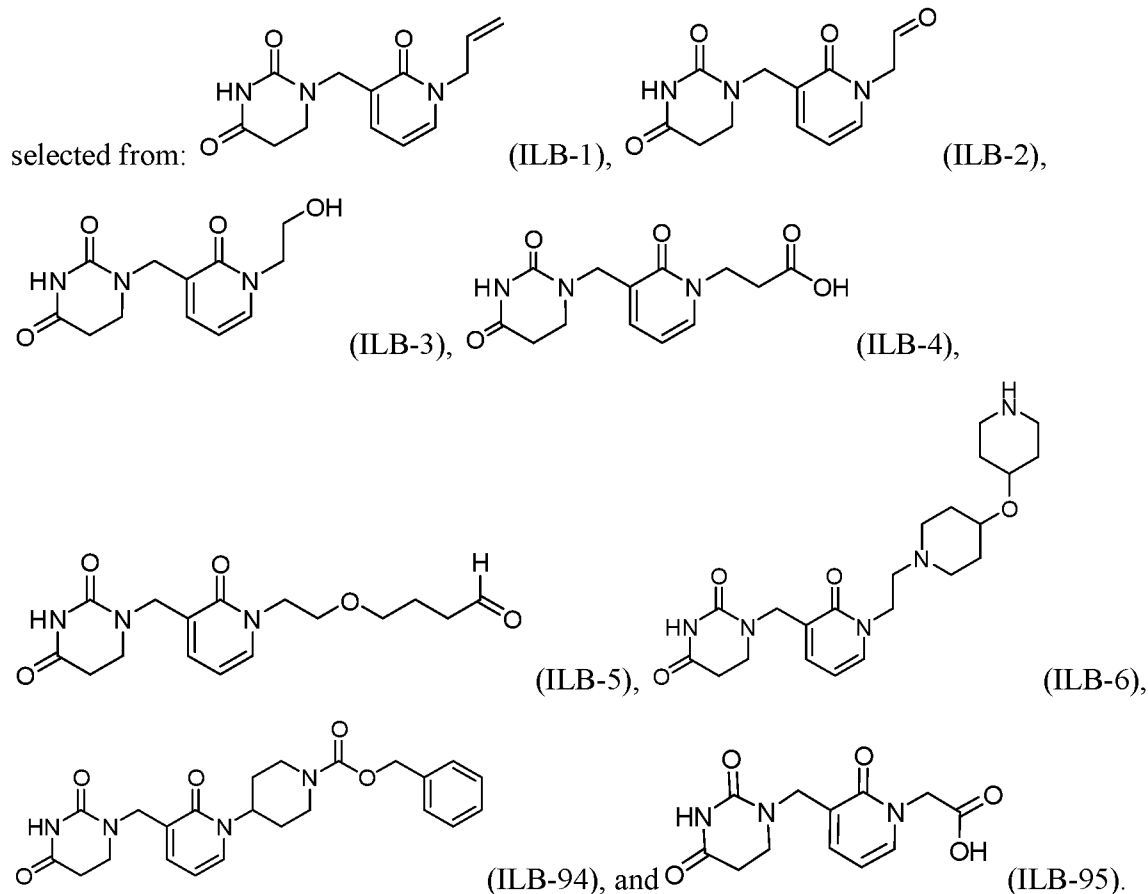
n is 1 or 2.

20 In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H. In an embodiment, R^{d4} is H.

In an embodiment, R^{L1} is selected from the group consisting of C_{2-6} alkenyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{1-3}O(CH_2)_{1-3}C(O)H$, $-(CH_2)_{0-3}$ heterocyclyl, wherein the heterocyclyl, is substituted with 0–2 occurrences of $-O$ -heterocyclyl.

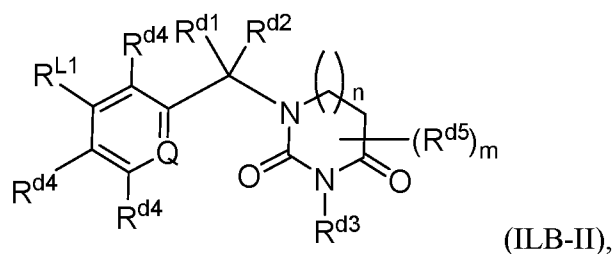
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Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



5

Another embodiment is a compound of Formula (ILB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,
wherein:

10 Q is N or CR^{d4};

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, -CH₂(O)(CH₂)₂Si(CH₃)₃, -CH₂OC(O)R^p, -CH₂OP(O)(OH)OR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

- 5 or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;
or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L1} is selected from the group consisting of C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, C_{3-6} heteroalkyl, C_{2-6} haloalkyl, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C_{3-7}$ carbocyclyl, $-(CH_2)_{0-3}$ heterocyclyl, C_6 aryl, and
10 heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and heteroaryl is substituted with 0-2 occurrences of $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, or C_{1-6} heteroalkyl;

15 R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

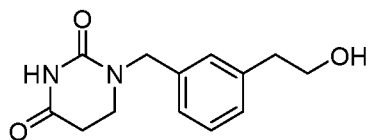
n is 1 or 2.

In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d3} is $-CH_2OP(O)(OR^p)_2$. In an embodiment, R^{d3} is H.

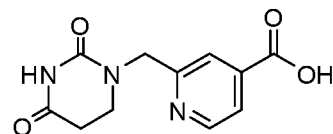
20 In an embodiment, Q is N; and R^{L1} is $-(CH_2)_{0-3}C(O)OH$.

In an embodiment, Q is CR^{d4} ; and R^{L1} is C_{2-6} hydroxyalkyl, $-(CH_2)_{0-3}C(O)OH$, and $-(CH_2)_{0-3}C(O)H$.

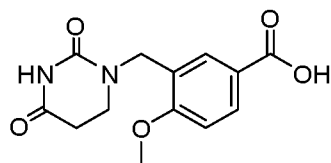
Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



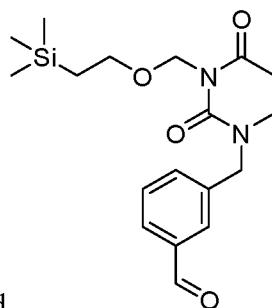
(ILB-7),



(ILB-8),

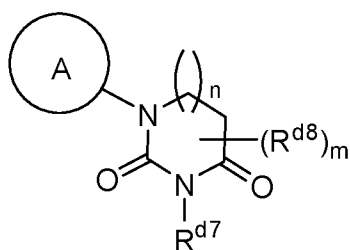


(ILB-9), and



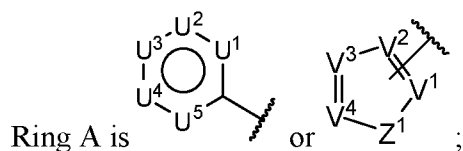
(ILB-10).

Another embodiment is a compound of Formula (ILB-III):



(ILB-III),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:



denotes the point of attachment to the base molecule of (ILB-III);

- 10 U^1 , U^2 , U^3 , U^4 , and U^5 are each independently N or CR^{d6} or CR^{L2} , wherein no more than three of U^1 , U^2 , U^3 , U^4 , and U^5 can be N, and wherein one of U^1 , U^2 , U^3 , U^4 , and U^5 is CR^{L2} and the remaining are CR^{d6} ;

Z^1 is selected from the group consisting of O, S, NR^{d6a} , or NR^{L2a}

- 15 V^1 , V^2 , V^3 , and V^4 are each independently N or C, wherein no more than two of V^1 , V^2 , V^3 , and V^4 can be N, and wherein one of Z^1 , V^1 , V^2 , V^3 , and V^4 is substituted with R^{L2} , one of V^1 , V^2 , V^3 , and V^4 is the point of attachment to the base molecule of (ILB-III), and the remaining are substituted with R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

each R^{d6a} is independently selected from the group consisting of H, polyethylene glycol (PEG), C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-6} haloalkyl, and C_{2-6} heteroalkyl;

R^{d7} is H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L2} is selected from the group consisting of H, hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{1-8} heteroalkyl, C_{1-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^c$, $-\text{O}-C_{2-6}$ alkenyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})$ -heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{N}(\text{R}^c)_2$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^{L2a} is selected from the group consisting of H, C_{3-6} alkenyl, C_{3-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, C_{2-8} heteroalkyl, C_{2-6} haloalkyl, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-C_{3-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, C_{1-6} heteroalkyl, and $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl;

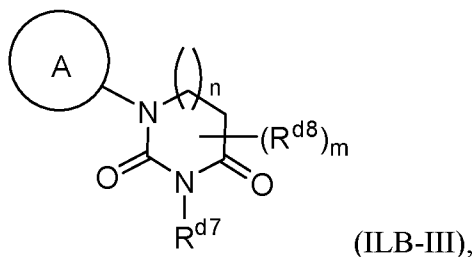
R^d is H or C_{1-4} alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0–2 occurrences of $-\text{O}$ -heterocyclyl,

R^p is H or C_{1-6} alkyl;

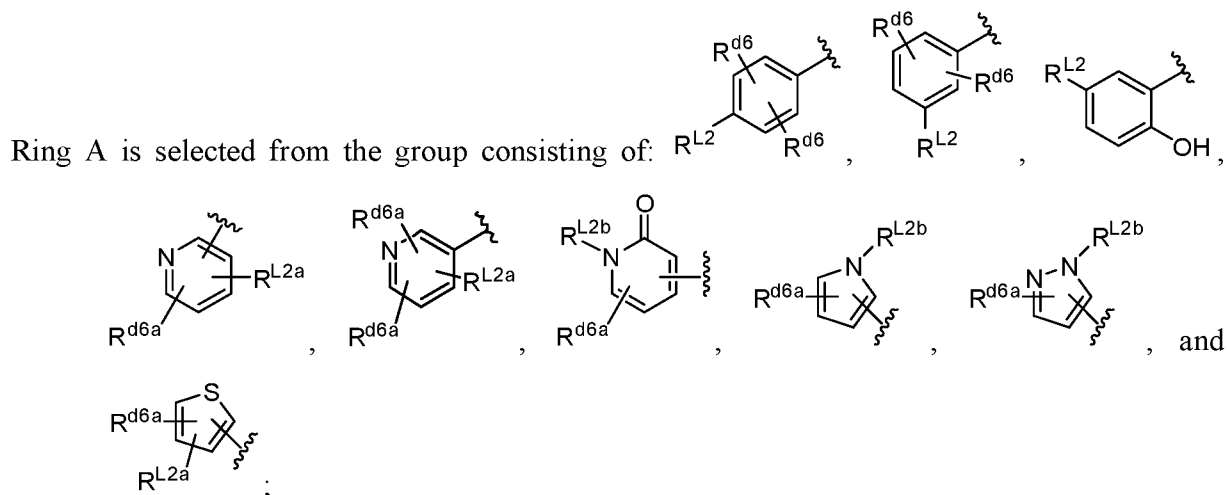
m is 1 or 2; and

n is 1 or 2.

Another embodiment is a compound of Formula (ILB-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:



— denotes the point of attachment to the base molecule of (ILB-III);

each R^{d6} is independently selected from the group consisting of H, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

15 each R^{d6a} is independently selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

R^{d7} is H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

20 each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

R^{L2} is selected from the group consisting of hydroxyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, $-O-(CH_2)_{2-6}NHR^c$, C₄₋₈ heteroalkyl, C₂₋₆ haloalkyl, $-SO_2-NH-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)OR^c$, $-O-C_{2-6}$ alkenyl, $-O-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C(O)H$, $-O-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}C(O)-$ heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}N(R^c)_2$, heterocyclyl, heteroaryl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl, wherein the heterocyclyl and heteroaryl is substituted with 0-2 occurrences of halogen;

R^{L2a} is selected from the group consisting of H, hydroxyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, $-O-(CH_2)_{2-6}NHR^c$, C₁₋₈ heteroalkyl, C₁₋₆ haloalkyl, $-SO_2-NH-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)OR^c$, $-O-C_{2-6}$ alkenyl, $-O-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C(O)H$, $-O-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}C(O)-$ heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}N(R^c)_2$, heterocyclyl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl, wherein the heterocyclyl is substituted with 0-2 occurrences of halogen;

R^{L2b} is selected from the group consisting of H, polyethylene glycol (PEG), C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, C₂₋₈ heteroalkyl, C₂₋₆ haloalkyl, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-C_{3-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, heterocyclyl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl,

–C(O)-carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C₁₋₄ alkyl, C₁₋₆ heteroalkyl, and –C(O)OC₁₋₆ alkyl;

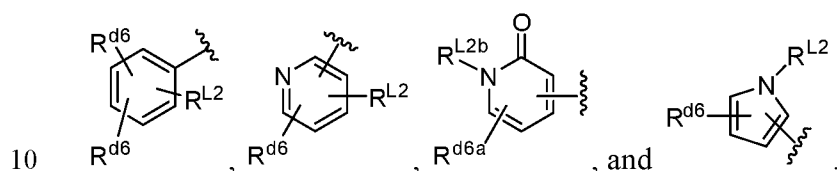
R^d is H or C₁₋₄ alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form
5 a heterocyclyl substituted with 0–2 occurrences of –O-heterocyclyl,

R^p is H or C₁₋₆ alkyl;

m is 1 or 2; and

n is 1 or 2.

In an embodiment, ring A is selected from the group consisting of:



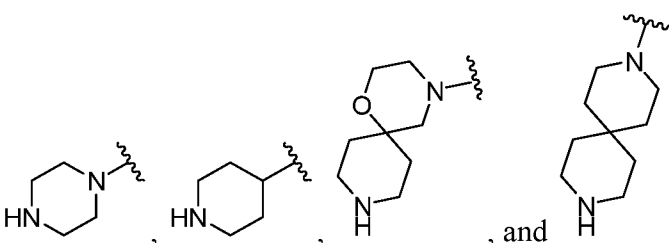
In an embodiment, n is 1. In an embodiment, n is 2. In an embodiment, R^{d7} is –CH₂OP(O)(OR^p)₂. In an embodiment, R^{d7} is H.

In an embodiment, each R^{d6} is independently selected from the group consisting of H, polyethylene glycol (PEG), halogen, C₁₋₃ alkyl, and C₁₋₃ alkoxy.

15 In an embodiment each R^{d6a} is independently halogen.

In an embodiment, R^{L2} is selected from the group consisting of hydroxyl, C₂₋₆ alkynyl, –O–(CH₂)₂₋₆NHR^c, C₄₋₈ heteroalkyl, –SO₂–NH–(CH₂)₂₋₆NHR^c, –O–C₂₋₆ alkenyl, –(CH₂)₀₋₃C(O)H, –O–(CH₂)₁₋₃C(O)OH, –(CH₂)₀₋₃ heterocyclyl, –C(O)–(CH₂)₀₋₃ heterocyclyl, –O–(CH₂)₀₋₃ heterocyclyl, –O–(CH₂)₀₋₃C(O)–heterocyclyl, –C₂₋₆ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, –(CH₂)₂₋₆NHR^c, heterocyclyl, heteroaryl, –C(O)–heterocyclyl, wherein the heterocyclyl and heteroaryl is substituted with 0–2 occurrences of halogen.
20

In an embodiment, the heterocyclyl is selected from the group consisting of:

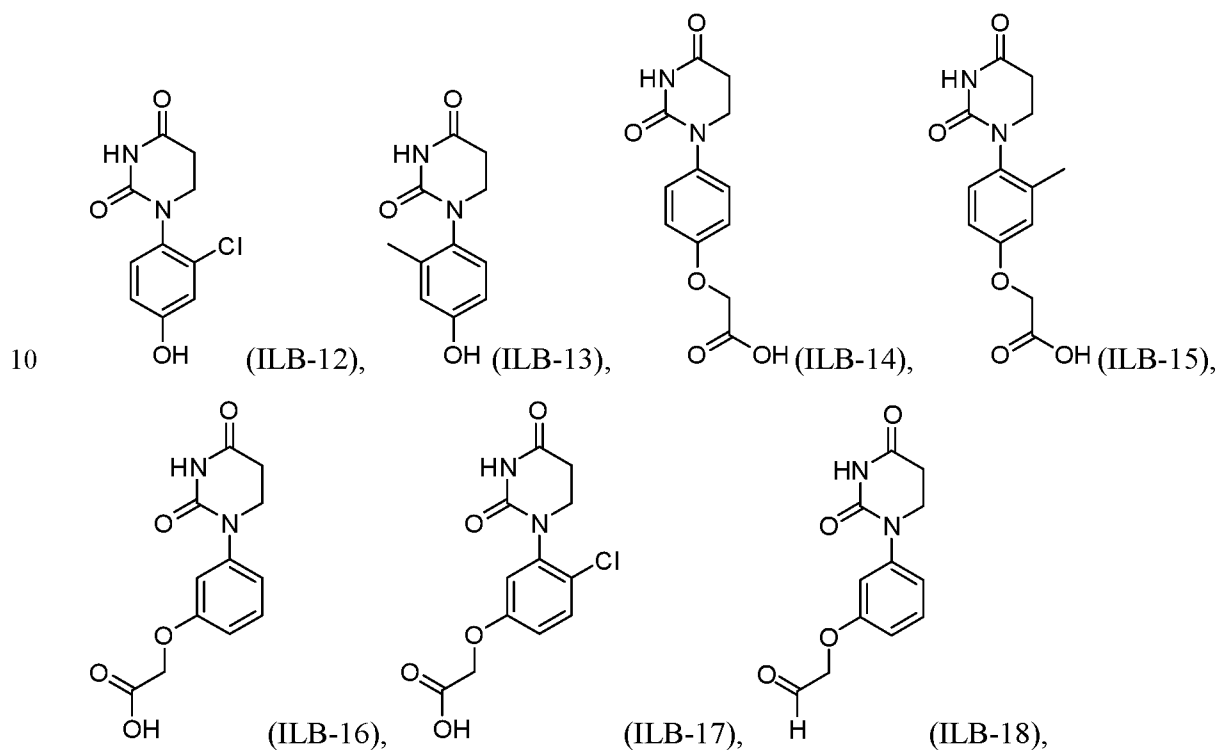

, wherein  denotes the point of attachment to the base molecule of (ILB-III).

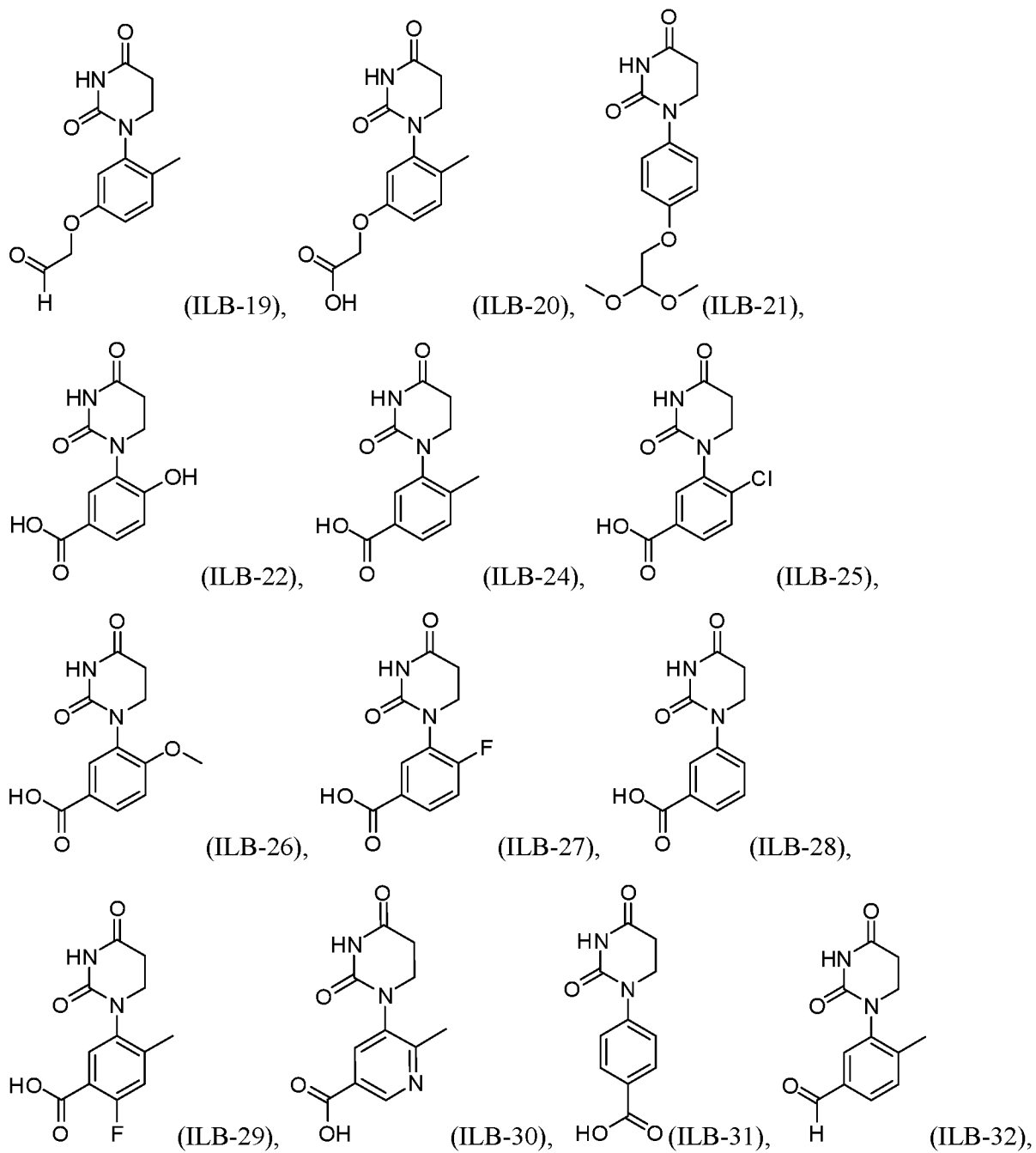
In an embodiment, R^{L2a} is H.

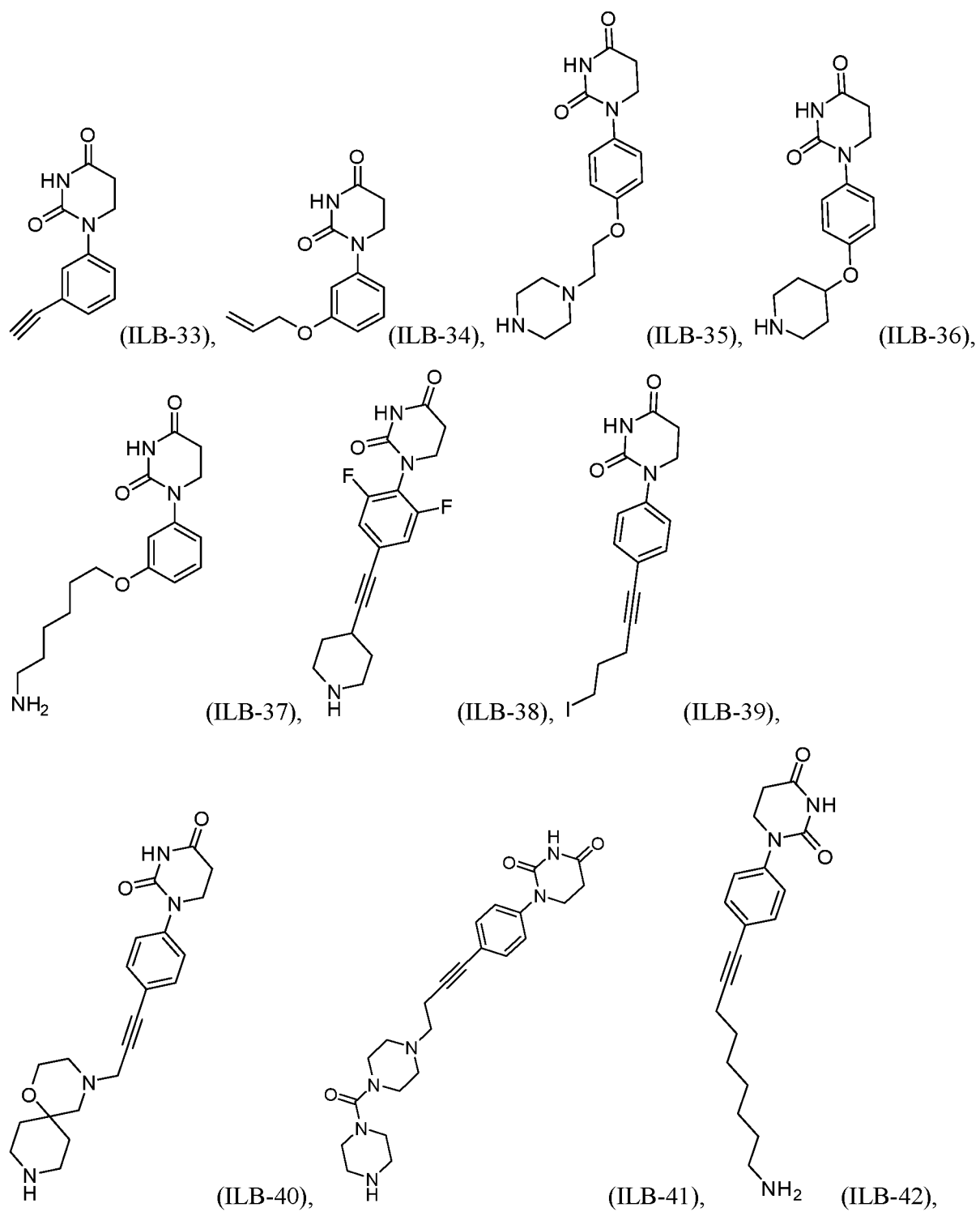
5 In an embodiment, R^c is H or $-C(O)OC_{1-6}$ alkyl.

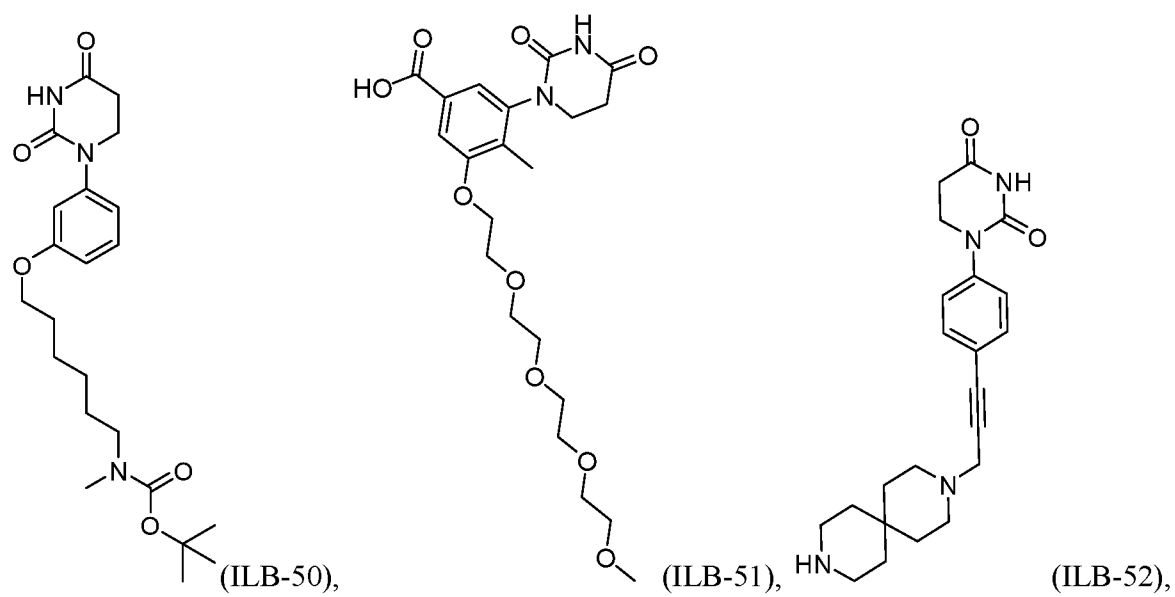
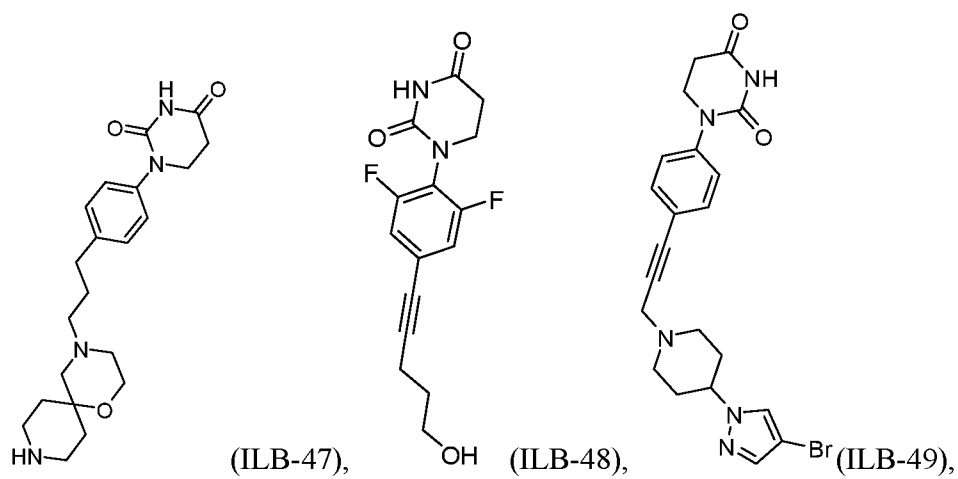
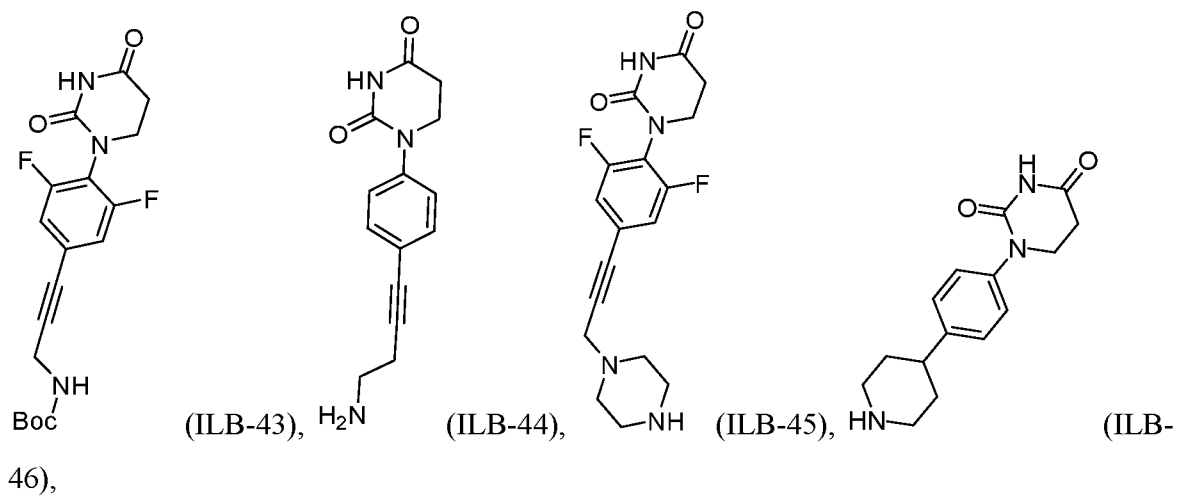
In an embodiment, R^d is H or C_{1-4} alkyl.

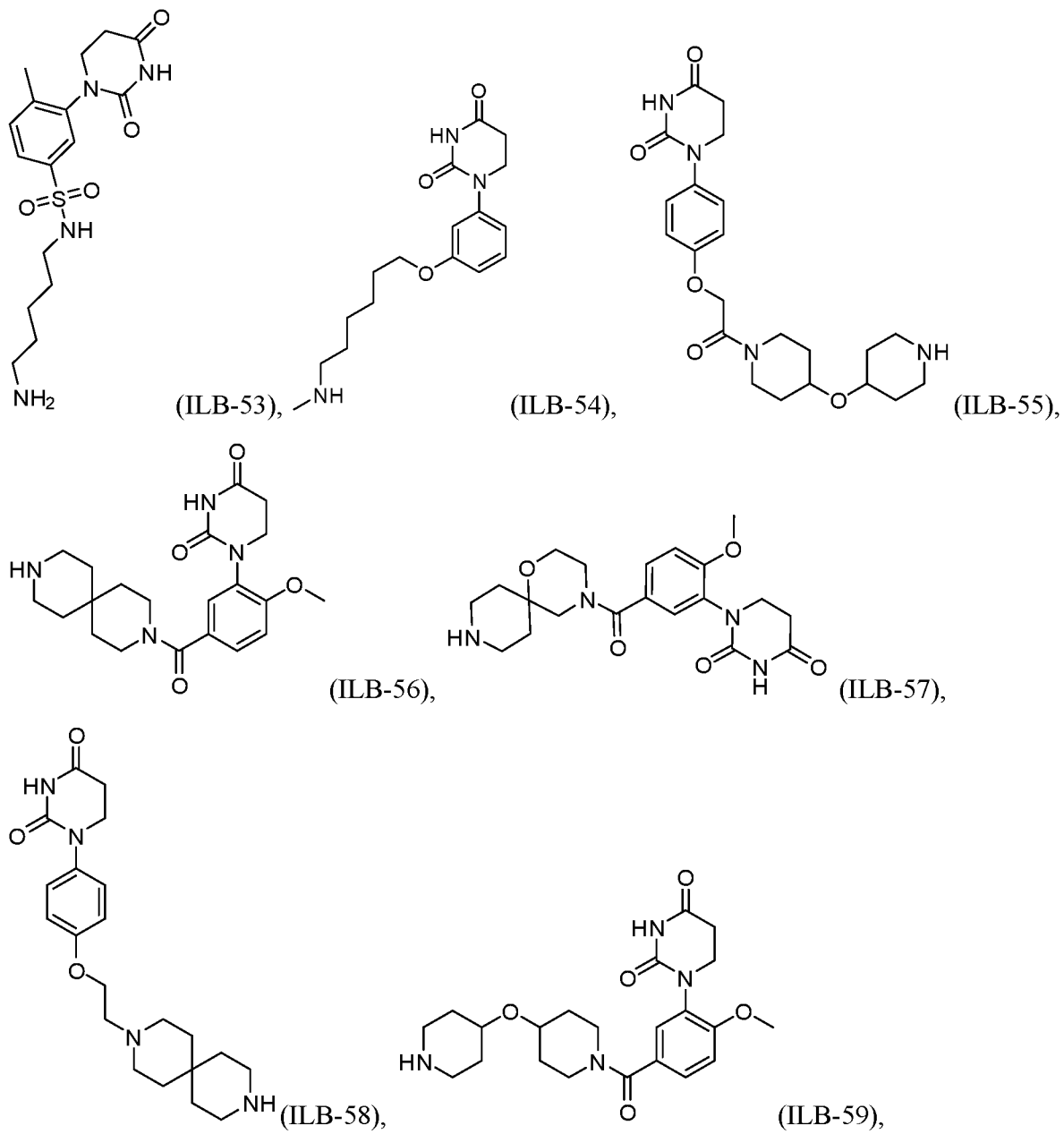
Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:

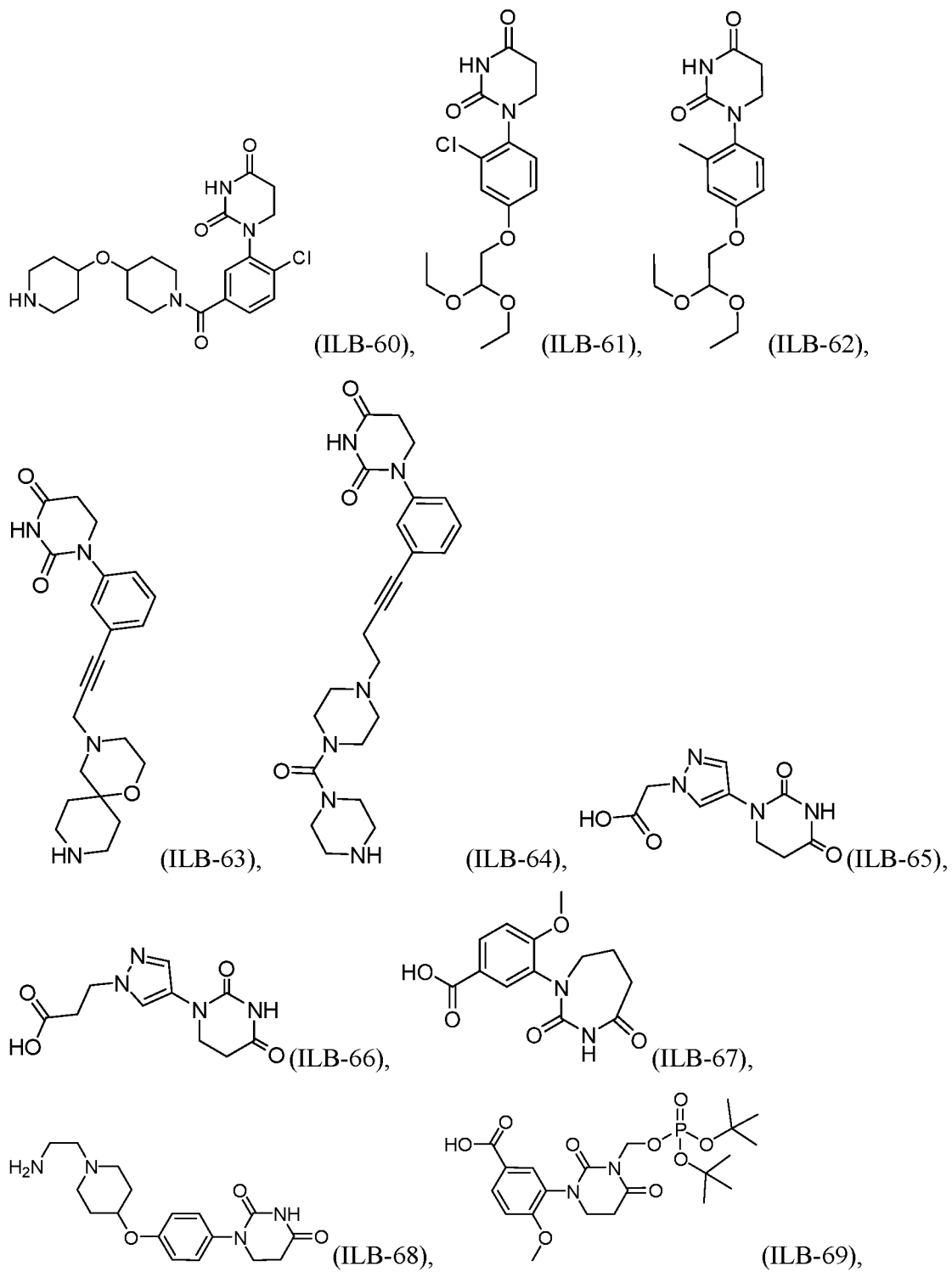


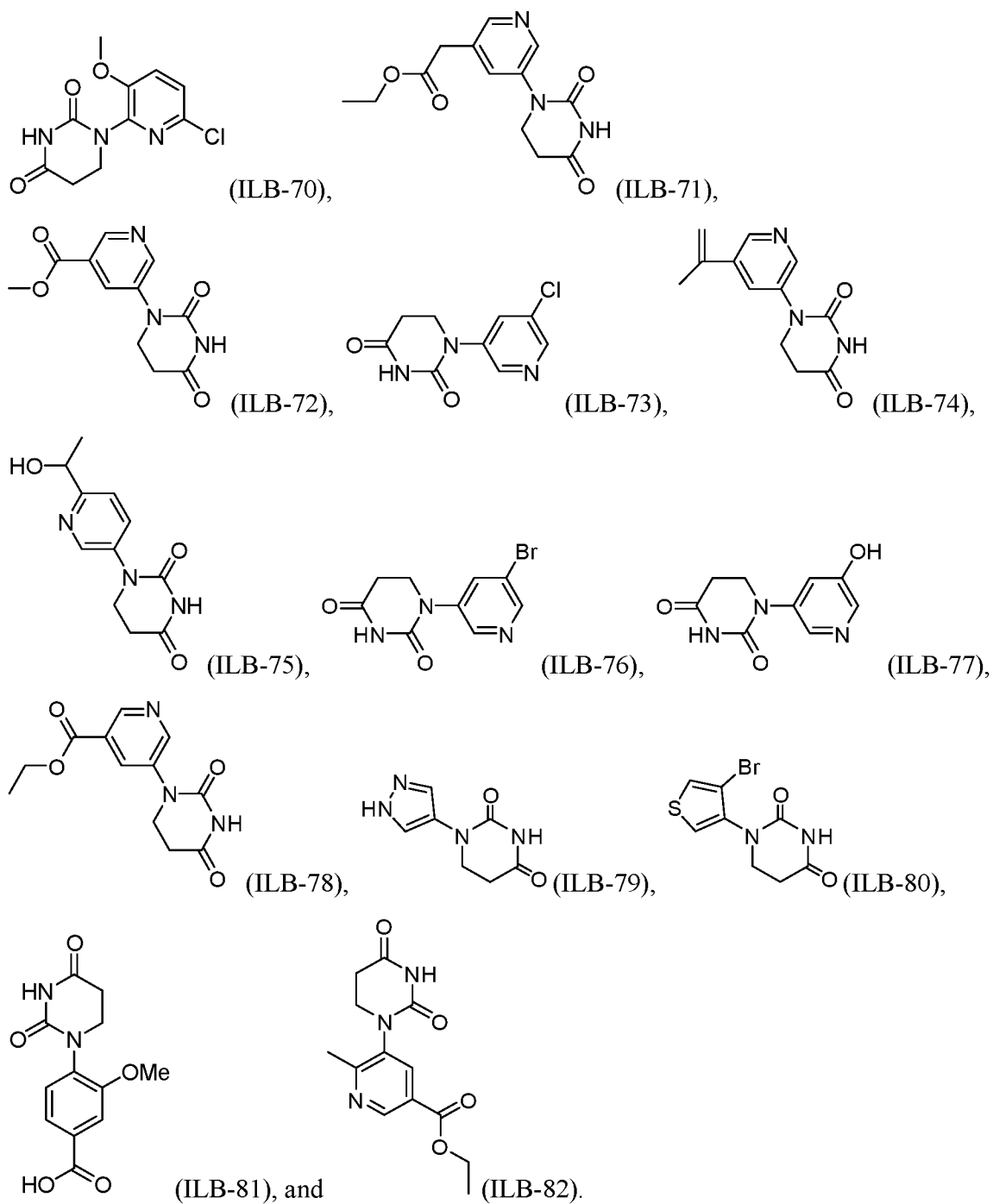




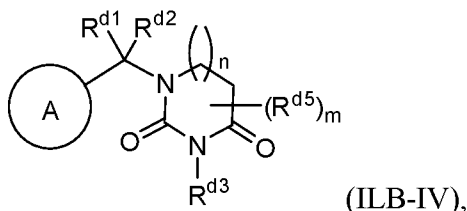




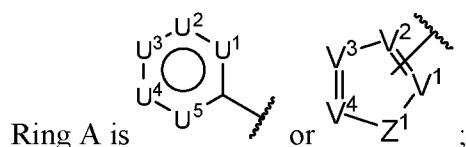




Another embodiment is a compound of Formula (ILB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:



5 denotes the point of attachment to the base molecule of (ILB-IV);

U^1 , U^2 , U^3 , U^4 , and U^5 are each independently N or CR^{d4} or CR^{L2} , wherein no more than three of U^1 , U^2 , U^3 , U^4 , and U^5 can be N, and wherein one of U^1 , U^2 , U^3 , U^4 , and U^5 is CR^{L2} and the remaining are CR^{d4} ;

Z^1 is selected from the group consisting of O, S, NR^{d4a} , or NR^{L2a}

10 V^1 , V^2 , V^3 , and V^4 are each independently N or C, wherein no more than two of V^1 , V^2 , V^3 , and V^4 can be N, and wherein one of Z^1 , V^1 , V^2 , V^3 , and V^4 is substituted with R^{L2} and the remaining are substituted with R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

15 R^{d3} is H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

20 each R^{d4a} is independently selected from the group consisting of H, polyethylene glycol (PEG), C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{2-6} haloalkyl, and C_{2-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L2} is selected from the group consisting of hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, $-O-(CH_2)_{2-6}NHR^c$, C_{4-8} heteroalkyl, C_{2-6} haloalkyl, $-SO_2-NH-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)OR^c$, $-O-C_{2-6}$ alkenyl, $-O-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C(O)H$, $-O-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}C(O)-$ heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}N(R^c)_2$, heterocyclyl, heteroaryl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl, wherein the heterocyclyl and heteroaryl is substituted with 0-2 occurrences of halogen;

R^{L2a} is selected from the group consisting of H, hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, $-O-(CH_2)_{2-6}NHR^c$, C_{1-8} heteroalkyl, C_{1-6} haloalkyl, $-SO_2-NH-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)OR^c$, $-O-C_{2-6}$ alkenyl, $-O-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C(O)H$, $-O-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}$ heterocyclyl, $-O-(CH_2)_{0-3}C(O)-$ heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}N(R^c)_2$, heterocyclyl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl, wherein the heterocyclyl is substituted with 0-2 occurrences of halogen;

R^c is H, C_{1-4} alkyl, C_{1-6} heteroalkyl, and $-C(O)OC_{1-6}$ alkyl;

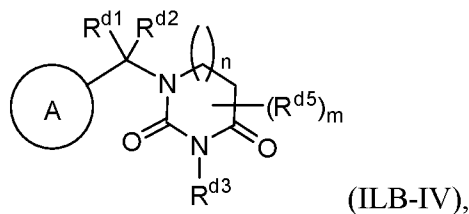
R^d is H or C_{1-4} alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0–2 occurrences of $-O$ -heterocyclyl,

R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

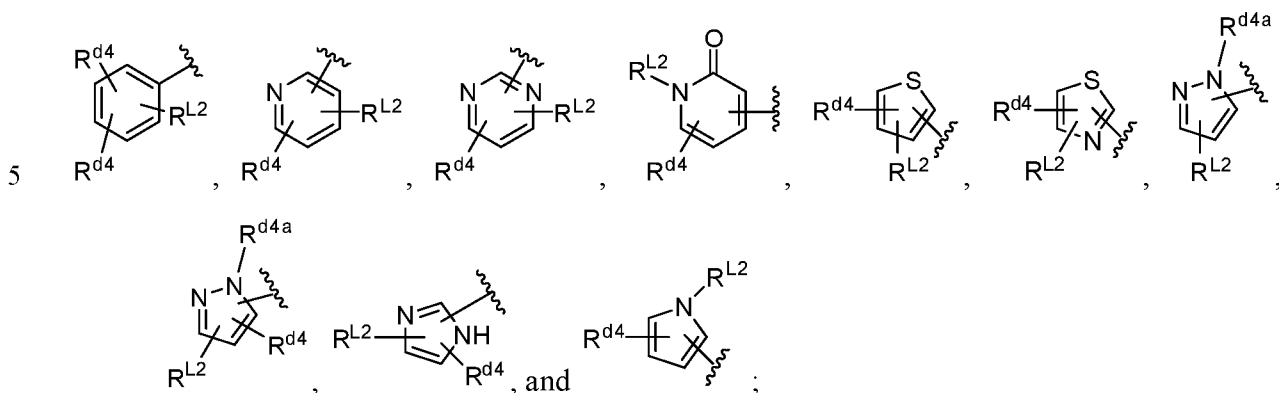
n is 1 or 2.

Another embodiment is a compound of Formula (ILB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

Ring A is selected from the group consisting of:



 denotes the point of attachment to the base molecule of (ILB-IV);

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

10 R^{d3} is H, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₁₋₃ alkoxy, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and -OC₁₋₇ heteroalkyl;

each R^{d4a} is independently selected from the group consisting of H, polyethylene glycol (PEG),

15 C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₂₋₆ haloalkyl, and C₂₋₆ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

20 R^{L2} is selected from the group consisting of hydroxyl, halogen, C₂₋₆ alkyl, C₁₋₃ alkoxy, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ hydroxyalkyl, -(CH₂)₂₋₆NHR^c, -(CH₂)₀₋₆NR^cR^d, -O-(CH₂)₂₋₆NHR^c, C₃₋₈ heteroalkyl, C₁₋₆ haloalkyl, -SO₂-NH-(CH₂)₂₋₆NHR^c, -(CH₂)₀₋₃C(O)OH,

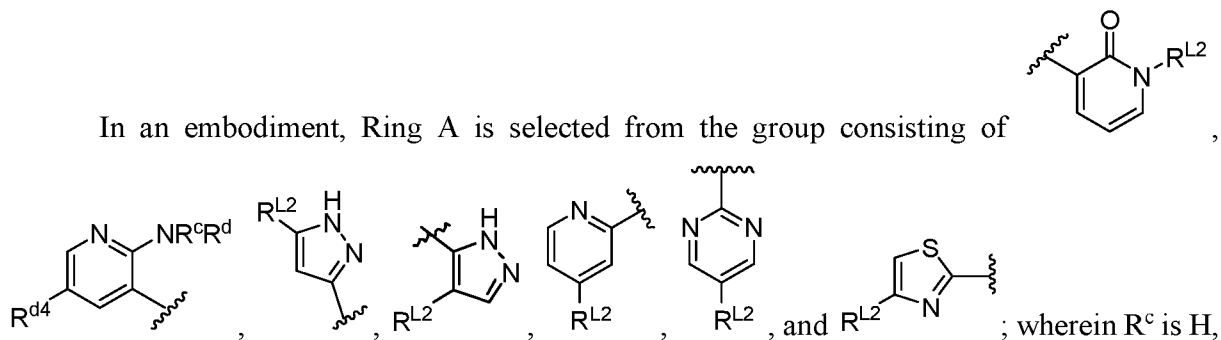
$-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}_{3-7}$ carbocyclyl, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}_{2-6}$ alkynyl-heterocyclyl, $-\text{C}_{2-6}$ alkynyl-heterocyclyl-heteroaryl, C_6 aryl, and heteroaryl, wherein the alkynyl, alkoxy, heterocyclyl, heteroalkyl, carbocyclyl, aryl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-\text{C}(\text{O})\text{O}$ -benzyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2.

In an embodiment, Ring A is selected from the group consisting of



wherein R^c is H, C_{1-4} alkyl, C_{1-6} heteroalkyl, and $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl; and R^d is H or C_{1-4} alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0–2 occurrences of $-\text{O}$ -heterocyclyl.

In an embodiment, R^{d4} is H or halogen.

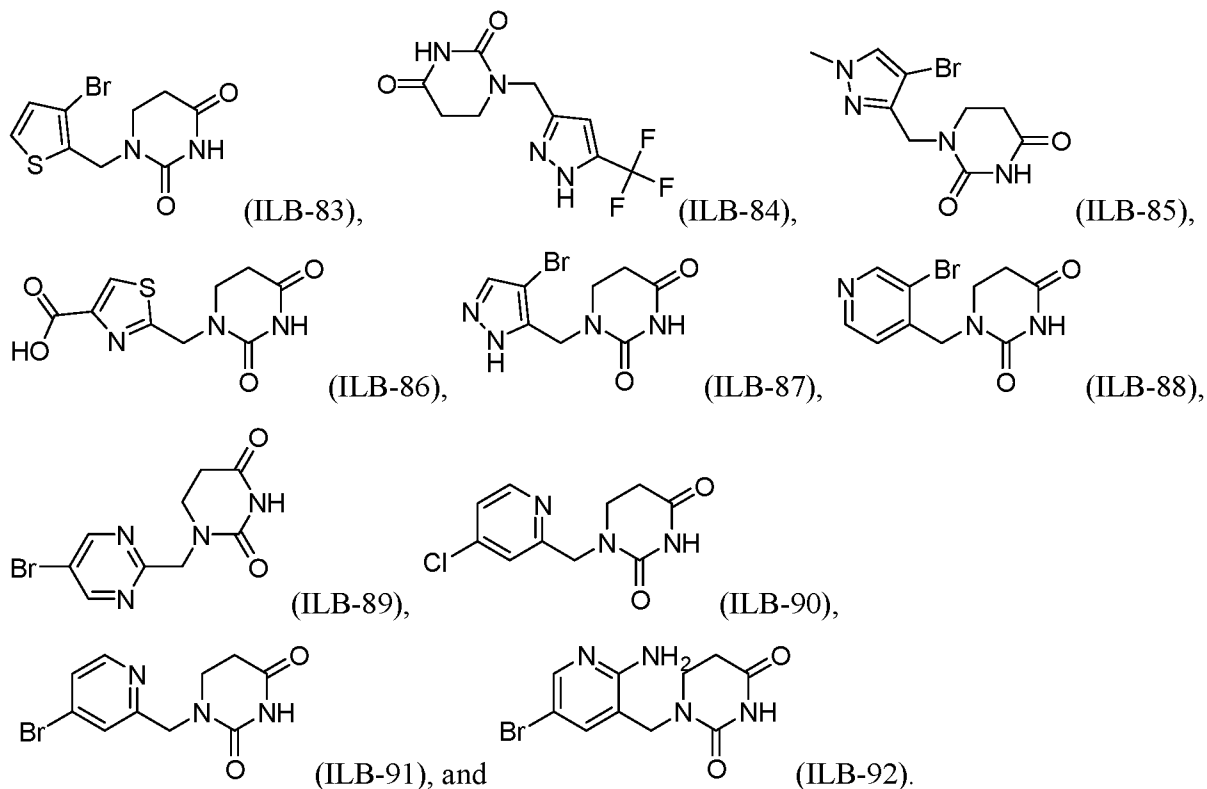
In an embodiment, each R^{d4a} is independently H.

In an embodiment, R^{L2} is selected from the group consisting of halogen, $-(\text{CH}_2)_{0-6}\text{NR}^c\text{R}^d$, C_{1-6} haloalkyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, and $-\text{C}(\text{O})\text{O}$ -benzyl.

In an embodiment, R^c is H, C_{1-4} alkyl, or $-\text{C}(\text{O})\text{OC}_{1-6}$ alkyl.

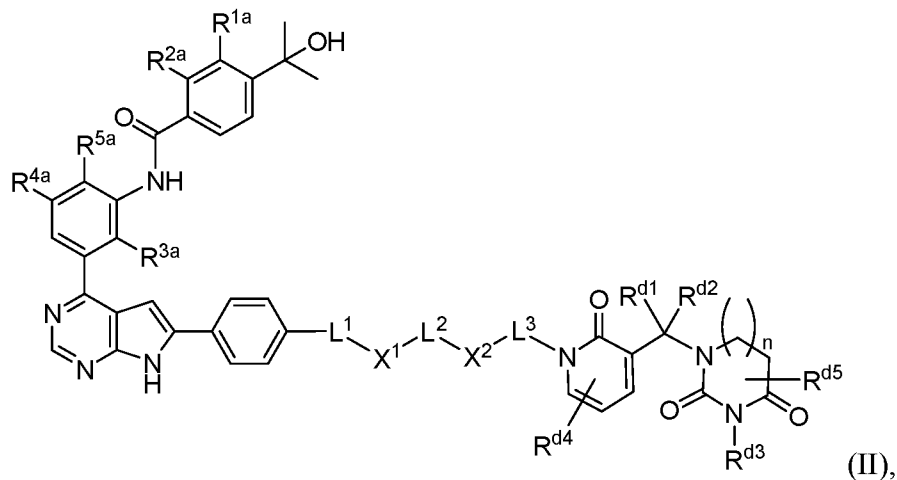
In an embodiment, R^d is H or C_{1-4} alkyl.

Another embodiment is a compound or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



5 Compounds

Another embodiment is a bifunctional compound of Formula (II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

- 10 R^{1a} is H or halo;
 R^{2a} is halo;
 R^{3a} is C_{1-6} alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

L¹ is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, *C(O)-C₁₋₆ alkylene, *C(O)-C₁₋₆ heteroalkylene, *C₁₋₆ alkylene-C(O), and
 5 *C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and *C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of
 10 L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O)-, -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, *C(O)-C₁₋₆ alkylene-O, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in
 15 Formula (BF-III);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;
 20

R^{d3} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

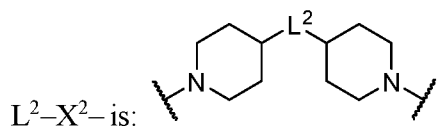
R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl; and
 25

R^p is H or C₁₋₆ alkyl.

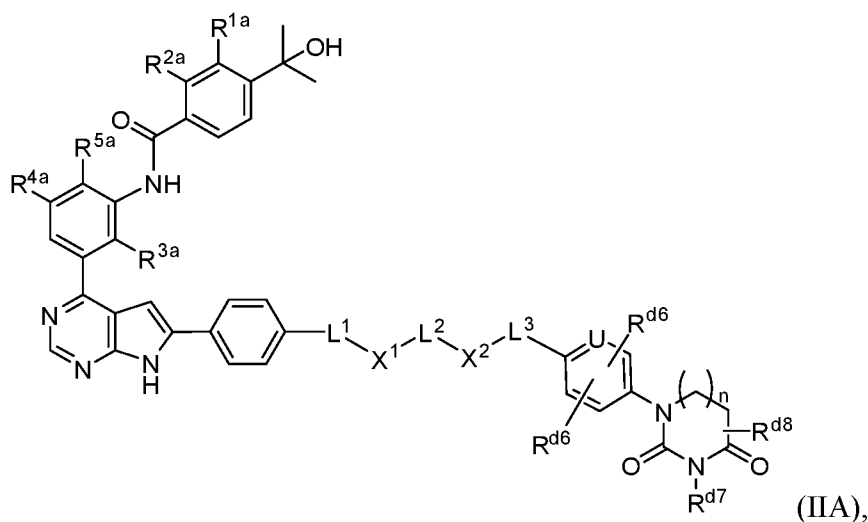
In an embodiment, R^{2a} is fluoro. In an embodiment, R^{3a} is C₁₋₃ alkyl. In an embodiment, R^{3a} is methyl.

In an embodiment, R^{4a} is fluoro. In an embodiment, L^1 is C_{1-9} alkylene. In an embodiment, $-X^1-$



In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene. In an embodiment, R^{d4} is H. In an embodiment, R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H. In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d5} is H or C_{1-3} alkyl. In an embodiment, R^{d5} is H.

Another embodiment is a bifunctional compound of Formula (IIA):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, $*C(O)-C_{1-6}$ alkylene- O , and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

U is $-CR^{d6}$ or N ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

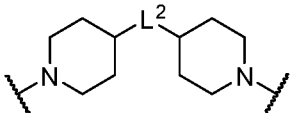
R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

In an embodiment, R^{2a} is fluoro. In an embodiment, R^{3a} is C_{1-3} alkyl. In an embodiment, R^{3a} is methyl.

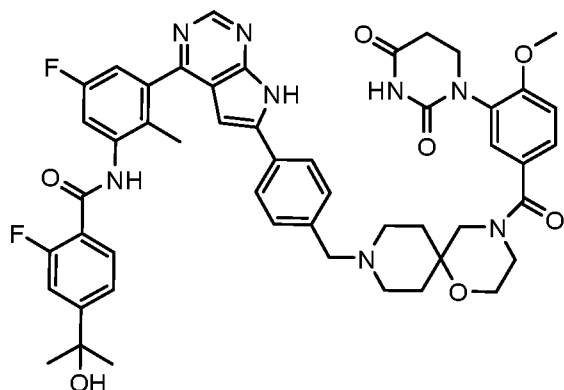
In another aspect, R^{4a} is fluoro. In an embodiment, L^1 is C_{1-9} alkylene. In an embodiment,

$-X^1-L^2-X^2-$ is: . In an embodiment, L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene. In an embodiment, L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6}

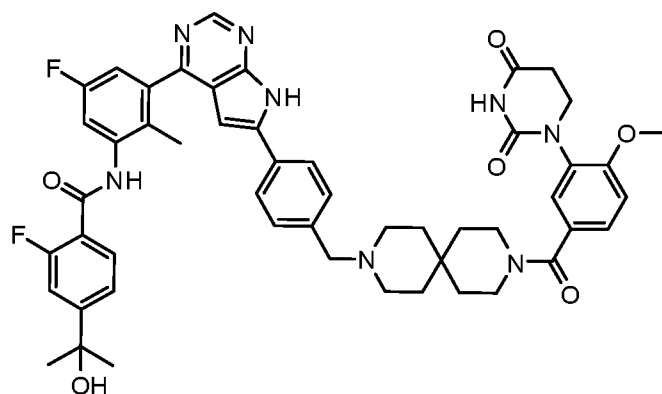
alkylene, C₂₋₆ alkynylene, and C₁₋₆ heteroalkylene. In an embodiment, R^{d4} is H. In an embodiment, R^{d1} is H. In an embodiment, R^{d2} is H. In an embodiment, R^{d1} and R^{d2} are both H. In an embodiment, n is 1. In an embodiment, R^{d3} is H. In an embodiment, R^{d5} is H or C₁₋₃ alkyl.

In an embodiment, R^{d5} is H.

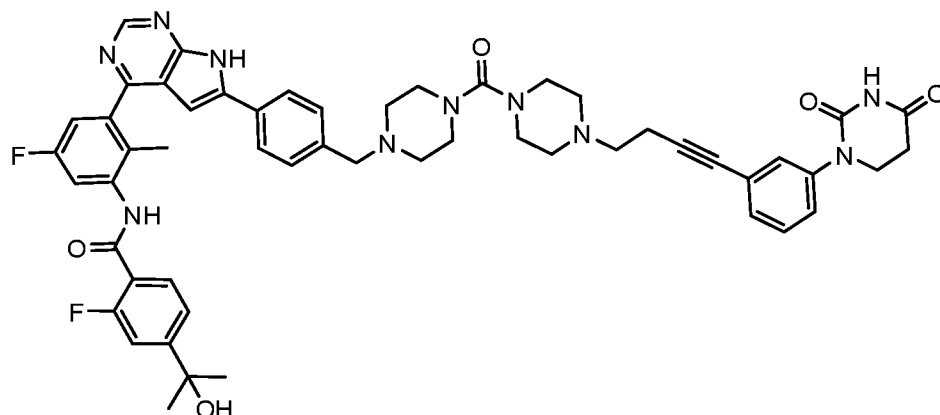
- 5 Another embodiment is a bifunctional compound, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



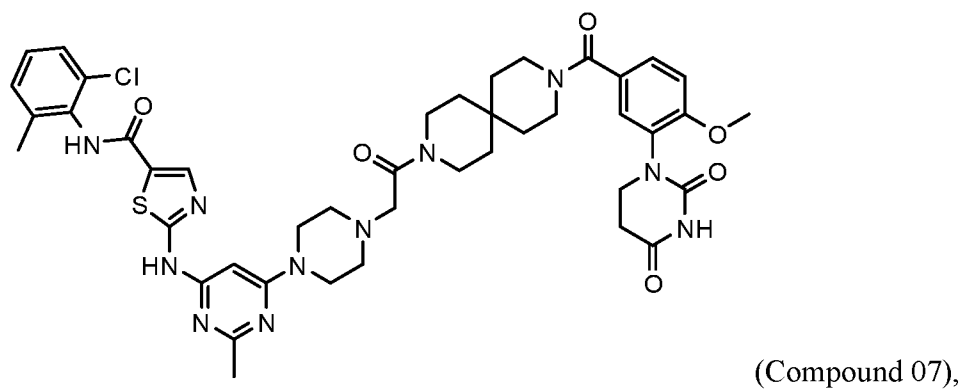
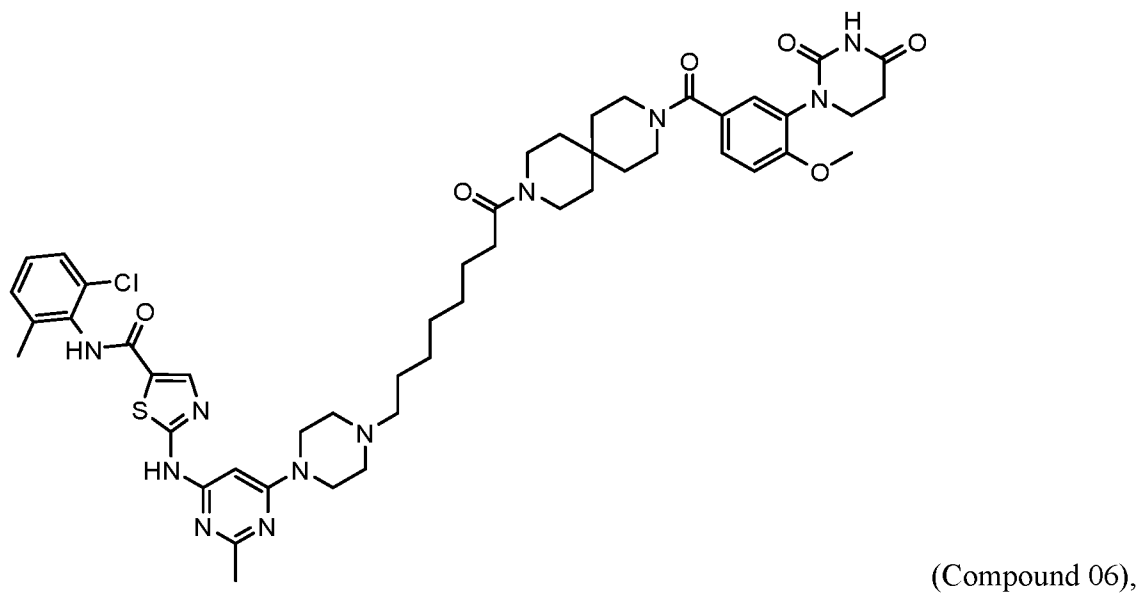
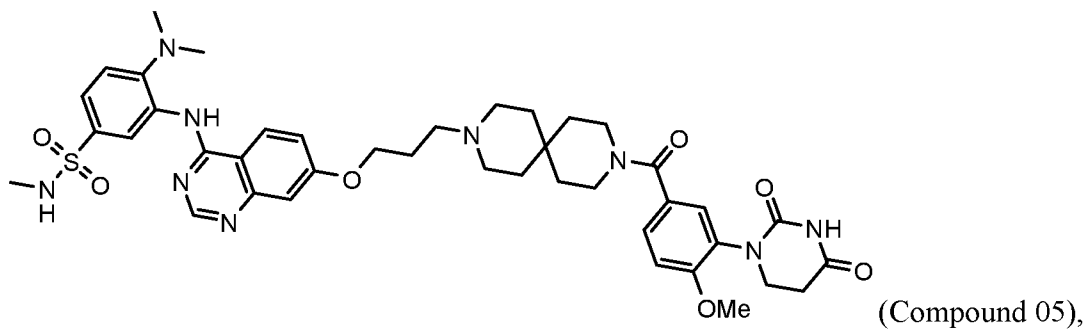
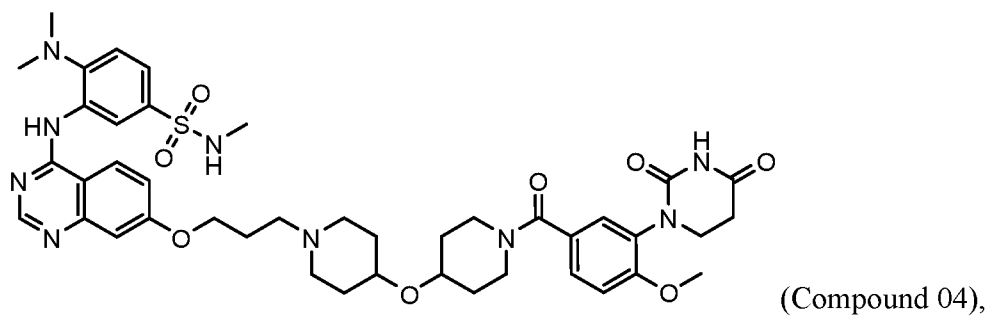
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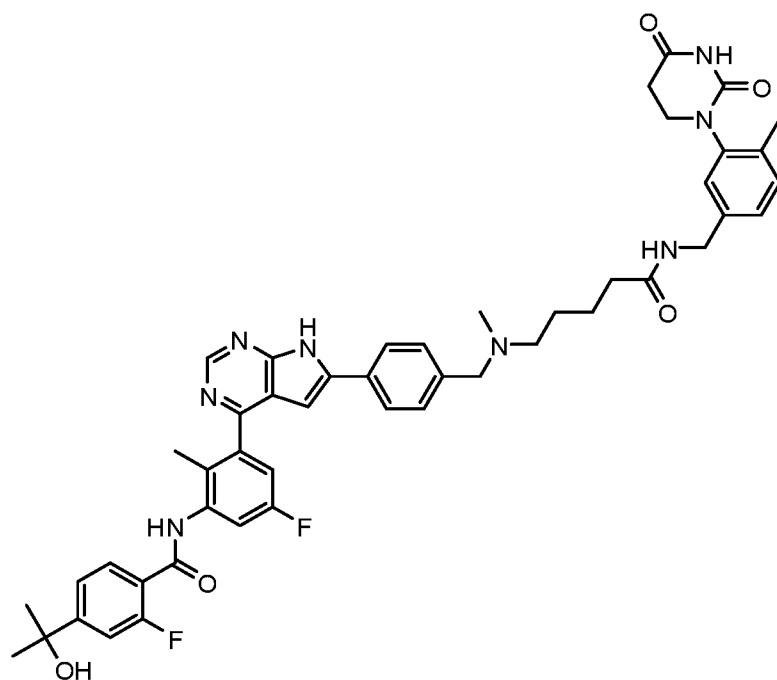


(Compound 02),

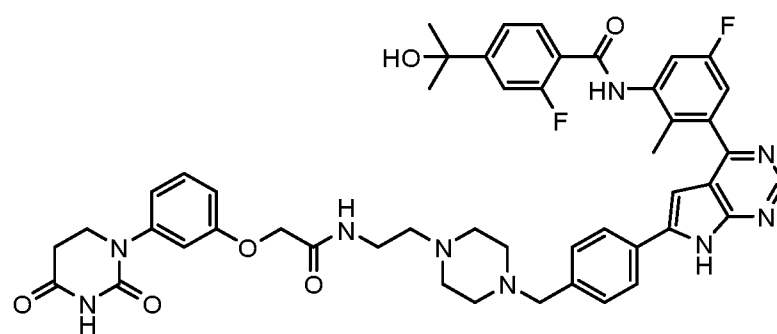


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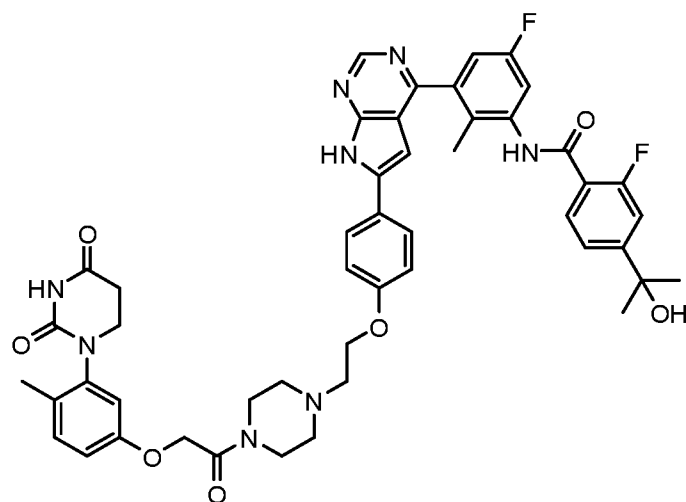




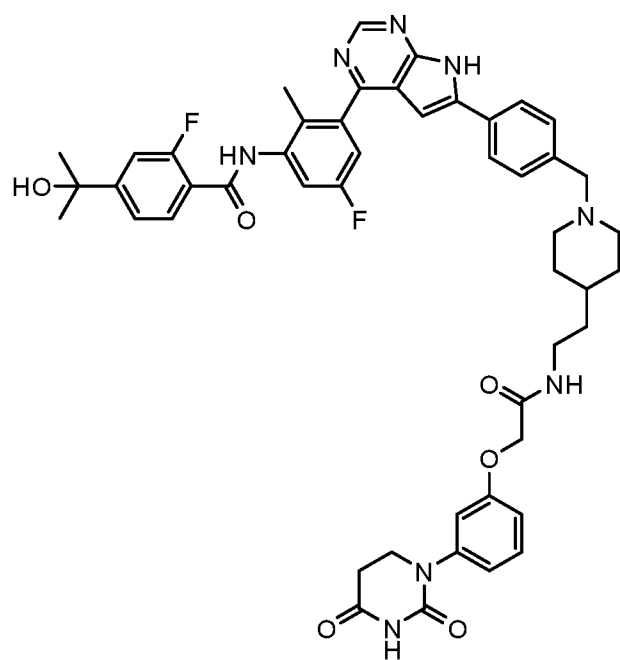
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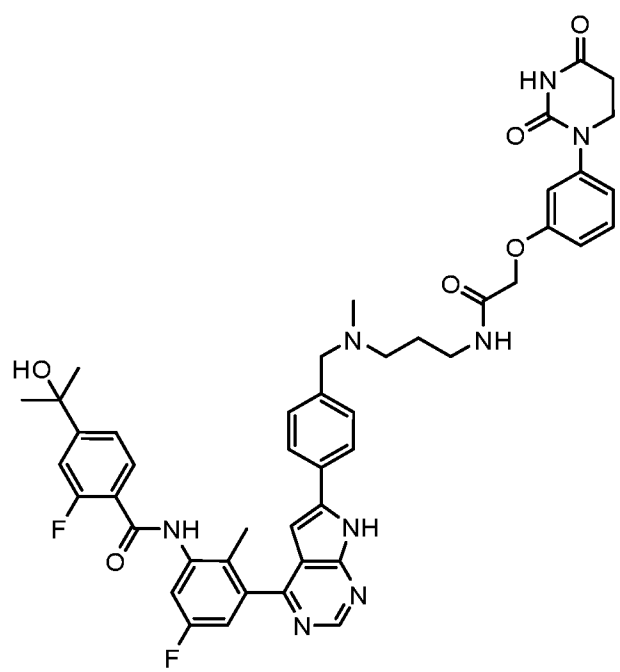
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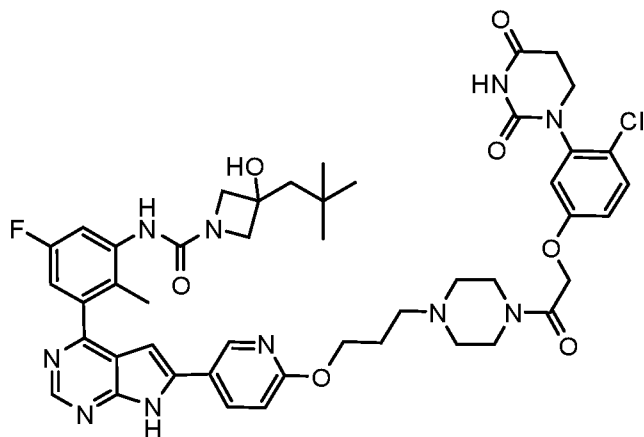
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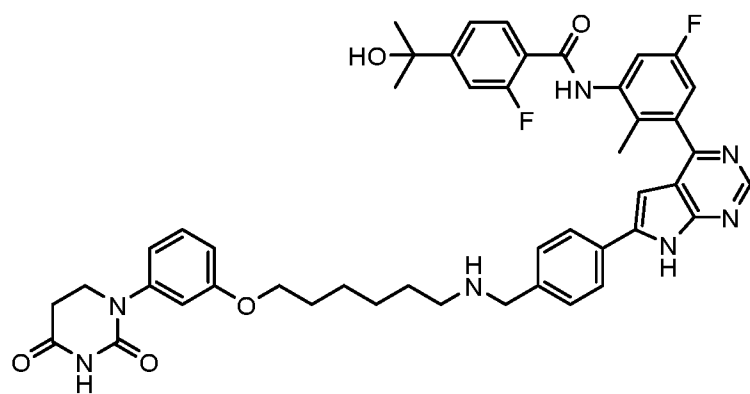
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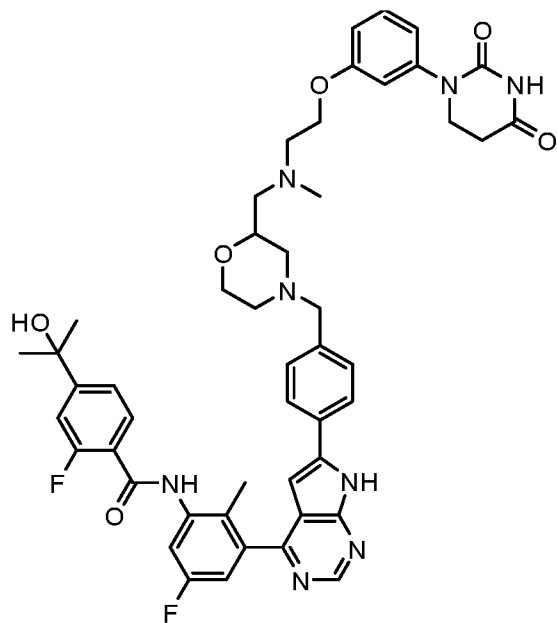
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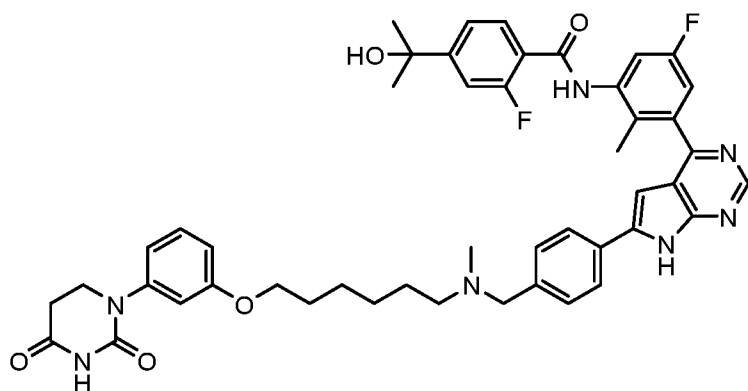
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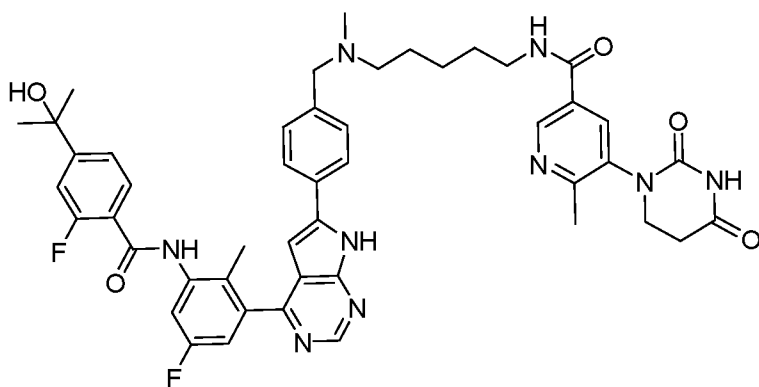
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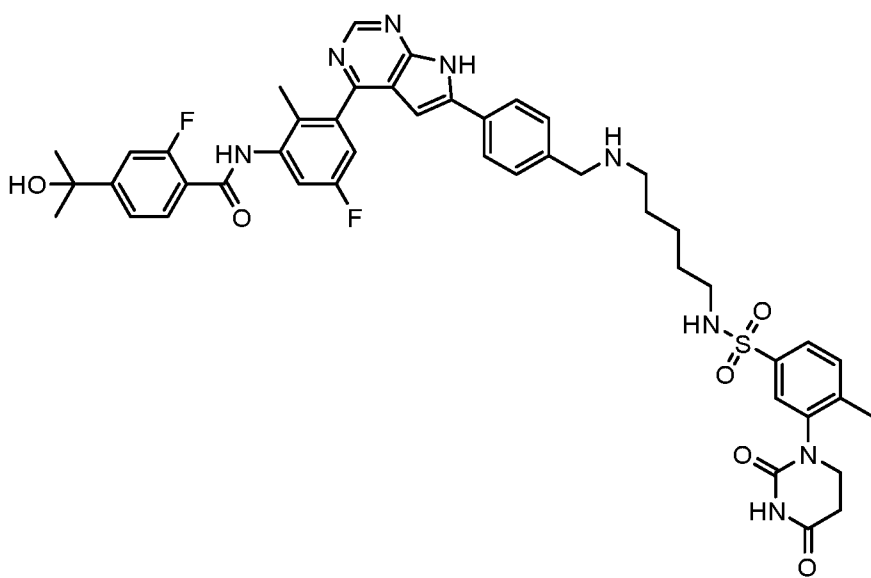
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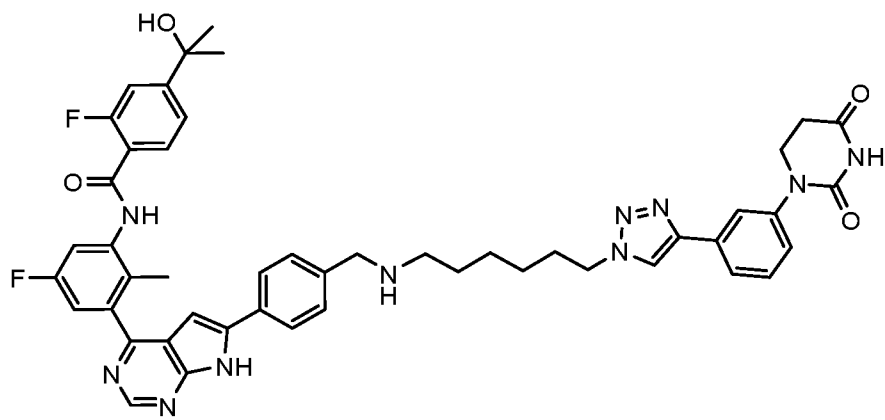
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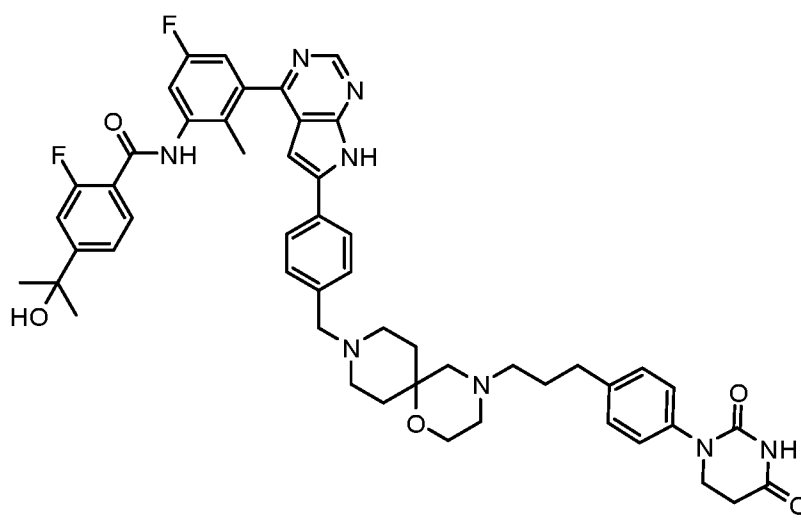
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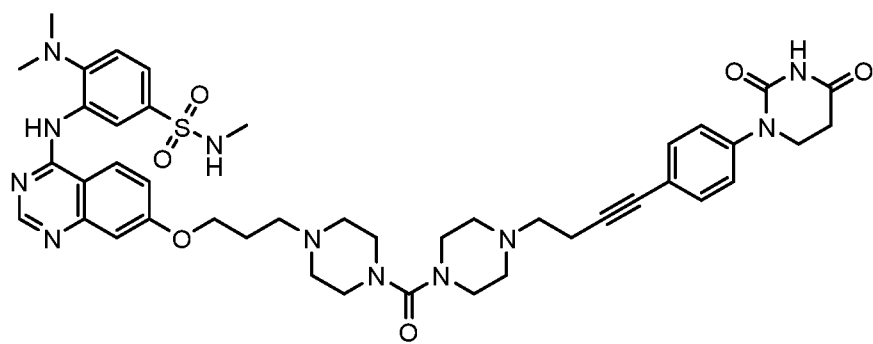
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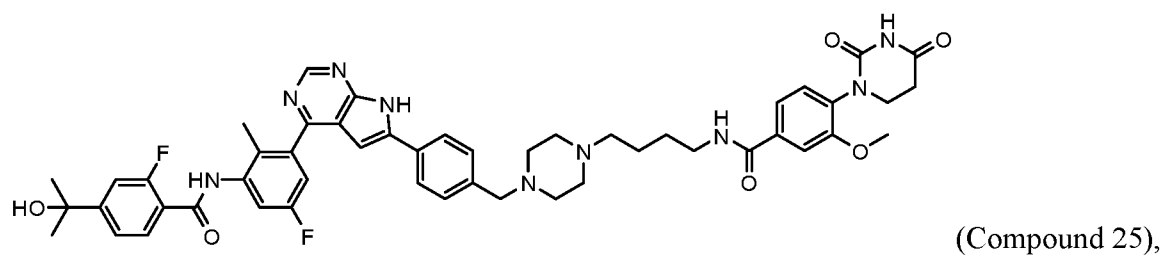
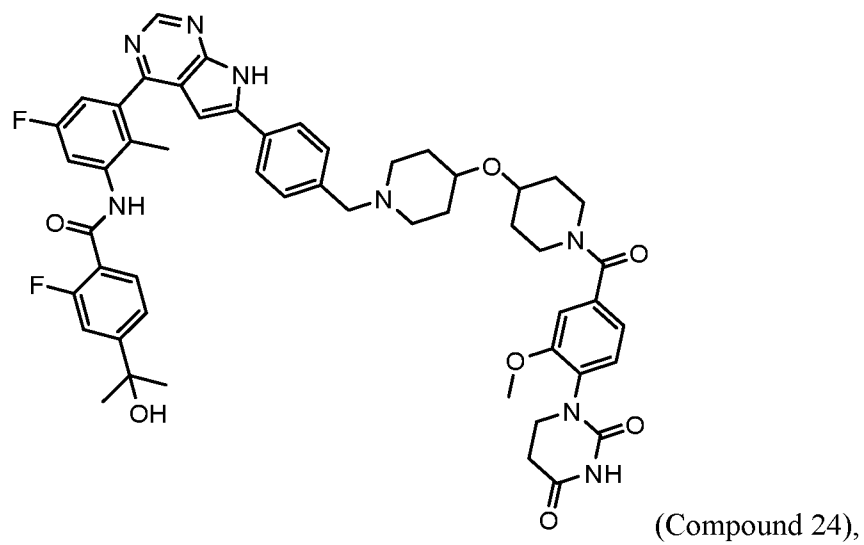
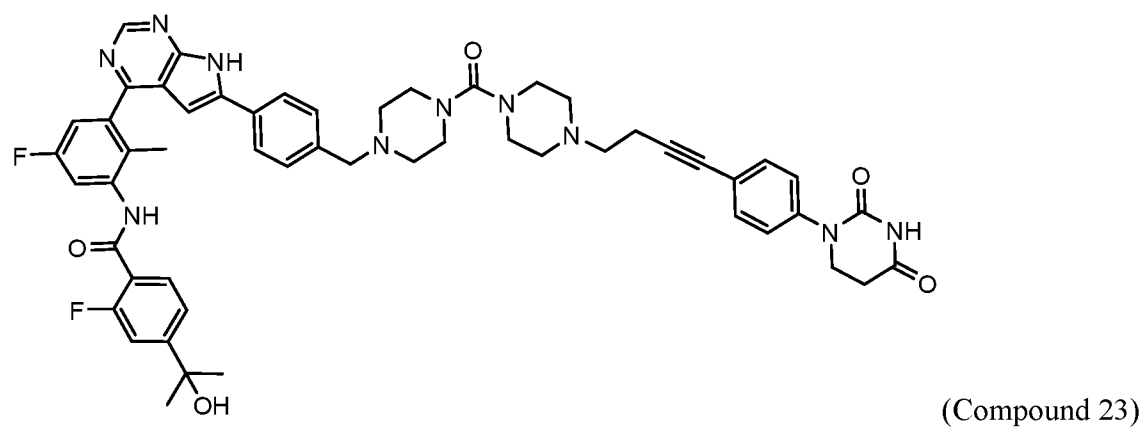
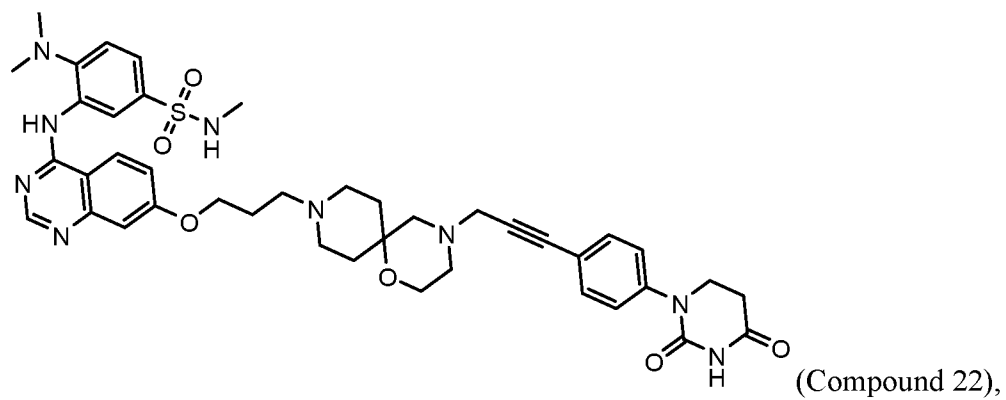
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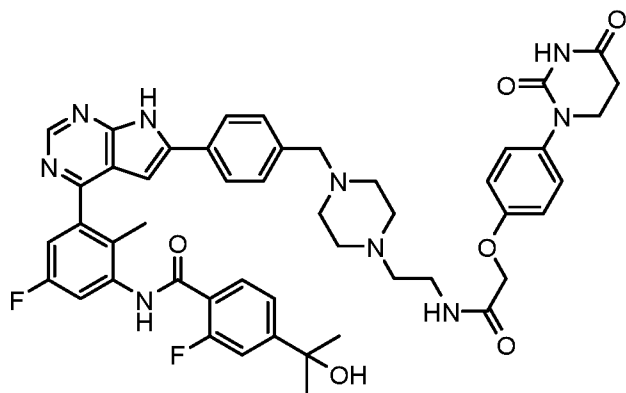


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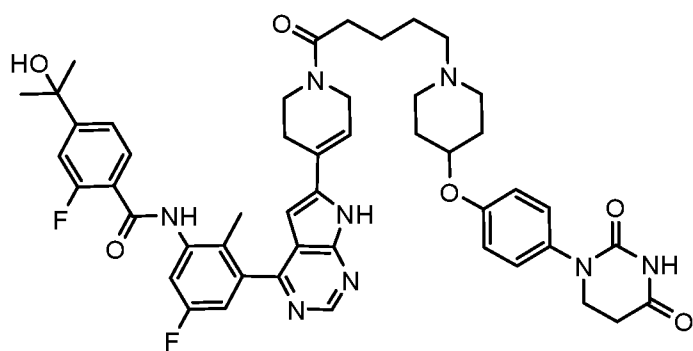


(Compound 21),

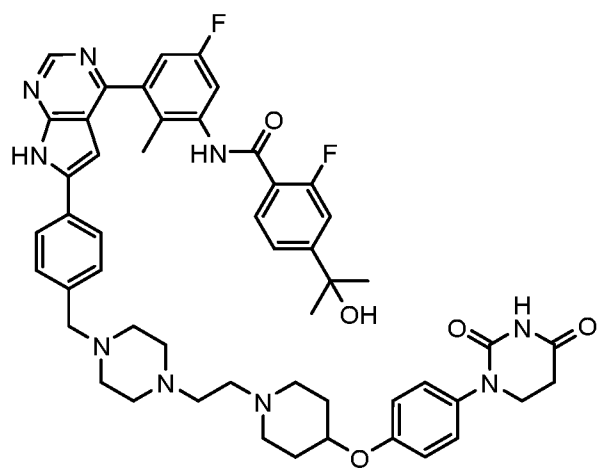




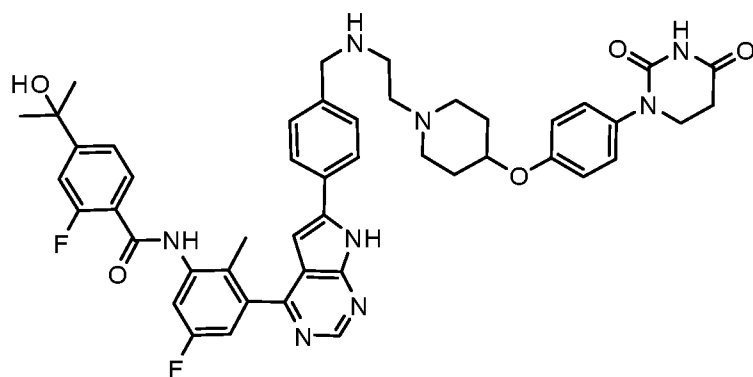
(Compound 26),



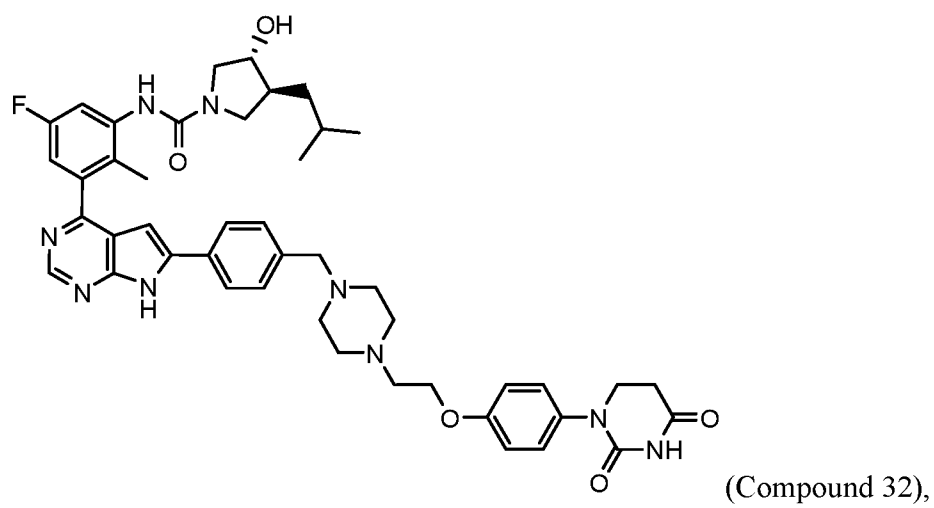
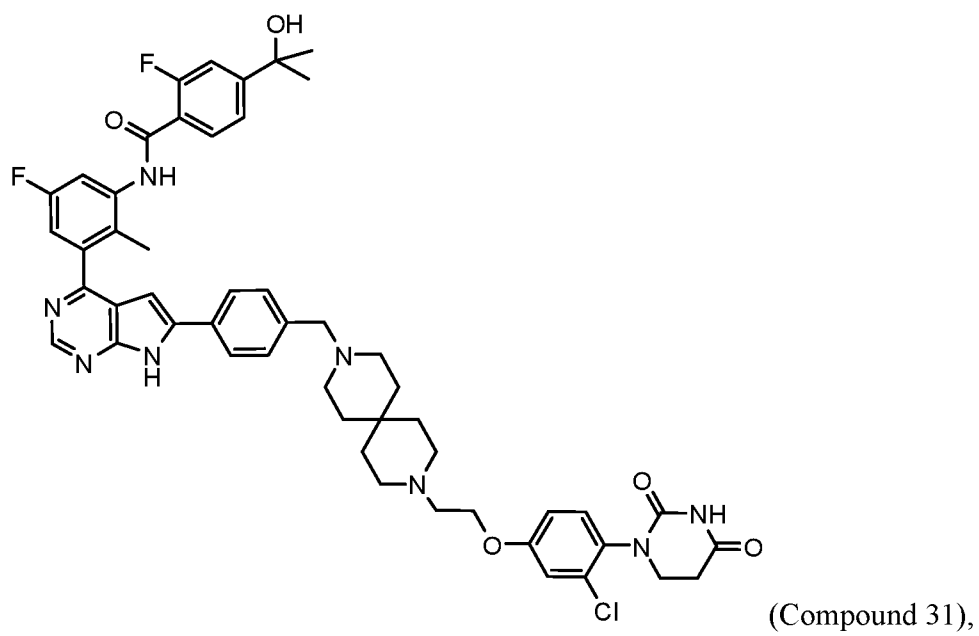
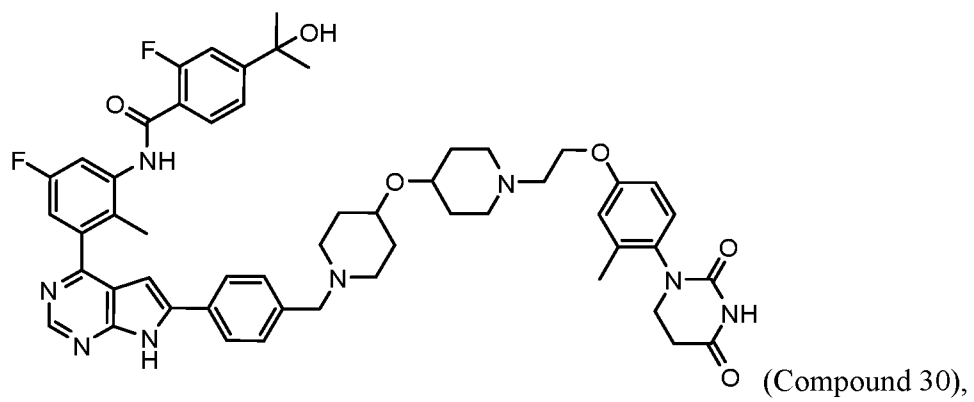
(Compound 27),

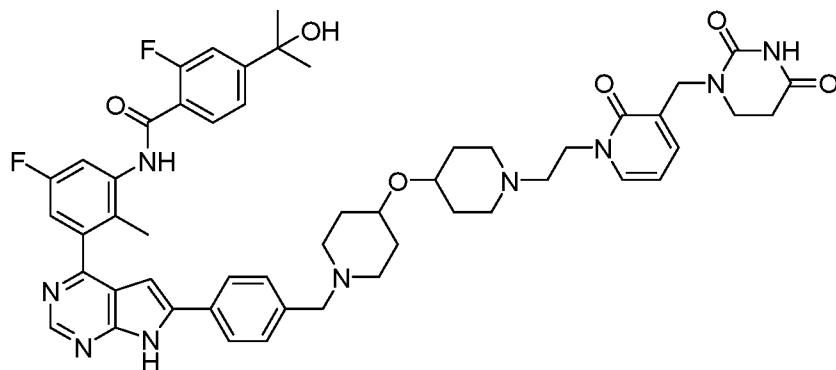


(Compound 28),

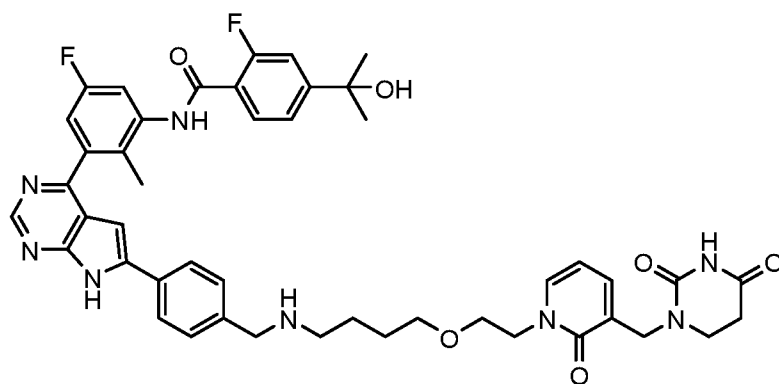


(Compound 29),

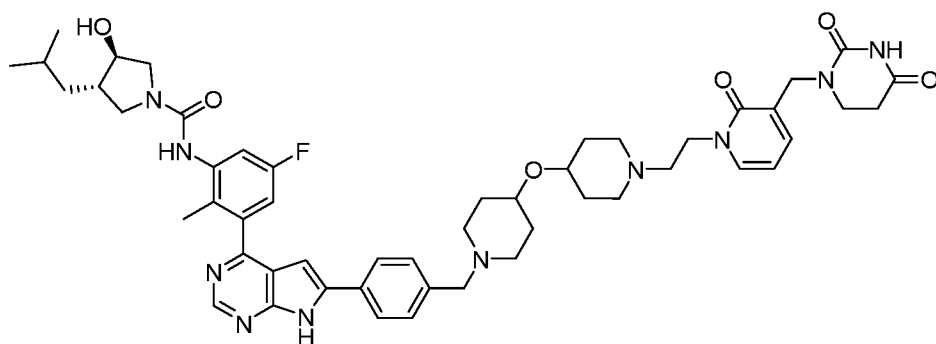




(Compound 33),



(Compound 34), and



(Compound 35).

5 In an embodiment, when the compound is a compound of Formula (IIA), then the compound is not a compound selected from:

rac-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-7-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

10 (R)-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-7-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

(S)-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-7-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-ethoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-fluorobenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)oxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)methyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)oxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-fluorobenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1-(3-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)propyl)piperidin-4-yl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

rac-N-(3-(6-(4-(((1-(2-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)-3-hydroxypropyl)piperidin-4-yl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)methyl)piperidin-4-yl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-methylpropyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)ethyl)piperidin-4-yl)oxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazine-1-carbonyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

rac-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

(S)-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

(R)-N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-(hydroxymethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)butyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoro-N-(5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)amino)pentyl)-N,4-dimethylbenzamide,

5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoro-N-(5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)amino)pentyl)-4-methylbenzamide,

3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-N-(5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)amino)pentyl)-N,4-dimethylbenzamide,

N-(3-(6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-2,7-diazaspiro[3.5]nonan-7-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidine-4-carbonyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((8-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)ethyl)-2,8-diazaspiro[4.5]decan-2-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(4-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)ethyl)amino)butoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(2-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamido)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)ethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)butyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1s,4s)-4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)cyclohexyl)oxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-N-(5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)amino)pentyl)-N-methylbenzamide,

N-(3-(6-(4-((1-(2-(1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)ethyl)piperidin-4-yl)methoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)ethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((3-((2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)ethyl)amino)propoxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1r,4r)-4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)cyclohexyl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-fluorobenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamido)propyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((8-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-2,8-diazaspiro[4.5]decan-2-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((1-(2-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperazin-1-yl)ethyl)piperidin-4-yl)methoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)ethyl)-2,7-diazaspiro[3.5]nonan-7-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzamido)ethyl)-2,8-diazaspiro[4.5]decan-8-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1s,4s)-4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)cyclohexyl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-2,8-diazaspiro[4.5]decan-8-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-(((1r,4r)-4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)cyclohexyl)oxy)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide,

N-(3-(6-(4-((9-(3-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzamido)propyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide, and

N-(3-(6-(4-((1-(2-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)ethyl)piperidin-4-yl)oxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide, or a pharmaceutically acceptable salt thereof.

Definitions

One embodiment is a compound of any of the formulae described herein, *e.g.*, a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, that modulates, *e.g.*, decreases the amount of a targeted protein or protein of interest, *e.g.*, one or more proteins from **Table 1** or **Table 2**.

Another embodiment is a compound of any of the formulae described herein, *e.g.*, a compound of Formula (I), (II), (III), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, that degrades a targeted protein through the ubiquitin-proteasome pathway (UPP).

The formation of a viable ternary complex among the target protein, the bifunctional degrader, and the E3 ligase substrate receptor is enabled by the use of targeted bifunctional degraders, relying on three components, the “targeting ligand” and the “targeting ligase binder” (also termed “warheads”) and the joining segment, termed the “linker.” The likelihood that a bifunctional degrader may form an energetically favored viable complex can be assessed using an *in silico* computational approach. Energetic unfavorability can arise through enthalpic contributions (steric or electronic clashes between the protein targets and the degrader), entropic contributions (reduction in the degrees of freedom upon formation of the ternary complex), or a combination of the two. Using *in silico* methods, unfavorable linkers can be quickly identified and deprioritized. Various methods have been described for designing bifunctional degraders. *See* Drummond and Williams, *J. Chem. Inf. Model.* 59:1634-1644 (2019). The *in silico* ternary complex modelling protocol consists of four steps (*see* FIG. 2): (1) generate the conformational ensemble of the bifunctional degraders. For this task, various conformational searches methods available in standard modelling programs can be used. (2) Rigidly superimpose using the coordinates one of the warheads (either the “targeting ligand” or the “targeting ligase binder”) with the same warhead bound in the binary complex structure, as observed in crystal structure or by docking it in the respective protein. (3) Filter to retain sterically competent conformations of the bifunctional degrader with the first protein. (4) Rigidly superimpose the warhead bound in the other binary complex structure to the coordinates of the corresponding warhead in the degrader. Conformations of the targeted bifunctional degraders causing serious clashes between any of the three components of the ternary complexes are filtered out. The saved generated conformations could be further clustered and refined using standard molecular dynamics approaches. This allows the relaxation of minor steric clashes and electrostatic mismatches. It also gives an indication of the stability of the ternary complex; linkers that do not bring the proteins into contact can be said to be entropically disfavored.

For example, the method described herein has been applied to Compounds 01 and 02. Despite both compounds binding to CRBN (**Table 4**), Compound 2 enabled the ternary complex formation according to the method described herein, and as such degrades BTK (>95%). However, Compound 01 was predicted to not form a ternary complex and experimentally no degradation of BTK was observed (**Table 4**).

It is also possible to design modified linkers using *de novo* or generative methods to enhance physicochemical properties or some other scoring metric. See Ertl and Lewis, *J. Comput Aided Mol. Des.* 26(11): 1207-1215 (2012). It is possible to combine both the assessment for ternary complex formation and having favorable properties, to identify an optimal linker space.

5 The term “a therapeutically effective amount” of a compound described herein refers to an amount of the compound described herein that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one embodiment, the term “a therapeutically effective amount” refers to the amount of the compound
10 described herein that, when administered to a subject, is effective to (1) at least partially alleviate, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by a target protein, (ii) associated with activity of a target protein, or (iii) characterized by activity (normal or abnormal) of a target protein; or (2) reduce or inhibit the activity of a target protein; or (3) reduce or inhibit the expression of a target protein. These effects may be achieved for example by reducing
15 the amount of a target protein by degrading of the target protein. In one embodiment, the term “a therapeutically effective amount” refers to the amount of the compound described herein that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reduce or inhibit the activity of target protein; or at least partially reduce or inhibit the expression of a target protein, for example by degrading a target protein.

20 As used herein, the term cancer refers to a neoplastic disease and includes for instance solid tumors, such as, *e.g.* sarcomas or carcinomas or blood cancer, such as, *e.g.* leukemia or myeloma, or cancers of lymphatic system such as lymphoma, or mixed types thereof.

 As used herein, the terms “degrades”, “degrading”, or “degradation” refers to the partial or full breakdown of a target protein by the cellular proteasome system to an extent that reduces or
25 eliminates the biological activity (especially aberrant activity) of target protein. Degradation may be achieved through mediation of an E3 ligase, in particular, E3-ligase complexes comprising the protein Cereblon. As used herein, the term “modulation of target protein activity” or “modulating target activity” means the alteration of, especially reduction, suppression or elimination, of target protein’s activity. This may be achieved by degrading the target protein *in vivo* or *in vitro*. The
30 amount of target protein degraded can be measured by comparing the amount of target protein remaining after treatment with a compound described herein as compared to the initial amount or

level of target protein present as measured prior to treatment with a compound described herein.
In an embodiment, at least about 30% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 40% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 50% of the target protein is degraded compared to initial levels.
5 In an embodiment, at least about 60% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 70% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 80% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 90% of the target protein is degraded compared to initial levels.
In an embodiment, at least about 95% of the target protein is degraded compared to initial levels.
10 In an embodiment, over 95% of the target protein is degraded compared to initial levels. In an
embodiment, at least about 99% of the target protein is degraded compared to initial levels.

In an embodiment, the target protein is degraded in an amount of from about 30% to about
99% compared to initial levels. In an embodiment, the target protein is degraded in an amount of
from about 40% to about 99% compared to initial levels. In an embodiment, the target protein is
15 degraded in an amount of from about 50% to about 99% compared to initial levels. In an
embodiment, the target protein is degraded in an amount of from about 60% to about 99%
compared to initial levels. In an embodiment, the target protein is degraded in an amount of from
about 70% to about 99% compared to initial levels. In an embodiment, the target protein is
degraded in an amount of from about 80% to about 99% compared to initial levels. In an
20 embodiment, the target protein is degraded in an amount of from about 90% to about 99%
compared to initial levels. In an embodiment, the target protein is degraded in an amount of from
about 95% to about 99% compared to initial levels. In an embodiment, the target protein is
degraded in an amount of from about 90% to about 95% compared to initial levels.

As used herein, the term “selectivity for the target protein” means, for example, a
25 compound described herein degrades the target protein in preference to, or to a greater extent than,
another protein or proteins.

As used herein, the term “subject” refers to an animal. Typically, the animal is a mammal.
A subject also refers to, for example, primates (*e.g.*, humans, male or female), cows, sheep, goats,
horses, dogs, cats, rabbits, rats, mice, fish, birds, and the like. In an embodiment, the subject is a
30 primate. In a preferred embodiment, the subject is a human.

As used herein, the terms “inhibit”, “inhibition”, or “inhibiting” refer to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the terms “treat”, “treating”, or “treatment” of any disease or disorder refer
5 In an embodiment, to ameliorating the disease or disorder (*i.e.*, slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In an embodiment, “treat”, “treating”, or “treatment” refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient.

As used herein, the term “preventing” refers to a reduction in the frequency of, or delay in
10 the onset of, symptoms of the condition or disease.

As used herein, a subject is “in need of” a treatment if such subject would benefit biologically, medically, or in quality of life from such treatment.

As used herein, the term “a,” “an,” “the” and similar terms used in the context of the disclosure (especially in the context of the claims) are to be construed to cover both the singular
15 and plural unless otherwise indicated herein or clearly contradicted by the context.

The term “alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 6 carbon atoms (“C₁₋₆ alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In
20 some embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“C₂₋₆ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), propyl (C₃) (*e.g.*, *n*-propyl, isopropyl), butyl (C₄) (*e.g.*, *n*-butyl, *tert*-butyl, *sec*-butyl, isobutyl), pentyl (C₅) (*e.g.*, *n*-pentyl, 3-pentanyl, amyl, neopentyl, 3-methyl-2-butanyl, tertiary amyl), and hexyl (C₆)
25 (*e.g.*, *n*-hexyl).

“Alkylene” refers to a divalent radical of an alkyl group, *e.g.*, –CH₂–, –CH₂CH₂–, and –CH₂CH₂CH₂–.

“Heteroalkyl” refers to an alkyl group, which further includes at least one heteroatom (*e.g.*, 1, 2, 3, or 4 heteroatoms) selected from oxygen, nitrogen, or sulfur within (*i.e.*, inserted between
30 adjacent carbon atoms of) and/or placed at one or more terminal position(s) of the parent chain. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon

atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₁₀ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₉ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₈ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₇ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 6 carbon atoms and 1 or more heteroatoms within the parent chain (“heteroC₁₋₆ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₅ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₁₋₄ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₃ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom within the parent chain (“heteroC₁₋₂ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ alkyl”). In some embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms within the parent chain (“heteroC₂₋₆ alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC₁₋₁₀ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₀ alkyl.

“Heteroalkylene” refers to a divalent radical of a heteroalkyl group.

“Alkoxy” or “alkoxyl” refers to an -O-alkyl radical. In some embodiments, the alkoxy groups are methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, and 1,2-dimethylbutoxy. In some embodiments, alkoxy groups are lower alkoxy, *i.e.*, with between 1 and 6 carbon atoms. In some embodiments, alkoxy groups have between 1 and 4 carbon atoms.

As used herein, the term “aryl” refers to a stable, aromatic, mono- or bicyclic ring radical having the specified number of ring carbon atoms. Examples of aryl groups include, but are not

limited to, phenyl, 1-naphthyl, 2-naphthyl, and the like. The related term “aryl ring” likewise refers to a stable, aromatic, mono- or bicyclic ring having the specified number of ring carbon atoms.

As used herein, the term “heteroaryl” refers to a stable, aromatic, mono- or bicyclic ring radical having the specified number of ring atoms and comprising one or more heteroatoms individually selected from nitrogen, oxygen and sulfur. The heteroaryl radical may be bonded via a carbon atom or heteroatom. Examples of heteroaryl groups include, but are not limited to, furyl, pyrrolyl, thienyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, pyrimidyl, pyridyl, quinoliny, isoquinoliny, indolyl, indazolyl, oxadiazolyl, benzothiazolyl, quinoxaliny, and the like. The related term “heteroaryl ring” likewise refers to a stable, aromatic, mono- or bicyclic ring having the specified number of ring atoms and comprising one or more heteroatoms individually selected from nitrogen, oxygen and sulfur.

As used herein, the term “carbocyclyl” refers to a stable, saturated or unsaturated, non-aromatic, mono- or bicyclic (fused, bridged, or spiro) ring radical having the specified number of ring carbon atoms. Examples of carbocyclyl groups include, but are not limited to, the cycloalkyl groups identified above, cyclobutenyl, cyclopentenyl, cyclohexenyl, and the like. In an embodiment, the specified number is C₃–C₁₂ carbons. The related term “carbocyclic ring” likewise refers to a stable, saturated or unsaturated, non-aromatic, mono- or bicyclic (fused, bridged, or spiro) ring having the specified number of ring carbon atoms. In an embodiment, the carbocyclyl can be substituted or unsubstituted. In an embodiment, the carbocyclyl can be substituted with 0-4 occurrences of R^a, wherein each R^a is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, and halogen.

As used herein, the term “heterocyclyl” refers to a stable, saturated or unsaturated, non-aromatic, mono- or bicyclic (fused, bridged, or spiro) ring radical having the specified number of ring atoms and comprising one or more heteroatoms individually selected from nitrogen, oxygen and sulfur. The heterocyclyl radical may be bonded via a carbon atom or heteroatom. In an embodiment, the specified number is C₃–C₁₂ carbons. Examples of heterocyclyl groups include, but are not limited to, azetidiny, oxetany, pyrroliny, pyrrolidiny, tetrahydrofuryl, tetrahydrothienyl, piperidyl, piperaziny, tetrahydropyrany, morpholiny, perhydroazepiny, tetrahydropyridiny, tetrahydroazepiny, octahydropyrrolopyrroly, and the like. The related term “heterocyclic ring” likewise refers to a stable, saturated or unsaturated, non-aromatic, mono- or bicyclic (fused, bridged, or spiro) ring having the specified number of ring atoms and comprising

one or more heteroatoms individually selected from nitrogen, oxygen and sulfur. In an embodiment, the heterocyclyl can be substituted or unsubstituted. In an embodiment, the heterocyclyl can be substituted with 0-4 occurrences of R^a, wherein each R^a is independently selected from the group consisting of C₁₋₆ alkyl, C₁₋₆ alkoxy, and halogen.

5 As used herein, “spirocycloalkyl” or “spirocyclyl” means carbogenic bicyclic ring systems with both rings connected through a single atom. The rings can be different in size and nature, or identical in size and nature. Examples include spiropentane, spirohexane, spiroheptane, spirooctane, spirononane, or spirodecane. One or both of the rings in a spirocycle can be fused to another ring carbocyclic, heterocyclic, aromatic, or heteroaromatic ring. For example, a (C₃–
10 C₁₂)spirocycloalkyl is a spirocycle containing between 3 and 12 carbon atoms.

As used herein, “spiroheterocycloalkyl” or “spiroheterocyclyl” means a spirocycle wherein at least one of the rings is a heterocycle wherein one or more of the carbon atoms can be substituted with a heteroatom (*e.g.*, one or more of the carbon atoms can be substituted with a heteroatom in at least one of the rings). One or both of the rings in a spiroheterocycle can be fused to another
15 ring carbocyclic, heterocyclic, aromatic, or heteroaromatic ring.

As used herein, “halo” or “halogen” refers to fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), or iodine (iodo, -I).

As used herein, “haloalkyl” means an alkyl group substituted with one or more halogens. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, and trichloromethyl.
20

As used herein, “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent.

As used herein, the definition of each expression, *e.g.*, alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same
25 structure.

Various embodiments of the disclosure are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features, including as indicated in the embodiments below, to provide further embodiments of the present disclosure.

It is understood that in the following embodiments, combinations of substituents or
30 variables of the depicted formulae are permissible only if such combinations result in stable compounds.

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

Certain compounds described herein may exist in particular geometric or stereoisomeric forms. If, for instance, a particular enantiomer of a compound described herein is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Unless otherwise stated, structures depicted herein are also meant to include geometric (or conformational) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, *Z* and *E* double bond isomers, and *Z* and *E* conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the disclosed compounds are within the scope of the disclosure.

Unless otherwise stated, all tautomeric forms of the compounds described herein are within the scope of the disclosure. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the disclosed structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C or ¹⁴C enriched carbon are within the scope of this disclosure. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the disclosure.

The “enantiomeric excess” or “% enantiomeric excess” of a composition can be calculated using the equation shown below. In the example shown below a composition contains 90% of one enantiomer, *e.g.*, the *S* enantiomer, and 10% of the other enantiomer, *i.e.*, the *R* enantiomer. $ee = (90-10)/100 \times 100 = 80\%$.

Thus, a composition containing 90% of one enantiomer and 10% of the other enantiomer is said to have an enantiomeric excess of 80%. The compounds or compositions described herein may contain an enantiomeric excess of at least 50%, 75%, 90%, 95%, or 99% of one form of the compound, *e.g.*, the *S*-enantiomer. In other words such compounds or compositions contain an enantiomeric excess of the *S* enantiomer over the *R* enantiomer.

Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as “optically enriched.” “Optically enriched,” as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments, the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments, the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or prepared by asymmetric syntheses. *See e.g.*, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen, et al., *Tetrahedron* 33:2725 (1977); Eliel, E.L. *Stereochemistry of Carbon Compounds* (McGraw Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (*e.g.* “such as”) provided herein is intended merely to better illuminate the disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with

an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds described herein into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Pharmaceutically Acceptable Salts

Pharmaceutically acceptable salts of the compounds described herein are also contemplated for the uses described herein. As used herein, the terms “salt” or “salts” refer to an acid addition or base addition salt of a compound described herein. “Salts” include in particular “pharmaceutical acceptable salts.” The term “pharmaceutically acceptable salts” refers to salts that retain the biological effectiveness and properties of the compounds disclosed herein and, which typically are not biologically or otherwise undesirable. In many cases, the compounds disclosed herein are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like.

Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium, and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, choline, diethanolamine, diethylamine, lysine, meglumine, piperazine, and tromethamine.

Another embodiment is a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35 as an acetate, ascorbate, adipate, aspartate, benzoate, besylate, bromide/hydrobromide, bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, caprate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, glutamate, glutarate, glycolate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, mucate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, sebacate, stearate, succinate, sulfosalicylate, sulfate, tartrate, tosylate, trifluoroacetate, or xinafoate salt form.

Pharmaceutical Compositions

Another embodiment is a pharmaceutical composition comprising one or more compounds described herein or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more pharmaceutically acceptable carrier(s). The term “pharmaceutically acceptable carrier” refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition or component thereof. Each carrier must be “acceptable” in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene

glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

5 The compositions described herein may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In some embodiments, the compositions of the disclosure are administered
10 orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this disclosure 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
15 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 diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation
20 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 carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tween®, Spans
25 and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutically acceptable compositions described herein may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets,
30 aqueous suspensions or solutions. In the case of tablets for oral use, carriers 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 cornstarch. 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.

Alternatively, the pharmaceutically acceptable compositions of this disclosure 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 that 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.

The pharmaceutically acceptable compositions of this disclosure may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. 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-transdermal patches may also be used.

For topical applications, the pharmaceutically acceptable 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. Alternatively, the pharmaceutically acceptable 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.

The pharmaceutically acceptable 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. The amount of the compounds of the present disclosure that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the

particular mode of administration. Preferably, the compositions should be formulated so that a dosage of between 0.01–100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

5 Isotopically Labelled Compounds

A compound described herein or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}F , ^{31}P , ^{32}P , ^{35}S , ^{36}Cl , ^{123}I , ^{124}I , ^{125}I , respectively. The disclosure includes various isotopically labeled compounds as defined herein, for example, those into which radioactive isotopes, such as ^3H and ^{14}C , or those into which non-radioactive isotopes, such as ^2H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds described herein or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (*i.e.*, ^2H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound described herein or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term “isotopic enrichment factor” as used herein means the

ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound described herein is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Dosages

Toxicity and therapeutic efficacy of compounds described herein, including pharmaceutically acceptable salts and deuterated variants, can be determined by standard pharmaceutical procedures in cell cultures or experimental animals. The LD₅₀ is the dose lethal to 50% of the population. The ED₅₀ is the dose therapeutically effective in 50% of the population. The dose ratio between toxic and therapeutic effects (LD₅₀/ED₅₀) is the therapeutic index. Compounds that exhibit large therapeutic indexes 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.

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 may lie within a range of circulating concentrations that include the ED₅₀ 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, 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 IC₅₀ (*i.e.*, the concentration of the test compound that 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.

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 being treated. The amount of a compound described herein in the composition will also depend upon the particular compound in the composition.

5

Methods of Use

Another embodiment is a method of modulating a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another embodiment is a method of inhibiting a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another embodiment is a method for inducing degradation of a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In another aspect, the disclosure provides a method of inhibiting, reducing, or eliminating the activity of a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, the method comprising administering to the subject a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In an embodiment, inhibiting, reducing, or eliminating the activity of a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, comprises recruiting a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase) with the Targeting Ligase Binder, *e.g.*, a Targeting Ligase Binder described herein, of the compound, *e.g.*, a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, forming a ternary complex of the Target

Protein, the compound, and the ligase, to thereby inhibit, reduce or eliminate the activity of the Target Protein.

Another embodiment is a method of treating or preventing a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder mediated by a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

Another embodiment is a method of treating or preventing a cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

In an embodiment, the cancer is a neoplastic disease and includes, for instance, solid tumors such as *e.g.* sarcomas or carcinomas or blood cancer such as *e.g.* leukemia or myeloma, or cancers of lymphatic system such as lymphoma, or mixed types thereof.

In another aspect, the disclosure provides compounds of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in inhibiting or modulating a target protein in a subject in need thereof.

In another aspect, the disclosure provides compounds of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in inhibiting a target protein in a subject in need thereof.

Another embodiment is a pharmaceutical composition comprising a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier, for use in inhibiting a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof.

Another embodiment is compounds of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating or preventing a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder mediated by a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof.

Another embodiment is compounds of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, for use in treating or preventing a cancer in a subject in need thereof.

In an embodiment, the cancer is a neoplastic disease and includes, for instance, solid tumors such as *e.g.* sarcomas or carcinomas or blood cancer such as *e.g.* leukemia or myeloma, or cancers of lymphatic system such as lymphoma, or mixed types thereof.

Another embodiment is the use of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for inhibiting or modulating a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof.

Another embodiment is a use of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for inhibiting a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof.

Another embodiment is a use of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating or preventing a cancer mediated by a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof.

In an embodiment, the cancer is a neoplastic disease and includes, for instance, solid tumors such as *e.g.* sarcomas or carcinomas or blood cancer such as *e.g.* leukemia or myeloma, or cancers of lymphatic system such as lymphoma, or mixed types thereof.

Another embodiment is a method for treating or preventing a cancer mediated by a Target Protein, *e.g.*, a Target Protein listed in **Table 1** or **Table 2**, in a subject in need thereof comprising administering a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof to the subject.

In an embodiment, the cancer is a neoplastic disease and includes, for instance, solid tumors such as *e.g.* sarcomas or carcinomas or blood cancer such as *e.g.* leukemia or myeloma, or cancers of lymphatic system such as lymphoma, or mixed types thereof.

Another embodiment is a use of a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating or preventing a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder in a subject in need thereof.

Combination Therapy

Another embodiment is a pharmaceutical combination comprising a compound of Formula (I), (II), (IIA), (BF-I), (BF-II), (BF-III), (BF-IV) (BF-V-A), (BF-V-B), or Compounds 1–35, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

In an embodiment, the additional therapeutic agent is selected from the group consisting of: an antiproliferative agent, anticancer agent, immunomodulatory agent, an anti-inflammatory agent, a neurological treatment agent, an anti-viral agent, an anti-fungal agent, anti-parasitic agent, an antibiotic, and a general anti-infective agent.

In an embodiment, the additional therapeutic agent is selected from the group consisting of: a second target protein inhibitor.

Methods of Making

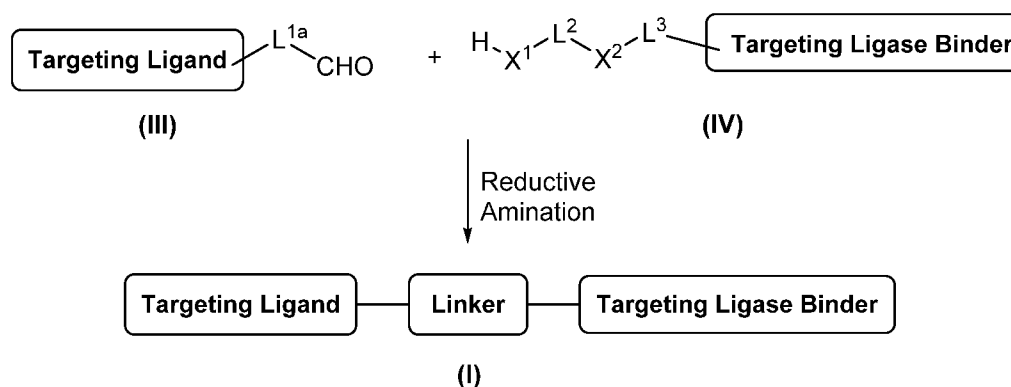
The compounds described herein can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in

the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below.

The disclosed compounds may be synthesized according to the general methods described in the following synthetic schemes 1, 1a, 1b, 2–4, 4a, 5, 5a, 6, 6a, 7–16, 16a, 17–18, 18a, 18b, 19, 19a, and 20–21. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

Compounds of formula (I) containing a linker of formula (L-I) wherein X^1 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl and X^2 , L^1 , L^2 , L^3 are as previously defined may be synthesized from a compound of formula (III) and a compound of formula (IV) according to Scheme 1 using a reductive amination reaction. If X^1 is a bond, then scheme 1 also provides for compounds of formula (IV) wherein L^2 is a primary or secondary amine to react with a compound of formula (III) to produce (I). L^{1a} is defined as a linker that is shorter by a single methylene group than L^1 , wherein the formula of L^1 allows (*e.g.*, in an embodiment where L^1 is $-\text{CH}_2\text{CH}_2-$, then L^{1a} is $-\text{CH}_2-$). Suitable L^1 include C_{1-6} alkylene and C_{1-6} heteroalkylene. Conditions such as ZnCl_2 and NaBH_3CN , in a solvent mixture such as THF/DMSO and MeOH may be employed. Alternative conditions include treatment with NaOAc, AcOH, and $\text{NaBH}(\text{OAc})_3$ in DCM.

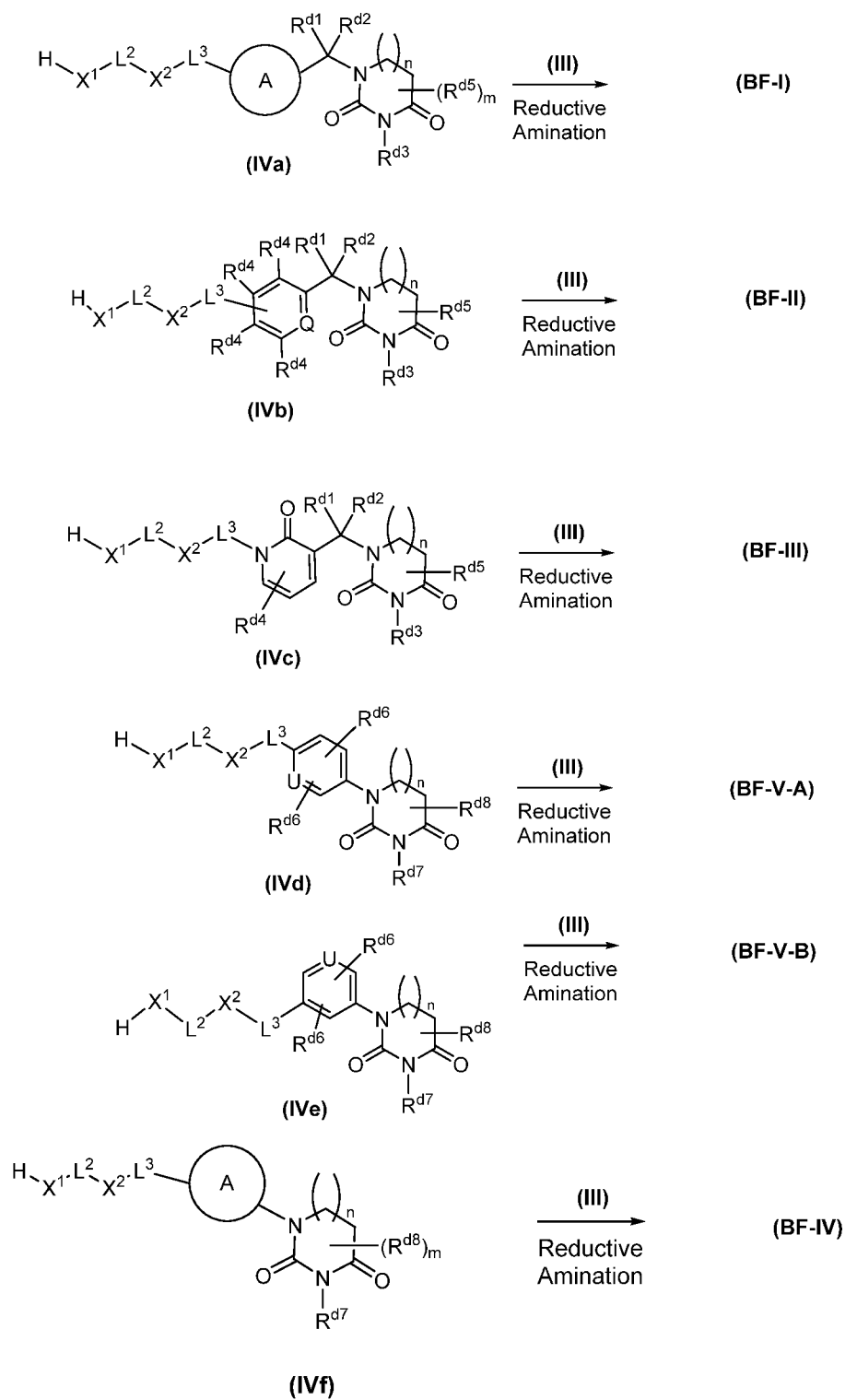
Scheme 1



By analogy, in further embodiments, bifunctional compounds of Formulae (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV) wherein X^1 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl and R^{d1} , R^{d2} , R^{d3} , R^{d4} , R^{d5} , R^{d6} , R^{d7} , R^{d8} , X^2 , L^1 , L^2 , L^3 , m and n are as

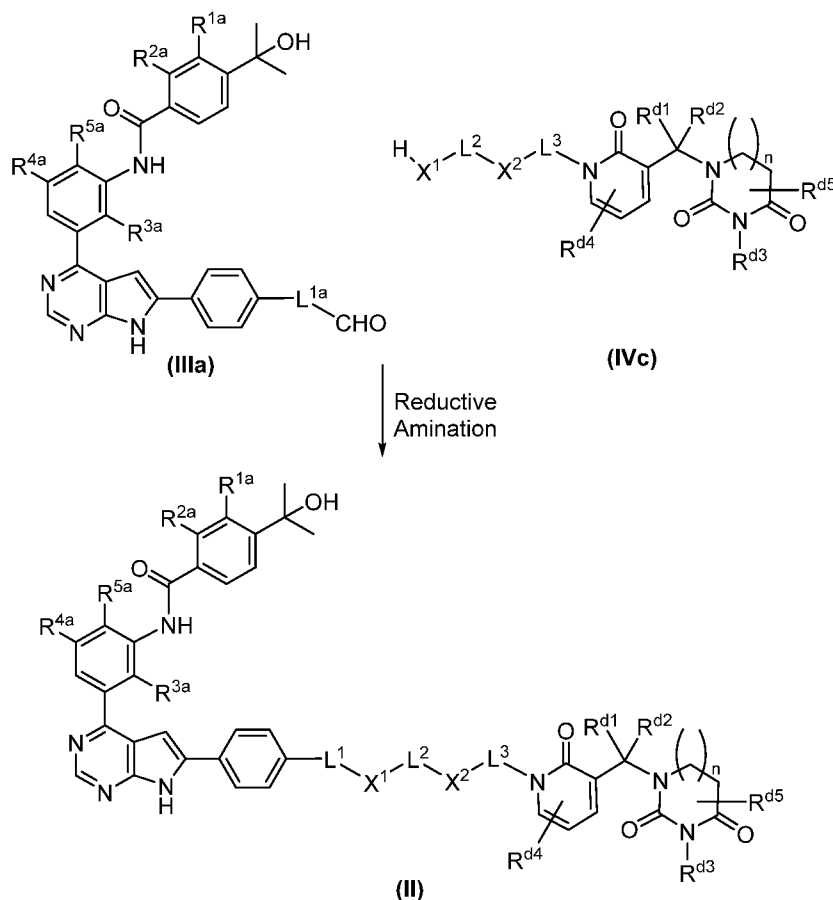
previously defined, may be made from a compound of formula (III) and compounds of formula (IVa), (IVb), (IVc), (IVd), (IVe), and (IVf), respectively, according to Scheme 1a.

Scheme 1a



In a further embodiment, a compound of formula (II) wherein X^1 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl and R^{d1} , R^{d2} , R^{d3} , R^{d4} , R^{d5} , R^{d6} , R^{d7} , R^{d8} , X^2 , L^1 , L^2 , L^3 , m and n are as previously defined, may be made from a compound of formula (IIIa), wherein R^{1a} , R^{2a} , R^{3a} , R^{4a} , R^{5a} and L^{1a} are as previously defined and a compound of formula (IVc) according to Scheme 1b. Conditions similar to those described herein above apply.

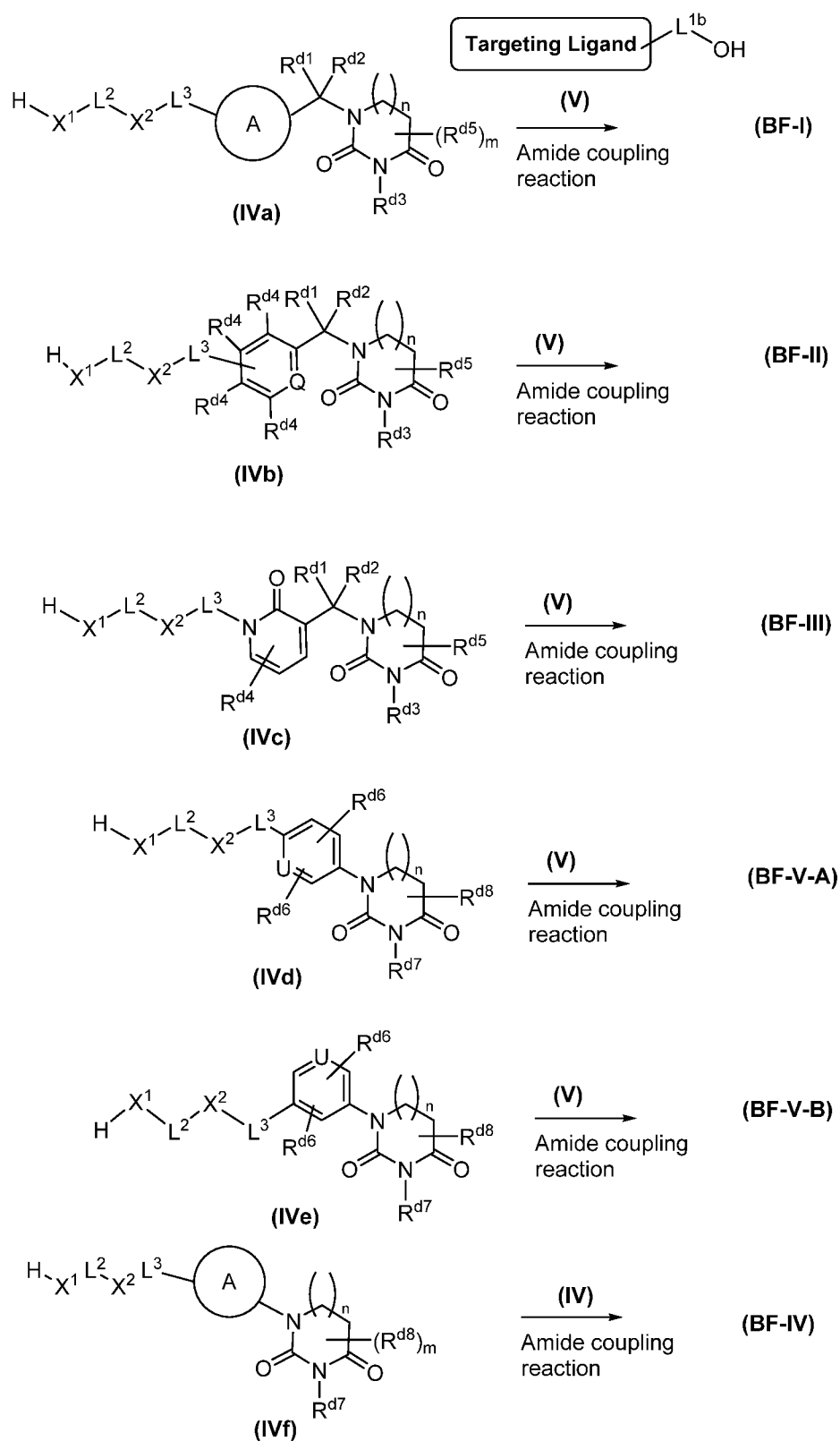
Scheme 1b



The intermediates of formulae (IVa), (IVb), (IVc), (IVd), (IVe) and (IVf) wherein X^1 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl, may also be applied to the synthesis of compounds of formulae (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV), respectively, which contain an amide linkage by reaction with a carboxylic acid of formula (V) using an amide coupling reaction according to Scheme 2. Similarly if X^1 is a bond, then scheme 2 also provides for compounds of formula (IV a-f) wherein L^2 is a primary or secondary amine to react with a compound of formula (III) to produce (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B),

and (BF-IV), respectively. For compounds of formula (V), L^{1b} is defined as the subset of linkers L^1 , that contain a carbonyl group and so are able to provide for compounds (V) containing a carboxylic acid functional group. Conditions include using an amide coupling reagent such as HATU, in a solvent such as DMF, in the presence of a base such as DIPEA.

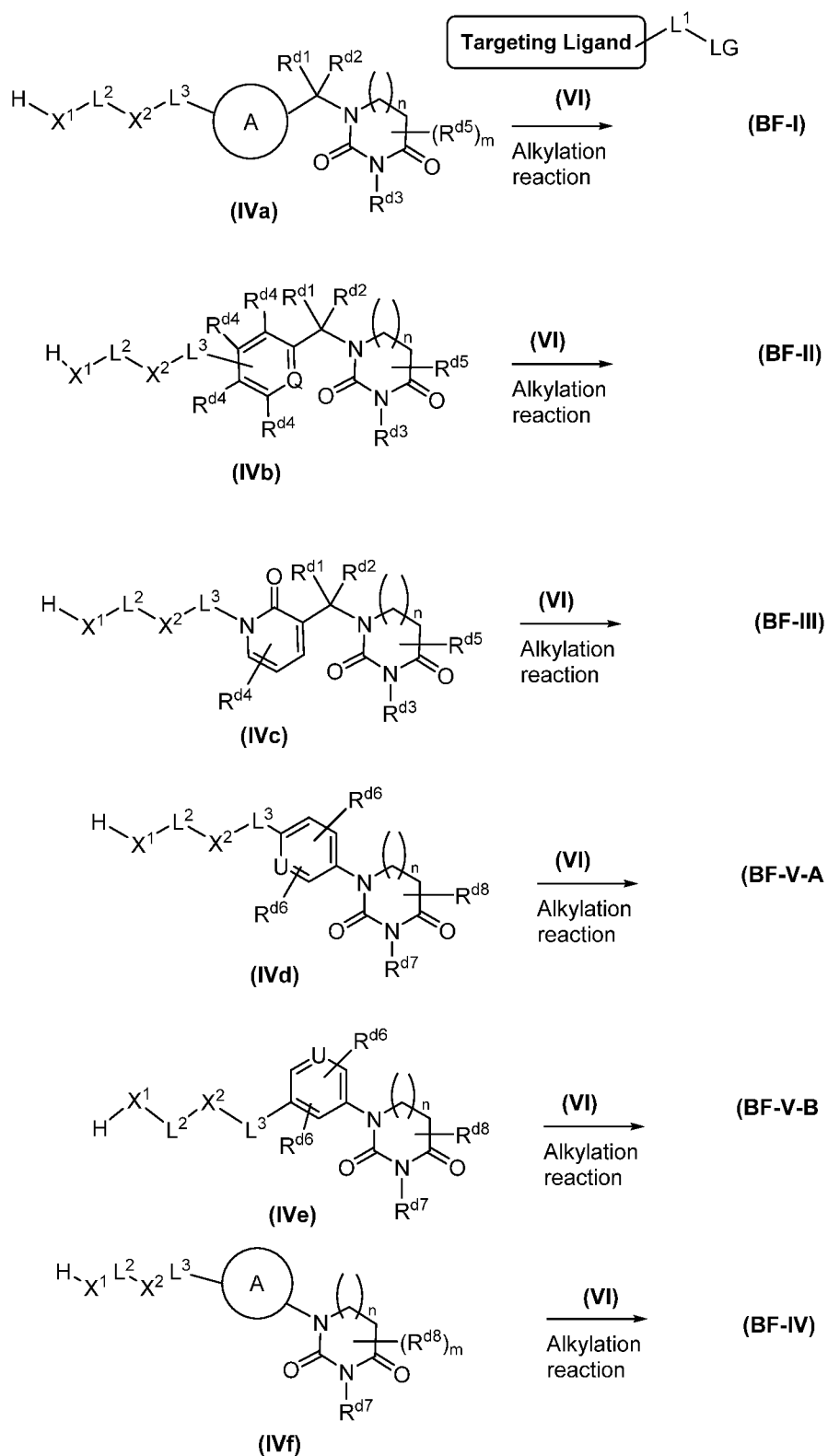
Scheme 2



In further embodiments, bifunctional compounds of formula (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV) wherein X^1 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl may be made from compounds of formula (VI), wherein LG represents a leaving group such as a halide or a mesylate, and compounds of formula (IVa), (IVb), (IVc), (IVd), (IVe), and (IVf), respectively using an alkylation reaction according to Scheme 3. Similarly if X^1 is a bond, then scheme 3 also provides for compounds of formula (IV a–f) wherein L^2 is a primary or secondary amine to react with a compound of formula (VI) to produce (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV) respectively.

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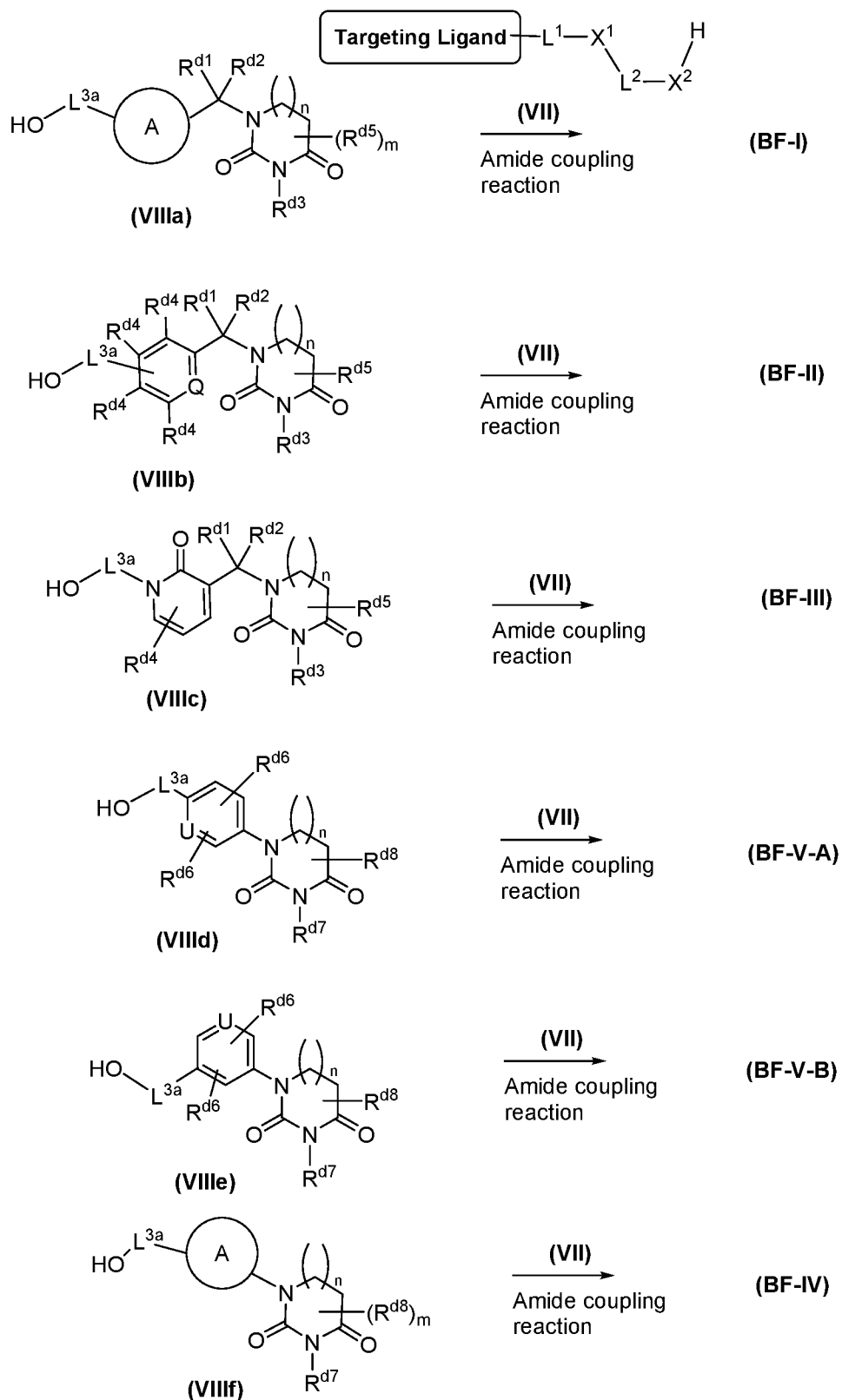
Scheme 3



Typical conditions would be to treat an alkyl chloride of formula (VI) with an iodinating reagent such as potassium iodide and a base such as DIPEA with the appropriate amine (IVa–f) in a solvent such as DMA at a temperature such as 80 °C.

Compounds of formula (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV) wherein X^2 is a nitrogen-containing heterocyclcyl, *e.g.*, a piperidinyl or piperazinyl may be made by reacting a compound of formula (VII) with compounds of formula (VIIIa), (VIIIb), (VIIIc), (VIIId), (VIIIe), and (VIIIf), respectively, in an amide coupling reaction according to Scheme 4. Similarly if X^2 is a bond, then scheme 4 also provides for compounds of formula (VIII a–f) wherein L^2 is a primary or secondary amine to react with a compound of formula (VII) to produce (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV), respectively.

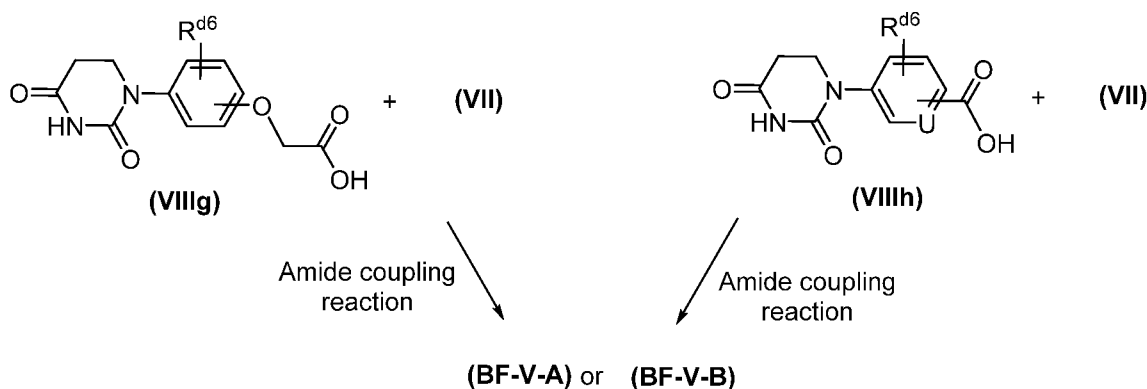
Scheme 4



In this embodiment, L^{3a} in compound (VIIIa-f) is defined as the subset of linkers L^3 that contain a carbonyl group and so are able to provide for compounds (VIIIa-f) containing a carboxylic acid functionality (*e.g.*, in an embodiment wherein L^{3a} is $-\text{CH}_2-\text{C}(\text{O})-$, then $L^{3a}-\text{OH}$ is defined as $-\text{CH}_2-\text{CO}_2\text{H}$). Suitable conditions include those for amide coupling reactions as already described herein above.

Further, more specific embodiments of carboxylic acid intermediates include compounds of formula (VIIIg) and (VIIIh), which can react with a compound of formula (VII) (in a similar fashion to that described herein above for compounds (VIIIa-f)), to provide compounds of formula (BF-V-A) or (BF-V-B), according to Scheme 4a.

Scheme 4a

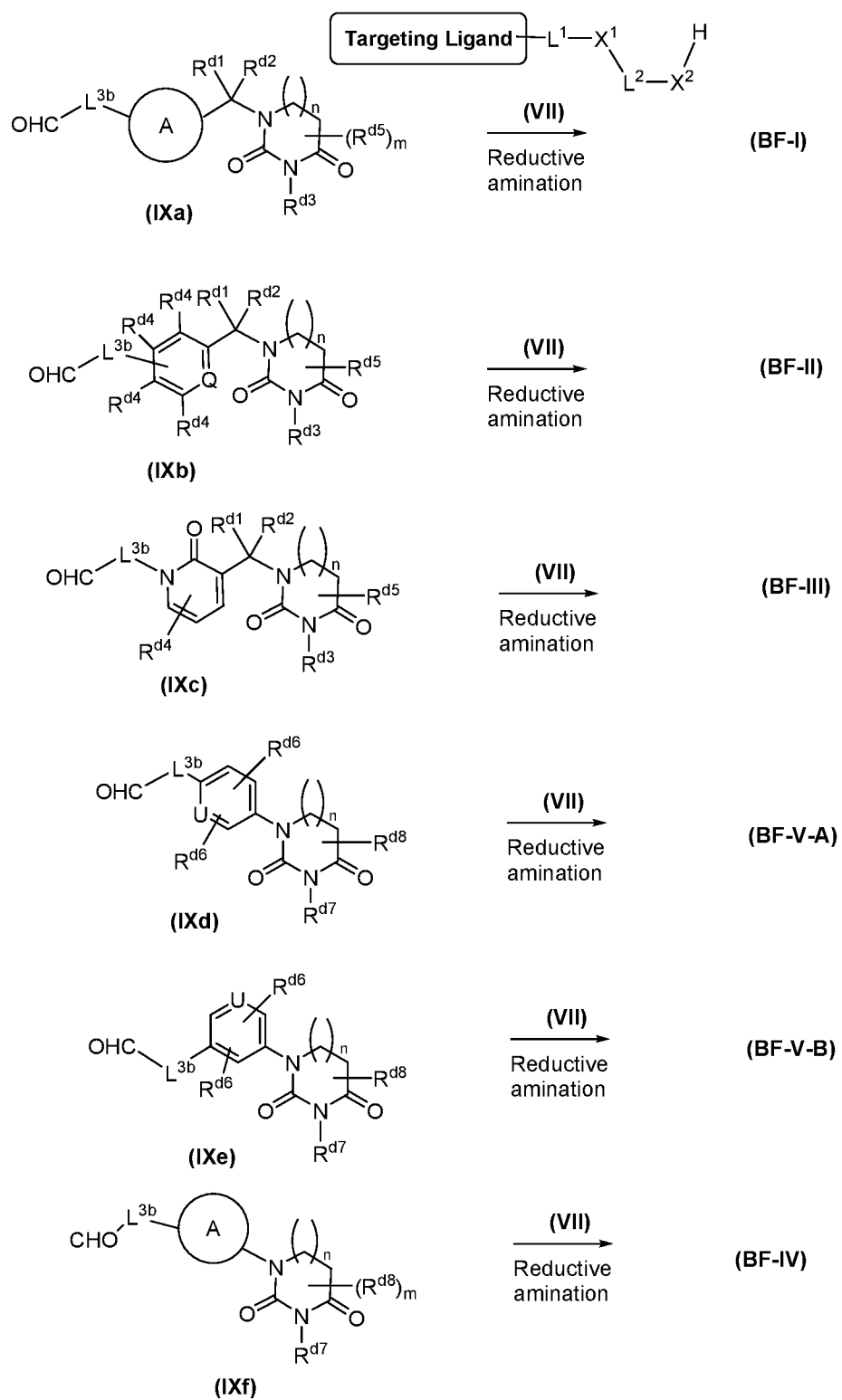


Compounds of formula (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV) wherein X^2 is a nitrogen-containing heterocyclyl, *e.g.*, a piperidinyl or piperazinyl may also be made by reacting a compound of formula (VII) with compounds of formula (IXa), (IXb), (IXc), (IXd), (IXe), and (IXf), respectively in a reductive amination reaction according to Scheme 5. Similarly if X^2 is a bond, then scheme 5 also provides for compounds of formula (IXa-f) wherein L^2 is a primary or secondary amine to react with a compound of formula (VII) to produce (BF-I), (BF-II), (BF-III), (BF-V-A), (BF-V-B), and (BF-IV), respectively.

For compounds (IXa-f), L^{3b} is defined as a linker that is shorter by a single methylene group than L^3 , wherein the formula of L^3 allows (*e.g.*, in an embodiment where L^3 is $-\text{CH}_2\text{CH}_2-$, then L^{3b} is $-\text{CH}_2-$). Suitable L^3 include C_{1-6} alkylene and C_{1-6} heteroalkylene. Conditions such as

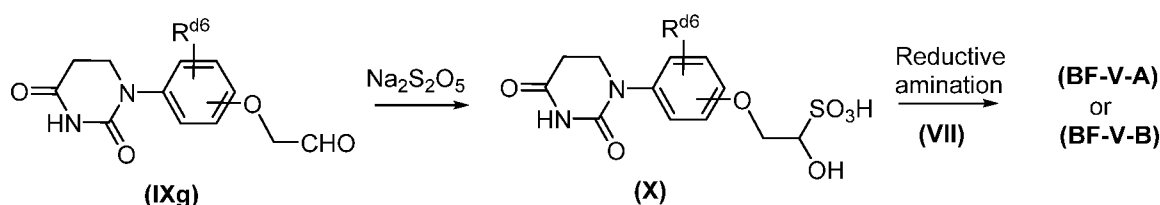
ZnCl₂ and NaBH₃CN, in a solvent mixture such as THF/DMSO and MeOH may be employed. Alternative conditions include treatment with NaOAc, AcOH, and NaBH(OAc)₃ in DCM.

Scheme 5



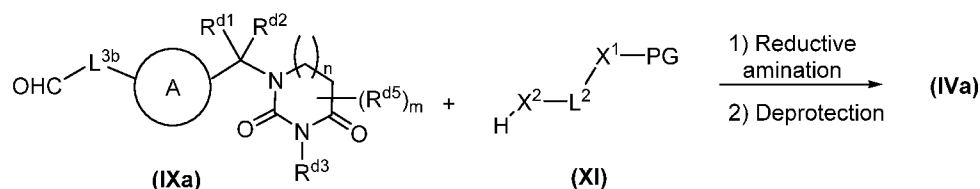
It will be apparent to those skilled in the art that masked aldehyde equivalents such as the corresponding adducts (*e.g.*, compounds of formula (X)) formed from an aldehyde such as (IXg) and sodium metabisulfite in aqueous ethanol are equally suitable reactants for effecting this overall reductive amination transformation, the embodiment depicted in Scheme 5a being a representative example. In this case, reaction of (X) with (VII) can occur in the presence of sodium acetate and picoline borane complex in a solvent such as methanol.

Scheme 5a



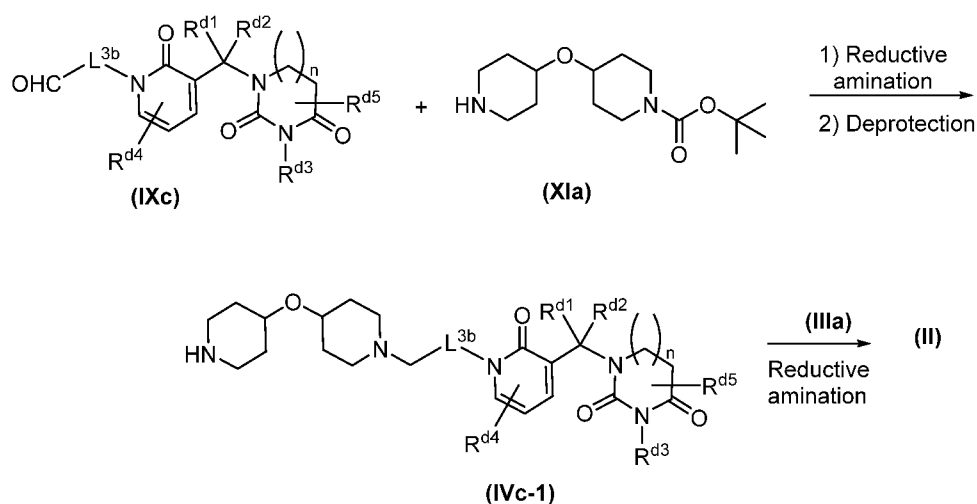
Compounds of formula (IV), more specifically compounds of formulae (IVa), (IVb), (IVc), (IVd), (IVe), and (IVf) such as those wherein both X^1 and X^2 are nitrogen-containing heterocyclyls, *e.g.*, piperidinyl or piperazinyl or $\text{X}^1\text{--L}^2\text{--X}^2$ is a spiroheterocyclyl, may be synthesized from the corresponding aldehydes (IXa), (IXb), (IXc), (IXd), (IXe), and (IXf), respectively according to Scheme 6. The aldehydes undergo a reductive amination reaction under conditions already described herein above using a compound of formula (XI), where PG represents a protecting group, such as *t*-butoxycarbonyl. A subsequent deprotection reaction using conditions such as TFA in DCM or HCl in 1,4-dioxane and methanol provides the compound of formula (IVa–f). Scheme 6 illustrates the transformation of (IXa) into (IVa) as a representative embodiment.

Scheme 6



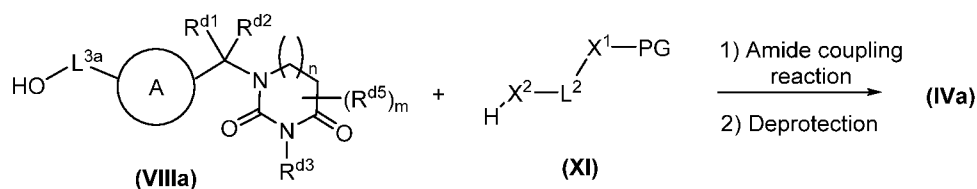
In an embodiment, a compound of formula (IXc) can undergo an analogous reductive amination with a specific example of (XI), such as (XIa), followed by deprotection under conditions already described herein above to provide a compound of formula (IVc-1) according to Scheme 6a. This compound (IVc-1) may then react in the same manner as other embodiments of (IVc) with a compound of formula (IIIa) in a reductive amination reaction to provide a compound of formula (II).

Scheme 6a



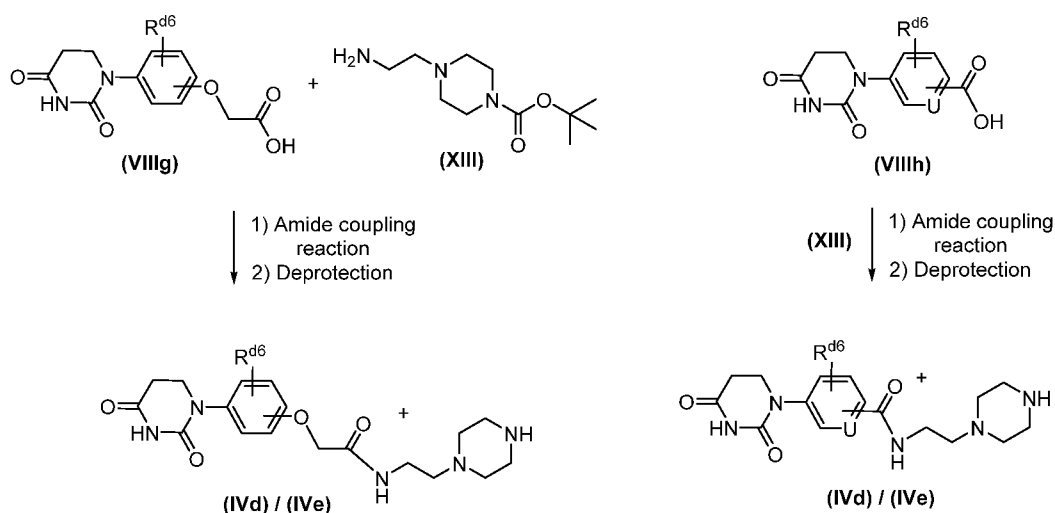
Compounds of formula (IV), and specifically compounds of formulae (IVa), (IVb), (IVc), (IVd), (IVe), and (IVf) such as those wherein both X¹ and X² are nitrogen-containing heterocyclyls, *e.g.*, piperidinyl or piperazinyl or X¹-L²-X² is a spiroheterocyclyl, may also be synthesized from the corresponding carboxylic acids (VIIIa), (VIIIb), (VIIIc), (VIId), (VIIIe), and (VIIf), respectively according to Scheme 7. In this embodiment, an amide coupling reaction is employed with a compound of formula (XI), using a reagent such as HATU, in a solvent such as DMF, in the presence of a base such as DIPEA, followed by a deprotection reaction using conditions such as TFA in DCM or HCl in 1,4-dioxane and methanol to provide the compound of formula (IVa-f). The scheme illustrates the transformation of (VIIIa) into (IVa) as a representative embodiment.

Scheme 7



In an embodiment, compounds of formula (IV), for example a compound of formula (IVd) or (IVe) may be synthesized from a carboxylic acid of formula (VIIIg) or (VIIIh) by reacting with a monoprotected diamine (such as compound (XIII)) in an amide coupling reaction followed by a deprotection reaction using conditions as already described herein above (Scheme 8). In the examples depicted, X^2 is absent.

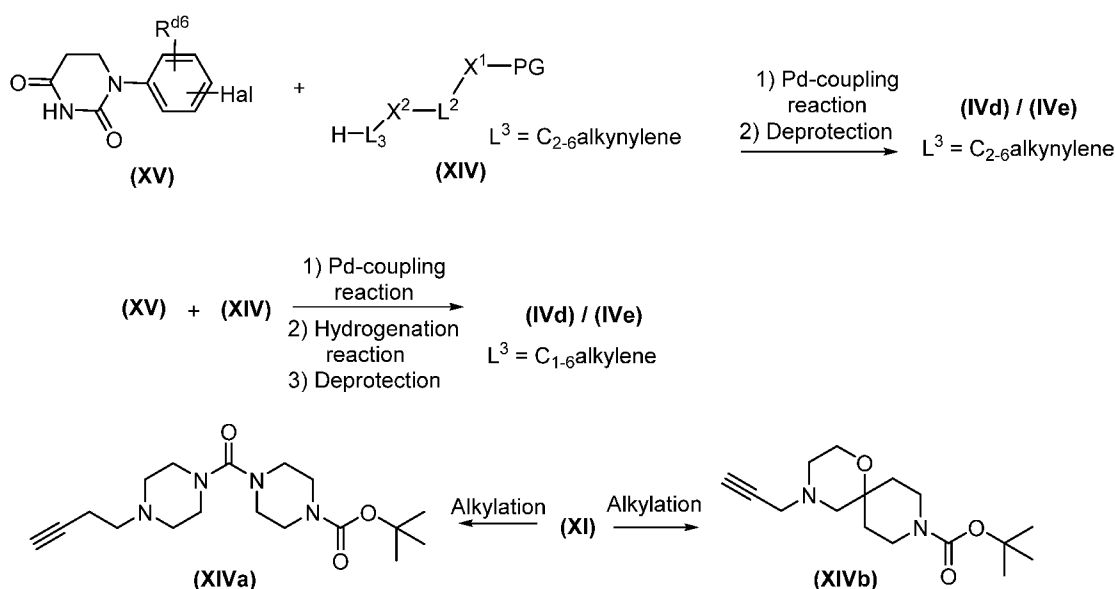
Scheme 8



Other compounds of formula (IV), for example compounds of formula (IVd) and (IVe) wherein L^3 is a C_{2-6} alkynylene, may be synthesized according to Scheme 9. Thus, a palladium-catalyzed coupling between an alkyne compound of formula (XIV) wherein PG is a protecting group such as a t-butoxycarbonyl and a compound of formula (XV), wherein Hal is a halogen atom such as iodine, followed by a deprotection reaction afford the compound of formula (IVd) or (IVe). The palladium catalyzed reaction is a Sonogashira reaction carried out using a catalyst such as $PdCl_2(PPh_3)_2$ and CuI and a base, such as triethylamine in a solvent such as DMF. Optionally, the product from the palladium-catalyzed reaction can be reduced under hydrogenation conditions, using for example H_2 gas and a Pd/C catalyst, prior to the deprotection reaction. In this case, the

final products (IVd/IVe) with L^3 being C_{1-6} -alkylene are produced. Compounds (XIVa) and (XIVb) are specific embodiments of compound (XIV) which can undergo these reaction sequences. Compounds (XIVa) and (XIVb) may in turn be synthesized for example by an alkylation reaction of a compound of formula (XI) using an alkynylene bromide such as 4-bromo-1-butyne or propargyl bromide respectively in the presence of a base such as K_2CO_3 in a solvent such as acetonitrile.

Scheme 9

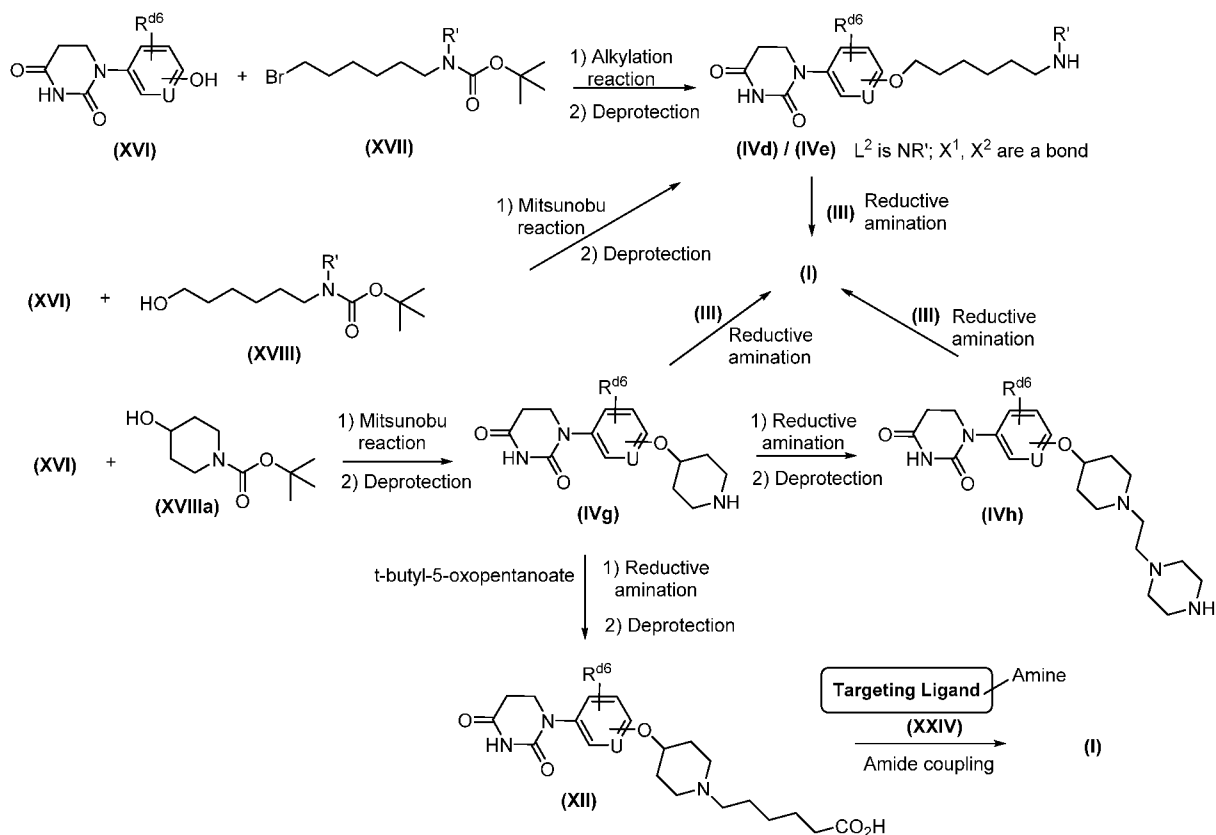


Other compounds of formula (IV), for example compounds of formula (IVd) and (IVe) wherein L^3 contains an ether link, may be synthesized according to Scheme 10 starting from a phenol of formula (XVI). Thus the alkylation of (XVI) using an alkyl bromide such as (XVII) with a base such as K_2CO_3 in a solvent such as DMF provides after deprotection a compound of formula (IVd/IVe); the particular example depicted represents a compound of formula (IVd/IVe) wherein both X^1 and X^2 are a bond and L^2 is NR' . Thus, this product is able to undergo a reductive amination with a compound of formula (III) under conditions already described herein above to provide a compound of formula (I). An alternative synthetic route is to react phenol (XVI) with a N-protected amino alcohol in a Mitsunobu reaction in the presence of a phosphine reagent such as triphenylphosphine and an azo carboxylate ester such as diethylazodicarboxylate to form the ether bond, followed by a deprotection reaction to provide the compound of formula (IVd/IVe). The linker may also be built up in a sequence of steps to convert a compound of formula (XVI) into a

compound of formula (IV), such as (IVg) or (IVh). In an embodiment, phenol (XVI) may react with an *N*-protected amino alcohol such as (XVIIIa) in a Mitsunobu reaction in the presence of a phosphine reagent such as triphenylphosphine and an azo carboxylate ester such as diethylazodicarboxylate to form an ether bond, followed by a deprotection reaction to provide a compound of formula (IVg). This compound can be extended, by a further reductive amination with a *N*-protected amino aldehyde such as *t*-butyl 4-(2-oxoethyl)piperazine-1-carboxylate to provide a chain extended compound of formula (IVh). Both (IVg) and (IVh) can react with a compound of formula (III) to provide a compound of formula (I) using a reductive amination using conditions already described herein above. In an embodiment, reductive amination with an aldehyde-ester such as *t*-butyl-5-oxopentanoate, followed by deprotection of the ester functionality using an acid such as TFA in DCM can give a carboxylic acid of formula (XII). Compound (XII) can react via an amide coupling under conditions described herein above, with a targeting ligand containing an available primary or secondary amine function (XXIV) to provide a compound of formula (I) wherein X^1 is a bond and L^1 is C(O).

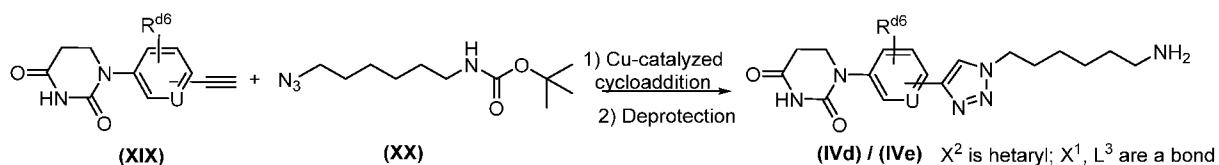
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Scheme 10



A compound of formula (IV), such as (IVd) or (IVe), wherein L³ and X¹ each represent a bond and X² is a 1,2,3-triazole can be made according to Scheme 11 using a Cu-catalyzed cycloaddition reaction between an alkyne of formula (XIX) and an azide of formula (XX) using a Cu(II) salt such as Cu(II)SO₄ and sodium L-ascorbate, in a solvent mixture such as THF and water. Deprotection of the protecting group under conditions already described herein above lead to the compound of formula (IV).

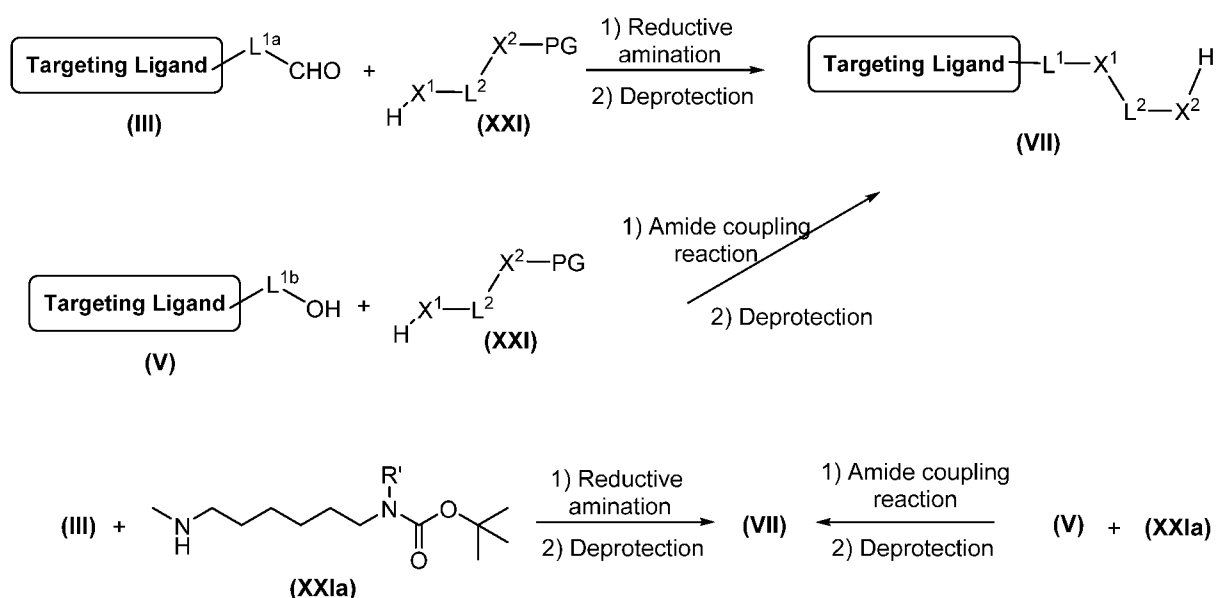
Scheme 11



A compound of formula (VII) wherein both X¹ and X² are nitrogen-containing heterocyclyls, *e.g.*, piperidinyl or piperazinyl or X¹-L²-X² is a spiroheterocyclyl, may be

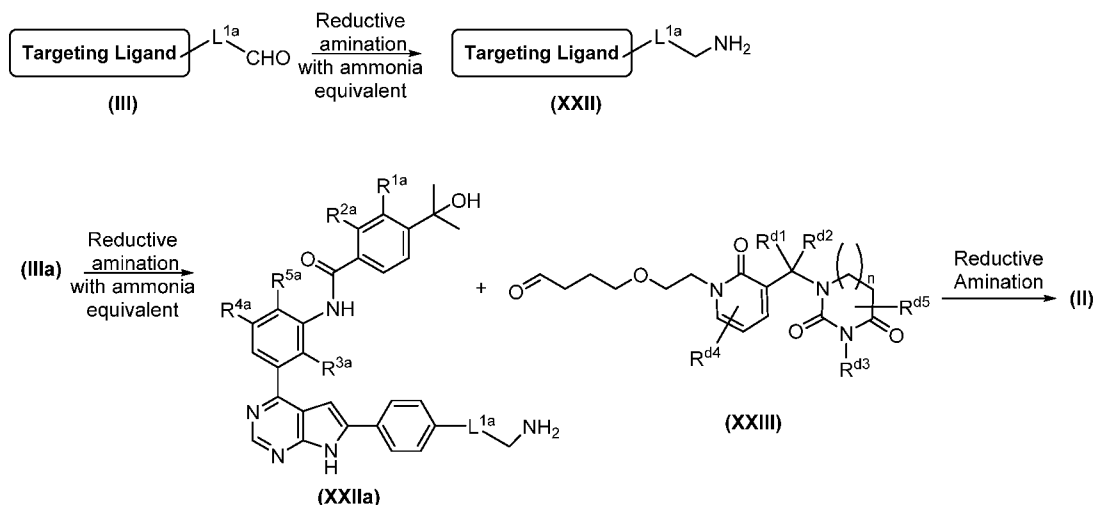
synthesized according to Scheme 12 from a compound of formula (III) and a compound of formula (XXI) following a reductive amination, deprotection sequence under conditions already described herein above. Alternatively, different compounds of formula (VII) can be prepared from carboxylic acids of formula (V), by reacting with a compound of formula (XXI) firstly in an amide coupling reaction, followed by a deprotection reaction under conditions already described herein above. This scheme also provides for compounds of certain cases of formula (VII) wherein certain linker elements are a bond, one example being when using the compound (XXIa) wherein both X^1 and X^2 are a bond.

10 Scheme 12



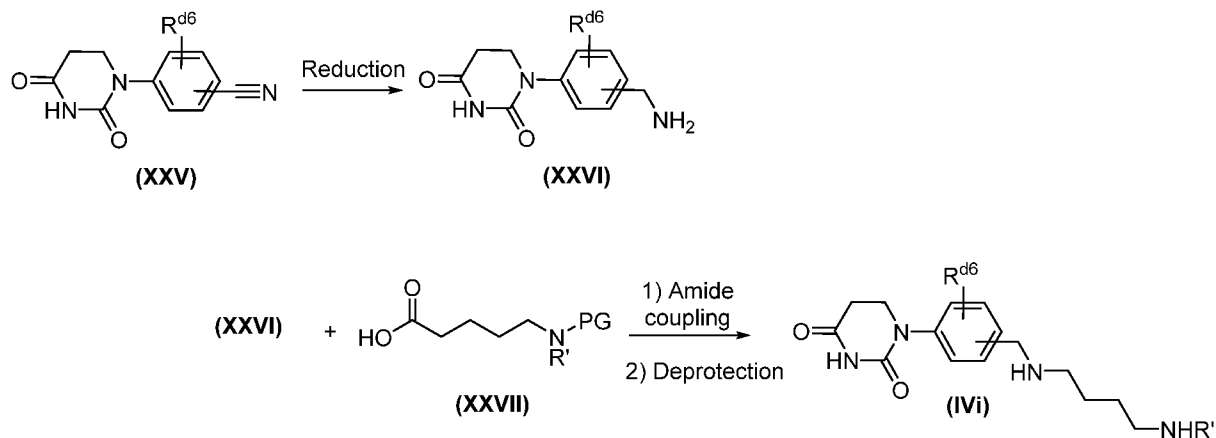
Compounds of formula (III) may also be converted to primary amines of formula (XXII) using a reductive amination using, for example, methanolic ammonia and hydrogen gas in the presence of a catalyst, such as Raney Nickel. In a specific embodiment, a compound of formula (IIIa) reacts under similar conditions to provide (XXIIa). Subsequent reductive amination with an aldehyde of formula (XXIII) using conditions such as ZnCl₂ and NaBH₃CN, in a solvent mixture, such as THF/DMSO and MeOH, provides an example compound of Formula (II), wherein X^1 and X^2 are each represented by a bond (Scheme 13).

Scheme 13



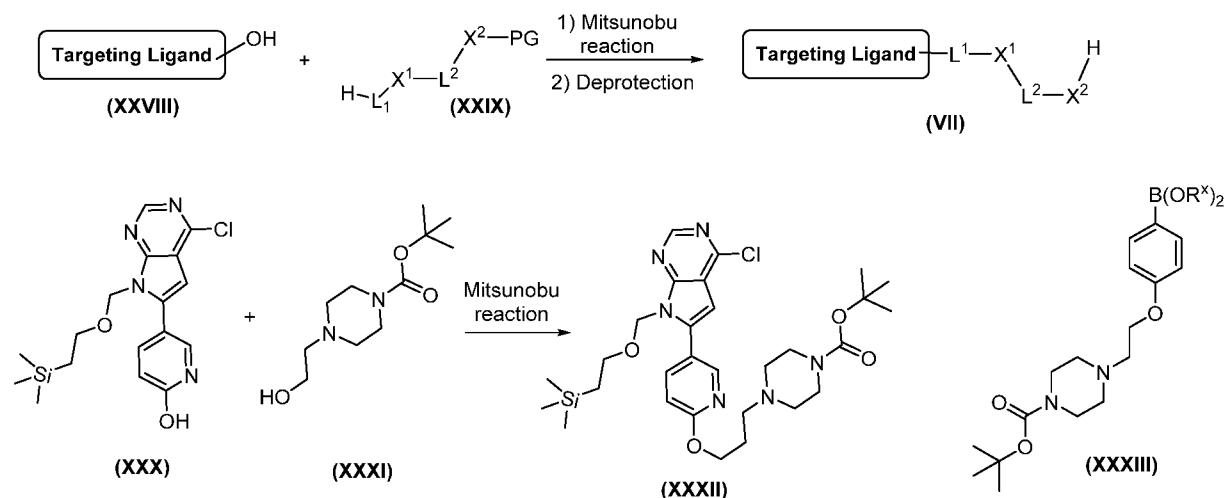
Nitriles of formula (XXV) may be reduced to amines of formula (XXVI) using conditions
 5 such as hydrogen gas and a catalyst such as Raney Nickel in the presence of aqueous ammonium hydroxide with a co-solvent such as MeOH, according to Scheme 14. These amines may react with N-protected amino acids, where in PG represents a protecting group such as a t-butoxycarbonyl group, in an amide coupling reaction, A subsequent deprotection reaction under acidic conditions provides compounds of formula (IV); in an embodiment (XXVI) may react with (XXVII) to
 10 provide the compounds of formula (IVi) wherein both X^1 and X^2 are a bond.

Scheme 14



A Mitsunobu coupling can be used to synthesize compounds of formula (VII) wherein the linker contains an ether linkage directly to the targeting ligand, from a compound of formula (XXVIII), wherein the hydroxy group is part of a phenol or a hydroxypyridine, followed by a deprotection reaction, according to Scheme 15.

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Scheme 15

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To those skilled in the art of organic synthesis, it will be understood that the molecules of the invention may be built up in a modular way which allows for different reaction orders. For example, the Mitsunobu coupling described in Scheme 15 may be applied to a synthesis fragment such as compound (XXX) wherein the pyridyl ring is part of the targeting ligand. Thus (XXX) can undergo reaction with the compound of formula (XXXI) to provide another reaction intermediate (XXXII). This intermediate (XXXII) then requires further synthetic procedures to construct the targeting ligand itself, in addition to synthetic procedures designed to link the molecule to a suitable ligase targeting fragment according to procedures fully described herein above. The compound of formula (XXXIII), wherein $B(OR^x)_2$ defines either a boronic acid or ester (including cyclic boronic esters such as pinacol esters), is another embodiment accessible by a Mitsunobu reaction. In this embodiment, the aryl ring is a fragment of the targeting ligand (which will require further elaboration), to which the Mitsunobu reaction appends some linker elements according to the definitions defined herein above.

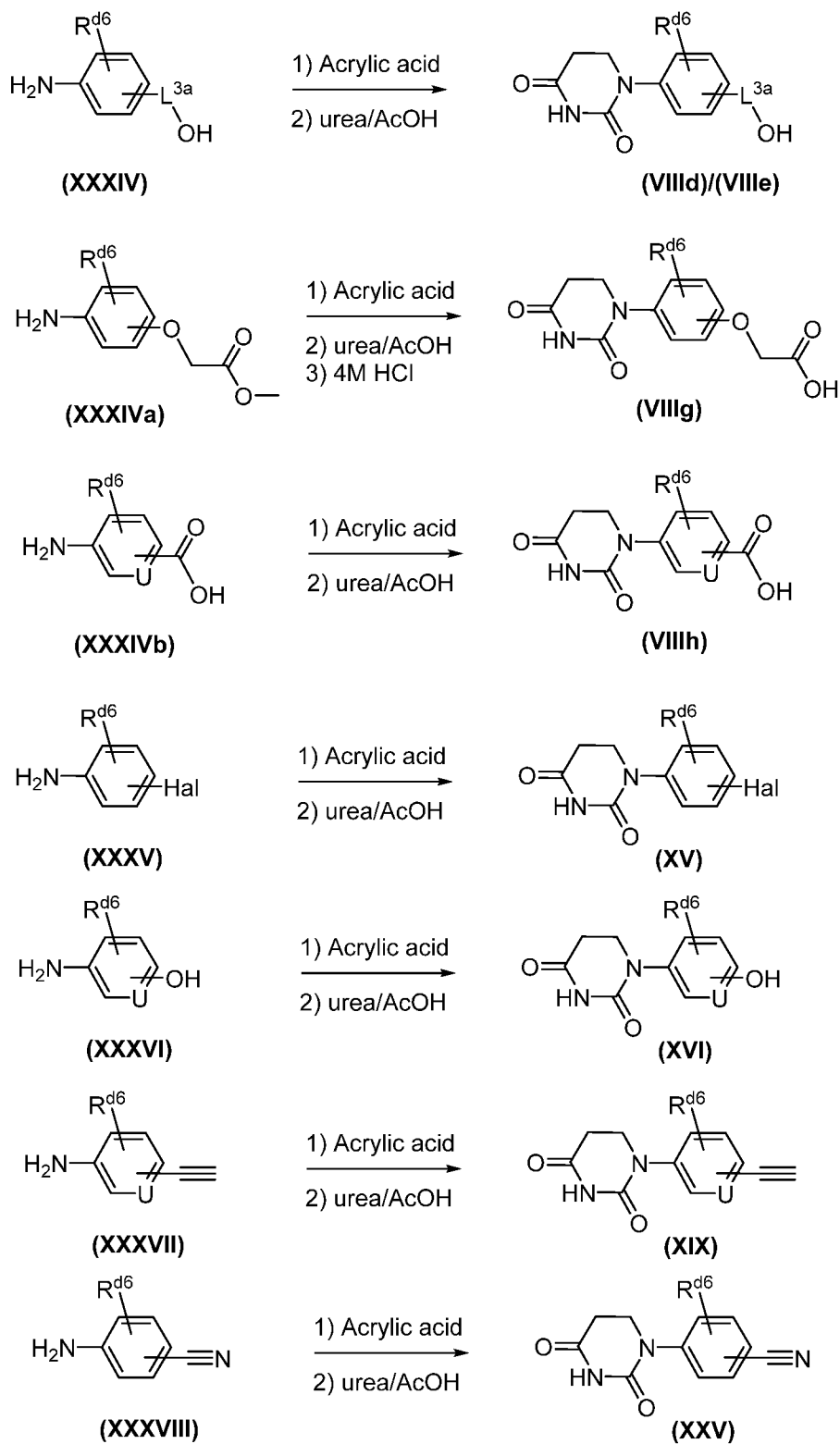
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Aryl dihydro uracil derivatives such as compounds of formula (VIIIId/VIIIe), (VIIIg), (VIIIh), (XV) (XVI), (XIX), and (XXV) may be synthesized according to Scheme 16 from the corresponding amines (XXXIV), (XXXIVa), (XXXIVb), (XXXV), (XXXVI), (XXXVII), and

(XXXVIII), respectively. The transformation proceeds through a conjugate addition to acrylic acid usually by heating above 70 °C with a co-solvent such as water, followed by reaction with urea and acetic acid, also at elevated temperature such as 120 °C, to form the dihydrouracil. In the case of (VIIIg), the dihydrouracil formation may be carried out on the corresponding phenolic acetate ester (XXXIVa) and the ester can be hydrolyzed using acidic conditions, such as HCl treatment in a final step.

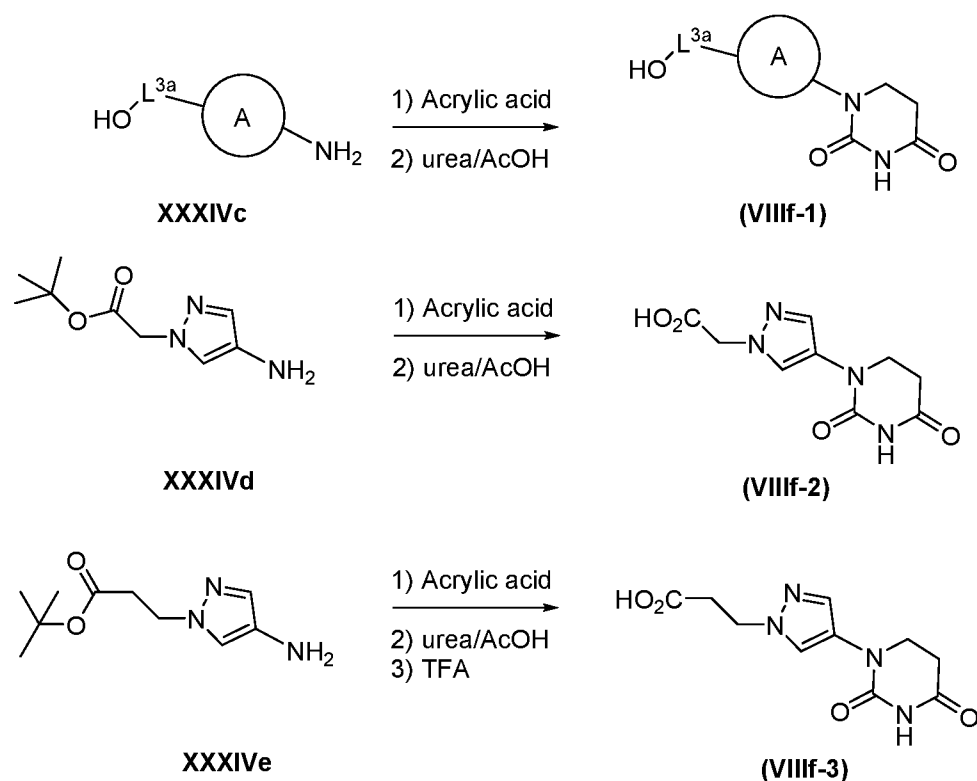
Scheme 16



The compounds of formula (XXXIVa) are available from aminophenols with a protected nitrogen (XXXIX), for example a Boc-protected nitrogen, in two steps according to Scheme 17. First, alkylation of the phenol using a base such as Cs_2CO_3 and a 2-haloacetate ester, such as methyl bromoacetate, in a solvent such as acetone with an additive such as potassium iodide provides an intermediate that can undergo *N*-deprotection using for example an acid such as TFA in a solvent such as dioxane to provide compounds of formula (XXXIXa). Also according to Scheme 17, dihydrouracil intermediates (IXg) can be synthesized, for example, by applying the dihydrouracil forming chemistry to an allyloxy aniline such as (XXXX). Oxidative cleavage of the allyl group using for example an ozonolysis reaction, provides the aldehydes of formula (IXg).

Dihydrouracil intermediates (IVj) bearing a sulfonamide linker chain can be synthesized from a compound of formula (XXXXI) in a similar method as for other dihydrouracil building blocks, followed by a deprotection reaction.

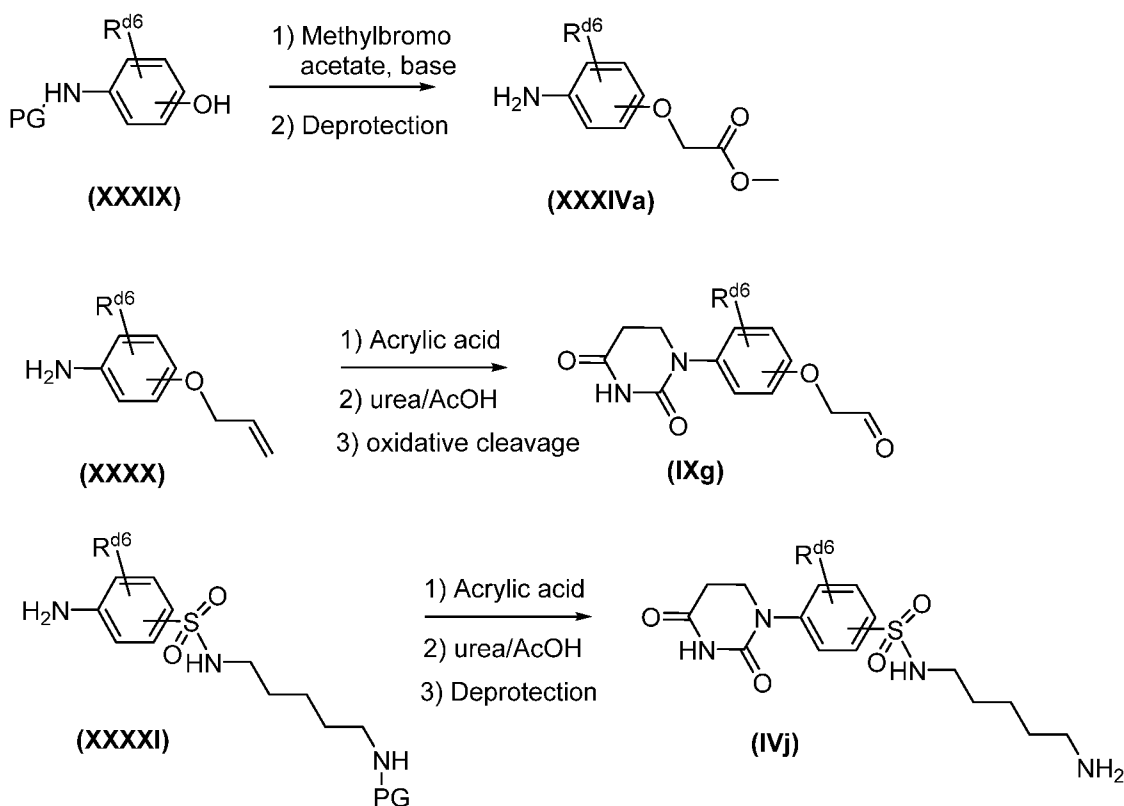
Scheme 16a



Heteroaryl dihydrouracil derivatives (VIIIf-1) bearing a carboxylic acid functionality, wherein A is a 5- or 6-membered heteroaryl ring may be made according to Scheme 16a using an analogous reaction sequence to that described in Scheme 16. In this case, reaction of the

corresponding amino acid (XXXIVc) or a derivative (*e.g.*, such as an amino ester) with acrylic acid at or above 70 °C with a co-solvent, *e.g.*, such as water, followed by reaction with urea and acetic acid, also at an elevated temperature such as 100 °C provides the heteroaryl dihydrouracil (VIIIf-1). Particular examples are the aminopyrazole derivatives (VIIIf-2) and (VIIIf-3), produced from the aminopyrazole tert-butyl ester derivatives (XXXIVd) and (XXXIVe), respectively. In some cases, such as for (VIIIf-2), the reaction conditions result in the concomitant hydrolysis of the tert-butyl ester to the carboxylic acid; for other cases, such as (VIIIf-3) a separate hydrolysis step using an acid such as TFA may be required to produce the free carboxylic acid.

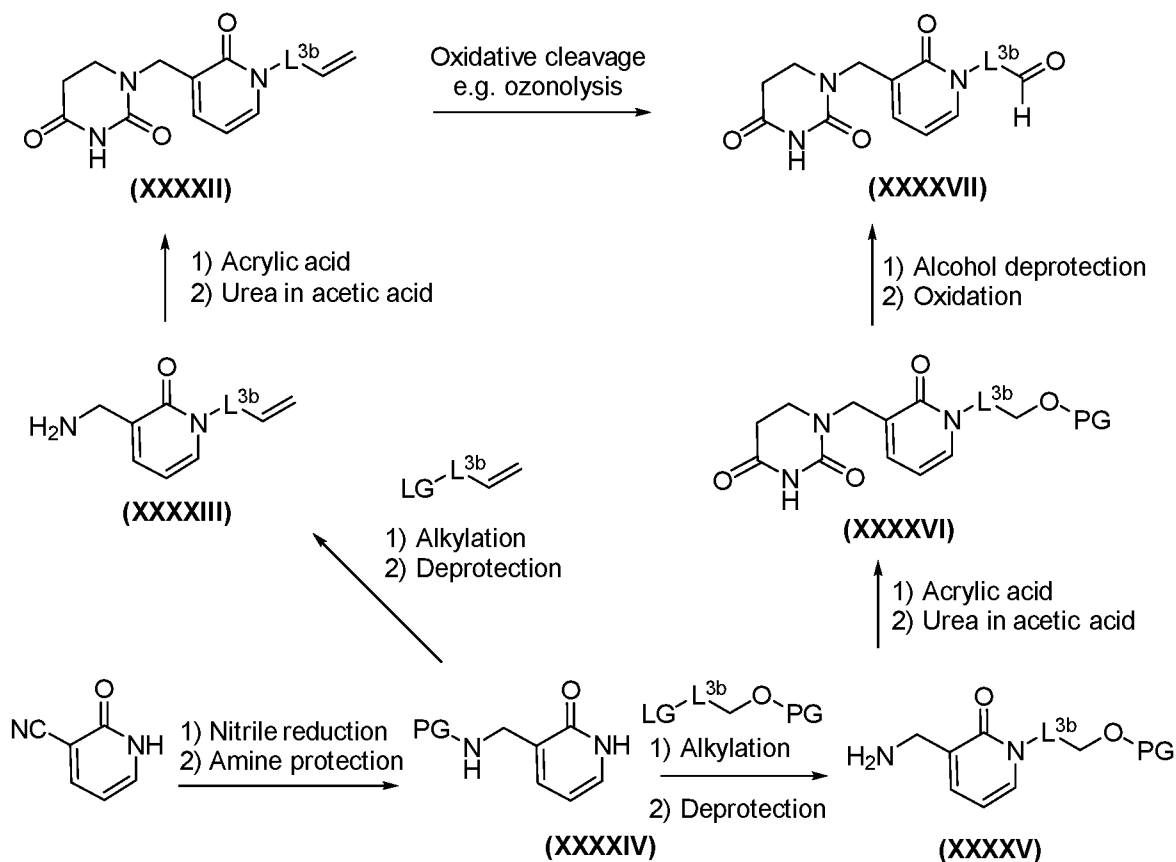
Scheme 17



A compound of Formula (XXXXVII), an embodiment of compounds (IXc), may be derived from a compound of Formula (XXXXII) using an oxidative cleavage reaction, such as an ozonolysis, as shown in Scheme 18. Compounds of Formula (XXXXII) may be derived from the corresponding amine of Formula (XXXXIII) through conjugate addition of the amine to acrylic acid, followed by reaction with urea and acetic acid to form the dihydrouracil using conditions already described herein above. Amines of Formula (XXXXIII) may be derived from 3-

cyanopyridin-2-one by first reducing the nitrile using conditions such as hydrogenation in the presence of Raney-Nickel in methanol/ammonia solution, then protecting the nitrogen to provide the compound of Formula (XXXXIV), for example, with a typical amine protecting group such as a *tert*-butoxycarbonyl group. Alkylation of Intermediate (XXXXIV) with an alkylating agent such as allyl bromide and a base such as potassium carbonate in a solvent such as DMF followed deprotection using, for example, HCl in a solvent mixture of DCM and dioxane provides the compound of Formula (XXXXIII). Alternatively, compounds of Formula (XXXXVII) may be synthesized from a compound of Formula (XXXXIV) through alkylation using an alkylating agent containing a protected alcohol to produce followed by removal of the protecting group PG to provide a molecule with Formula (XXXXV). Dihydrouracil formation using the method previously described provides compounds of Formula (XXXXVI). Alcohol deprotection followed by oxidation to the aldehyde using an oxidant such as Dess-Martin periodinane provides the compound of Formula (XXXXVII).

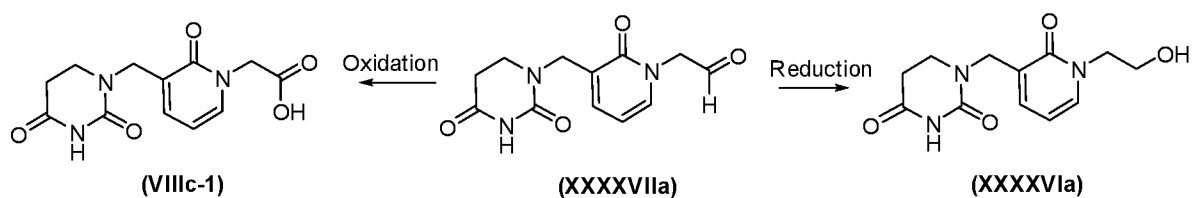
Scheme 18



Two alternative methods are described in scheme 19 and scheme 20 to exemplify the synthesis of Intermediates with the formula (ILB III). Hydrogenation of 2,4-dihydroxypyrimidines of formula (XXXVIII) under pressure (*e.g.*, 30 psi) using a catalyst such as Rhodium on charcoal in a solvent such as water followed by acetylation with PMBCl in a solvent mixture such as DMSO/DCM in the presence of a base such as Cs_2CO_3 provides compounds of formula (XXXIX) as depicted in scheme 19. Subsequent copper catalyzed arylation of (XXXIX) using heteroaryl substrates (L) or (LI), wherein Hal represents a halogen atom, preferentially bromine or iodine provides compounds of formula (ILB IIIa) and (ILB IIIb) respectively. Suitable conditions use a ligand, such as DMEDA and a base such as K_2CO_3 in a solvent such as DMF; subsequent deprotection occurs under acidic conditions, such as TFA/TfOH.

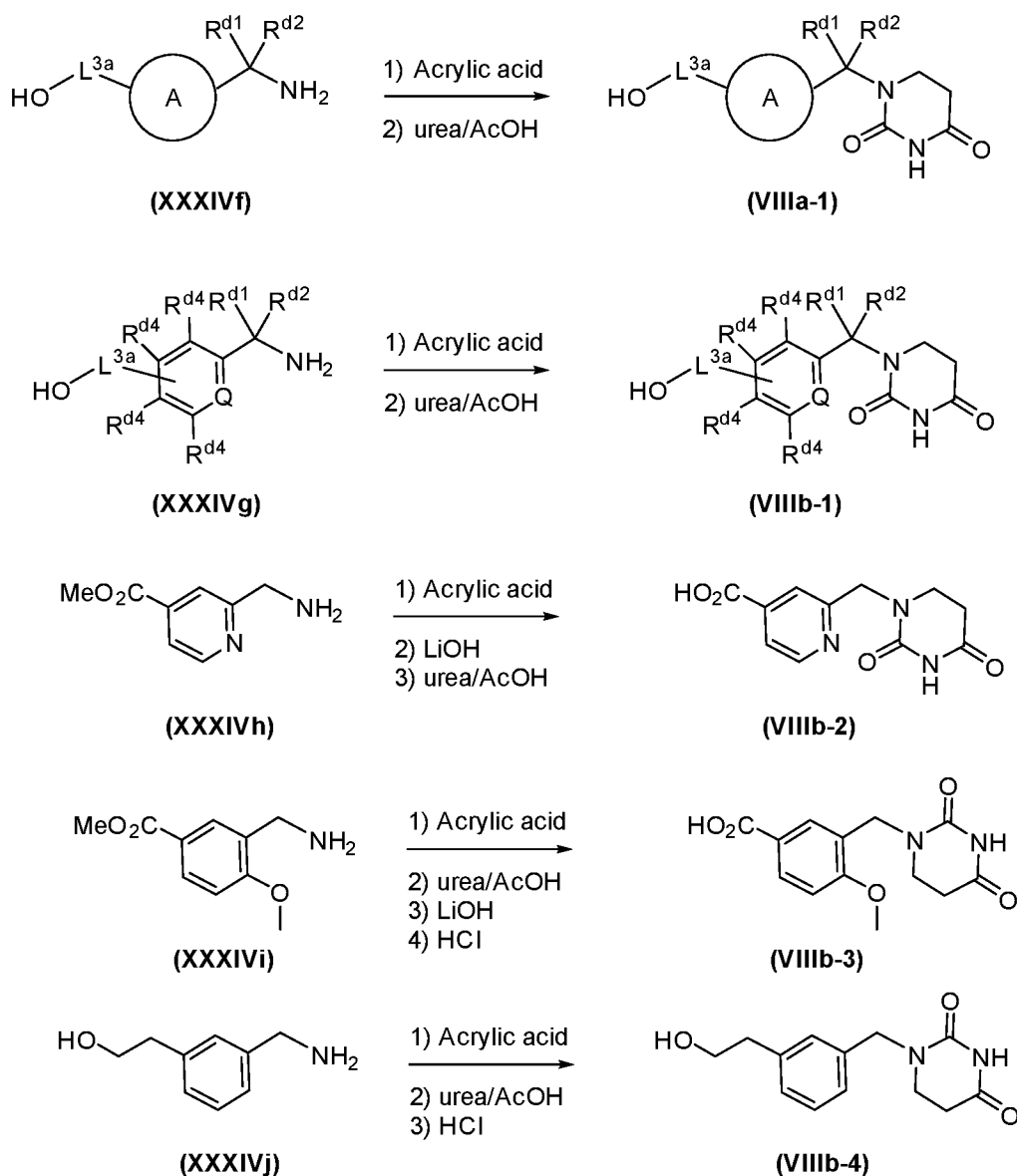
For compounds of formula (L) and (LI), U^1 , U^2 , U^3 , U^4 , U^5 , V^1 , V^2 , V^3 , V^4 and Z^1 are as previously defined herein above.

Scheme 18a



Aldehydes of compound classes (XXXXVII)/(IXc) such as the example (XXXXVIIa) may
5 undergo oxidation, for example by treatment with potassium permanganate in THF at room
temperature to give the corresponding carboxylic acid (VIIIc-1), or reduction, for example using
sodium borohydride in THF at room temperature to provide the alcohol derivative (XXXXVIa),
according to Scheme 18a.

Scheme 18b



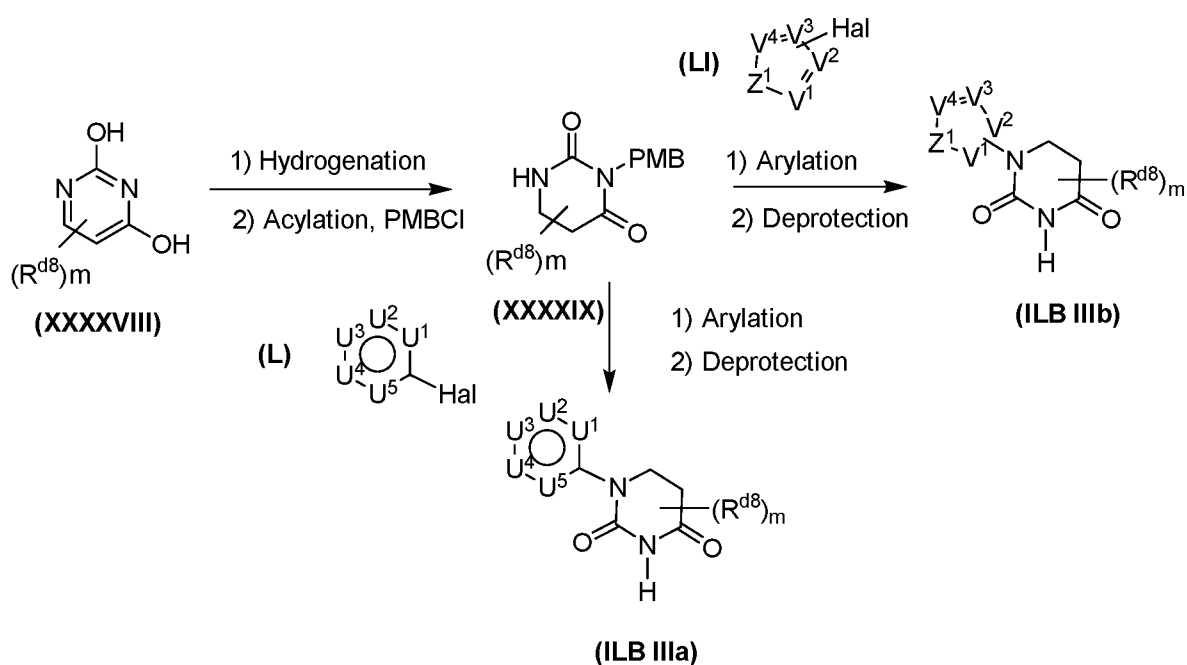
Benzylic and heterobenzylic dihydrouracil compounds bearing a carboxylic acid functionality belonging to classes (VIIIa)/(VIIIb), may be synthesized according to Scheme 18b.

- 5 Reaction of the amino acid (XXXIVf) or (XXXIVg) or a derivative (such as an amino ester) with acrylic acid at or above 70 °C with co-solvents such as water and MeCN, or toluene, followed by reaction with urea and acetic acid, also at an elevated temperature such as 100 °C provides the dihydrouracils (VIIIa-1) and (VIIIb-1), respectively.

Representative examples are the derivatives (VIIIb-2), (VIIIb-3) and (VIIIb-4), produced
 10 from the amines (XXXIVh), (XXXIVi) and (XXXIVj), respectively. To those skilled in the art, it

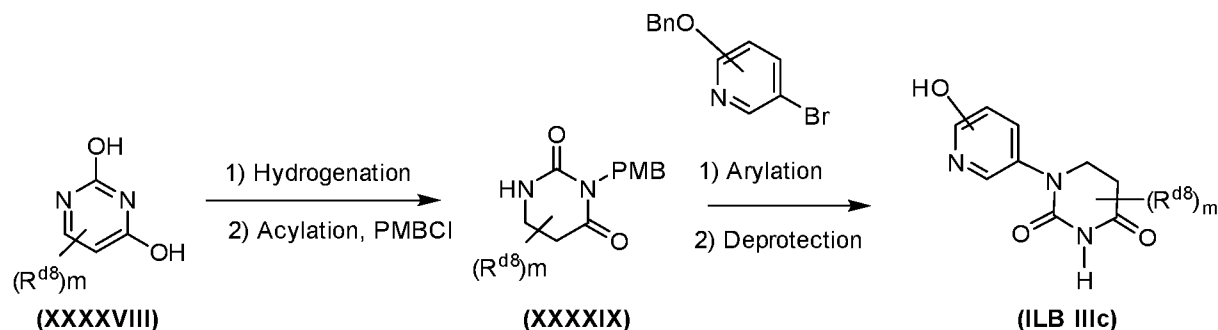
will be clear that protecting group removal may be effected at different stages of the synthesis, such as for (VIIIb-2) where hydrolysis of the ester using LiOH may be carried out prior to the cyclisation reaction, or such as for (VIIIb-3), where hydrolysis of the ester may be carried out after the cyclisation reaction. In the latter case, ring opening of the dihydrouracil necessitated a further treatment with acid to reform the dihydrouracil ring. Furthermore, use of a primary alcohol in this reaction sequence as for example (VIIIb-4) required a subsequent treatment with aqueous acid to hydrolyse the acetate ester that formed during the dihydrouracil cyclisation reaction.

Scheme 19



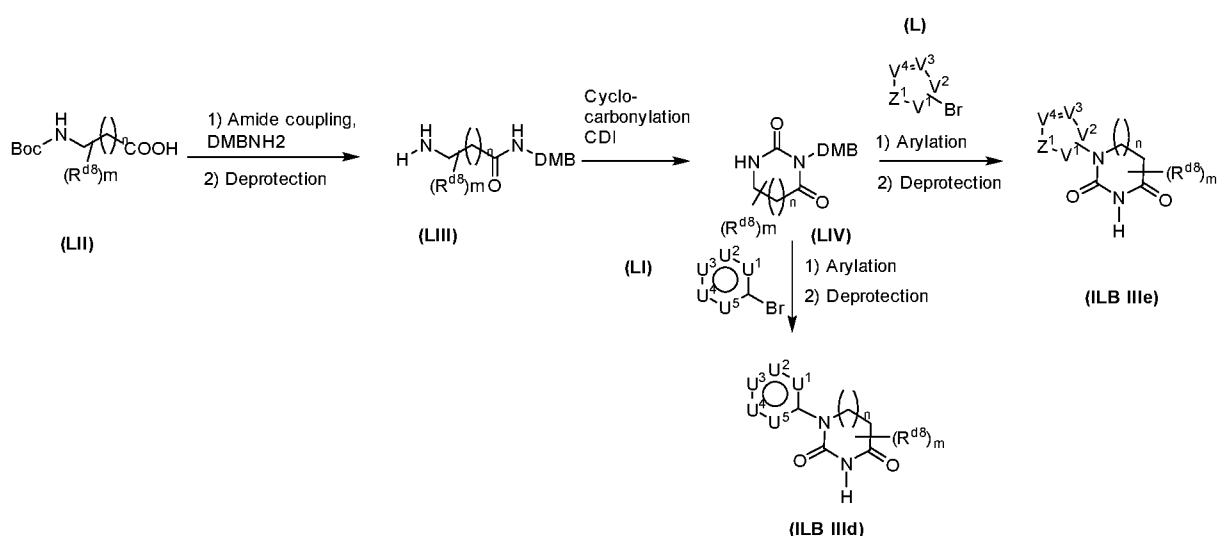
In an embodiment, the same reaction sequence has been applied to prepare structures of formula (ILB IIIc), wherein one of U^4 or U^2 is a nitrogen atom according to Scheme 19a. In certain cases, the deprotection of the PMB group also leads to deprotection of other functionality in the aromatic substituent, an example being debenzylation of a benzyl ether.

Scheme 19a



An alternative way to synthesize ILB III is shown in Scheme 20. An amide coupling of an *N*-protected amino acid (LII) with dimethoxybenzylamine using standard coupling reagents such as CDI in an aprotic solvent such as DCM, followed by Boc-deprotection under acidic conditions with *e.g.*, HCl in ethyl acetate provides compounds of formula (LIII). Cyclization to a compound of formula (LIV) occurs by reacting (LIII) with CDI in the presence of a base such as DIEA in an aprotic solvent such as DCE. A copper-catalyzed arylation of (LIV) using 6-membered heterocycles of formula (L) or 5-membered heterocycles of formula (LI) in the presence of a ligand and a catalyst under conditions already described herein above (in Scheme 19) provide compounds of formula ILB IIIc and ILB IIIe respectively.

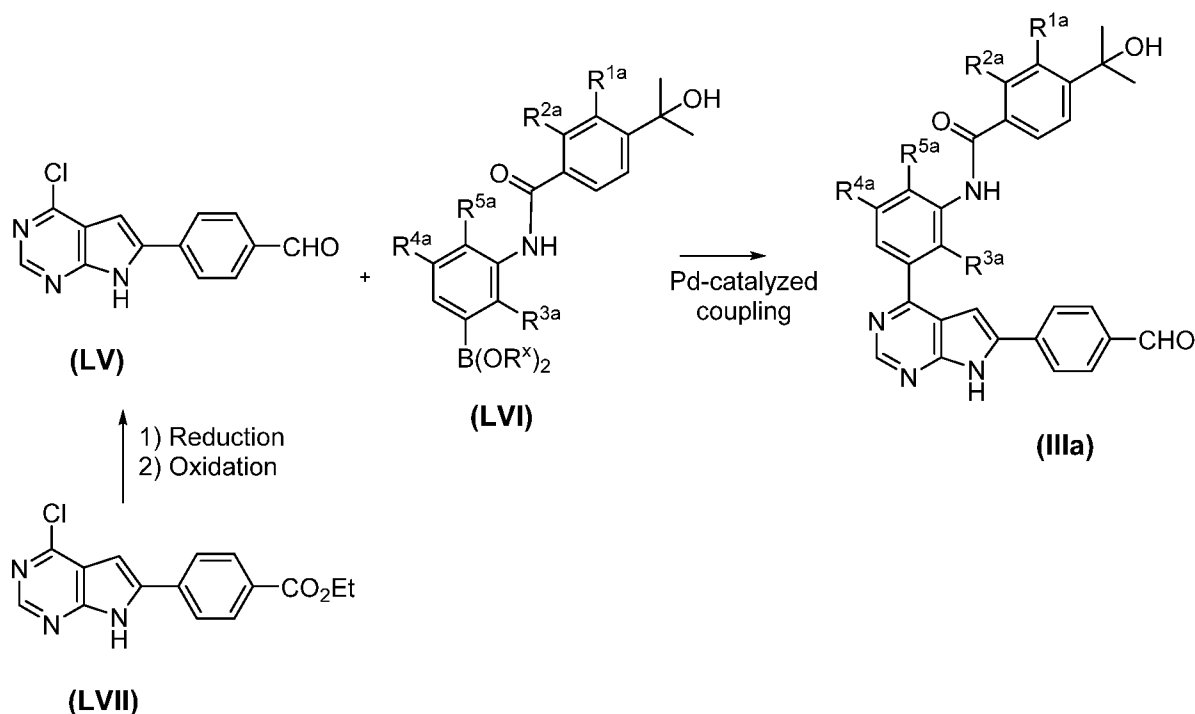
Scheme 20



Targeting ligands can be synthesized using a wide variety of methods. In an embodiment, a compound of formula (IIIa) is synthesized by a palladium-catalyzed coupling reaction, such as a

Suzuki reaction between a compound of formula (LV) and a compound of formula (LVI), using a catalyst (*e.g.*, PdCl₂(dppf)) and a base (*e.g.*, Cs₂CO₃) in a solvent mixture (*e.g.*, dioxane/water), according to Scheme 21. Compound (LV) may be made from the ester (LVII), by reduction to the alcohol using a reductant such as LiAlH₄ in a solvent such as THF, followed by oxidation to the aldehyde using MnO₂ in THF.

Scheme 21



Synthesis of other specific intermediates containing targeting ligands are described in the experimental section. The TNNI3K targeting binding moiety has been prepared by analogy to a literature procedure. *See* WO 2011/56740. The reported advanced intermediate 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (CAS No. [302964-08-5]) was also utilized in the preparation of bifunctional compounds.

The compounds of formula (III), (IIIa), (V), (VI), (XXIV), (XXII), (XXIIa), and (XXVIII) which contain targeting ligands and appropriate functional groups for attaching to a linker and ligase targeting ligand, can be prepared by a range of standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled chemist in light of the teachings herein. It is understood that depending on the nature of the targeting ligand it is possible to apply similar targeting ligands but with differing functional groups to the synthesis of

the compounds of this invention. Thus, compounds such as (III), (V), (VI), (XXIV), (XXII) and (XXVIII) may be interconverted using functional group interconversions well known to those skilled in organic synthesis.

A mixture of enantiomers, diastereomers, and cis/trans isomers resulting from the process described above can be separated into their single components by chiral salt technique, chromatography using normal phase, reverse phase or chiral column, depending on the nature of the separation.

Any resulting racemates of compounds of the present disclosure or of intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present disclosure into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid, or camphor-10-sulfonic acid. Racemic compounds of the present disclosure or racemic intermediates can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Any resulting mixtures of stereoisomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

It should be understood that in the description and formula shown above, the various groups and variables are as previously defined herein above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of schemes 1, 1a, 1b, 2–4, 4a, 5, 5a, 6, 6a, 7–16, 16a, 17–18, 18a, 18b, 19, 19a, and 20–21 are merely representative with elected radicals to illustrate the general synthetic methodology of the compounds disclosed herein. The preparation of specific intermediates and examples using the general methods described above is provided in detail in the experimental section.

EXAMPLES

The disclosure is further illustrated by the following examples, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof, which may suggest themselves to those, skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Compounds described herein may be prepared by methods known in the art of organic synthesis. In all of the methods it is understood that protecting groups for sensitive or reactive groups may be employed where necessary in accordance with general principles of chemistry. Protecting groups are manipulated according to standard methods of organic synthesis. *See, e.g.,* T.W. Green and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons (1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art.

Temperatures are given in degree Celsius. Abbreviations used are those conventional in the art and listed below.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art. Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

Abbreviations

ACN	acetonitrile
AcOH	acetic acid
app.	apparent
aq.	aqueous
ATP	adenosine 5'-triphosphate
BINAP	racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BISPIN	bis(pinacolato)diboron

BOC	<i>tert</i> -butoxycarbonyl
br	broad
BSA	bovine serum albumin
CDI	carbonyldiimidazole
CHX	cyclohexane
conc	concentrated
d	doublet
dd	doublet of doublets
DCE	1,2-dichloroethane
DCM	Dichloromethane
DEA	diethylamine
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminum hydride
DIEA	diethylisopropylamine
DIPEA	diisopropylethylamine
DMA	Dimethyl acetamide
DMBNH ₂	2,4-dimethoxy-benzyl chloride
DME	1,4-dimethoxyethane
DMEDA	1,2-dimethylethylenediamine
DMF	N,N-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
Dppf	1,1'-bis(diphenylphosphino)ferrocene
EDTA	ethylenediamine tetraacetic acid
<i>e.g.</i>	for example
eq.	equivalent
ESI	electrospray ionization
Et ₂ O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol

h	hour(s)
GC	gas chromatography
HATU	1-[bis(dimethylamino)methylene]-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HBTU	2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HCl	hydrogen chloride
HCOOH	formic acid
H ₂ O	water
HOAc	acetic acid
HOBt	1-hydroxy-7-azabenzotriazole
HPLC	high performance liquid chromatography
HV	high vacuum
iPrOH	isopropanol
K	kelvin
KOAc	potassium acetate
L	liter
LC-MS	liquid chromatography and mass spectrometry
LiHMDS	lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
MeOH	methanol
mg	milligram
MgSO ₄	magnesium sulfate
MHz	megahertz
min	minute(s)
mL	milliliter
mm	millimeter
μm	micrometer
mmol	millimol
mM	millimolar

MS	mass spectrometry
Ms	methanesulfonyl
MsCl	methanesulfonyl chloride
Ms ₂ O	methanesulfonic anhydride
MTBE	methyl <i>tert</i> -butyl ether
MW	molecular weight
m/z	mass to charge ratio
NaBH ₄	sodium borohydride
NaBH ₃ CN	sodium cyanoborohydride
NaBH(OAc) ₃	sodium triacetoxymethylborohydride
NaH	sodium hydride
NaHCO ₃	sodium bicarbonate
NaOAc	sodium acetate
NaOH	sodium hydroxide
NH ₄ Cl	ammonium chloride
NH ₄ OAc	ammonium acetate
NH ₄ OH	ammonium hydroxide
NMM	N-methylmorpholine
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
OAc	acetate
PdCl ₂ (dppf)	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride
PdCl ₂ (dppf)-CH ₂ Cl ₂	1,1'-Bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex
PdCl ₂ (PPh ₃) ₂	bis(triphenylphosphine)palladium dichloride
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium
PE	petroleum ether
PG	protecting group
PMBCl	para-methoxy-benzyl chloride
PPh ₃	triphenylphosphine
ppm	parts per million

PyBOP	benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate
rac	racemic
RM	reaction mixture
Rt	retention time
RT	room temperature
s	singlet
sat.	saturated
SEM-Cl	2-(trimethylsilyl)ethoxymethyl chloride
SFC	supercritical fluid chromatography
t	triplet
t-BuOH	<i>tert</i> -butyl alcohol
t-BuOK	potassium <i>tert</i> -butoxide
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate
TBDPS	<i>tert</i> -butyl diphenylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Tris·HCl	aminotris(hydroxymethyl)methane hydrochloride

Example 1

Analytical Methods

General Conditions

5

NMR

NMR spectra were run on Bruker AVANCE 400 MHz or 500 MHz NMR spectrometers using ICON-NMR, under TopSpin program control. Spectra were measured at 298 K, unless indicated otherwise, and were referenced relative to the solvent resonance.

10

LC-MS

Mass spectra were acquired on LC-MS, SFC-MS, or GC-MS systems using electrospray, chemical and electron impact ionization methods from a range of instruments of the following configurations: Waters Acquity UPLC/SQD system, using a photodiode array detector and a single quadrupole mass detector or Agilent 1200 systems with G 6110 series mass detector. [M+H]⁺ refers to protonated molecular ion of the chemical species.

Method LCMS1

Column: ACQUITY UPLC® HSS T3 (2.1 × 50 mm, 1.8 μm)

Column temperature: 60 °C

10 Eluents: A: water + 0.05% FA + 3.75 mM AA

B: ACN + 0.04% FA

Flow rate: 1.0 mL/min

Gradient: 5% to 98% B in 1.4 min

15 Method LCMS2

Column: ACQUITY UPLC® HSS T3 (2.1 × 50 mm, 1.8 μm)

Column temperature: 60 °C

Eluents: A: water + 0.05% FA + 3.75 mM AA

B: ACN + 0.04% FA

20 Flow rate: 1.0 mL/min

Gradient: concave from 1% to 98% B in 1.4 min

Method LCMS3

Column: ACQUITY UPLC® BEH C18 (2.1 × 50 mm, 1.7 μm)

25 Column temperature: 80 °C

Eluents: A: water + 0.05% FA + 3.75 mM AA

B: iPrOH + 0.05% FA

Flow rate: 0.6 mL/min

Gradient: from 5% to 98% B in 1.7 min

30

Method LCMS4

Column: XBridge® BEH™ C18 (2.1 × 50 mm, 2.5 µm)

Column temperature: 80 °C

Eluents: A: water + 5 mM NH₄OH

B: ACN + 5 mM NH₄OH

5 Flow rate: 1.0 mL/min

Gradient: from 2% to 98% B in 1.4 min

Method LCMS5

Column: ACQUITY UPLC® HSS T3 (2.1 × 100 mm, 1.8 µm)

10 Column temperature: 60 °C

Eluents: A: water + 0.05% FA + 3.75 mM AA

B: ACN + 0.04% FA

Flow rate: 0.8 mL/min

Gradient: 5% to 98% B in 9.4 min

15

Method LCMS6

Column: ACQUITY UPLC® BEH C18 (2.1 × 100 mm, 1.7 µm)

Column temperature: 80 °C

Eluents: A: water + 0.05% FA + 3.75 mM AA

20 B: iPrOH + 0.05% FA

Flow rate: 0.4 mL/min

Gradient: from 5 to 60% B in 8.4 min from 60 to 98% B in 1 min

Method LCMS7

25 Column: ACQUITY UPLC® BEH C18 (2.1 × 50 mm, 1.7 µm)

Column temperature: 80 °C

Eluents: A: water + 4.76% iPrOH + 0.05% FA + 3.75 mM AA

B: iPrOH + 0.04% FA

Flow rate: 0.6 mL/min

30 Gradient: from 1% to 98% B in 1.7 min

Method LCMS8

Column: Kinetex Evo C18 (2.1 × 50 mm, 1.7 μm)

Column temperature: 60 °C

Eluents: A: water + 0.05% FA + 3.75 mM AA

5 B: ACN + 0.04% FA

Flow rate: 1.0 mL/min

Gradient: 5% to 98% B in 1.4 min

Method LCMS9

10 Column: Ascentis® Express C18 2.7 μm 2.1 × 50 mm

Column temperature: 80 °C

Eluents: A: water + 4.76% isopropanol + 0.05% FA + 3.75 mM AA

B: isopropanol + 0.05% FA

Flow rate: 1.0 mL/min

15 Gradient: 1% to 50% B in 1.4 min, 50 to 98% B in 0.3 min

Method LCMS10

Column: Kinetex EVO C18 (30*2.1mm, 5um)

Column temperature: 50 °C

20 Eluents: A: 0.0375% TFA in water (v/v)

B: 0.01875% TFA in Acetonitrile (v/v)

Flow rate: 1.5 ml/min

Gradient: 0 % to 60 % B in 1.55 min

25 **Method LCMS11**

Column: Kinetex EVO C18 (30*2.1mm, 5um)

Column temperature: 50 °C

Eluents: A: 0.0375% TFA in water (v/v)

B: 0.01875% TFA in Acetonitrile (v/v)

30 Flow rate: 1.5 ml/min

Gradient: 0 % to 60 % B in 7 min

Method LCMS12

Column: CORTECS™ C18+ 2.7 µm

Column temperature: 80.0 °C

5 Eluents: A: water + 4.76% isopropanol + 0.05% FA + 3.75 mM AA

B: isopropanol + 0.05% FA

Flow rate: 1.0 mL/min

Gradient: from 1 to 50 % B in 1.4 min; 50 to 98 % B in 0.3 min

10 **Method LCMS13**

Column: Waters XSelect HSS T3 3.5µm 4.6*50mm

Column temperature: 50°C

Eluents: A: 0.0375% TFA in water (v/v)

B: 0.01875% TFA in ACN (v/v)

15 Flow rate: 1 ml/min

Gradient: 0 % to 30 % B in 5 min

Example 2**Analytical Methods**

20 **General Conditions:**

NMR

NMR spectra were run on Bruker AVANCE 400MHz or 500MHz NMR spectrometers using ICON-NMR, under TopSpin program control. Spectra were measured at 298K, unless indicated otherwise, and were referenced relative to the solvent resonance.

25

LC-MS

Mass spectra were acquired on LC-MS, SFC-MS, or GC-MS systems using electrospray, chemical and electron impact ionization methods from a range of instruments of the following configurations: Waters Acquity UPLC/SQD system, using a photodiode array detector and a single
30 quadrupole mass detector or Agilent 1200 systems with G 6110 series mass detector. [M+H]⁺ refers to protonated molecular ion of the chemical species.

Method A

Column: XBridge C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 50 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: ACN

5 Flow rate: 1.8 mL/min

Gradient: 5% to 95% B in 1.5 min

Method B

Column: SunFire C18 (4.6 × 50 mm, 3.5 μm)

10 Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: ACN containing TFA (0.01%)

Flow rate: 2.0 mL/min

Gradient: 5% to 95% B in 1.4 min

15 **Method C**

Column: SunFire C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: ACN containing TFA (0.01%)

Flow rate: 2.0 mL/min

20 Gradient: 5% to 95% B in 1.3 min

Method D

Column: HALO C18 (4.6 × 30 mm, 2.7 μm)

Column temperature: 50 °C

25 Eluents: A: aq. TFA (0.01%); B: ACN containing TFA (0.01%)

Flow rate: 2.2 mL/min

Gradient: 5% to 95% B in 1.0 min

Method E

30 Column: SunFire C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: ACN containing TFA (0.01%)
Flow rate: 2.0 mL/min
Gradient: 5% to 95% B in 1.2 min

5 **Method F**

Column: SunFire C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: ACN containing TFA (0.01%)

Flow rate: 2.0 mL/min

10 Gradient: 5% to 95% B in 1.2 min, followed by 95% B for 1.3 min

Method G

Column: XBridge C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 40 °C

15 Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: CAN

Flow rate: 1.8 mL/min

Gradient: 5% to 95% B in 1.4 min, followed by 95% B for 1.6 min

Method H

20 Column: XBridge C18 (4.6 × 50 mm, 3.5 μm)

Column temperature: 40 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: ACN

Flow rate: 2.0 mL/min

Gradient: 5% to 95% B in 1.5 min

25

Preparative chromatography methods

Normal and reverse phase chromatography purifications have been performed on a Biotage Isolera One system.

30 **Achiral preparative HPLC methods**

Method PB with basic modifier

Instrument: Gilson 281 (PHG012)
Column: Xtimate C18 (21.2 × 250 mm, 10 µm)
Column temperature: RT
Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: ACN
5 Flow: 30 mL/min
Detection: UV @ 254 nm, 214 nm

Method PA with acidic modifier

Instrument: Gilson 281 (PHG012)
10 Column: Xtimate C18 (21.2 × 250 mm, 10 µm)
Column temperature: RT
Eluents: A: aq. TFA (0.1%); B: ACN
Flow: 30 mL/min
Detection: UV @ 254 nm, 214 nm

15

Method PA2 with acidic modifier

Column: Waters Xbridge (150*25*10 µm)
Column temperature: 25 °C
Eluents: A: aq. TFA (0.1 %); B: ACN
20 Flow rate: 25.0 ml/min
Gradient: 34 % to 54 % B in 10 min

Method PA3 with acidic modifier

Instrument: Gilson GX-215&Shimadzu LCMS2020
25 Column: Waters Atlantis T3 150*30mm*5um
Column temperature: RT
Eluents: A: aq. TFA (0.1%); B: ACN
Flow: 25 mL/min
Detection: UV @ 254 nm, 220 nm

30

Example 3**Analytical Methods****General Conditions****NMR**

5 NMR spectra were recorded on Bruker AVANCE 400 MHz, 500 MHz or 600 MHz NMR spectrometers using ICON-NMR, under TopSpin program control. Spectra were measured at 298 K, unless indicated otherwise, and were referenced relative to the solvent resonance according to the values described in *J. Org. Chem.* 62: 7512-7515 (1997) (*e.g.* DMSO d₆ at 2.50 ppm, CDCl₃ at 7.26 ppm, D₂O at 4.79 ppm and MeOD-d₄ at 3.31 ppm). Significant peaks are tabulated in the
10 following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; v, very) and number of protons.

LC-MS

Mass spectra were acquired on LC-MS, SFC-MS, or GC-MS systems using electrospray,
15 chemical and electron impact ionization methods from a range of instruments of the following configurations: Waters Acquity UPLC/SQD system, using a photodiode array detector and a single quadrupole mass detector or Agilent 1200 systems with G 6110 series Mass Spectrometer. [M+H]⁺ refers to the protonated molecular ion of the chemical species.

20 Method XA

Column: Waters Acquity HSS T3 1.8 μm 2.1 × 50 mm or 2.1 × 100 mm

Column temperature: 60 °C

Eluents: A: aq. formic acid (0.05%) + aq. ammonium acetate (3.75 mM); B: ACN containing formic acid (0.04%)

25 Flow rate: 1.0 mL/min

Gradient: 5% to 98% B in 1.4 min

Method XB

Column: Waters Acquity HSS T3 1.8 μm 2.1 × 50 mm or 2.1 × 100 mm

30 Column temperature: 60 °C

Eluents: A: aq. formic acid (0.05%) + aq. ammonium acetate (3.75 mM); B: ACN containing formic acid (0.04%)

Flow rate: 0.8 mL/min

Gradient: 5% to 98% B in 9.4 min

5

Method XC

Column: Waters Acquity HSS T3 1.8 μ m 2.1 $\times$ 50 mm or 2.1 $\times$ 100 mm

Column temperature: 50 °C

Eluents: A: aq. formic acid (0.05%) + aq. ammonium acetate (3.75 mM); B: ACN containing formic acid (0.04%)

10

Flow rate: 1.2 mL/min

Gradient: 2% to 98% B in 1.4 min

Method XD

15 Column: SunFire C18, 4.6 $\times$ 50 mm, 3.5 μ m

Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: acetonitrile containing TFA (0.01%)

Flow rate: 2.0 mL/min

Gradient: 5% to 95% B in 1.4 min

20

Method XE

Column: SunFire C18, 4.6 $\times$ 50 mm, 3.5 μ m

Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: acetonitrile containing TFA (0.01%)

25 Flow rate: 2.0 mL/min

Gradient: 5% to 95% B in 1.2 min, 95% B for 1.3 min

Method XF

Column: Phenomenex, 3.0 $\times$ 30 mm, 5 μ m

30 Column temperature; 50 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: acetonitrile

Flow rate: 1.5 mL/min

Gradient: 5% to 95% B in 1.5 min, 95% B for 0.7 min

Method XG

5 Column: XBridge C18, 4.6 × 50 mm, 3.5 μm

Column temperature: 40 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: acetonitrile

Flow rate: 2.0 mL/min

Gradient: 5% to 95% B in 1.5 min

10

Method XH

Column: XBridge C18, 4.6 × 50 mm, 3.5 μm

Column temperature: 50 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: acetonitrile

15 Flow rate: 1.8 mL/min

Gradient: 5% to 95% B in 1.5 min, 95% B for 1.5 min

Method XI

Column: SunFire C18, 3 × 30 mm, 2.5 μm

20 Column temperature: 50 °C

Eluents: A: aq. TFA (0.01%); B: acetonitrile containing TFA (0.01%)

Flow rate: 1.5 mL/min

Gradient: 5% to 95% B in 1.5 min

25 Method XJ

Column: XBridge C18, 4.6 × 50 mm, 3.5 μm

Column temperature: 40 °C

Eluents: A: aq. ammonium hydrogen carbonate (10 mM); B: acetonitrile

Flow rate: 1.8 mL/min

30 Gradient: 5% to 95% B in 1.4 min, 95% B for 1.6 min

Chiral Analytical HPLC Methods**Method XK**

Instrument: Agilent 1200 system

Column: Chiralpak ID 5um 4.6 × 250 mm

5 Column temperature: RT

Eluents: Hept : DCM : MeOH (40 : 35 : 25) + DEA (0.1%)

Flow rate: 1.0 mL/min

Gradient: isocratic

Detection: UV at 254 nm

10

Preparative Chromatography Methods

Normal and reverse phase chromatography purifications have been performed on a CombiFlash Rf200 or Rf+ system. Alternatively, chromatography purifications on reverse phase have been performed on an Interchim Puriflash 4250 system.

15 Achiral SFC Chromatography separations have been performed using a Waters Preparative SFC-100-MS system with either a Waters 2998 Photodiode Array Detector or a Waters MS Single Quadrupole Detection using MeOH as modifier. The back pressure was 120 bar, the flow 100 g CO₂/min and the column temperature 40 °C. The type of the column varies and has been indicated in the individual experimental sections. Reverse phase HPLC purifications have been performed
20 on a Waters HPLC Preparative System with either a Waters 2998 Photodiode Array Detector or a Waters MS Single Quadrupole Detection.

Achiral Preparative HPLC Methods**Method XL**

25 Instrument: Gilson GX-281

Column: SunFire C18

Column temperature: RT

Mobile phase: ACN in water containing TFA (0.1%)

Flow: 40 mL/min

30 Detection: UV @ 254 nm

Chiral Preparative Chromatography Methods**Method XM**

Instrument: Gilson Trilution I HPLC System

Column: ChiralPak ID, 5 μ M, 250 $\times$ 20 mm

5 Column temperature: RT

Mobile phase: heptane/DCM/MeOH (40 : 35 : 25) containing DEA (0.05%)

Flow: 10 mL/min

Detection: UV @ 254 nm

10 **Method XN:**

Instrument: Gilson

Column: Reprosil 100 C18 (250 $\times$ 30 mm, 5 μ m)

Column temperature: Room temperature

Eluents: A: Water (0.1% TFA), B: ACN

15 Flow rate: 25 mL/min

Gradient: 0–2 min. 100% Eluent A, 2–26 min. 100% to 5% Eluent A

Detection: UV @ 254 nm

Method XN-A:

20 Instrument: Gilson

Column: Reprosil 100 C18 (250 $\times$ 30 mm, 5 μ m)

Column temperature: Room temperature

Eluents: A: Water (0.1% TFA), B: ACN

Flow rate: 25 mL/min

25 Gradient: 0–2 min. 100% Eluent A, 2–26 min. 100% to 50% Eluent A

Detection: UV @ 254 nm

Method XO

Column: AcQuity UPLC BEH C18, 2.1 $\times$ 30 mm, 1.7 μ m

30 Column temperature: 50 $^{\circ}$ C

Eluents: A: 5 mM NH₄OH in water; B: 5 mM NH₄OH in ACN

Flow rate: 1.0 mL/min

Gradient: 1% to 30% B in 1.20 min, 30% to 98% B in 0.95 min, 98% to 1% B in 0.04 min

Method XP

5 Column: AcQuity UPLC BEH C18, 2.1 × 50 mm, 1.7 μm

Column temperature: 50 °C

Eluents: A: 5 mM NH₄OH in water; B: 5 mM NH₄OH in ACN

Flow rate: 1.0 mL/min

Gradient: 1% to 30% B in 3.20 min, 30% to 98% B in 1.95 min, 98% to 1% B in 0.04 min

10

Method XP-A

Column: AcQuity UPLC BEH C18, 2.1 × 50 mm, 1.7 μm

Column temperature: 50 °C

Eluents: A: 0.1% Formic Acid in Water

15 B: 0.1% Formic Acid in Acetonitrile

Flow rate: 1.0 mL/min

Gradient: 1% to 30% B in 1.20 min, 30% to 98% B in 0.95 min, 98% to 1% B in 0.04 min

20 Method XQ

Column: AcQuity UPLC BEH C18 1.7μm 2.1 × 30 mm

Column temperature: 50 °C

Eluents: A: 0.1% Formic Acid in Water; B: 0.1% Formic Acid in Acetonitrile

Flow rate: 1.0 mL/min

25 Gradient: 2% B for 0.10 min, 2% to 98% B in 1.40 min, 98% B for 0.30 min, 98% to 2% B in 0.10 min, 2% B for 0.10 min

Method XR

Column: AcQuity UPLC BEH C18 1.7μm 2.1 × 50 mm

30 Column temperature: 50 °C

Eluents: A: 5 mM NH₄OH in water; B: 5 mM NH₄OH in ACN

Flow rate: 1.0 mL/min

Gradient: 2% to 98% B in 4.40 min, 98% B for 0.75 min, 98% to 2% B in 0.04 min

Method XR-A

5 Column: AcQuity UPLC BEH C18 1.7 μ m 2.1 $\times$ 50 mm

Column temperature: 50 °C

Eluents: A: 0.1% Formic Acid in Water

B: 0.1% Formic Acid in Acetonitrile

Flow rate: 1.0 mL/min

10 Gradient: 2% to 98% B in 5 min, 98% B for 0.75 min, 98% to 2% B in 0.04 min

Method XV-B

Column: AcQuity UPLC BEH C18 1.7 μ m 2.1 $\times$ 30 mm

Column temperature: 50 °C

15 Eluents: A: 5 mM Ammonium Hydroxide in Water; B: 5 mM Ammonium Hydroxide in Acetonitrile

Flow rate: 1.0 mL/min

Gradient: 2% to 98% B in 1.80 min

20 Method XS

Detection: - Waters 2998 Photodiode Array Detector

- Waters MS Single Quadrupole Detection

Column temperature: RT

Eluent A: water / Eluent B: acetonitrile, both containing 0.1% trifluoroacetic acid

25

Method XT

Detection: - Waters 2998 Photodiode Array Detector

- Waters MS Single Quadrupole Detection

Column temperature: RT

30 Eluent A: water / Eluent B: acetonitrile, both containing 0.1% NH₄OH

Method XU

Instrument: Waters Preparative SFC-100-MS system

Detection: - Waters 2998 Photodiode Array Detector
- Waters MS Single Quadrupole Detection

5 Modifier: Methanol
ABPR: 1 20 bar
Column temperature: 40°C
Flow rate: 100 g/min.

10 **Method XX**

Instrument: Gilson GX-281, Gilson 155, Gilson 331

Column: Sunfire C18 (30 × 100 mm, 5 µm)

Column temperature: RT

Eluents: A: aq. TFA (0.1%); B: ACN

15 Flow: 50 mL/min

Detection: UV @ 254 nm, 214 nm

Materials for Solid Phase Extraction

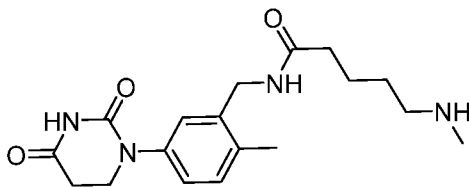
The following solid phase extraction (SPE) cartridges were used according to product instructions to generate the corresponding free base from different salts:

20 PL-HCO₃ MP SPE cartridges were purchased from Agilent StratosPhere–Ref: PL-HCO₃ MP-resin, 1.8 mmol/g, 100A, 150-300 µm, 500 mg, 6 mL.

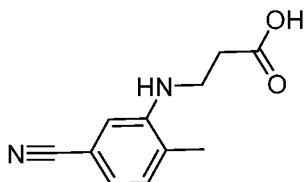
SCX cartridges were purchased from Agilent–Ref. : HF Mega DE-SCX, 2 g, 12 mL.

Example 425 **Synthetic Intermediate and Reagent Synthesis**

Intermediate AA: N-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)-5-(methylamino)pentanamide

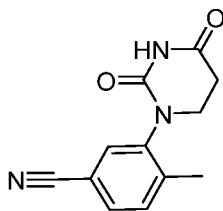


Step 1: 3-((5-cyano-2-methylphenyl)amino)propanoic acid



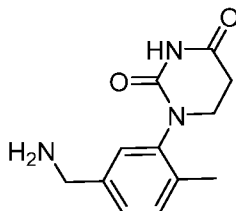
A solution of 3-amino-4-methylbenzonitrile (CAS No. [60710-80-7], 10 g, 75.66 mmol), and Acrylic acid (CAS No. [79-10-7], 3 g, 151.33 mmol), in toluene (25 mL) was stirred at 120°C for 16 h under N₂. The RM was concentrate to dryness to afford the title compound as a light yellow solid (15 g). Method G: Rt = 1.34 min; [M+H]⁺ = 204.

Step 2: 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzonitrile



To a solution of 3-((5-cyano-2-methylphenyl)amino)propanoic acid (7.8 g, 38.19 mmol) and Urea (CAS No. [57-13-6], 11.5 g, 191 mmol) in AcOH (CAS No. [64-19-7], 100 mL) was stirred at 120 °C for 16 h. The RM was poured on crushed ice (200 g), stirred for 30 min and filtered to afford the title compound as a light yellow solid (4 g). Method F: Rt = 1.31 min; [M+H]⁺ = 230.

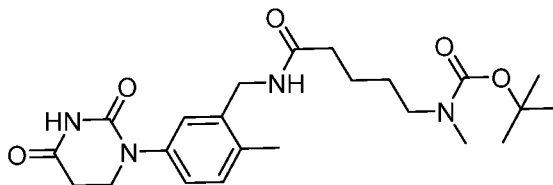
Step 3: 1-(5-(aminomethyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione



A solution of 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzonitrile (4 g, 17.45 mmol) and Raney Nickel (500 mg) in MeOH/NH₄OH (1000 mL/200 mL) was stirred under H₂ at RT for

16 h. The mixture was filtered through Celite[®] filter aid and concentrated to dryness. The crude compound was purified by reverse phase HPLC Method (5% to 95% ACN/H₂O, 0.01% TFA) to give the title compound as the TFA salt (1.1 g). Method F: Rt = 0.379 min; [M+H]⁺ = 234.

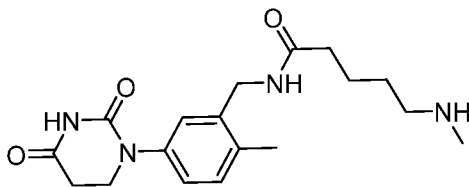
5 **Step 4:** *tert*-butyl (5-((5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)amino)-5-oxopentyl)(methyl)carbamate



HATU (CAS No. [148893-10-1], 324 mg, 0.85 mmol) was added to a stirred solution of 1-(5-(aminomethyl)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (250 mg, 0.72 mmol) and
 10 5-((*tert*-butoxycarbonyl)(methyl)amino)pentanoic acid (CAS No. [124073-08-1], 200 mg, 0.86 mmol) followed by the addition of DIEA (CAS No. [7087-68-5], 186 mg, 1.44 mmol). The resulting solution was stirred at RT for 16 h. The RM was purified by reverse phase HPLC (0%–50% ACN in H₂O, 0.1% NH₄CO₃) to afford the title compound as a white solid. Method G: Rt = 1.36 min; [M-BOC+H]⁺ = 347.

15

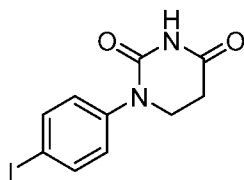
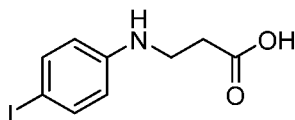
Step 5: N-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)-5-(methylamino)pentanamide



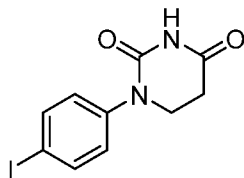
tert-Butyl (5-((5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)amino)-5-oxopentyl)(methyl)carbamate (200 mg, 0.45 mmol) was dissolved in DCM (2 mL). TFA (6 mL) was added and the RM was stirred at RT for 16 h. The solution was concentrate to afford the title compound as a dark liquid. Method G: Rt = 1.26 min; [M+H]⁺ = 347.

20

Intermediate BB: 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione

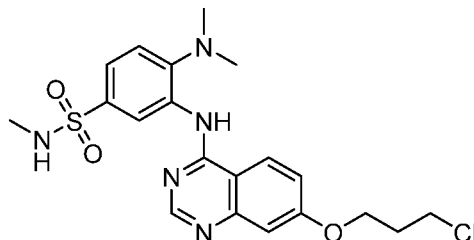
**Step 1:** 3-((4-iodophenyl)amino)propanoic acid

4-iodoaniline (4.0 g, 18.26 mmol) and acrylic acid (1.503 mL, 21.92 mmol) were dissolved in toluene (100 mL) and the reaction mixture was refluxed at 110 °C for 4 days. The reaction mixture was then cooled to room temp and concentrated. The crude solid was redissolved in a 1:1:1 solution of DMSO/water/ACN and purified via reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (1%) (from 10 to 80%) to afford the TFA salt of the title compound as a light brown solid (3.70 g, 9.14 mmol). Method XQ: RT = 0.85 min; [M+H]⁺ = 292.1.

Step 2: 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione

3-((4-iodophenyl)amino)propanoic acid (3.7 g, 12.71 mmol) was dissolved in acetic acid (50 mL) and sodium cyanate (2.479 g, 38.1 mmol) was added. The reaction was heated at 90 °C for 18 h. The reaction mixture was cooled to RT, neutralized with 1N NaOH, and extracted with EtOAc (3 × 50 mL). The combined organics were washed with water (1 × 25 mL) and brine (1 × 25 mL), dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified via FCC (0–15% MeOH/DCM) and further via reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of NH₄OH (0.1%) (from 10 to 75%) to afford the title compound (400 mg). Method XR: Rt = 1.38 min; [M+H]⁺ = 317.0. ¹H NMR (400 MHz, DMSO-d₆) δ 10.41 (s, 1H), 7.81–7.65 (m, 2H), 7.23–7.10 (m, 2H), 3.78 (t, J = 6.6 Hz, 2H), 2.70 (t, J = 6.6 Hz, 2H).

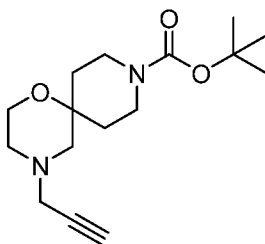
Intermediate CC: **3-((7-(3-chloropropoxy)quinazolin-4-yl)amino)-4-(dimethylamino)-N-methylbenzenesulfonamide**



This compound was prepared according to a procedure published in WO 2011/56740 A1; page 49,

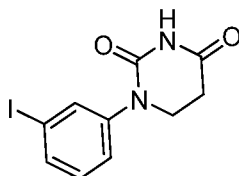
5 Example 16.

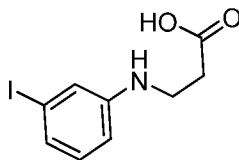
Intermediate DD: ***tert*-butyl 4-(prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate**



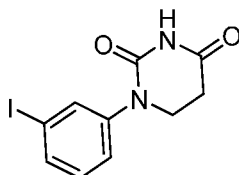
10 To a solution of K_2CO_3 (415 mg, 3.00 mmol) in acetonitrile (10 mL) was added *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (CAS No. [930785-40-3], 550 mg, 2.146 mmol) under argon. After 10 minutes, a solution of propargyl bromide in toluene (0.335 mL, 3.00 mmol) was added. The mixture was heated at reflux for 18 h, at which point, an additional 8 mg of K_2CO_3 and 10 mg of propargyl bromide was added to the reaction mixture. The reaction mixture was refluxed
15 for an additional 24 hours, then cooled to room temperature and filtered to remove solids. The filtrate was concentrated and purified via Flash chromatography (0–100% EtOAc/Cyclohexane) to afford the title compound (594 mg, 2.018 mmol). Method LCMS1: R_t = 0.95 min; $[M+H]^+$ = 295.3.

20 Intermediate EE: **1-(3-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione**



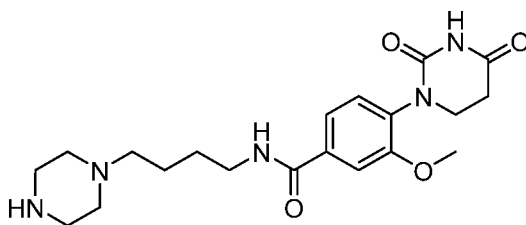
Step 1: 3-((3-iodophenyl)amino)propanoic acid

To a solution of 3-iodoaniline (10 g, 45.66 mmol) in toluene (131 mL) was added acrylic acid (4.28 g, 59.36 mmol). The mixture was stirred at 115 °C for 48 h. The solvent was removed to
 5 obtain the title compound as an orange oil (15 g, crude). Method H: $R_t = 1.36$ min; $[M+H]^+ = 291.9$.

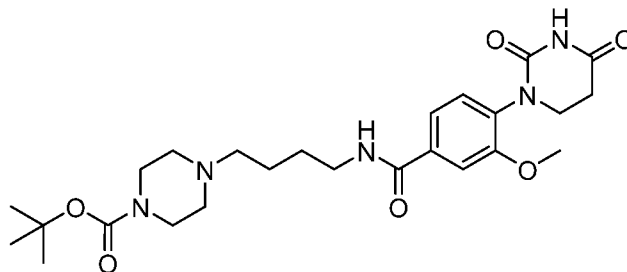
Step 2: 1-(3-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione

To a solution of 3-((3-iodophenyl)amino)propanoic acid (15 g, 51.5 mmol) in AcOH (125 mL) was added urea (9.284 g, 154.6 mmol). The mixture was stirred at 120 °C for 16 h. The solvent was removed and water (200 mL) was added. The mixture was filtered. The filter cake was washed with water (2×20 mL) and dried in vacuum. The solid was suspended in EtOAc (60 mL), triturated for 16 h at RT. The mixture was filtered. The filter cake was washed with EtOAc (2×5 mL) and
 15 dried to afford the title compound as a pale solid (7.9 g). Method E: $R_t = 1.43$ min; $[M+H]^+ = 317.0$.

Intermediate FF: **4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxy-N-(4-(piperazin-1-yl)butyl)benzamide**

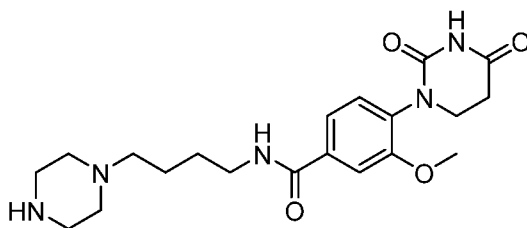


Step 1: *tert*-Butyl 4-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzamido)butyl)piperazine-1-carboxylate



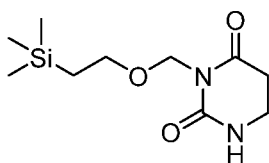
A solution of 4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzoic acid (ILB-81, 155 mg, 0.539 mmol), 4-(4-amino-butyl)-piperazine-1-carboxylic acid *tert*-butyl ester (CAS No. [745048-07-1], 146 mg, 0.539 mmol), HATU (293 mg, 0.755 mmol) and NMM (0.30 mL, 2.70 mmol) in DMF (5 mL) was stirred for 3 h at RT. The crude product was loaded on a Redisep® C18 column and eluted from (water + 0.1% TFA)/ACN 98:2 to 1:9 to afford the title compound as a white powder (179 mg). Method LCMS1: Rt = 0.59 min; [M+H]⁺ = 504.

Step 2: 4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxy-N-(4-(piperazin-1-yl)butyl)benzamide



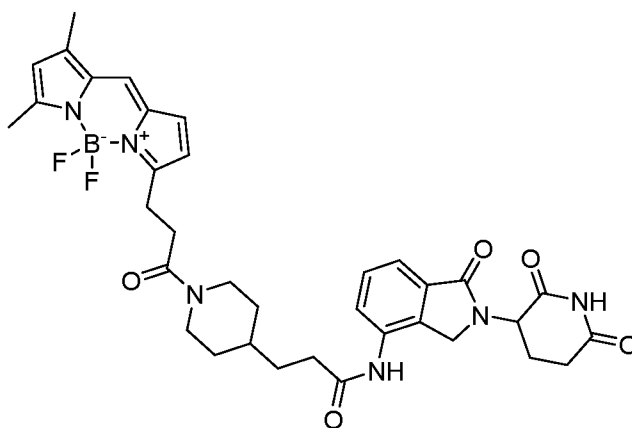
A solution of *tert*-butyl 4-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzamido)butyl)piperazine-1-carboxylate (175 mg, 0.269 mmol) and HCl 4 N in dioxane (4 mL, 16 mmol) was stirred in methanol (2 mL) for 1.5 h at RT. The solvent was removed, the residue redissolved in ACN/H₂O and freeze dried to afford the title compound as a pale beige powder (131 mg). Method LCMS2: Rt = 0.69 min; [M+H]⁺ = 404.

Intermediate GG: 3-((2-(trimethylsilyl)ethoxy)methyl)dihydropyrimidine-2,4(1H,3H)-dione

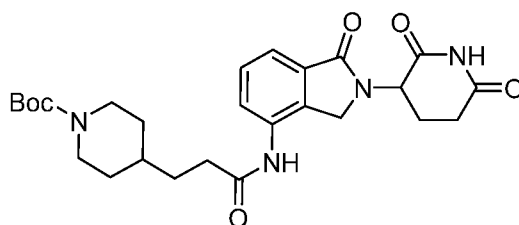


To a 100 mL round bottom flask were added dihydropyrimidine-2,4(1H,3H)-dione (2.7 g, 23.66 mmol) and anhydrous DMPU (35 mL). A solution of LiHMDS (1 M) in THF (25 mL, 25.00 mmol) was added under argon and the RM was vigorously stirred at 60°C for 40 min. The RM was cooled to RT. SEM-Cl (5 mL, 28.20 mmol) was added and the RM was stirred at 60°C for 18 h. The RM was diluted with sat. NaHCO₃ sol. and brine, extracted with EtOAc (×3). The organic phase was washed with water and brine, dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel eluting with EtOAc in CHX (from 0% to 100%) and then with MeOH (from 0% to 20%) to afford the title compound as a slightly yellow oil (4.7 g). Method LCMS4: Rt = 0.76 min; [M-H]⁻ = 243.

Compound HH: 4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butanal



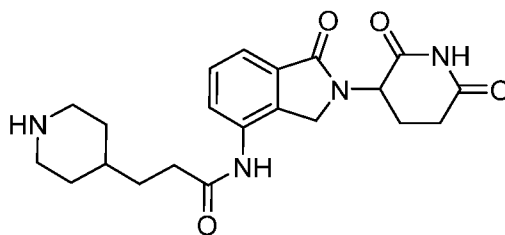
Step 1: *tert*-butyl 4-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)-3-oxopropyl)piperidine-1-carboxylate



In a MW vial were put lenalidomide (CAS No. [191732-72-6], 50 mg, 0.193 mmol), N-Boc-4-piperidinepropionic acid (CAS No. [154775-43-6], 65 mg, 0.212 mmol) and HATU (83 mg, 0.212 mmol) followed by 1.25 mL ACN and 0.5 mL DMF. DIPEA (0.1 mL, 0.579 mmol) was added before the vial was flushed with N₂ and capped. The pale yellow mixture was stirred for 21 h. The

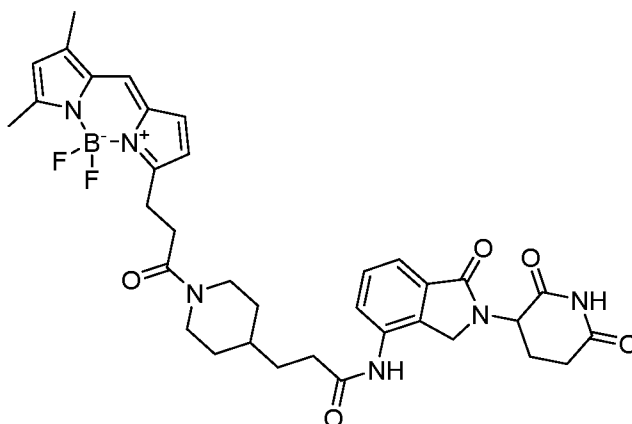
RM was concentrated and partitioned between EtOAc (5–6 mL) and buffer pH = 4 (commercial solution, Fluka product number 33643, containing citric acid, sodium hydroxide and sodium chloride, 5 mL). Layers were separated and the aq. layer was extracted with EtOAc (5 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated under HV overnight to give a pale yellow resin. The crude product was purified by Redisep[®] ISCO - column 12 g SiO₂ with a DCM/iPrOH gradient to afford the title compound as white solid (87 mg). Method LCMS1: Rt = 0.89 min; [M-H]⁺ = 499.1. ¹H NMR (400 MHz, DMSO-d₆): 0.92 - 1.03 (m, 2 H) 1.34 - 1.46 (m, 10 H) 1.54 (q, J = 7.09 Hz, 2 H) 1.64 (br d, J = 11.86 Hz, 2 H) 1.96 - 2.06 (m, 1 H) 2.30 - 2.40 (m, 3 H) 2.55 - 2.75 (m, 3 H) 2.83 - 2.97 (m, 1 H) 3.91 (br d, J = 12.10 Hz, 2 H) 4.25 - 4.42 (m, 2 H) 5.13 (dd, J = 13.27, 5.07 Hz, 1 H) 7.42 - 7.54 (m, 2 H) 7.79 (dd, J = 6.97, 1.47 Hz, 1 H) 9.76 (s, 1 H) 11.00 (s, 1 H).

Step 2: N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)-3-(piperidin-4-yl)propanamide



tert-Butyl 4-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)-3-oxopropyl)piperidine-1-carboxylate (265 mg, 0.532 mmol) and 3.98 mL of 4M HCl yielded a white suspension which was stirred at RT under N₂ atmosphere. After 1 hour, the RM was concentrated until dryness, and dried under HV pump. The solid residue was then co-evaporated with DCM (2×) to give a pale yellow powder which was dried at HV over night to yield the final product in 86% purity determined by NMR. The compound was used without further purification in the next reaction. Method LCMS1: Rt = 0.43 min; [M-H]⁺ = 399.2.

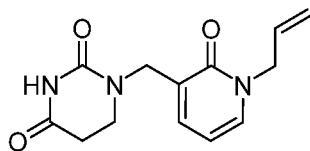
Step 3: *tert*-butyl 4-(3-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)-3-oxopropyl)piperidine-1-carboxylate



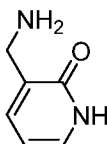
N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)-3-(piperidin-4-yl)propanamide (20 mg, 0.046 mmol) and BODIPY-FL propionic acid (13.43 mg, 0.046 mmol) have been dissolved in DMF (Volume: 0.5 mL) to give a fluorescence reddish solution [commercial, preparation *see* 5 Krajcovicova et al., *Chemistry - A European Journal*, 24(19): 4957-4966 (2018)]. DIPEA (0.060 mL, 0.343 mmol) was added and the reaction was stirred in the dark and was monitored by UPLC/MS after 45 minutes. Trifluoroacetic acid (14.17 μ L, 0.184 mmol) was added until the color changed to greenish. The crude product was submitted for RP purification using the method XS (Sunfire C18 (5 μ m, 30 x 100 mm), 40 mL/min, 29-49% over 16 min, total 21 min). Pure fractions 10 were lyophilized overnight to afford the title compound as bright orange fluffy powder, which turns into fluorescent yellow upon solution in DMSO (27 mg). Method LCMS1: R_t = 0.93 min; $[M-H]^+ = 673.4$.

Example 5: Intermediate Compound Synthesis

ILB-1: 1-((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

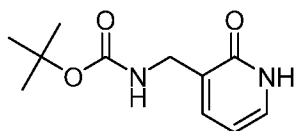


5 **Step 1:** 3-(aminomethyl)pyridin-2(1H)-one



To a 1 L round bottom flask were added 2-oxo-1,2-dihydropyridine-3-carbonitrile (CAS No. [20577-27-9], 12 g, 100 mmol), Raney Ni (3 g), a solution of NH₃ (7 M) in MeOH (100 mL) and MeOH (150 mL). The reaction mixture was stirred under H₂ (1 atm) at RT for 48 h, filtered and
 10 the filtrate was concentrated, yielding a yellow oil (13.5 g), which was used for the next step without further purification. Method A: Rt = 0.48 min; [M+H]⁺ = 125.

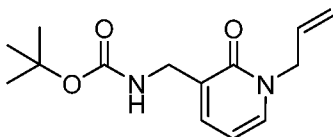
Step 2: *tert*-butyl ((2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate



15 To a 1 L round bottom flask were added 3-(aminomethyl)pyridin-2(1H)-one (13.5 g, 100 mmol), DIEA (25.8 g, 200 mmol), MeOH (200 mL), DCM (300 mL) and di-*tert*-butyl dicarbonate (21.8 g, 100 mmol). The reaction mixture was stirred at RT for 16 h, concentrated and the residue was purified by chromatography on silica gel eluting with MeOH in DCM from 0% to 8% to afford the title compound as an oil (10.0 g). Method B: Rt = 1.61 min; [M+H]⁺ = 225.

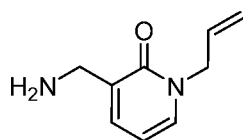
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Step 3: *tert*-butyl ((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate



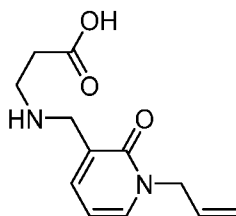
To a 250 mL round bottom flask were added *tert*-butyl ((2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (10.0 g, 45 mmol), K₂CO₃ (12.4 g, 90 mmol), DMF (80 mL) and 3-bromoprop-1-ene (CAS No. [106-95-6], 8.1 g, 67 mmol). The RM was stirred at RT for 16 h, filtered and the filtrate was poured into water (500 mL). The mixture was extracted with EtOAc (4 × 300 mL) and the combined organic phases were dried over Na₂SO₄, yielding the title compound as an oil (14.0 g). Method B: Rt = 1.78 min; [M+H]⁺ = 265.

Step 4: 1-allyl-3-(aminomethyl)pyridin-2(1H)-one



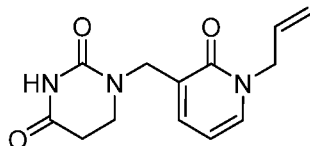
To a 1 L round bottom flask were added *tert*-butyl ((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (14.0 g), DCM (300 mL), and a solution of HCl (4 M) in 1,4-dioxane (50 mL). The reaction mixture was stirred at RT for 16 h, the solvents were removed and the residue was purified by reversed phase chromatography on a Biotage Agela C18 column (120 g, spherical 20–35 μm, 100 Å) eluting with ACN in aq. ammonium hydrogen carbonate (0.1%) from 5% to 40%, yielding the title compound as an oil (7.2 g). Method B: Rt = 1.14 min; [M+H]⁺ = 165.

Step 5: 3-(((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)propanoic acid



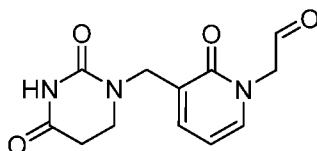
To a 250 mL round bottom flask were added 1-allyl-3-(aminomethyl)pyridin-2(1H)-one (3.28 g, 20 mmol), acrylic acid (4.32 g, 60 mmol) and toluene (100 mL). The RM was stirred at 100 °C for 18 h, concentrated to afford the crude title compound used to the next step without further purification. Method C: Rt = 0.34 min; [M+H]⁺ = 237.

Step 6: 1-(((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione



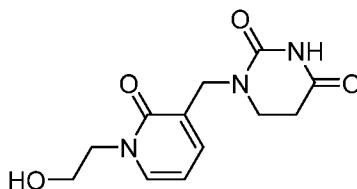
To a 250 mL round bottom flask were added 3-(((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)propanoic acid (8 g), urea (3.6 g, 60 mmol) and acetic acid (40 mL). The reaction mixture was stirred at 120 °C for 18 h, concentrated and the residue was purified by reversed phase chromatography on a Biotage Agela C18 column (120 g, spherical 20–35 μm, 100 Å) eluting with ACN in aq. ammonium hydrogen carbonate (0.1%) from 5% to 50%, yielding the title compound as a solid (3.4 g). Method B: $R_t = 1.40$ min; $[M+H]^+ = 262$.

ILB-2: **2-(3-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)acetaldehyde**



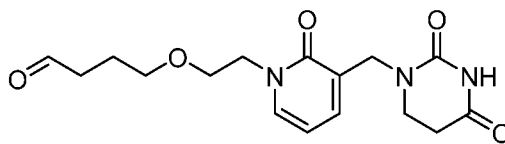
To a 250 mL round bottom flask were added 1-(((1-allyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)di)hydropyrimidine-2,4(1H,3H)-dione (ILB-1, 3.9 g, 15 mmol), THF (120 mL), and a solution of OsO_4 (4%) in water (8 mL). The reaction mixture was stirred under nitrogen atmosphere at RT for 45 min. Solid $NaIO_4$ (9.6 g, 45 mmol) was added and the reaction mixture was stirred under nitrogen atmosphere at RT for 16 h. The mixture was filtered, the solvents were removed and the residue was purified by reversed phase chromatography on a Biotage Agela C18 column (120 g, spherical 20–35 μm, 100 Å) eluting with ACN in aq. ammonium hydrogen carbonate (0.1%) from 0% to 30%, yielding the title compound as a solid (3.6 g). Method D: $R_t = 0.42$ min; $[M+H]^+ = 264$

ILB-3: **1-(((1-(2-Hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)di)hydropyrimidine-2,4(1H,3H)-dione**

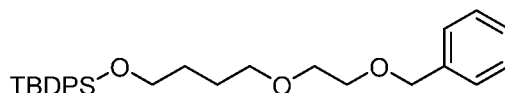


To a mixture of ILB-2 (80 mg, 0.30 mmol) in THF (3 mL) at 25 °C was added NaBH₄ (17 mg, 0.46 mmol) and the reaction mixture was stirred at 25 °C for 0.5 h. The RM was then cooled to 0°C and water (1 mL) was added carefully. The solvent was removed *in vacuo* and the crude mixture was purified by flash chromatography on silica gel eluting with 0–10% MeOH in DCM to afford the desired product, 1-((1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione, as a white solid (52 mg). Method G: Rt = 0.466; [M+H]⁺ = 266. ¹H NMR (500 MHz, DMSO) δ 10.16 (s, 1H), 7.55 (m, 1H), 7.28 (d, J = 6.8 Hz, 1H), 6.20 (t, J = 6.8 Hz, 1H), 4.88 (t, J = 5.4 Hz, 1H), 4.27 (s, 2H), 3.96 (t, J = 5.4 Hz, 2H), 3.62 (q, J = 5.4 Hz, 2H), 3.42 (t, J = 6.8 Hz, 2H), 2.57 (t, J = 6.8 Hz, 2H).

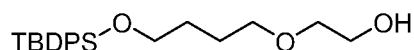
ILB-5: 4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butanal



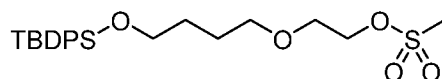
Step 1: 12,12-Dimethyl-1,11,11-triphenyl-2,5,10-trioxa-11-silatrdecane



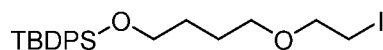
To a solution of 2-(benzyloxy)ethan-1-ol (CAS No. [622-08-2], commercially available, 9.91 g, 65.15 mmol) in THF (150 mL) was slowly added NaH (6.95 g, 173.73 mmol). The reaction mixture was warmed to 80 °C and stirred at this temperature for 1 h. After cooling to RT, (4-bromobutoxy)(*tert*-butyl)diphenylsilane (CAS No. [125010-58-4], *Angew. Chem. Int. Ed.* 54 (51): 15717-15720 (2015), 17 g, 43.43 mmol) was added dropwise. The reaction mixture solution was stirred at 80 °C for 16 h. The reaction mixture was slowly added to water (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine (2 × 60 mL), dried with Na₂SO₄ and concentrated *in vacuo* to obtain crude product. The crude mixture was purified by flash chromatography on silica gel eluting with petroleum ether and a 0–5% gradient of EtOAc yielding of desired product as colorless oil (7 g). Method G: R_f = 2.88 min, [M+NH₄]⁺ = 480.3.

Step 2: 2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethan-1-ol

To a solution of 12,12-dimethyl-1,11,11-triphenyl-2,5,10-trioxa-11-silatridecane (10.8 g, 23.34 mmol) in EtOH/H₂O (100 mL / 4 mL) was slowly added Pd/C (150 mg). The mixture was stirred at 40 °C for 16 h under H₂ atmosphere. The RM solution filtered and the solvent evaporated. The crude mixture was purified by chromatography on silica gel eluting with petroleum ether and a 0–50% gradient of EtOAc yielding the title compound as light yellow oil (8.1 g). Method G: R_f = 2.310 min, [M+H]⁺ = 373.3.

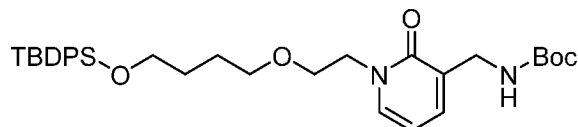
Step 3: 2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethyl methanesulfonate

To a solution of 2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethan-1-ol (8.1 g, 21.74 mmol) and TEA (6.60 g, 65.22 mmol) in DCM (50 mL) was slowly added MsCl (2.49 g, 21.74 mmol) dissolved in DCM (20 mL) via drop funnel at 0 °C. After completed addition, the mixture was stirred for 3 h at 0 °C. Water (20 mL) was added slowly and the mixture was extracted with DCM (3 × 100 mL). The combined organic layers were washed with brine (2 × 50 mL), dried with Na₂SO₄ and concentrated *in vacuo* to afford the crude title compound as a yellow oil (9.23 g) which was used directly in the next step without further purification. Method G: R_f = 2.355 min, [M+NH₄]⁺ = 468.

Step 4: *tert*-butyl(4-(2-iodoethoxy)butoxy)diphenylsilane

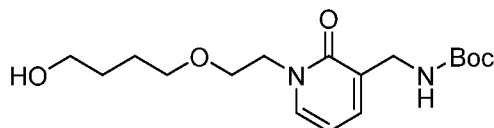
To a solution of 2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethyl methanesulfonate (9.23 g, 20.48 mmol) in MeCN (100 mL) was added KI (34 g, 204.81 mmol) at RT and the mixture was stirred at 80 °C for 16 h. The mixture was poured into water (200 mL), extracted with EtOAc (2 × 100 mL), the combined organic layers were concentrated *in vacuo* to afford the crude title compound as a yellow oil (9.25 g), which was used directly in the next step without further purification. Method G: R_f = 2.879 min, No mass observed (no ionization) purity: 100% (254 nm).

Step 5: *tert*-butyl ((1-(2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate



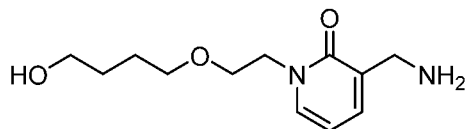
To a solution of *tert*-butyl ((2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (ILB-1 Step 2, 4.3 g, 19.17 mmol) and *tert*-butyl(4-(2-iodoethoxy)butoxy)diphenylsilane (9.25 g, 19.17 mmol) in DMF (20 mL) was added K₂CO₃ (7.95 g, 33.44 mmol) and the mixture was stirred for 16 h at RT. The mixture was poured into water (200 mL), extracted with EtOAc (2 × 100 mL); the combined organic layers were washed with brine (5 × 5 mL) to remove the DMF. The organic layer was concentrated to give the crude product as yellow oil which was purified by flash chromatography on silica gel (petroleum ether, 10% to 60% ethyl acetate) to afford the title compound as light yellow oil (6.3 g). Method G: R_f = 2.48 min, [M+H]⁺ = 579.

Step 6: *tert*-butyl ((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate



TBAF (3.4 g, 13.06 mmol) was added to a solution of *tert*-butyl ((1-(2-(4-((*tert*-butyldiphenylsilyl)oxy)butoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (6.3 g, 10.88 mmol) in 20 mL THF and the mixture was stirred at RT for 2 h. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (10 to 100% EtOAc in petroleum ether followed by 0 to 10% MeOH in DCM) yielding the title compound as light yellow oil (3.3 g). Method G: R_f = 1.56 min, [M+H]⁺ = 341.

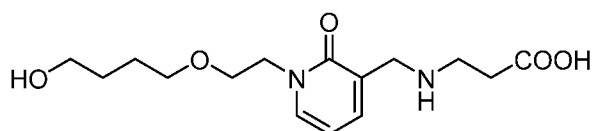
Step 7: 3-(aminomethyl)-1-(2-(4-hydroxybutoxy)ethyl)pyridin-2(1H)-one



To a solution of *tert*-butyl ((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)carbamate (1.8 g, 5.29 mmol) in DCM/MeOH (30 mL / 3 mL) at 0 °C was slowly added

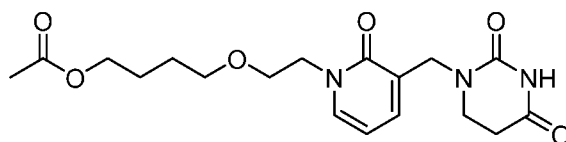
a solution of HCl in 1,4-dioxane (4M) (13.2 mL, 52.9 mmol). The RM was allowed to warm to RT and stirring was continued for 16 h. After removing the volatile components under reduced pressure, the residue was dissolved in H₂O/MeOH (8 mL/2 mL) and the pH was adjusted to 7.0 with aqueous Na₂CO₃ solution. The mixture solution was purified by reverse-phase chromatography using Method PB to afford the title compound as a white solid (800 mg). Method H: R_f = 0.94 min, [M+H]⁺ = 241.3.

Step 8: 3-(((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)propanoic acid



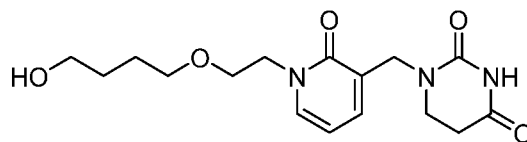
A mixture of 3-(aminomethyl)-1-(2-(4-hydroxybutoxy)ethyl)pyridin-2(1H)-one (1.3 g, 5.42 mmol) and acrylic acid (780 mg, 10.8 mmol) in ACN (30 mL) was stirred at 80 °C for 4 h. The solvent was removed *in vacuo* to afford the title compound as a yellow oil (1.5 g) was used for the next step without further purification. Method H: R_f = 0.89 min, [M+H]⁺ = 313.2.

Step 9: 4-(2-(3-(((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butyl acetate



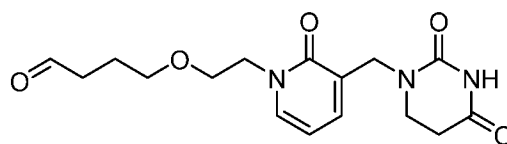
A mixture of 3-(((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)amino)propanoic acid (1.5 g, crude, 4.8 mmol) and urea (1.15 g, 19.2 mmol) in HOAc (20 mL) was stirred at 100 °C for 16 h. The solvent was evaporated and the residue was purified by reverse-phase chromatography using Method PB to afford the title compound as a white solid (800 mg). Method XH: R_f = 1.44 min, [M+H]⁺ = 380.0.

Step 10: 1-(((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione



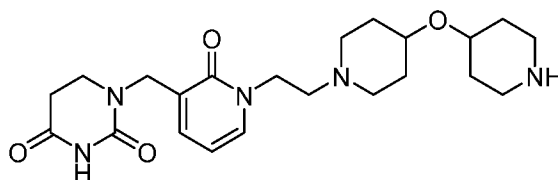
To a solution of 4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butyl acetate (800 mg, 2.11 mmol) in 1,4-dioxane (10 mL) was added HCl (aq., 6 M, 20 mL). The reaction mixture was stirred at 90 °C for 30 min. The volatile components were removed under reduce pressure and the evaporation residue dissolved in water/MeCN (8 mL/2 mL) and the pH value was adjusted to 7.0 with aqueous Na₂CO₃ solution. The crude product solution was purified by reverse-phase chromatography using Method PB to afford the title compound as an off-white solid (600 mg). Method H: R_f = 1.10 min, [M+H]⁺ = 338.3.

Step 11: 4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butanal

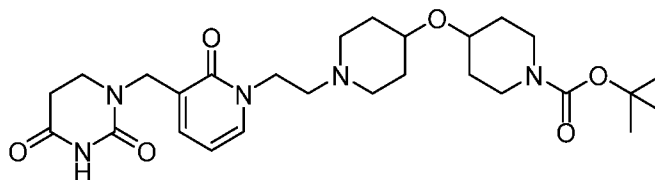


A mixture of 1-((1-(2-(4-hydroxybutoxy)ethyl)-2-oxo-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.593 mmol) and pyridinium chlorochromate (255 mg, 1.187 mmol) in DCM (10 mL) was stirred at RT for 4 h. The solids were removed by filtration and the filtrate was evaporated. The residue after evaporation was purified by reverse-phase chromatography using Method PB to afford the title compound as a light yellow solid (70 mg). Method G: R_f = 1.50 min, [M+H]⁺ = 336.1.

ILB-6: 1-((2-oxo-1-(2-(4-(piperidin-4-yloxy)piperidin-1-yl)ethyl)-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

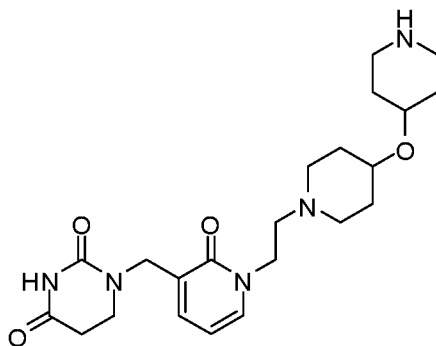


Step 1: *tert*-butyl 4-(1-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethyl)piperidin-4-yloxy)piperidine-1-carboxylate



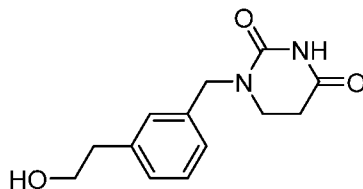
To a 250 mL round bottom flask were added 2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)acetaldehyde (ILB-2, 3.6 g, 13.6 mmol), *tert*-butyl 4-(piperidin-4-yloxy)piperidine-1-carboxylate (CAS No. [845305-83-1], 3.86 g, 13.6 mmol), a solution of ZnCl₂ (1 M) in THF (20.4 mL, 20.4 mmol) and DMSO (40 mL). The RM was stirred at RT for 2 h, solid NaBH₃CN (2.57 g, 40.8 mmol) and MeOH (8 mL) were added, the reaction mixture was stirred at RT for 16 h, concentrated and purified by reverse phase chromatography on a Biotage Agela C18 column (120 g, spherical 20–35 μm, 100 Å) eluting with ACN in aq. ammonium hydrogen carbonate (0.1%) from 5% to 60%, yielding the title compound as a solid (2.8 g). Method A: Rt = 1.81 min; [M+H]⁺ = 532.

Step 2: 1-((2-oxo-1-(2-(4-(piperidin-4-yloxy)piperidin-1-yl)ethyl)-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

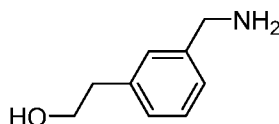


To a 250 mL round bottom flask were added *tert*-butyl 4-(1-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethyl)piperidin-4-yloxy)piperidine-1-carboxylate (2.8 g, 5.2 mmol), DCM (30 mL), and a solution of HCl (4 M) in 1,4-dioxane (10 mL). The reaction mixture was stirred at RT for 6 h, the mixture was concentrated and the residue purified by reversed phase chromatography on a Biotage Agela C18 column (120 g, spherical 20–35 μm, 100 Å) eluting with ACN in aq. ammonium hydrogen carbonate (0.1%) from 0% to 50%, yielding the title compound as a solid (1.8 g). Method B: Rt = 1.36 min; [M+H]⁺ = 432.

ILB-7: 1-(3-(2-Hydroxyethyl)benzyl)dihydropyrimidine-2,4(1H,3H)-dione

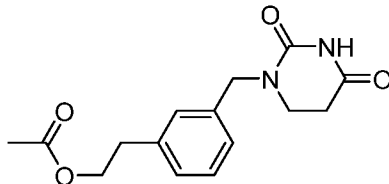


Step 1: 2-(3-(Aminomethyl)phenyl)ethan-1-ol



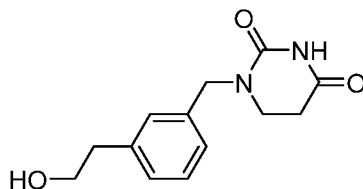
To a solution of ethyl 2-(3-(aminomethyl)phenyl)acetate (600 mg, 4.0 mmol) in THF (30 mL) at 0°C was added dropwise a solution of LiAlH₄ (1M in THF, 8 mL, 8 mmol) and the mixture was stirred at RT for 4h. An aqueous solution of Na₂SO₄ was added dropwise at 0 °C to quench the reaction and the mixture was filtered, then evaporated. The residue was purified by reverse phase chromatography eluting with ACN in an aq. solution of NH₄CO₃H (0.1 %), providing the desired product, 2-(3-(aminomethyl)phenyl)ethan-1-ol (240 mg), as a yellow solid. LCMS Method XJ: Rt = 1.45 min; [M+H]⁺ = 152.

Step 2: 3-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)phenethyl acetate



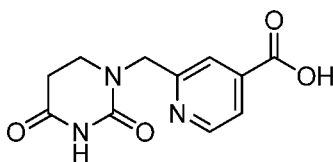
A mixture of 2-(3-(aminomethyl)phenyl)ethan-1-ol (240 mg, 1.6 mmol) and acrylic acid (137 mg, 1.9 mmol) in toluene (10 mL) was heated at 100 °C for 16 h, then cooled to RT. The solvent was removed under vacuum to provide a yellow solid. Acetic acid (5 mL) was added, then urea (384 mg, 6.4 mmol). The reaction mixture was heated at 120 °C for 72 h, then cooled to RT and the acetic acid was removed under vacuum. Purification by reverse phase chromatography, eluting with ACN in an aq. solution of formic acid (0.1 %), provided the desired product (170 mg) as a yellow solid. LCMS Method XJ: Rt = 1.57 min; [M+H]⁺ = 291.

Step 3: 1-(3-(2-Hydroxyethyl)benzyl)dihydropyrimidine-2,4(1H,3H)-dione

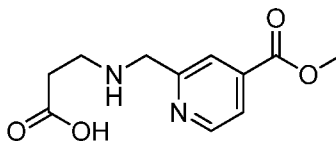


Aqueous hydrochloric acid (6M, 2 mL) was added to 3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)phenethyl acetate (170 mg, 0.6 mmol) in dioxane (4 mL). The reaction mixture was stirred at 80 °C for 1 h, then cooled to RT. The solvent was removed under vacuum and the residue was purified by reverse phase chromatography (Method PB) eluting with ACN in an aq. solution of $\text{NH}_4\text{CO}_3\text{H}$ to provide the title compound (50 mg) as a white solid. LCMS Method XE: $R_t = 1.27$ min; $[\text{M}+\text{H}]^+ = 249$. ^1H NMR (500 MHz, DMSO) δ 7.25 (t, $J = 7.9$ Hz, 1H), 7.13-7.09 (m, 3H), 4.63 (br. s, 1H), 4.49 (s, 2H), 3.60-3.57 (m, 2H), 3.27 (t, $J = 6.8$ Hz, 2H), 2.71 (t, $J = 7$ Hz, 2H), 2.53 (t, $J = 6.8$ Hz, 2H).

ILB-8: 2-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)isonicotinic acid

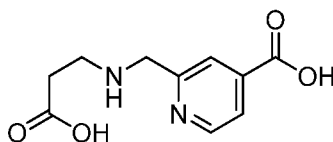


Step 1: 3-(((4-(Methoxycarbonyl)pyridin-2-yl)methyl)amino)propanoic acid



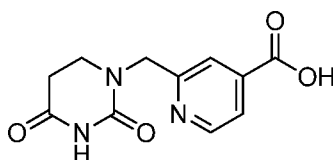
To a mixture of methyl 2-cyanoisonicotinate (7 g, 43.2 mmol) in MeOH (100 mL) was added Pd/C (500 mg) and conc. HCl (5 mL). The mixture was then stirred at 30 °C for 2 hours under a H_2 (15 psi) atmosphere. The mixture was filtered to remove Pd/C, then the filtrate was concentrated under reduced pressure to give methyl 2-(aminomethyl)isonicotinate (7 g, crude) as a yellow solid. To this material (7 g, 42.1 mmol), which was used without further purification, was added MeCN (35 mL), water (7 mL) and finally acrylic acid (3.96 g, 54.7 mmol). The mixture was stirred at 80 °C for 16 hrs, then the mixture was concentrated under vacuum to dryness. The solid was purified by flash column chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0-100% DCM/MeOH) to afford the title compound 3-(((4-(methoxycarbonyl)pyridin-2-yl)methyl)amino)propanoic acid as yellow oil (5 g, 92 % purity). Method LCMS10: $R_t = 0.26$ min; $[\text{M}+\text{H}]^+ = 239.0$.

Step 2: 2-(((2-Carboxyethyl)amino)methyl)isonicotinic acid



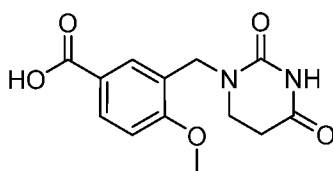
To a solution of 3-(((4-(methoxycarbonyl)pyridin-2-yl)methyl)amino)propanoic acid (2 g, 8.39 mmol) in MeOH (5 mL) was added THF (5 mL), H₂O (5 mL) and LiOH (1.01 g, 42 mmol). The mixture was stirred at 25 °C for 12 hours. The mixture was then concentrated to afford the crude
 5 2-(((2-carboxyethyl)amino)methyl)isonicotinic acid (2 g) as a yellow solid. Method LCMS10: Rt = 0.13 min; [M+H]⁺ = 225.0.

Step 3: 2-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)isonicotinic acid

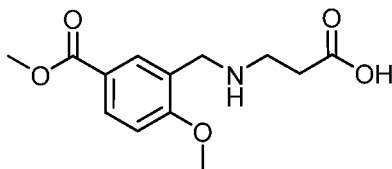


To a solution of 2-(((2-carboxyethyl)amino)methyl)isonicotinic acid (2 g, 8.92 mmol) in HOAc (20 mL) was added urea (1.61 g, 26.8 mmol) at 25 °C. The reaction mixture was then heated with
 10 stirring at 100 °C for 12 hours. After cooling to RT, the reaction mixture was concentrated in vacuum to remove the HOAc to afford an oil (2.5g, crude). The oil was purified by flash silica gel chromatography (ISCO[®]; 10 g SepaFlash[®] Silica Flash Column, Eluent of 0-100% DCM/MeOH) to afford, after lyophilization, a yellow solid (500 mg, 91% purity). This product was further
 15 purified by Prep-HPLC (Method PA2) to afford the title compound, 2-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)isonicotinic acid which was obtained as a white solid (156 mg, 0.6 mmol, 97.8 % purity). Method LCMS11: Rt = 2.66 min; [M+H]⁺ = 250.1. ¹H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 8.75 - 8.69 (m, 1H), 7.74 - 7.70 (m, 2H), 4.71 (s, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.59 (t, J = 6.8 Hz, 2H).

ILB-9: 3-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)-4-methoxybenzoic acid

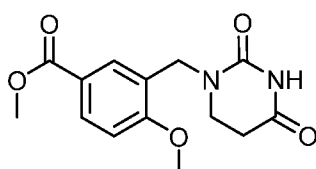


Step 1: 3-((2-Methoxy-5-(methoxycarbonyl)benzyl)amino)propanoic acid



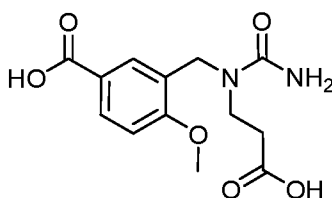
A mixture of methyl 3-(aminomethyl)-4-methoxybenzoate (CAS [771579-95-4], 1.90 g, 9.73 mmol) and acrylic acid (2.004 mL, 29.2 mmol) in toluene (48.7 mL) was stirred at 100 °C overnight. The RM was concentrated to dryness to afford the title compound as a yellow resin (3.75g). Method LCMS7: Rt = 0.41 min; [M+H]⁺ = 268.

Step 2: Methyl 3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-4-methoxybenzoate



Under argon, a mixture of 3-((2-methoxy-5-(methoxycarbonyl)benzyl)amino)propanoic acid (3.7 g, 13.84 mmol) and urea (1.663 g, 27.7 mmol) in acetic acid (18.5 mL) was stirred at 120 °C overnight. The mixture was cooled to RT, then mixed with ca. 100 mL ice and 20 mL conc. HCl. The opaque beige mixture was left to stir for 30 min, then stored in the fridge overnight. The cooled mixture was filtered, the residue washed with a little water, then Et₂O, then dried under high vacuum to afford 1.82 g of the desired product as an off-white solid. Method LCMS7: Rt = 0.69 min; [M+H]⁺ = 293

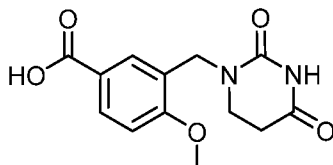
Step 3: 3-((1-(2-Carboxyethyl)ureido)methyl)-4-methoxybenzoic acid



A solution of lithium hydroxide monohydrate (CAS [1310-66-3], 2.58 g, 61.6 mmol) in water (30.8 mL) was added to a mixture of methyl 3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-4-methoxybenzoate (1.80 g, 6.16 mmol) in THF (30.8 mL). The mixture was stirred for 2.5 h at RT. The THF was then removed under reduced pressure and the aqueous layer was washed with DCM, then acidified with 1N HCl to ca. pH3 (a white precipitate emerged on standing for few minutes). The mixture was then sonicated and filtered. The residue washed with water, then Et₂O,

then dried to afford 1.69 g of the product as an off-white solid. Method LCMS7: $R_t = 0.54$ min; $[M+H]^+ = 297$

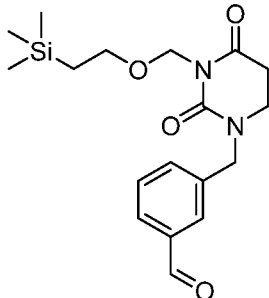
Step 4: 3-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)-4-methoxybenzoic acid



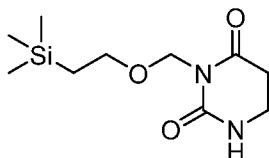
- 5 A mixture of 3-((1-(2-carboxyethyl)ureido)methyl)-4-methoxybenzoic acid (1.52 g, 5.13 mmol) in conc. HCl (15.6 mL, 513 mmol) was stirred for 1 hour at 100 °C. The mixture was then cooled to RT and diluted with ice water. The precipitate was filtered off, washed with water and Et₂O, then dried to afford 1.23 g of the desired product as white solid. Method LCMS7: $R_t = 0.60$ min; $[M+H]^+ = 279$

10

ILB-10: **3-((2,4-Dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)tetrahydropyrimidin-1(2H)-yl)methyl)benzaldehyde**



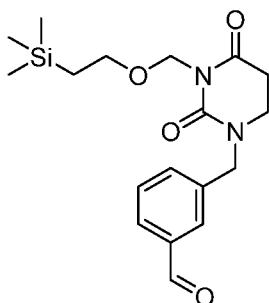
- 15 **Step 1:** 3-((2-(trimethylsilyl)ethoxy)methyl)dihydropyrimidine-2,4(1H,3H)-dione



- To a 100 mL round bottom flask were added under an argon atmosphere dihydropyrimidine-2,4(1H,3H)-dione (2.7 g, 23.66 mmol) and DMPU (35 mL). A solution of LiHMDS (1M) in THF (25 mL, 25.00 mmol) was added and the RM was vigorously stirred at 60 °C for 40 min. The RM was cooled to RT, 2-(trimethylsilyl)ethoxymethyl chloride (5 mL, 28.20 mmol) was added and the RM was stirred at 60 °C for 18 h. The RM was diluted with a sat. solution of NaHCO₃ and brine,
- 20

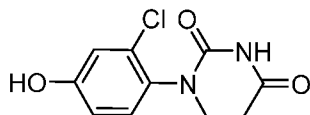
the mixture was extracted with EtOAc, the combined organic phases were washed with water and brine, dried over MgSO_4 and the residue was purified by chromatography on silica gel eluting with EtOAc (from 0% to 100%) in CHX followed by MeOH (from 0% to 20%) in EtOAc, yielding the title compound as an oil (4.7 g). Method LCMS4: $R_t = 0.76$ min; $[\text{M}-\text{H}]^+ 243$.

5
Step 2: 3-((2,4-dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)tetrahydropyrimidin-1(2H)-yl)methyl)benzaldehyde

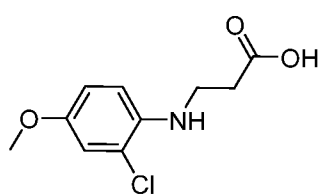


To a 10 mL round bottom flask were added under an argon atmosphere 3-((2-
 10 (trimethylsilyl)ethoxy)methyl)dihydropyrimidine-2,4(1H,3H)-dione (150 mg, 0.602 mmol) and DMF (3 mL). The mixture was cooled to 0 °C, solid NaH (60% dispersion in mineral oil, 16 mg, 25.0 mmol) was added and the mixture was stirred at RT for 10 min. 3-(Bromomethyl)-benzaldehyde (132 mg, 0.632 mmol) was added and the RM was stirred at RT for 2 h. An aq. sat. solution of NH_4Cl and water were added, the aq. phase was extracted with EtOAc, and the
 15 combined organic phases were washed with brine, dried over MgSO_4 and the residue was purified by reversed phase chromatography on a RediSep[®] Gold HP C18 column (15.5 g) eluting with ACN (from 1% to 100%) in an aq. solution of NH_4HCO_3 (0.1%), yielding the title compound as an oil (62 mg). Method LCMS1: $R_t = 1.06$ min; $[\text{M}+\text{H}]^+ = 380$.

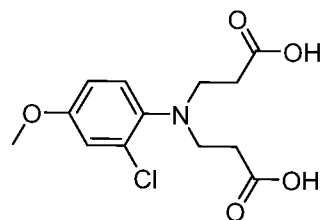
20 **ILB-12: 1-(2-chloro-4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione**



Step 1: 3-((2-chloro-4-methoxyphenyl)amino)propanoic acid, 3,3'-((2-chloro-4-methoxyphenyl)azanediyl)dipropanoic acid



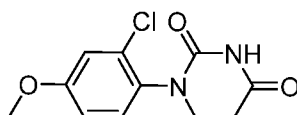
Structure I



Structure II

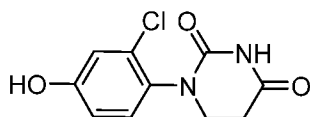
A mixture of 4-methoxy-2-methylaniline (4.82 g, 30.6 mmol) and acrylic acid (8.40 mL, 122 mmol) in Toluene (Volume: 10 mL) was heated for 1 h at 100 °C. After 1.5 h, the RM was evaporated to dryness to obtain 7.02g of a mixture of Structure I and II as a black resin. UPLC-MS showed 47% structure I / 19% structure II. Method LCMS1 for structure I: Rt = 0.78 min; [M+H]⁺ = 230.1. Method LCMS1 for structure II: Rt = 0.84 min; [M+H]⁺ = 302.1.

Step 2: 1-(2-chloro-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



To a mixture of 3-((2-chloro-4-methoxyphenyl)amino)propanoic acid, 3,3'-((2-chloro-4-methoxyphenyl)azanediyl)dipropionic acid (7.02 g, 30.6 mmol) in toluene (35 mL, ratio: 1.0) / acetic acid (35.0 mL, ratio: 1.0) was added urea (9.18 g, 153 mmol). The RM was heated overnight at 120 °C. The RM was evaporated to dryness. The greasy residue was poured into 300 mL ice and stirred until reaching room temperature. The formed precipitate was filtered off and washed with water. The filter cake was washed with diisopropyl ether before drying overnight *in vacuo* at 50 °C to afford the title compound as a violet solid (5.11 g). Method LCMS1: Rt = 0.66 min; [2M+H]⁺ = 509.2.

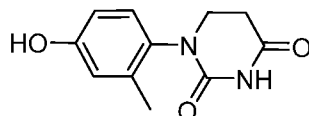
Step 3: 1-(2-chloro-4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



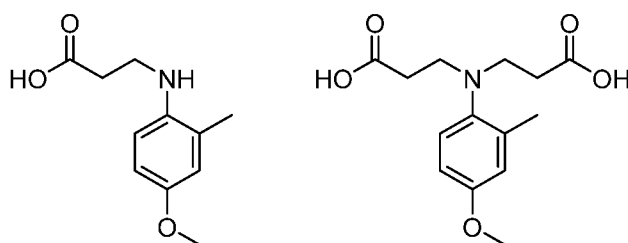
To a mixture of 1-(2-chloro-4-methoxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (2.29 g, 8.27 mmol) in DCM (40 mL) was added dropwise BBr₃ 1 M in CH₂Cl₂ (23.16 mL, 23.16 mmol) at RT. The RM was stirred at room temperature for 1.5 h. The RM was evaporated and absorbed on silica

gel and purified by flash chromatography on a Silica flash column 24 g eluting with DCM/MeOH to afford the title compound (1.69 g). Method LCMS1: $R_t = 0.47$ min; $[M-H]^+ = 239.1$.

ILB-13: 1-(4-hydroxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione

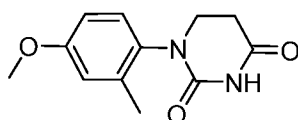


5 **Step 1:** 3-((4-Methoxy-2-methylphenyl)amino)propanoic acid, 3,3'-((4-methoxy-2-methylphenyl)azanediyl)dipropionic acid

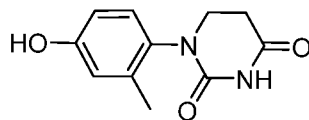


10 A mixture of 4-methoxy-2-methylaniline (4.82 g, 35.1 mmol) and acrylic acid (9.65 mL, 141 mmol) in toluene (10 mL) was heated for 1.5 h at 100 °C. The RM was evaporated to dryness to obtain a black resin. The black resin was used directly in 1-(4-methoxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione. Method LCMS1: $R_t = 0.53$ min; $[M+H]^+ = 210.1$ structure I. Method LCMS1: $R_t = 0.49$ min; $[M+H]^+ = 282.2$ structure II.

15 **Step 2:** 1-(4-methoxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione

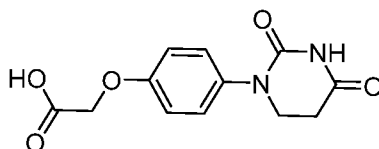


20 To a mixture of 3-((4-methoxy-2-methylphenyl)amino)propanoic acid (7.34 g, 35.1 mmol) in toluene (35 mL, ratio: 1.0) / acetic acid (35.0 mL, ratio: 1.0) was added urea (10.54 g, 176 mmol). The RM was heated overnight at 120 °C. The RM was evaporated to dryness. The greasy residue was poured into 300 mL ice and stirred until reaching room temperature. The formed precipitate was filtered off and washed well with water. The cake was taken up in diisopropyl ether (soluble in acetonitrile) and filtered before drying overnight *in vacuo* at 50 °C to afford the title compound as a violet solid (4.34 g). Method LCMS1: $R_t = 0.61$ min; $[M+H]^+ = 235.1$.

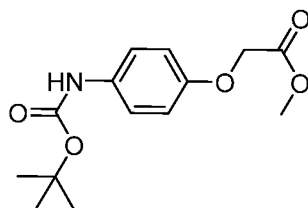
Step 3: 1-(4-hydroxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione

To a mixture of 1-(4-methoxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (2.5 g, 10.03 mmol) in DCM (30 mL) was added dropwise BBr_3 1 M in CH_2Cl_2 (27.1 mL, 27.1 mmol) at RT.

- 5 The RM was stirred at RT for 2 h. The RM was evaporated to dryness. The residue was used without purification in 1-(4-hydroxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione. Method LCMS1: $R_t = 0.43$ min; $[\text{M}+\text{H}]^+ = 221.1$.

ILB-14: 2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid

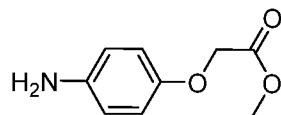
10

Step 1: Methyl 2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)acetate

To a solution of *tert*-butyl (4-hydroxyphenyl)carbamate (7 g, 31.8 mmol) in acetone (75 mL) was added cesium carbonate (11.4 g, 35 mmol) and potassium iodide (50 mg, 0.301 mmol). Methyl bromoacetate (3 mL, 32.6 mmol) was added and the RM was stirred at reflux for 4 h. The RM was cooled to RT, filtered and the filtrate was concentrated to dryness. The residue was dissolved in EtOAc and washed with sat. aq. NaHCO_3 sol., dried over MgSO_4 , and concentrated to dryness. The residue was purified by chromatography on silica gel eluting with EtOAc in CHX (from 10% to 25%) yielding the title compound as a white solid (8.83 g). Method LCMS1: $R_t = 0.97$ min; $[\text{M}+\text{H}]^+ = 282.2$.

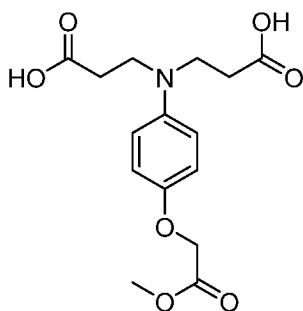
20

Step 2: Methyl 2-(4-aminophenoxy)acetate



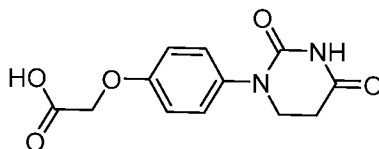
To a solution of methyl 2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)acetate (8.83 g, 31.4 mmol) in 1,4-dioxane (30 mL) was added TFA (30 mL). The RM was stirred at RT overnight. The RM was concentrated to dryness and the residue dissolved in DCM. The organic phase was washed
 5 with sat. aq. NaHCO₃ sol., dried over MgSO₄, and concentrated to dryness to afford the title compound as an oil (5.35 g). Method LCMS1: Rt = 0.37 min; [M+H]⁺ = 182.1.

Step 3: 3,3'-((4-(2-Methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid

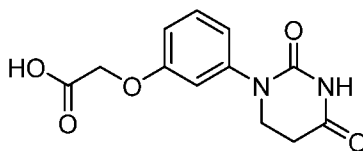
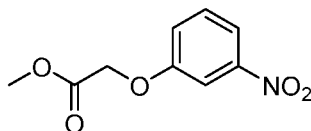


To a solution of methyl 2-(4-aminophenoxy)acetate (5347 mg, 25.7 mmol) in water (5 mL) at RT was added acrylic acid (11 mL, 160 mmol). The RM was stirred at 70 °C for 90 min. The RM was cooled to RT and adsorbed onto silica gel. The crude material was purified by chromatography on silica gel eluting with iPrOH in DCM (from 0% to 10%) yielding the title compound as a grey solid (8.24 g). Method LCMS1: Rt = 0.47 min; [M+H]⁺ = 326.2.

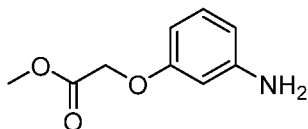
Step 4: 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid



A suspension of 3,3'-((4-(2-methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid (8243 mg, 25.09 mmol) and urea (2260 mg, 37.6 mmol) in AcOH (60 mL) was stirred at 120 °C overnight.
 20 The RM was cooled to 0 °C and filtered to afford the title compound as an off-white solid (4.93 g). Method LCMS2: Rt = 0.75 min; [M+H]⁺ = 265.2.

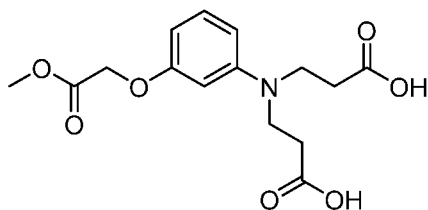
ILB-16: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid**Step 1: Methyl 2-(3-nitrophenoxy)acetate**

- 5 To a mixture of 3-nitrophenol (3.0 g, 21.57 mmol) and K_2CO_3 (4.0 g, 28.9 mmol) in acetone (10 mL) was added methyl bromoacetate (2.58 mL, 28.1 mmol) dropwise at RT. The mixture was stirred at 70 °C for 6 h. The RM was cooled to RT and diluted with water (40 mL). The resulting mixture was filtered and the filter cake was dried under HV, yielding the title compound as a slightly orange powder (4323 mg). ^1H NMR (400 MHz, $DMSO-d_6$) δ 7.85 (m, 1H), 7.73 (m, 1H),
 10 7.59 (m, 1H), 7.45 (m, 1H), 4.99 (s, 2H), 3.72 (s, 3H).

Step 2: Methyl 2-(3-aminophenoxy)acetate

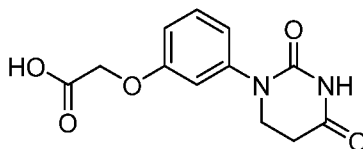
- To a solution of methyl 2-(3-nitrophenoxy)acetate (1000 mg, 4.74 mmol) in MeOH (30 mL) at RT
 15 under argon was added palladium 10% on carbon (150 mg, 1.41 mmol). The flask was purged twice with argon and replaced three times by hydrogen gas taken from a balloon. The RM was stirred at RT for 22 h. The RM was diluted with MeOH (25 mL), filtered through Hyflow Super Cel[®], and rinsed with MeOH (2×20 mL). The filtrate was concentrated. The residue was purified by filtration over silica gel 60 (230–400 mesh) using DCM/2% MeOH as eluent (3×50 mL),
 20 yielding the title compound as a brown oil (875 mg). Method LCMS1: R_t = 0.57 min; $[M+H]^+$ = 182.0.

Step 3: 3,3'-((3-(2-Methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid



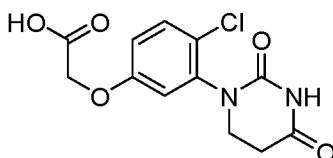
To a mixture of methyl 2-(3-aminophenoxy)acetate (800 mg, 4.42 mmol) in H₂O (0.5 mL) was added acrylic acid (1.740 mL, 27.8 mmol) at RT. The RM was stirred at 70 °C under argon for 1.5 h. The residue was purified by chromatography on silica gel eluting with iPrOH in DCM (from 0.4% to 20%) yielding the title compound (1.30 g). Method LCMS1: Rt = 0.66 min; [M+H]⁺ = 326.1.

Step 4: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid

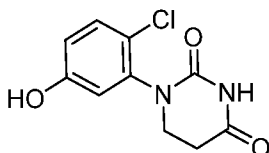


A mixture of 3,3'-((3-(2-methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid (1.30 g, 4.00 mmol) and urea (0.360 g, 5.99 mmol) in AcOH (8 mL) was stirred at 120 °C under argon overnight. A 10% aq. HCl sol. (20 mL) was added and the RM was refluxed for 1 h. The RM was cooled to RT and evaporated to dryness. The remaining solid was suspended in 10% aq. HCl sol, cooled to 0 °C and filtered yielding the title compound as a beige solid (575 mg). Method LCMS1: Rt = 0.43 min; [M+H]⁺ = 265.1.

ILB-17: 2-(4-Chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid

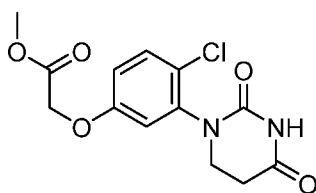


Step 1: 1-(2-Chloro-5-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



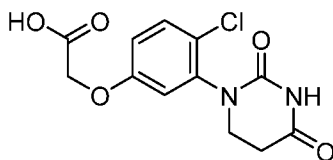
To a mixture of 3-amino-4-chlorophenol (1436 mg, 10.00 mmol) in H₂O (1 mL) was added acrylic acid (2.057 mL, 30.00 mmol) at RT. The RM was stirred at 70 °C under argon for 5.5 h. The RM was cooled to RT and dried. The residue was diluted in AcOH (15 mL). Urea (901 mg, 15.00 mmol) was added and the RM was stirred at 130 °C under argon overnight. Urea (500 mg, 8.33 mmol) was added and the RM was stirred at 130 °C under argon for 4.5 h. Urea (1000 mg, 16.65 mmol) was added and the RM was stirred at 130 °C under argon overnight. The RM was cooled to RT. 10% aq. HCl (20 mL) was added and the RM was refluxed for 30 min. The RM was cooled to RT and partially evaporated. EtOH (20 mL) was added and the mixture was cooled to 0 °C for 20 min and filtered. The filtrate was partially evaporated, adsorbed on Isolute[®] and purified by chromatography on silica gel eluting with EtOAc in CHX (from 80% to 100%). Fractions containing target compound were combined, evaporated, and recrystallized from hot acetone yielding the title compound as a white powder (1.09 g). Method LCMS1: Rt = 0.53 min; [M+H]⁺ = 241.1.

Step 2: Methyl 2-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetate



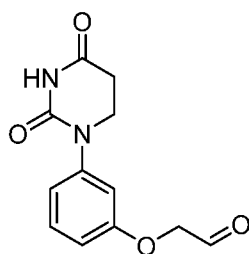
To a solution of 1-(2-chloro-5-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (353 mg, 1.467 mmol) and cesium carbonate (478 mg, 1.467 mmol) in DMF (15 mL) was added methyl 2-bromoacetate (0.135 mL, 1.467 mmol) at RT. The RM was stirred at RT overnight, concentrated, adsorbed on Isolute[®] and purified by chromatography on silica gel eluting with EtOAc in hexane (from 20% to 100%) and then with AcOH (from 0% to 1%), yielding the title compound as a white powder (400 mg). Method LCMS1: Rt = 0.97 min; [M+H] = 313.1.

Step 3: 2-(4-Chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid

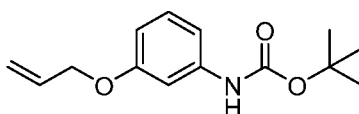


To a mixture of methyl 2-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetate (310 mg, 0.991 mmol) in THF (6 mL) was added lithium hydroxide monohydrate (74.9 mg, 1.784 mmol) at RT under argon. The RM was stirred at RT for 30 min. An aq. solution of HCl 1 M was added and the RM was concentrated to remove THF. The resulting white suspension was diluted with a cold 0.1N HCl solution and filtered off. The filter cake was washed with water and dried yielding the title compound as a white solid (222 mg). Method LCMS1: Rt = 0.48 min; [M+H]⁺ = 299.1.

ILB-18: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde

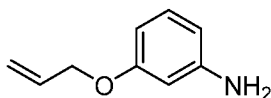


Step 1: *tert*-Butyl (3-(allyloxy)phenyl)carbamate



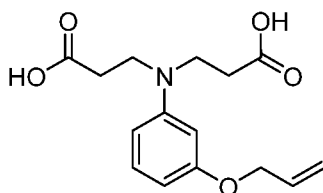
To a solution of *tert*-butyl (3-hydroxyphenyl)carbamate (CAS No. [19962-06-2], commercially available, 5.025 g, 24.02 mmol) in DMF (200 mL) under argon at RT was added potassium carbonate (5.0 g, 36.2 mmol) followed by allyl bromide (CAS No. [106-95-6], commercially available, 2.4 mL, 28.4 mmol) which was added dropwise. The resulting RM was stirred for 3 days at RT and was filtered then rinsed with diethyl ether. The filtrate was taken up in Et₂O and washed with a large amount of water and then with brine. The organic phase was dried over MgSO₄ and then evaporated to dryness to afford the title compound as a pale beige solid (5.59 g). Method LCMS1: Rt = 1.20 min; [M+H]⁺ = 250.

Step 2: 3-(Allyloxy)aniline



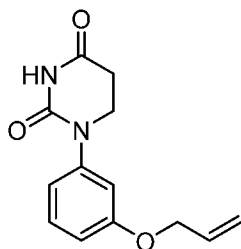
To a solution of *tert*-butyl (3-(allyloxy)phenyl)carbamate (5.547 g, 21.14 mmol) in DCM (80 mL) was added TFA (8.0 mL, 104 mmol). The resulting solution was stirred at RT overnight. RM was concentrated *in vacuo*. The crude was taken up in DCM and washed with sat. bicarbonate aq. solution. The organic layer was dried over MgSO₄ and evaporated to dryness to afford the title compound (3181 mg). Method LCMS1: Rt = 0.74 min; [M+H]⁺ = 150.1.

Step 3: 3,3'-((3-(Allyloxy)phenyl)azanediyl)dipropionic acid



To a suspension of 3-(allyloxy)aniline (CAS No. [74900-81-5], commercially available, 3174 mg, 18.51 mmol) in water (5 mL) was added acrylic acid (CAS No. [79-10-7], commercially available, 8 mL, 117 mmol) at RT and the RM was heated at 70 °C under argon for 1.5 h. The RM was allowed to cool to RT and adsorbed on Isolute[®] and purified by normal phase flash chromatography eluting with methanol in DCM (from 0 to 10%) to afford the title compound as a brown foam (5.27 g). Method LCMS1: Rt = 0.79 min; [M+H]⁺ = 294.1.

Step 4: 1-(3-(Allyloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

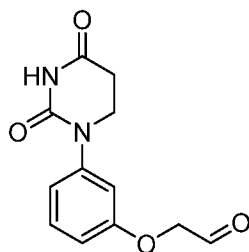


A suspension of 3,3'-((3-(allyloxy)phenyl)azanediyl)dipropionic acid (5.27 g, 16.89 mmol) and urea (1.5 g, 24.98 mmol) in AcOH (20 mL) was heated at 120 °C under argon overnight. The RM was partially evaporated and then allowed to cool to RT. 10% aq. HCl solution was added and the RM was cooled to 0 °C and then filtered over a P4 filter frit. 3105 mg of the solid containing about 55% of the product was obtained. The filtrate also contained about 56% of the product. They were both purified separately. The solid was purified by normal phase flash chromatography eluting with methanol in DCM (from 0 to 10%) to afford the title compound as a yellow solid (2383 mg

but with about 75% purity). The filtrate was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 90%) to afford, after freeze drying, 1213 mg of the title compound (purity 95%). Method LCMS1: Rt = 0.74 min; [M+H]⁺ = 247.1.

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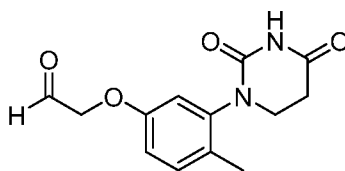
Step 5: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde



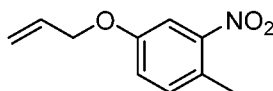
A solution of 1-(3-(allyloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (460 mg, 1.775 mmol) in anhydrous DCM (10.0 mL) was cooled to -78 °C. Ozone generator was used and the resulting RM was stirred for 10 min. The RM was allowed to warm up to RT and triphenylphosphine polymer bound (2218 mg, 7.10 mmol) was added to destroy ozonolides. RM was stirred for 30 minutes at RT and then filtered over Celite® filter aid and washed with DCM to remove triphenylphosphine oxide. The filtrate was evaporated to dryness yielding the title compound as a white solid (435 mg). Method LCMS2: Rt = 0.76 min; [M+H]⁺ = 249.1.

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ILB-19: 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetaldehyde



Step 1: 4-(allyloxy)-1-methyl-2-nitrobenzene

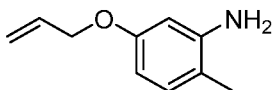


A mixture of 4-methyl-3-nitrophenol (CAS No. [2042-14-0], 15.3 g, 100 mmol) and K₂CO₃ (27.8 g, 200 mmol) in ACN (100 mL) was stirred at RT, then allyl bromide (CAS No. [106-95-6], 15.5 g, 130 mmol) was added, and the mixture was stirred at RT for 16 h. The mixture was filtered and

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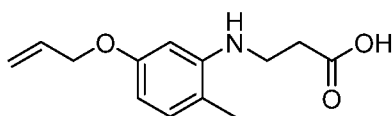
the resulting solution was concentrated *in vacuo* to afford the title compound 4-(allyloxy)-1-methyl-2-nitrobenzene as a yellow oil (19 g). Method XF: $R_t = 1.39$ min.

Step 2: 5-(allyloxy)-2-methylaniline



5 A mixture of 4-(allyloxy)-1-methyl-2-nitrobenzene (19 g, 100 mmol) and Zn (39 g, 600 mmol) in EtOH (250 mL) was stirred at RT, then AcOH (9 g, 75 mmol) was added and the mixture was stirred at RT for 16 h. After filtration, the solution was concentrated *in vacuo*, the residue was poured into EtOAc (500 mL), and water (200 mL) was added. The mixture was basified with
10 K_2CO_3 to reach pH = 9. The organic layer was separated, dried over Na_2SO_4 , and concentrated *in vacuo* to afford the title compound 5-(allyloxy)-2-methylaniline as a yellow solid (17.4 g). Method XF: $R_t = 1.13$ min; $[M+H]^+ = 164$.

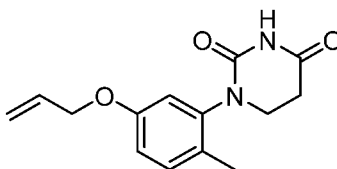
Step 3: 3-((5-(allyloxy)-2-methylphenyl)amino)propanoic acid



15 A mixture of 5-(allyloxy)-2-methylaniline (17.4 g, 100 mmol) and acrylic acid (CAS No. [79-10-7], 12.4 g, 200 mmol) in toluene (50 mL) was stirred at 100 °C for 16 h. The solvent was removed *in vacuo* to afford the title compound 3-((5-(allyloxy)-2-methylphenyl)amino)propanoic acid as a brown oil (26 g). Method XF: $R_t = 0.78$ min; $[M+H]^+ = 236$.

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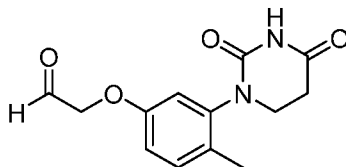
Step 4: 1-(5-(allyloxy)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione



A mixture of 3-((5-(allyloxy)-2-methylphenyl)amino)propanoic acid (26 g, 100 mmol) and urea (CAS No. [57-13-6], 48 g, 800 mmol) in AcOH (500 mL) was stirred at 120 °C for 30 h. The
25 solvent was removed *in vacuo*, the residue was poured into water (500 mL) and the resulting mixture was adjusted to pH = 7 with $NaHCO_3$. Then the solid was filtered, washed with water and

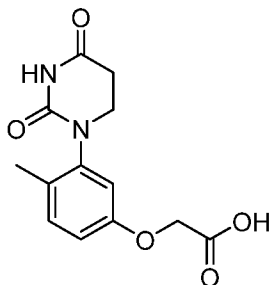
MTBE to afford the title compound as a light pink solid (16 g). Method XF: $R_t = 1.05$ min; $[M+H]^+ = 261$.

Step 5: 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetaldehyde

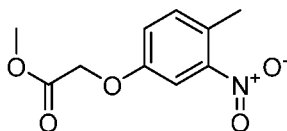


5 A mixture of 1-(5-(allyloxy)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (8 g, 30 mmol) in DCM (200 mL) was stirred at -78 °C, then bubbled with O_3 for 20 min. The mixture was then bubbled with N_2 at -78 °C for 30 min, Me_2S (15 mL) was added and the mixture was stirred at -78 °C for 2 h. The solvent was removed and the residue was purified by flash
10 chromatography on silica gel eluting with a 1:3 mixture of THF in DCM to afford the title compound as a white solid (6.1 g). Method XF: $R_t = 0.65$ min; $[M+H]^+ = 263$. ^1H NMR (500 MHz, $DMSO-d_6$) δ 10.34 -10.30 (m, 1 H) 9.67 (s, 1 H) 7.18–7.16 (m, 1 H) 6.97–6.75 (m, 2 H) 4.84–4.64 (m, 2 H) 3.77–3.75 (m, 1 H) 3.51-3.47 (m, 1H) 2.74–2.64 (m, 2 H) 2.10 (s, 3 H).

15 **ILB-20: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetic acid**



Step 1: Methyl 2-(4-methyl-3-nitrophenoxy)acetate

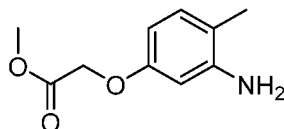


To a solution of 4-methyl-3-nitrophenol (6.34 g, 41.4 mmol) in acetone (140 mL) was added cesium carbonate (2023 g, 62.1 mmol). Methyl bromoacetate (5.10 mL, 53.8 mmol) was added
20 and the RM was stirred at 50 °C for 1 h. The RM was cooled to RT, and diluted with water and extracted with Et_2O three times. The organic phase was washed with brine, dried over $MgSO_4$ and

concentrated. The crude was purified by chromatography on silica gel eluting with MeOH in DCM (from 0% to 12.5%) yielding the title compound as a beige solid (1183 mg). ^1H NMR (400 MHz, DMSO- d_6) δ 7.51 (d, J = 2.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.24 (dd, J = 8.5, 2.9 Hz, 1H), 4.90 (s, 2H), 3.69 (s, 3H), 2.41 (s, 3H).

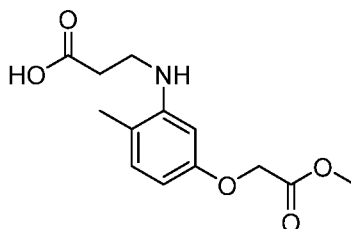
5

Step 2: Methyl 2-(3-amino-4-methylphenoxy)acetate



To a solution of methyl 2-(4-methyl-3-nitrophenoxy)acetate (9120 mg, 39.6 mmol) in MeOH (100 mL) at RT under argon was added palladium 10% on carbon (421 mg, 0.396 mmol). The RM was stirred at RT under hydrogen atmosphere for 18 h. The RM was filtered through Celite[®] filter aid and rinsed with MeOH. The filtrate was concentrated, yielding the title compound (7411 mg), directly used in next step without further purification. Method LCMS1: R_t = 0.70 min; $[M+H]^+$ = 196.2.

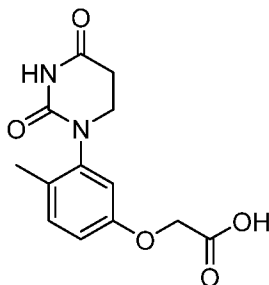
15 **Step 3:** 3-((5-(2-Methoxy-2-oxoethoxy)-2-methylphenyl)amino)propanoic acid



To a mixture of methyl 2-(3-amino-4-methylphenoxy)acetate (7350 mg, 35.0 mmol) in H₂O (10 mL) was added acrylic acid (15 mL, 219 mmol) at RT. The RM was stirred at 70 °C overnight. The residue was cooled to RT, adsorbed on Isolute[®], and purified by chromatography on silica gel eluting with MeOH in DCM (from 0% to 25%) yielding the title compound (23.7 g). Method LCMS1: R_t = 0.76 min; $[M+H]^+$ = 268.2.

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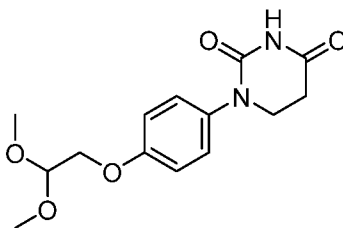
Step 4: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetic acid



A mixture of 3-((5-(2-methoxy-2-oxoethoxy)-2-methylphenyl)amino)propanoic acid (23.7 g, 35.00 mmol) and urea (3.15 g, 52.5 mmol) in AcOH (60 mL) was stirred at 120 °C under argon overnight. An HCl solution 4 M in water (50 mL) was added and the RM was refluxed for 45 min.

5 The RM was cooled to RT, then stirred at 0 °C and filtered. The filter cake was rinsed with MTBE and dried yielding the title compound as a beige solid (4.31 g). Method LCMS1: Rt = 0.49 min; [M+H]⁺ = 279.2.

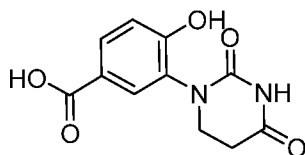
ILB-21: 1-(4-(2,2-dimethoxyethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



2-Bromo-1,1-dimethoxyethane (4.54 mL, 38.4 mmol) was added to a mixture of ILB-36, step 1 (8 g, 38.4 mmol), potassium iodide (7 g, 42.3 mmol) and potassium carbonate (8 g, 57.6 mmol) at 115 °C in 100 mL DMF. The RM was stirred at 115 °C for 16 h. After cooling to RT, the solids were removed by filtration, and washed with ACN. The filtrate was concentrated on the rotavap,

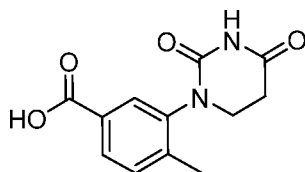
15 the residue dissolved in 20 mL DMSO and purified by reverse phase flash chromatography (C18, 275 g) eluting with 5–40% ACN/water over 25 min. Lyophilization yielded the title compound (4.1 g). Method XQ: Rt = 0.63 min; [M+H]⁺ = 295.3. ¹H NMR (400 MHz, Chloroform-d) δ 7.65 (s, 1H), 7.26 - 7.19 (m, 2H), 7.02 - 6.94 (m, 2H), 4.75 (t, J = 5.2 Hz, 1H), 4.03 (d, J = 5.2 Hz, 2H), 3.84 (t, J = 6.7 Hz, 2H), 3.48 (s, 6H), 2.84 (t, J = 6.7 Hz, 2H).

ILB-22: 3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-4-hydroxybenzoic acid



To a white suspension of 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid (ILB-26, 50 mg, 0.189 mmol) in dry ACN (1.9 mL) flushed with N₂ was added aluminum iodide (CAS No. [7784-23-8], 231 mg, 0.568 mmol). The resulting yellow mixture was flushed again
 5 with N₂ then stirred at 80 °C for 2.5 h, then allowed to stand overnight at RT. The RM was diluted with ACN and water, adsorbed on Isolute[®], concentrated, and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound (39 mg). Method LCMS1: Rt = 0.41 min; [M-H]⁻ = 249.0. ¹H NMR (400 MHz, DMSO-*d*₆) δ 2.71 (t, J = 6.71 Hz, 2H), 3.62 (t, J = 6.71 Hz, 2H),
 10 6.99 (d, J = 8.36 Hz, 1H), 7.67 - 7.88 (m, 2H), 10.33 (s, 1H), 10.50 (s, 1H), 12.60 (s, 1H).

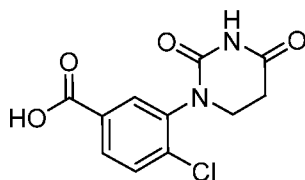
ILB-24: 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzoic acid



This compound was prepared as described in PCT/IB2019/052346 intermediate 8.

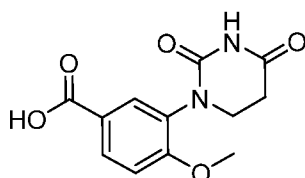
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ILB 25: 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoic acid



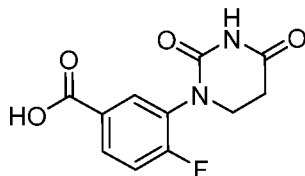
This compound was prepared as described in PCT/IB2019/052346 compound 37, step 4.

20 **ILB-26: 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid**



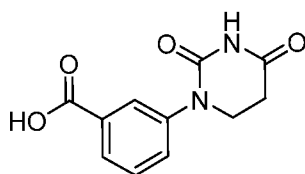
This compound was prepared as described in PCT/IB2019/052346 intermediate 5.

ILB-27: 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-fluorobenzoic acid



5 This compound was prepared as described in PCT/IB2019/052346 intermediate 9.

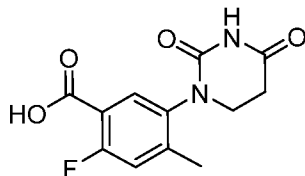
ILB-28: 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoic acid



This compound was prepared as described in PCT/IB2019/052346 compound 12, step 8.

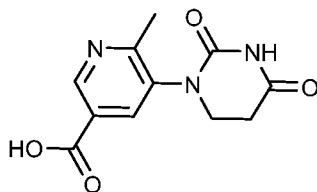
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ILB-29: 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-fluoro-4-methylbenzoic acid



This compound was prepared as described in PCT/IB2019/052346 intermediate 22.

15 **ILB-30: 5-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-6-methylnicotinic acid**

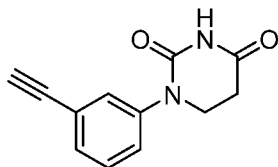
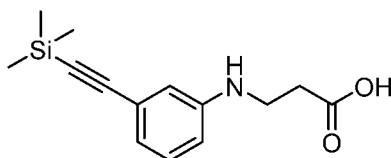


To a cloudy solution of ethyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-6-methylnicotinate (ILB-82, 22 mg, 0.079 mmol) in dry ACN (2 mL) flushed with N₂ at RT was added aluminum iodide (97 mg, 0.238 mmol). The yellow-brown mixture was stirred at 80 °C for 4.5 h, then the

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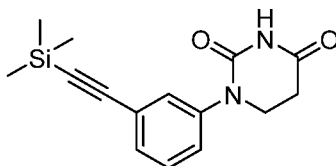
RM was diluted with ACN and water, adsorbed on Isolute[®], concentrated until dryness and purified by reverse phase chromatography on a Redise[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%) to afford, after freeze drying, the title compound as a white solid TFA salt (22 mg). Method LCMS1: Rt = 0.19 min; [M+H]⁺ = 250.1.

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ILB-33: 1-(3-ethynylphenyl)dihydropyrimidine-2,4(1H,3H)-dione**Step 1: 3-((3-((Trimethylsilyl)ethynyl)phenyl)amino)propanoic acid**

10 A mixture of 3-((trimethylsilyl)ethynyl)aniline (155 mg, 0.819 mmol) and acrylic acid (225 μ L, 3.27 mmol) was stirred at RT for 30 minutes, then stirred at 50 °C for 3 h. The reaction mixture was dissolved in MeOH and the crude mixture purified by reverse phase preparative HPLC using Method XN to afford the title compound as a TFA salt (0.11 g). Method LCMS1: Rt = 1.13 min; [M+H]⁺ = 262.2.

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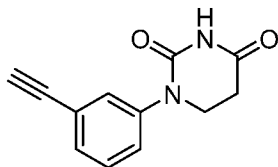
Step 2: 1-(3-((Trimethylsilyl)ethynyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

To 3-((3-((trimethylsilyl)ethynyl)phenyl)amino)propanoic acid (0.11 g, 0.332 mmol) was added urea (0.998 g, 16.62 mmol) followed by AcOH (2.85 mL, 49.9 mmol). The reaction mixture was stirred at 120 °C overnight. The reaction mixture was concentrated to dryness and the residue diluted with EtOAc. The organic phase was washed with aqueous HCl solution and brine, dried over Na₂SO₄, filtered and concentrated to dryness. The crude mixture purified by reverse phase preparative HPLC using method XN. The appropriate fractions were combined, treated with NaHCO₃, the ACN evaporated down and the resultant aqueous extracted with EtOAc. The organic

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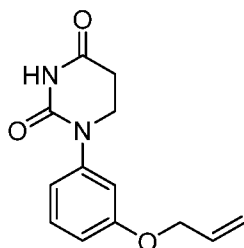
phase was separated and concentrated to dryness to afford the title compound as an off-white solid (0.05 g). Method LCMS1: $R_t = 1.05$ min; $[M+H]^+ = 288.2$.

Step 3: 1-(3-Ethynylphenyl)dihydropyrimidine-2,4(1H,3H)-dione

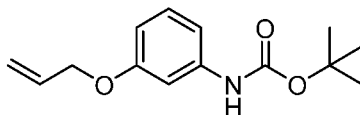


A solution of 1-(3-((trimethylsilyl)ethynyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (0.11 g, 0.384 mmol) in THF (3 mL) was cooled using an ice-bath, to which TBAF 1.0M in THF (0.461 mL, 0.461 mmol) was added. The reaction mixture was stirred while cooling with an ice bath for 90 minutes. The reaction mixture was concentrated to dryness. The crude mixture purified by reverse phase preparative HPLC using method XN-A to afford the title compound as a TFA salt (0.19 g). Method LCMS1: $R_t = 0.63$ min; $[M+H]^+ = 215.1$.

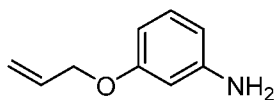
ILB-34: 1-(3-(allyloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



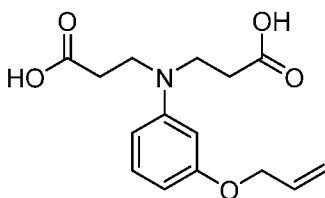
Step 1: *tert*-butyl (3-(allyloxy)phenyl)carbamate



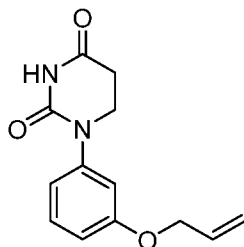
To a 500 mL round bottom flask were added *tert*-butyl (3-hydroxyphenyl)carbamate (5025 mg, 24.02 mmol), potassium carbonate (5000 mg, 36.20 mmol) and DMF (200 mL). Allyl bromide (2.4 mL, 28.40 mmol) was added dropwise and the RM was stirred at RT for 3 days. The RM was filtered and rinsed with Et₂O. The filtrate was taken up in Et₂O and washed with water and brine. The organic phase was dried over MgSO₄ and evaporated to dryness, yielding the title compound as a beige solid (5599 mg). Method LCMS1: $R_t = 1.20$ min; $[M+H]^+ = 250.2$.

Step 2: 3-(allyloxy)aniline

To a 250 mL round bottom flask were added *tert*-butyl (3-(allyloxy)phenyl)carbamate (5547 mg, 21.14 mmol) and DCM (80 mL). TFA (8 mL, 104 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated. The residue was taken up in DCM and washed with sat. aq. NaHCO₃ solution. The organic was dried over MgSO₄ and evaporated to dryness, yielding the title compound as an orange liquid (3181 mg). Method LCMS1: Rt = 0.74 min; [M+H]⁺ = 150.1.

Step 3: 3,3'-((3-(allyloxy)phenyl)azanediyl)dipropionic acid

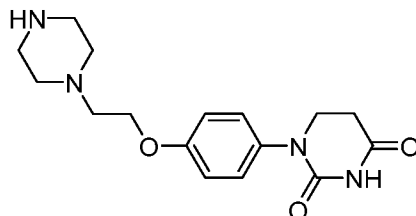
To a 100 mL round bottom flask were added 3-(allyloxy)aniline (3174 mg, 18.51 mmol) and water (5 mL). Acrylic acid (8 mL, 117.00 mmol) was added at RT and the mixture was stirred at 70 °C for 1.5 h. The RM was cooled to RT, adsorbed on Isolute[®], and purified by chromatography on silica gel eluting with iPrOH (from 0% to 10%) in DCM, yielding the title compound as a brown foam (5.27 g). Method LCMS1: Rt = 0.79 min; [M+H]⁺ = 294.1.

Step 4: 1-(3-(allyloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

A suspension of 3,3'-((3-(allyloxy)phenyl)azanediyl)dipropionic acid (713 mg, 0.778 mmol) and urea (200 mg, 3.33 mmol) in AcOH (6 mL) was stirred at 120 °C overnight. The RM was partially evaporated. The residue was purified by reversed phase chromatography on a RediSep[®] Gold HP C18 column (50 g) eluting with ACN (from 2% to 100%) in an aq. solution of TFA (0.1%). Fractions containing pure target compound were filtered through PL-HCO₃ MP SPE cartridges

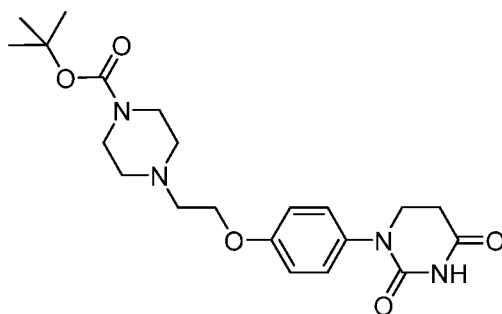
and freeze dried to afford the title compound (176 mg). Method LCMS1: $R_t = 0.74$ min; $[M+H]^+ = 247.1$.

ILB-35: 1-(4-(2-(piperazin-1-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



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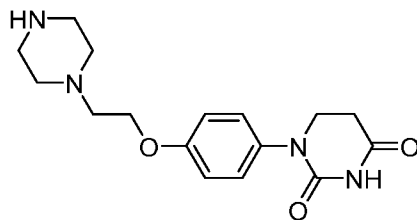
Step 1: *tert*-Butyl 4-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)piperazine-1-carboxylate



To a stirred brown suspension of 1-(4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-36 step 1, 600 mg, 2.91 mmol), 1-Boc-4-(2-hydroxyethyl)piperazine (804 mg, 3.49 mmol), and PPh_3 (916 mg, 3.49 mmol) in 29 mL of dry THF flushed with N_2 and cooled down at 0–5 °C with an ice-water bath was added slowly DEAD 40% in toluene (1.382 mL, 3.49 mmol.) over 10 minutes. The resulting RM was then stirred in the bath for 1 h, before being allowed to stir at RT over 3 days. RM was diluted with ACN and concentrated until dryness. Crude: 3.09 g. The dark residue was then re-dissolved in a minimum of ACN, adsorbed on Isolute and purified by reverse phase chromatography on a Redisep® C18 column of 275 g eluting with ACN/aq. Solution of TFA 0.1% to afford the title compound as the TFA salt (550 mg). Method LCMS1: $R_t = 0.58$ min; $[M+H]^+ = 419.3$.

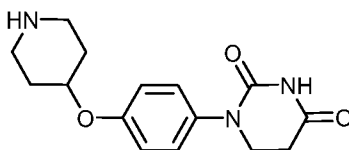
Step 2: 1-(4-(2-(piperazin-1-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

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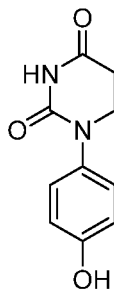


To a colorless solution of *tert*-Butyl 4-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)piperazine-1-carboxylate (548 mg, 1.029 mmol) in 15 mL of DCM was added TFA (2.38 mL, 30 eq). The resulting RM (solution) was stirred at RT for 1 h. RM was diluted with DCM and concentrated until dryness, then co-evaporated with DCM (2×) and dried under HV pump a few hours. The residue was then lyophilized over a long weekend to afford the TFA salt of the title compound as a beige hygroscopic solid (590 mg). Method LCMS1: Rt = 0.36 min; [M+H]⁺ = 319.2.

10 ILB-36: **1-(4-(piperidin-4-yloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**



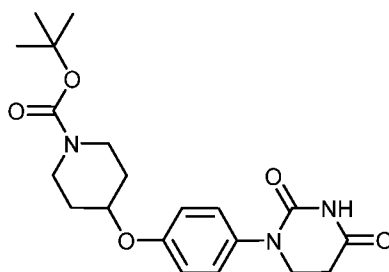
Step 1: 1-(4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



A purple mixture of 4-aminophenol (CAS No. [123-30-8], 5.5 g, 50.4 mmol), methyl acrylate (CAS No. [96-33-3], 5 mL, 55.5 mmol), AcOH (0.5 mL, 8.73 mmol) and hydroquinone (CAS No. [123-31-9], 20 mg, 0.182 mmol) in iPrOH (5 mL) was refluxed at 85°C for 17 h, then concentrated. The resulting crude mixture was dissolved in 20% aq. HCl (20 mL), stirred for 1 h at RT and refluxed overnight, then the RM was concentrated *in vacuo*. To the resulting crude mixture was added urea (CAS No. [57-13-6], 6.1 g, 102 mmol), then it was heated overnight at 120 °C in AcOH (20 mL), and cooled down to RT. Then, 10% aq. HCl was added, the solution was cooled to 0 °C

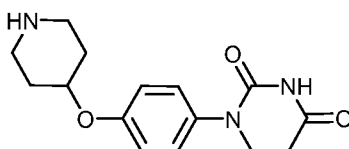
and then filtered through a frit. The solid was dried under reduced pressure to afford the title compound as dark crystals (4.325 g). Method LCMS2: $R_t = 0.72$ min; $[M+H]^+ = 207.1$.

Step 2: *tert*-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidine-1-carboxylate



To a stirred brown mixture of 1-(4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 1.455 mmol), 1-Boc-4-hydroxypiperidine (CAS No. [109384-19-2], 351 mg, 1.746 mmol), and PPh_3 (CAS No. [603-35-0], 458 mg, 1.746 mmol) in dry THF (14.5 mL) flushed with N_2 and cooled down to 0–5 °C was slowly added DEAD 40% in toluene (CAS No. [1972-28-7], 691 μ L, 1.746 mmol) over 10 min. The resulting RM was then stirred at 0–5 °C for 10 min before being allowed to stir at RT. After 3 h at RT, the RM was diluted with EtOAc (75 mL) and water (30 mL). More EtOAc (30 mL) and brine (15 mL) were added to help separation. Layers were separated, the aq. layer was extracted with EtOAc (1 $\times$ 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under HV to afford a light brown solid (1.47 g). Purification of the crude product by flash chromatography on silica gel eluting with 1–20% (DCM / *i*PrOH 80/20) in DCM afforded the title compound as an off-white solid (388 mg). Method LCMS1: $R_t = 0.96$ min; $[M+H]^+ = 390.3$.

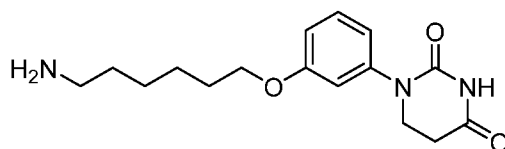
Step 3: 1-(4-(piperidin-4-yloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



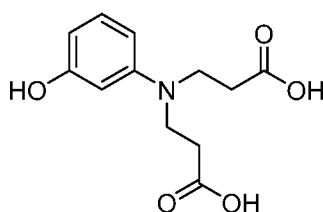
To a colorless solution of *tert*-butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidine-1-carboxylate (387 mg, 0.994 mmol) in DCM (3.8 mL) was added TFA (2.297 mL, 29.8 mmol). The resulting solution was stirred at RT for 1 h, diluted with DCM and concentrated until dryness, then co-evaporated with DCM (1 $\times$), and dried under HV pump to

afford a resin. The resin was redissolved in a mixture of ACN and water, then freeze dried to afford the title compound as an off-white solid TFA salt (419 mg). Method LCMS1: $R_t = 0.37$ min; $[M+H]^+ = 290.3$.

5 ILB-37: 1-(3-((6-Aminohexyl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

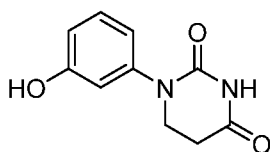


Step 1: 3,3'-((3-hydroxyphenyl)azanediyl)dipropionic acid



To a suspension of 3-aminophenol (CAS No. [591-27-5], commercially available, 10.9 g, 100
 10 mmol) in water (9 mL) at RT was added acrylic acid (CAS No. [79-10-7], commercially available, 18.5 mL, 295 mmol) and the RM was heated at 70 °C under argon for 3 h. The RM was allowed to cool to RT, EtOH (18 mL) was added, and the RM was stored at 4 °C for 12 h. The heterogeneous mixture was filtered over a P4 filter frit, the solid was carefully washed with EtOAc and then dried in vacuum over P₂O₅ affording the title compound as a white powder (15.77 g).
 15 Method LCMS1: $R_t = 0.44$ min; $[M+H]^+ = 254.1$.

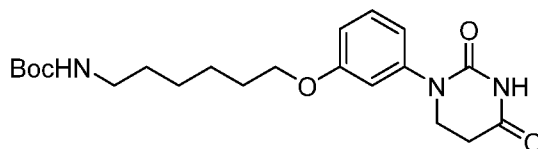
Step 2: 1-(3-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



A suspension of 3,3'-((3-hydroxyphenyl)azanediyl)dipropionic acid (1266 mg, 5 mmol) and urea
 20 (450 mg, 7.5 mmol) in AcOH (7.5 mL) was heated at 130 °C under argon overnight. The RM was allowed to cool to RT, 10% aq. solution of HCl (20 mL) was added and the RM was heated until reflux for 30 min. The RM was allowed to cool to RT and 3/4 of the solvent was evaporated yielding a heterogeneous orange mixture. The mixture was cooled to 0 °C for 20 min and filtered over a P4 filter frit. The solids were washed with an ice cold aq. solution of HCl (0.1 M) (2 × 3

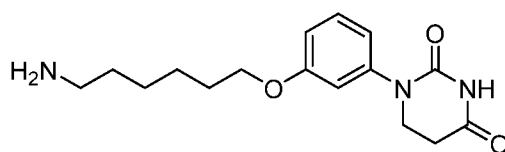
mL) and then dried under vacuum over P_2O_5 affording the title compound as a slightly yellow powder (506 mg). Method LCMS1: $R_t = 0.44$ min; $[M+H]^+ = 207.1$.

Step 3: *tert*-butyl (6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)carbamate



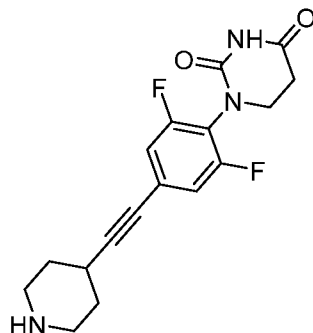
To a solution of *tert*-butyl (6-bromohexyl)carbamate (CAS No. [142356-33-0], commercially available, 326 mg, 1.164 mmol) in DMF (3 mL) under argon at RT was added 1-(3-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (200 mg, 0.970 mmol) followed by potassium carbonate (402 mg, 2.91 mmol). The resulting RM was stirred overnight at RT. The RM was diluted with water (30 mL) and EtOAc (30 mL) and after stirring for 5 min the phases were separated. The aq. phase was extracted with EtOAc (5×20 mL) and the combined organic phases were dried over $MgSO_4$. Evaporation gave a colorless oil which was adsorbed on Isolute[®] and purified by reverse phase chromatography on a Redise[®] Rf Gold 50 g HP C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2 to 100%) to afford 170 mg of a colorless oil containing the expected product. It was then purified further by SFC using method XU on a Reprospher PEI column (250×30 mm, 100A, $5\mu m$) eluting with methanol from 16% to 22% to afford the title compound (110 mg). Method LCMS1: $R_t = 1.05$ min; $[M+H]^+ = 406.3$.

Step 4: 1-(3-((6-aminohexyl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



To *tert*-butyl (6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)carbamate (105 mg, 0.259 mmol) was added HCl (4.0 M) in dioxane (4.0 mL, 16.00 mmol) at RT. The resulting solution was stirred at RT for 1 h, then evaporated to dryness and further dried under vacuum over P_2O_5 overnight to afford the title compound as an HCl salt (85 mg). Method LCMS1: $R_t = 0.51$ min; $[M+H]^+ = 306.2$.

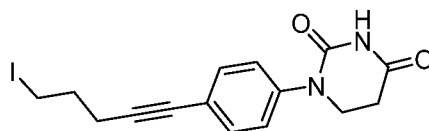
ILB-38: 1-(2,6-difluoro-4-(piperidin-4-ylethynyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



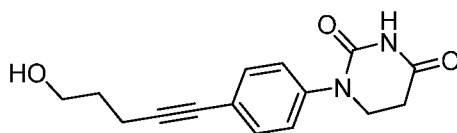
The mixture of 1-(4-bromo-2,6-difluorophenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-45
 5 step 2, 20 mg, 0.066 mmol), 1-(prop-2-yn-1-yl)piperazine (20 mg, 0.066 mmol), 1-(prop-2-yn-1-yl)piperazine (48.8 mg, 0.393 mmol) copper (I) iodide (4.99 mg, 0.026 mmol), tetrakis(triphenylphosphine)palladium (0) (15.15 mg, 0.013 mmol), TEA (0.091 mL, 0.656 mmol) in DMF (0.5 mL) was stirred at 115 °C for 0.5 h. After cooling to RT, the mixture was diluted EtOAc, washed with water, brine, the organic phase was dried over anhydrous sodium sulfate,
 10 filtered and concentrated. The residue was purified with reverse phase C18 chromatography, eluted with 10-100% 0.1%TFA in ACN/ water to provide the desired product as a white solid TFA salt (4 mg). Method XR-A: Rt = 0.65 min; MS [M+H]⁺ = 334.2. ¹H NMR (400 MHz, DMSO-d₆) δ 10.67 (s, 1H), 8.45 (s, 1H), 7.65–7.06 (m, 2H), 3.70 (t, J = 6.7 Hz, 2H), 3.36–2.78 (m, 7H), 2.15–1.92 (m, 4H).

15

ILB-39: 1-(4-(5-iodopent-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



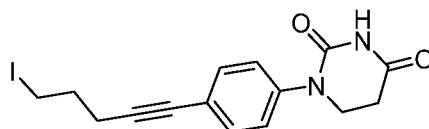
Step 1: 1-(4-(5-hydroxypent-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



20 A yellow solution of 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (CAS No. [1528991-21-0], 203 mg, 0.642 mmol), DBU (0.232 mL, 1.541 mmol) and Pd(PPh₃)₄ (18.55 mg, 0.016 mmol) in DMSO (2 mL) was bubbled with Argon for 5 min, then pent-4-yn-1-ol (0.034 mL, 0.357

mmol) was added, and the RM was stirred at 80 °C for 1 h. Then, TPGS-750-M 2 wt.% solution in water (= DL- α -Tocopherol methoxypolyethylene glycol succinate solution) (CAS No. [1309573-60-1], 1 mL) was added, the mixture was stirred at 80 °C for 1 h and allowed to stand overnight at RT. The RM was dissolved in a mixture of EtOAc and MeOH (9:1, 50 mL) and washed with sat. aq. Na₂CO₃ (2 × 50 mL). The aqueous layers were extracted with a mixture of EtOAc and MeOH (9:1, 50 mL). The organic layers were combined and evaporated to afford a yellow solid, which was purified by flash chromatography on silica gel eluting with 5–100% EtOAc in CHX to afford the title compound as a white solid (118 mg). Method LCMS1: Rt = 0.59 min; [M+H]⁺ = 273.2.

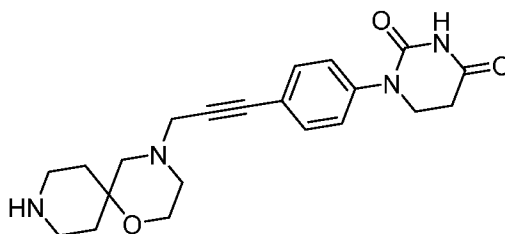
Step 2: 1-(4-(5-iodopent-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



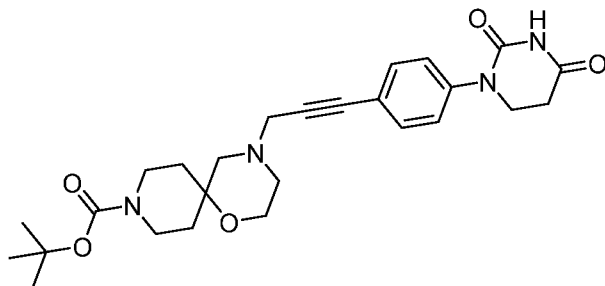
To a yellow suspension of 1-(4-(5-hydroxypent-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (162 mg, 0.595 mmol) and imidazole (CAS No. [288-32-4], 60.8 mg, 0.892 mmol) in THF (2 mL) was added DCM (2 mL), followed by PPh₃ (203 mg, 0.773 mmol) and I₂ (226 mg, 0.892 mmol) in one portion. The vial was covered with aluminum foil and the brown suspension was stirred at RT for 4 h. The RM was dissolved in EtOAc (50 mL) and extracted with sat. aq. Na₂CO₃ (50 mL), followed by 20% aq. Na₂S₂O₃ (50 mL) and water (50 mL). The aqueous layers were extracted with EtOAc (30 mL). The organic layers were combined and evaporated to afford a yellow solid, which was purified by flash chromatography on silica gel eluting with 5–100% EtOAc in CHX to afford the title compound as a white solid (186 mg). Method LCMS1: Rt = 0.99 min; [M+H]⁺ = 383.1.

ILB-40:

1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

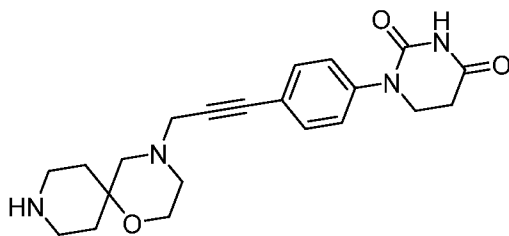


Step 1: *tert*-butyl 4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



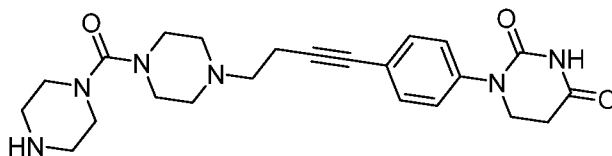
To a solution of *tert*-butyl 4-(prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (Intermediate DD, 51.2 mg, 0.174 mmol), 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BB, 50 mg, 0.158 mmol), PdCl₂(PPh₃)₂ (5.55 mg, 7.91 μmol), and CuI (1.506 mg, 7.91 μmol) in DMF (1582 μL) under an atmosphere of nitrogen, was added TEA (110 μL, 0.791 mmol). The reaction mixture was stirred at 80 °C for 90 min, then was cooled to room temperature and diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over magnesium sulfate, filtered, and concentrated. The crude residue was purified via flash chromatography (0–30% MeOH/DCM) to afford the title compound (50 mg). Method XV: Rt = 0.95 min; [M+H]⁺ = 483.4.

Step 2: 1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

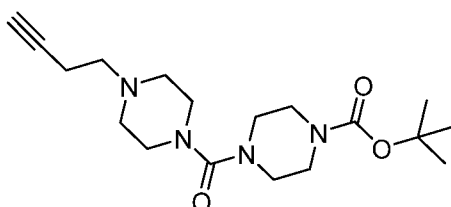


A solution of 4 N HCl in dioxane (777 μL, 3.11 mmol) was added to *tert*-butyl 4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (50 mg, 0.104 mmol), and the resulting solution was stirred at RT for 18 h. The solvent was concentrated to afford the title compound as an HCl salt (43.4 mg). Method XV: Rt = 0.71 min; [M+H]⁺ = 383.3.

ILB-41: **1-(4-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

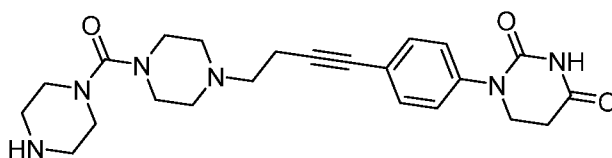


Step 1: *tert*-butyl 4-(4-(but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate



5 To a solution of *tert*-butyl 4-(piperazine-1-carbonyl)piperazine-1-carboxylate (150 mg, 0.503 mmol) in ACN (5.0 mL), was added K₂CO₃ (208 mg, 1.508 mmol), followed by 4-bromobut-1-yne (0.090 mL, 1.005 mmol). The resulting solution was stirred at 75 °C for 72 h. The RM was then cooled to RT, diluted with EtOAc, and washed with water (2 × 25 mL). The combined
10 aqueous layers were then extracted again with EtOAc (3 × 15 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford the title compound as a white solid (160 mg). Method XV: Rt = 0.87 min; [M+H]⁺ = 351.3.

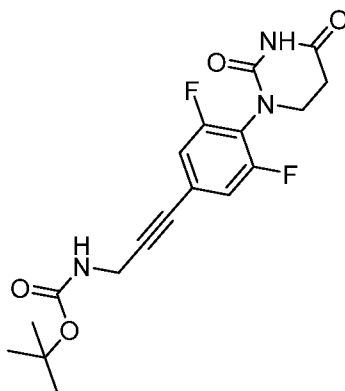
Step 2: **1-(4-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**
15



To a solution of *tert*-butyl 4-(4-(but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate (14.41 mg, 0.041 mmol), 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (CAS No. [1528991-21-0], Intermediate BB, 10 mg, 0.032 mmol), PdCl₂(PPh₃)₂ (1.110 mg, 1.582 μmol),
20 and CuI (0.301 mg, 1.582 μmol) in dioxane (300 μL) was added TEA (150 μL, 1.076 mmol), and the resulting solution was stirred at 80 °C for 30 min. The RM was then cooled to RT and a solution of HCl (4M in dioxane) (395 μL, 1.582 mmol) was added and the RT was stirred at RT for 72 h.

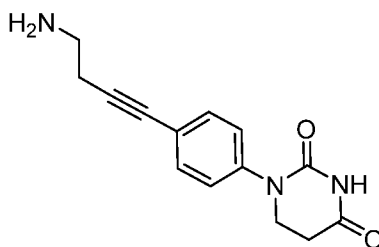
The solution was filtered, diluted with a 1:1:1 solution of H₂O:ACN:DMSO and purified via preparative HPLC (XBridge C18 30x50 mm 10-30% MeCN/H₂O (5 mM NH₄OH) to afford the title compound as a white powder (5 mg). Method XV: Rt = 0.61 min; [M+H]⁺ = 439.4.

5 ILB-43: ***tert*-Butyl (3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3,5-difluorophenyl)prop-2-yn-1-yl)carbamate**

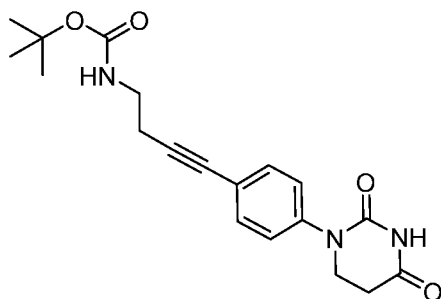


The mixture of 1-(4-bromo-2,6-difluorophenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-45 step 2, 20 mg, 0.066 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (61.0 mg, 0.393 mmol), 1-(prop-2-yn-1-yl)piperazine (48.8 mg, 0.393 mmol) copper (I) iodide (4.99 mg, 0.026 mmol), tetrakis(triphenylphosphine)palladium (0) (15.15 mg, 0.013 mmol), TEA (0.091 mL, 0.656 mmol) in DMF (0.5 mL) was stirred at 115 °C for 0.5 hr. After cooling to RT, the mixture was diluted EtOAc, washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with flash chromatography (0-10% MeOH/DCM) to provide the desired product as a light brown solid (10 mg). Method XR-A: Rt = 1.81 min; [M-55]⁺ = 324.1. ¹H NMR (400 MHz, Acetonitrile-*d*₃) δ 8.40 (s, 1H), 7.24–7.08 (m, 2H), 5.68 (s, 1H), 4.07 (d, J = 6.0 Hz, 2H), 3.74 (t, J = 6.6 Hz, 2H), 2.79 (s, 2H), 1.46 (s, 9H).

ILB-44: **1-(4-(4-aminobut-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

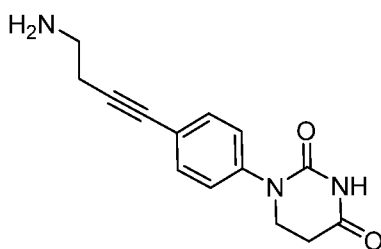


Step 1: *tert*-Butyl (4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)carbamate



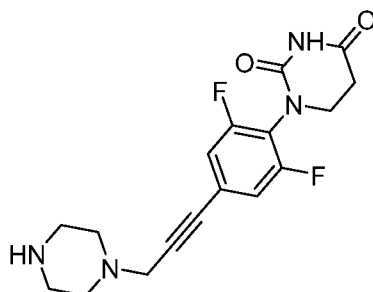
To 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (CAS No. :[1528991-21-0], 300 mg, 0.949 mmol), CuI (36.2 mg, 0.190 mmol) and PdCl₂(PPh₃)₂ (66.6 mg, 0.095 mmol) in DMF (8 mL) was slowly added TEA (0.794 mL, 5.69 mmol). The RM was stirred under argon atmosphere at 80 °C for 30 min. The residue was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound as a grey solid (346 mg). Method LCMS1: Rt = 0.87 min; [M-H]⁻ = 356.2.

Step 2: 1-(4-(4-aminobut-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

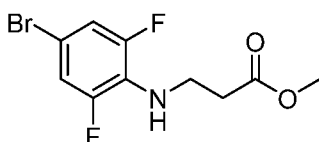


To a solution of *tert*-butyl (4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)carbamate (346 mg, 0.661 mmol) in dioxane (2 mL) was added HCl 4 N in dioxane (6.61 mL, 26.4 mmol) and the RM was stirred at RT for 1.5 h. The mixture was concentrated, then dried *in vacuo* to afford the title compound as an orange powder HCl salt (250 mg). Method LCMS2: Rt = 0.66 min; [M+H]⁺ = 258.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 8.06 (s, 3H), 7.49 - 7.43 (m, 2H), 7.36 - 7.31 (m, 2H), 3.80 (t, J = 6.6 Hz, 2H), 3.03 (q, J = 6.7 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 2.70 (t, J = 6.6 Hz, 2H).

ILB-45: **1-(2,6-difluoro-4-(3-(piperazin-1-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

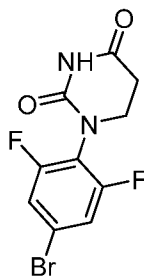


5 **Step 1:** Methyl 3-((4-bromo-2,6-difluorophenyl)amino)propanoate



Trifluoromethanesulfonic acid (0.021 mL, 0.240 mmol) was added to the mixture of 4-bromo-2,6-difluoroaniline (1 g, 4.81 mmol), methyl acrylate (4.33 mL, 48.1 mmol). The mixture was stirred at 80 °C overnight. After cooling to RT, the mixture was diluted with EtOAc, washed with water,
10 brine, the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with flash chromatography (0–30% EtOAc/heptane) to provide the desired product as a glassy solid (470 mg). Method XQ: Rt = 1.07 min; MS [M+H]⁺ = 294.1.

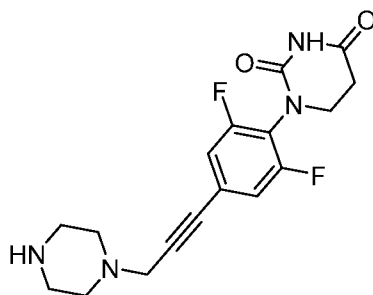
Step 2: 1-(4-bromo-2,6-difluorophenyl)dihydropyrimidine-2,4(1H,3H)-dione



15 2,2,2-Trichloroacetyl isocyanate (169 mg, 0.898 mmol) in THF (2 mL,) was added to the mixture of methyl 3-((4-bromo-2,6-difluorophenyl)amino)propanoate (240 mg, 0.816 mmol) in THF (8 mL) at 0 °C. After stirred for 30 minutes, ammonia in methanol (2.332 mL, 16.32 mmol) was added to the mixture. The resulting mixture was stirred at RT overnight. Then, more ammonia in
20 methanol (2.332 mL, 16.32 mmol) was added, and the mixture was allowed to warm up to 60 °C.

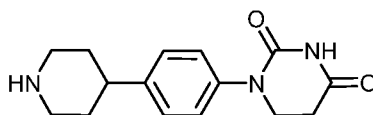
After stirred overnight, the mixture was concentrated. The residue was purified with flash chromatography (0–60% EtOAc/heptane) to provide the desired product as a solid (130 mg). Method XQ: Rt = 0.71 min; $[M+H]^+ = 304.9$.

5 **Step 3:** 1-(2,6-difluoro-4-(3-(piperazin-1-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

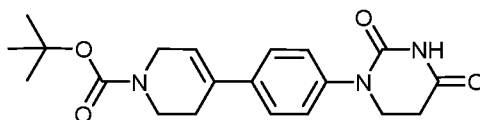


The mixture of 1-(4-bromo-2,6-difluorophenyl)dihydropyrimidine-2,4(1H,3H)-dione (20 mg, 0.066 mmol), 1-(prop-2-yn-1-yl)piperazine (48.8 mg, 0.393 mmol), copper (I) iodide (4.99 mg, 0.026 mmol), tetrakis(triphenylphosphine)palladium (0) (15.15 mg, 0.013 mmol), TEA (0.091 mL, 0.656 mmol) in DMF (0.5 mL) was stirred at 115 °C for 0.5 h. After cooling to RT, the mixture was diluted EtOAc, washed with water, brine, the organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified with reverse phase C18 chromatography, eluted with 10–100% 0.1%TFA in ACN/ water to provide the desired product as a white solid TFA salt (2.7 mg). Method XR-A: Rt = 0.62 min; $[M+H]^+ = 349.1$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.69 (s, 1H), 8.75 (s, 1H), 7.33–6.94 (m, 2H), 3.79–3.42 (m, 6H), 3.28–3.05 (m, 4H), 2.87–2.65 (m, 5H).

ILB-46: 1-(4-(piperidin-4-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

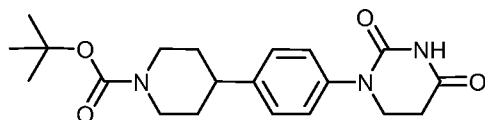


20 **Step 1:** *tert*-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate



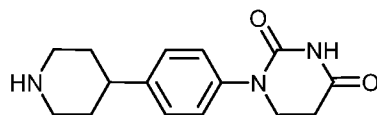
To a mixture of 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (CAS No. [1528991-21-0], 200 mg, 0.633 mmol), 3,6-dihydro-2H-pyridine-1-*tert*-butoxycarbonyl-4-boronic acid pinacol ester (CAS No. [286961-14-6], 215 mg, 0.696 mmol) and K₃PO₄ (403 mg, 1.898 mmol) in dioxane (10.5 mL) at RT flushed with N₂ was added PdCl₂(dppf) (46.3 mg, 0.063 mmol), followed by water (2.1 mL). The RM was flushed with N₂, the vial was capped and heated under microwave irradiation at 120 °C for 30 min. The RM was diluted with ACN, adsorbed on Isolute[®], concentrated until dryness and purified by flash chromatography on silica gel eluting with 1–25% (DCM/iPrOH 80/20) in DCM to afford the title compound as a yellow solid (154 mg). Method LCMS1: Rt = 0.98 min; [M-*t*Bu+H]⁺ = 316.3.

Step 2: *tert*-Butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)piperidine-1-carboxylate



A pale yellow mixture of *tert*-butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (151 mg, 0.386 mmol) in dry EtOH (12 mL) was treated with 10% palladium on activated charcoal (CAS No. [7440-05-3], 41.1 mg, 0.039 mmol) and the RM was stirred under H₂ atmosphere at RT for 20 h. Then, the RM diluted with EtOAc, filtered through Hyflo[®] and rinsed with a mixture of EtOH and EtOAc. The pale yellow filtrate was then concentrated until dryness to afford the title compound as a beige solid (154 mg). Method LCMS1: Rt = 0.99 min; [M+H₂O]⁺ = 391.4.

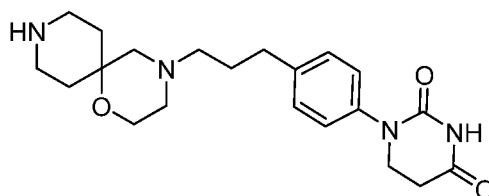
Step 3: 1-(4-(piperidin-4-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



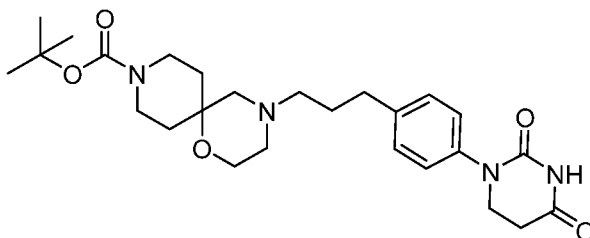
To a colorless solution of *tert*-butyl 4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)piperidine-1-carboxylate (153 mg, 0.373 mmol) in DCM (5.4 mL) was added TFA (862 μL, 11.18 mmol) and the resulting solution was stirred at RT for 1 h. The RM was diluted with DCM, concentrated until dryness, co-evaporated with DCM, then dried under HV pump and freeze

dried to afford the title compound as a solid TFA salt (166 mg). Method LCMS1: $R_t = 0.36$ min; $[M+H]^+ = 274.3$.

ILB-47: 1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)propyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

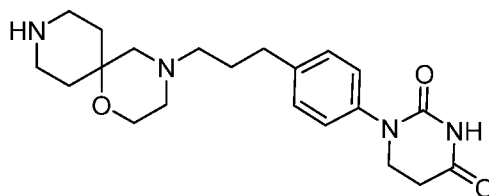


Step 1: *tert*-Butyl 4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)propyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



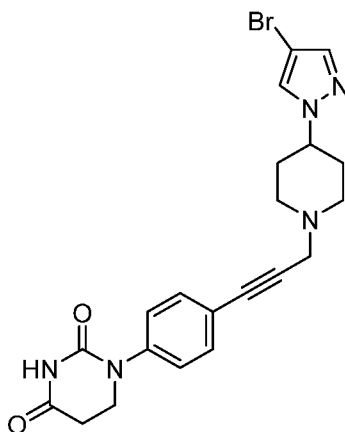
To a mixture of *tert*-butyl 4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (ILB-40 step 2, 200 mg, 0.41 mmol) in EtOH (10 mL) was added Pd/C (50 mg, 10% w/w). The mixture was purged with H_2 and heated at 25 °C for 8 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on a 12 g silica Biotage[®] column eluting with EtOAc in DCM (from 30 to 90%), 20 mL/min, to afford the title compound as a white solid (122 mg). Method G: $R_t = 1.92$ min; $[M+H]^+ = 487.3$

Step 2: 1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)propyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

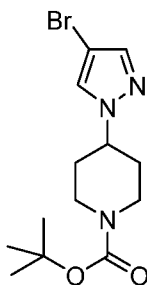


To a mixture of *tert*-butyl 4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)propyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (118 mg, 0.24 mmol) in DCM (3 mL) was added TFA (1 mL). The mixture was stirred at 25 °C for 3 h. The mixture was concentrated *in vacuo*. The residue was diluted with DCM (5 mL) and basified with ammonia in MeOH (7N) to pH 9. Silica gel (100–200 mesh, 10 mL) was added and the mixture was concentrated *in vacuo*. The residue was purified by chromatography on a 12 g silica Biotage[®] column eluting with a methanolic ammonia solution (0.7 N) in DCM (from 5 to 25%), 20 mL/min, to afford the title compound as a colorless oil (85 mg). Method G: Rt = 1.47 min; [M+H]⁺ = 387.2

- 10 ILB-49: **1-(4-(3-(4-(4-bromo-1H-pyrazol-1-yl)piperidin-1-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**



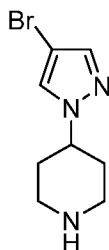
Step 1: *tert*-Butyl 4-(4-bromo-1H-pyrazol-1-yl)piperidine-1-carboxylate



- 15 4-bromo-1H-pyrazole (CAS No. [2075-45-8], 1.104 g, 7.51 mmol) was dissolved in DMF (15.02 mL) and cooled down to 0 °C. NaH (0.330 g, 8.26 mmol) was added, the RM was stirred at 0 °C for 1 h, then *tert*-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (CAS No. [141699-59-4], 2.098 g, 7.51 mmol) was added and the resulting suspension was stirred at 100 °C for 1 h. The RM was quenched with water and extracted with EtOAc. The organic layer was washed with water

and brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel eluting with 0–50% EtOAc in CHX to afford the title compound (1.876 g). Method LCMS1: Rt = 1.16 min; [M+H]⁺ = 330.2 / 332.2.

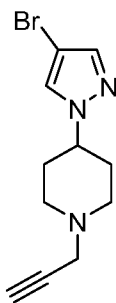
5 **Step 2:** 4-(4-bromo-1H-pyrazol-1-yl)piperidine



tert-Butyl 4-(4-bromo-1H-pyrazol-1-yl)piperidine-1-carboxylate (1.850 g, 5.60 mmol) was dissolved in DCM (56 mL), then TFA (2.158 mL, 28 mmol) was added and the RM was stirred at RT for 18 h. More TFA (2.158 mL, 28.0 mmol) was added and the RM was stirred at RT for 3 h.

10 The RM was basified with NH₄OH and extracted with DCM. The organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated to afford the title compound (1.250 g). Method LCMS1: Rt = 0.44 min; [M+H]⁺ = 230.1 / 232.1.

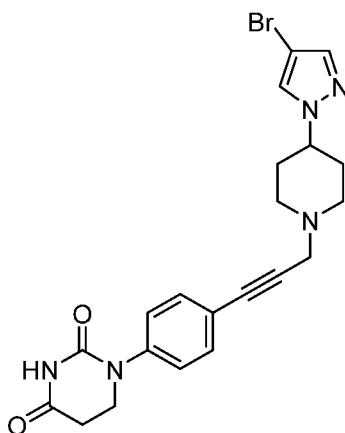
15 **Step 3:** 4-(4-bromo-1H-pyrazol-1-yl)-1-(prop-2-yn-1-yl)piperidine



4-(4-bromo-1H-pyrazol-1-yl)piperidine (1.24 g, 5.39 mmol) was dissolved in THF (53.9 mL), Cs₂CO₃ (1.756 g, 5.39 mmol) was added, followed by propargyl bromide 80% in toluene (0.581 mL, 5.39 mmol) and the RM was stirred at RT for 18 h. The RM was quenched with water and
 20 extracted with EtOAc, the organic layer was washed with brine, dried over Na₂SO₄, filtered, concentrated and purified by flash chromatography on silica gel eluting with 0–100% EtOAc in

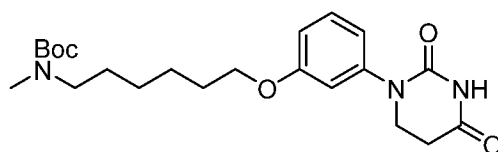
CHX to afford the title compound (1.140 g). Method LCMS1: Rt = 0.51 min; $[M+H]^+ = 268.2 / 270.2$.

Step 4: 1-(4-(3-(4-(4-bromo-1H-pyrazol-1-yl)piperidin-1-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

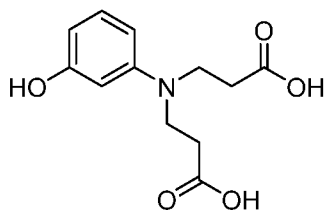


1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (CAS No. [1528991-21-0], 50 mg, 0.158 mmol) was dissolved in DMF (1.582 mL), 4-(4-bromo-1H-pyrazol-1-yl)-1-(prop-2-yn-1-yl)piperidine (42.4 mg, 0.158 mmol) was added, followed by CuI (6.03 mg, 0.032 mmol), TEA (132 μ L, 0.949 mmol), and $PdCl_2(PPh_3)_2$ (11.10 mg, 0.016 mmol). The RM was stirred at RT for 18 h, then filtered through a silica gel pre-column, washing with DCM/MeOH (95/5), and concentrated *in vacuo* to afford a residue. The residue was purified by flash chromatography on silica gel eluting with 0–5% MeOH in DCM to afford the title compound (52 mg). Method LCMS1: Rt = 0.61 min; $[M+H]^+ = 456.2 / 458.2$.

ILB-50: ***tert*-Butyl (6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)(methyl)carbamate**

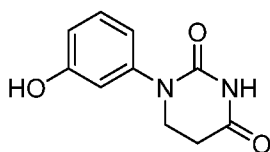


Step 1: 3,3'-((3-Hydroxyphenyl)azanediyl)dipropionic acid



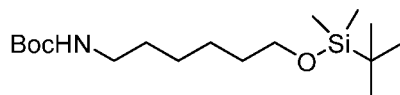
To a suspension of 3-aminophenol (CAS No. [591-27-5], commercially available, 10.9 g, 100 mmol) in water (9 mL) at RT was added acrylic acid (CAS No. [79-10-7], commercially available, 18.5 mL, 295 mmol) and the RM was heated at 70 °C under argon for 3 h. The RM was allowed to cool to RT, EtOH (18 mL) was added and the RM was stored at 4 °C for 12 h. The heterogeneous mixture was filtered over a P4 filter frit, the solid was carefully washed with EtOAc and then dried in vacuum over P₂O₅ affording the title compound as a white powder (15.77 g). Method LCMS1: Rt = 0.44 min; [M+H]⁺ = 254.1.

Step 2: 1-(3-Hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione



A suspension of 3,3'-((3-hydroxyphenyl)azanediyl)dipropionic acid (1266 mg, 5 mmol) and urea (450 mg, 7.5 mmol) in AcOH (7.5 mL) was heated at 130 °C under argon overnight. The RM was allowed to cool to RT, 10% aq. solution of HCl (20 mL) was added and the RM was heated until reflux for 30 min. The RM was allowed to cool to RT and 3/4 of the solvent was evaporated yielding a heterogeneous orange mixture. The mixture was cooled to 0 °C for 20 min and filtered over a P4 filter frit. The solids were washed with an ice cold aq. solution of HCl (0.1 M) (2 × 3 mL) and then dried under vacuum over P₂O₅ affording the title compound as a slightly yellow powder (506 mg). Method LCMS1: Rt = 0.44 min; [M+H]⁺ = 207.1.

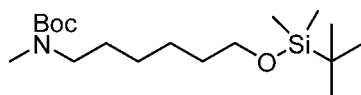
Step 3: *tert*-Butyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)carbamate



To a solution of *tert*-butyl (6-hydroxyhexyl)carbamate (CAS No. [75937-12-1], commercially available, 5.0 g, 23.01 mmol) and imidazole (2.036 g, 29.9 mmol) in DCM (30 mL) under argon at 0 °C was added dropwise a solution of *tert*-butylchlorodimethylsilane (3.81 g, 25.3 mmol) in

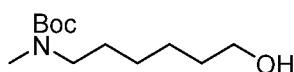
DCM (10 mL) over 15 min. After the addition, the RM was stirred at 0 °C for 15 min, then the cooling bath was removed and stirring was continued at RT for 2 days. The RM was filtered over a P4 filter frit and the solid was washed with PE (3 × 20 mL). The combined filtrates were evaporated, redissolved in DCM (150 mL) and washed with an aq. solution of HCl (1 M) (3 × 30 mL) and brine (2 × 30 mL), dried over Na₂SO₄, and concentrated under vacuum to afford a colorless oil. It was then adsorbed on Isolute® and purified by normal phase flash chromatography on a Redisep® Rf 220 g column eluting with EtOAc in CHX (from 0 to 10%) to afford the title compound as a colorless oil (7.35 g).

Step 4: *tert*-Butyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)(methyl)carbamate



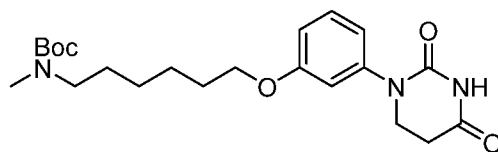
To a suspension of NaH (60% in mineral oil) (3.64 g, 91 mmol) in THF (80 mL) at 0 °C under argon was added dropwise a solution of *tert*-butyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)carbamate (7.3 g, 22.02 mmol) in THF (20 mL) over 15 min. After the addition the RM was stirred at 0 °C for 30 min, then iodomethane (3.38 mL, 54 mmol) was added dropwise over 10 min and after the addition the reaction mixture was allowed to RT. The resulting RM was stirred overnight at RT. Aq. sat. NH₄Cl (100 mL) was carefully added to the reaction mixture at 0 °C, the mixture was allowed to warm to RT under stirring for 30 min and filtered over a P4 filter frit. The solids were washed with MTBE (3 × 25 mL) and the phases were separated. The aq. phase was extracted with MTBE (3 × 50 mL), the combined organic phases were washed with brine (2 × 50 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum yielding a yellow oil (8.70 g). It was then adsorbed on Isolute® and purified by normal phase flash chromatography on a Redisep® Rf 220 g column eluting with EtOAc in CHX (from 0 to 10%) to afford the title compound as a colorless oil (7.03 g). ¹H NMR (400 MHz, Chloroform-*d*₆) δ 3.59 (t, *J* = 6.5 Hz, 2H), 3.18 (t, *J* = 7.3 Hz, 2H), 2.82 (s, 3H), 1.56 - 1.47 (m, 4H), 1.45 (s, 9H), 1.39 - 1.22 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).

Step 5: *tert*-Butyl (6-hydroxyhexyl)(methyl)carbamate



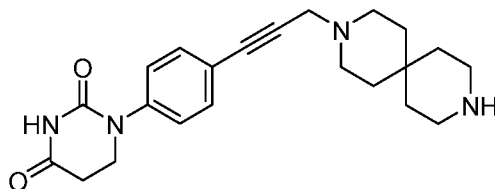
To a solution of *tert*-butyl (6-((*tert*-butyldimethylsilyl)oxy)hexyl)(methyl)carbamate (2.0 g, 5.8 mmol) in THF (30.0 mL) was added tetrabutylammonium fluoride (1.0 M) in THF (17.36 mL, 17.36 mmol) dropwise at RT. The resulting RM was stirred overnight at RT. The solvent was removed then ice cold water (30 mL) was added and the mixture was stirred 30 min at RT. Cyclohexane (50 mL) was added and after stirring additional 10 min, the phases were separated. The aq. phase was extracted with cyclohexane (4 × 50 mL) and the combined organic phases were dried over Na₂SO₄, filtered, and concentrated yielding a yellow oil: 1.97 g. It was then adsorbed on Isolute[®] and purified by normal phase flash chromatography on a Redisep[®] Rf 80 g column eluting with EtOAc in cyclohexane (from 0 to 100%) to afford the title compound as a colorless oil (1.26 g). ¹H NMR (400 MHz, Chloroform-*d*) δ 3.63 (t, J = 6.5 Hz, 2H), 3.19 (t, J = 7.2 Hz, 2H), 2.84 - 2.79 (m, 3H), 1.62 - 1.46 (m, 4H), 1.45 (s, 9H), 1.42 - 1.34 (m, 2H), 1.34 - 1.24 (m, 2H).

Step 6: *tert*-Butyl (6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)(methyl)carbamate

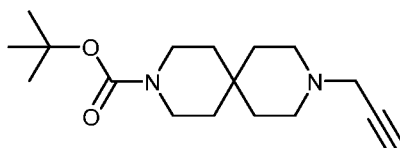


1-(3 hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (step 2, 200 mg, 0.970 mmol), *tert*-butyl (6-hydroxyhexyl)(methyl)carbamate (step 5, 269 mg, 1.164 mmol) and triphenylphosphine (356 mg, 1.358 mmol) were added to the reaction flask which was then flushed with argon and THF (5 mL) was added via a syringe. The suspension was cooled to 0 °C and DEAD 40% in toluene (0.537 mL, 1.358 mmol) was added dropwise. After the addition, stirring was continued at 0 °C and the reaction mixture was allowed to warm to RT without withdrawing the cooling bath. The resulting RM was stirred overnight at RT. Solvent was partially evaporated and then adsorbed on Isolute[®] and purified by reverse phase chromatography on a Redisep[®] Rf Gold 50 g HP C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100% ACN) to afford 176 mg of a colorless oil containing the expected product. It was then purified further by SFC on a Reprospher PEI column (250 × 30 mm, 100 Å, 5 μm) eluting with methanol from 12% to 18% to afford the title compound (105 mg). Method LCMS1: Rt = 1.12 min; [M+H]⁺ = 420.3.

ILB-52: 1-(4-(3-(3,9-diazaspiro[5.5]undecan-3-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



Step 1: *tert*-Butyl 9-(prop-2-yn-1-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

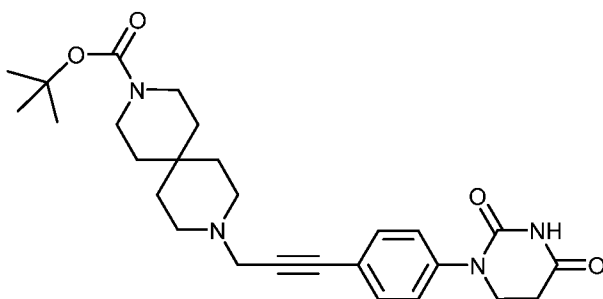


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To a stirred colorless solution of *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (CAS No. [173405-78-2], 8 g, 31.5 mmol) in ACN (175 mL) at RT flushed with N₂ was added K₂CO₃ (6.52 g, 47.2 mmol) to give a white suspension. After 10 min stirring at RT, propargyl bromide 80% in toluene (4.20 mL, 37.7 mmol) was slowly added and the RM was stirred at 60 °C for 22 h. The RM was filtered to remove inorganics, rinsed with ACN, and the filtrate was concentrated until dryness to afford a yellow-orange solid. The solid was purified by flash chromatography on silica gel eluting with 10–50% EtOAc in CHX to afford the title compound as a pale yellow solid (6.31 g). Method LCMS1: Rt = 0.64 min; [M+H]⁺ = 293.3.

10

15 **Step 2:** *tert*-Butyl 9-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

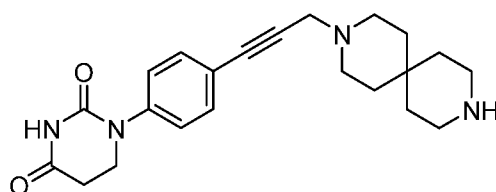


A mixture of 1-(4-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BB, CAS No. [1528991-21-0], 300 mg, 0.949 mmol), *tert*-butyl 9-(prop-2-yn-1-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (305 mg, 1.044 mmol), CuI (36.2 mg, 0.190 mmol) and PdCl₂(PPh₃)₂ (68 mg, 0.095 mmol) in dry DMF (4.5 mL) was flushed with N₂. Then, while stirring,

20

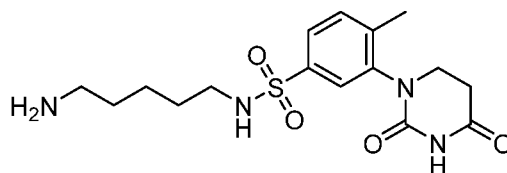
TEA (0.789 mL, 5.69 mmol) was slowly added, the resulting yellow mixture was then flushed with N₂, heated at 80 °C for 3 h, then allowed to stand overnight at RT. The RM was diluted with DCM (30 mL) and washed with a mixture of water and brine (15 mL). The aq. layer was extracted twice with DCM (20 mL, then 10 mL). Combined organics were dried then over MgSO₄, filtered, concentrated and dried to afford a brown solid. The solid was purified by flash chromatography on silica gel eluting with 2–30% (DCM/MeOH 80/20) in DCM to afford the title compound as a brown solid (358 mg). Method LCMS1: Rt = 0.69 min; [M+H]⁺ = 481.6.

Step 3: 1-(4-(3-(3,9-diazaspiro[5.5]undecan-3-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

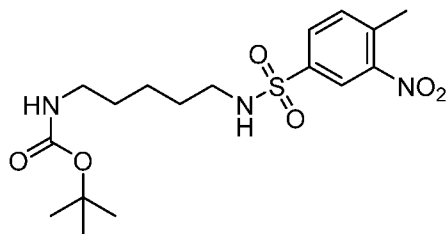


tert-Butyl 9-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (87 mg, 0.163 mmol) was dissolved in DCM (2 mL). TFA (2 mL, 26.0 mmol) was added and the clear solution was stirred at RT for 20 min, then evaporated on Isolute[®] and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound as a yellow solid bis-TFA salt (76 mg). Method LCMS1: Rt = 0.32 min; [M+H]⁺ = 381.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.47 (s, 1H), 10.06 (s, 1H), 8.40 (s, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 4.36 (s, 2H), 3.82 (t, J = 6.6 Hz, 2H), 3.45 (s, 2H), 3.14 (s, 2H), 3.06 (s, 4H), 2.72 (t, J = 6.6 Hz, 2H), 1.92 (s, 2H), 1.74 (s, 2H), 1.52 (s, 4H).

ILB-53: **N-(5-aminopentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzenesulfonamide**

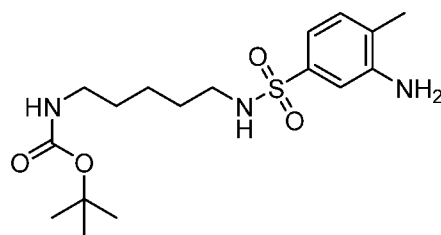


Step 1: *tert*-Butyl (5-(4-methyl-3-nitrophenylsulfonamido)pentyl)carbamate



A solution of N-Boc-cadaverine (650 mg, 3.12 mmol) and TEA (0.900 mL, 6.39 mmol) in DCM (25 mL) was cooled at 0 °C, to which a solution of 4-methyl-3-nitrobenzenesulfonyl chloride (795 mg, 3.27 mmol) in DCM (50 mL) was added dropwise. The reaction was allowed to warm to RT and stirred at RT for 2 h. The RM was partially concentrated under reduced pressure and washed with water (×3), dried over magnesium sulfate, filtered and concentrated to dryness. The crude material was purified by silica gel chromatography eluting with EtOAc in CHX (from 0% to 100%) to afford the title compound (1165 mg). Method LCMS1: Rt = 1.09 min; [M+H]⁺ = 402.3.

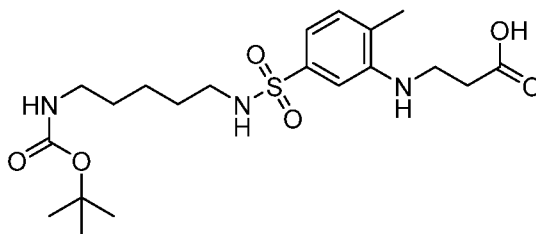
10 **Step 2:** *tert*-Butyl (5-(3-amino-4-methylphenylsulfonamido)pentyl)carbamate



A solution of *tert*-butyl (5-(4-methyl-3-nitrophenylsulfonamido)pentyl)carbamate (1150 mg, 2.86 mmol) in MeOH (15 mL) was purged three times with argon. Then palladium 10% on carbon (305 mg, 0.286 mmol) was added. The RM was vigorously stirred for 2 h under hydrogen atmosphere.

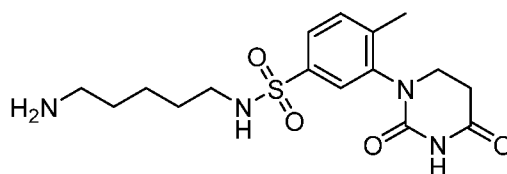
15 The RM was flushed with argon and the black suspension was filtered over a Celite[®] filter aid plug, rinsing with MeOH. The filtrate was concentrated to dryness to afford the title compound (1056 mg). Method LCMS1: Rt = 0.96 min; [M+H]⁺ = 372.3.

Step 3: 3-((5-(N-(5-((*tert*-Butoxycarbonyl)amino)pentyl)sulfamoyl)-2-methylphenyl)amino)propanoic acid



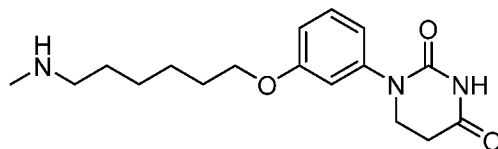
To a solution of *tert*-butyl (5-(3-amino-4-methylphenylsulfonamido)pentyl)carbamate (1045 mg, 2.67 mmol) in water (5 mL) at RT was added acrylic acid (1.2 mL, 17.48 mmol). The resulting dark solution was stirred at 70 °C for 5 h and then at RT for 2 days. The RM was concentrated to dryness and used in the next step without further purification.

Step 4: N-(5-Aminopentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzenesulfonamide



To a solution of 3-((5-(N-(5-((*tert*-butoxycarbonyl)amino)pentyl)sulfamoyl)-2-methylphenyl)amino)propanoic acid (crude, 2.56 mmol) in AcOH (10 mL) was added urea (0.5 g, 8.33 mmol). The RM was stirred at 120 °C overnight. The RM was concentrated to dryness. The crude material was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aqueous solution of TFA (0.1%) (from 2% to 100%) to afford the TFA salt of the title compound as a liquid (245 mg). Method LCMS1: $R_t = 0.42$ min; $[M+H]^+ = 369.2$.

ILB-54: 1-(3-((6-(Methylamino)hexyl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



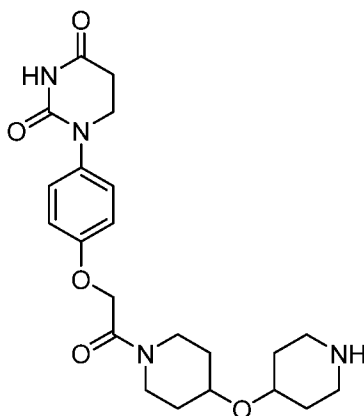
To *tert*-butyl (6-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)(methyl)carbamate (ILB-50, 105 mg, 0.250 mmol) in solution in THF (5 mL) was added HCl (4 M) in dioxane (2.0 mL, 8.00 mmol). The resulting solution was stirred at RT for 2 h, then evaporated to dryness and

further dried under vacuum over P₂O₅ overnight to afford the title compound as an HCl salt (85 mg). Method LCMS1: Rt = 0.56 min; [M+H]⁺ = 320.2.

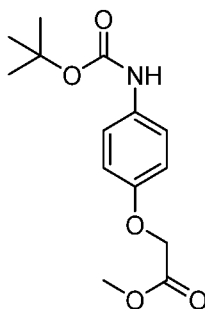
ILB-55:

1-(4-(2-Oxo-2-(4-(piperidin-4-yloxy)piperidin-1-

5 yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

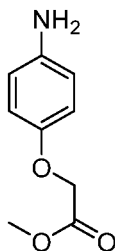


Step 1: methyl 2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)acetate



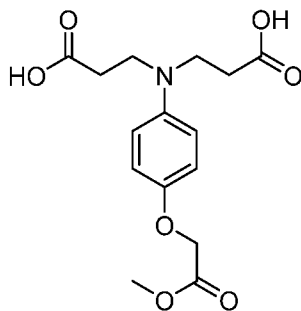
To a 250 mL round bottom flask were added *tert*-butyl (4-hydroxyphenyl)carbamate (7 g, 31.8 mmol), Cs₂CO₃ (11.4 g, 35.0 mmol), KI (5 mg, 0.301 mmol), and acetone (75 mL). Methyl bromoacetate was added and the RM was stirred at 70 °C for 4 h. The RM was cooled to RT, filtered and the filtrate was concentrated. The residue was diluted with EtOAc, washed with a sat. aq. solution of NaHCO₃, dried over MgSO₄, and evaporated. The residue was purified by chromatography on silica gel eluting with EtOAc (from 0% to 25%) in CHX, yielding the title compound as a solid (8.83 g). Method LCMS1: Rt = 0.97 min; [M+H]⁺ = 282.

Step 2: methyl 2-(4-aminophenoxy)acetate



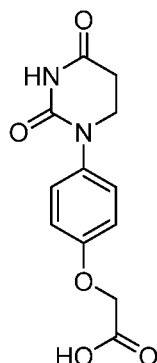
To a 100 mL round bottom flask were added methyl 2-(4-((*tert*-butoxycarbonyl)amino)phenoxy)acetate (8.83 g, 31.4 mmol), TFA (30 mL, 389 mmol) and 1,4-dioxane (30 mL). The RM was stirred at RT for 18 h and concentrated. The residue was diluted with DCM, the organic phase was washed with a sat. aq. solution of NaHCO₃ and dried over MgSO₄, yielding the title compound as an oil (5.35 g), which was directly used for next step without further purification. Method LCMS1: Rt = 0.37 min; [M+H]⁺ = 182.

Step 3: 3,3'-((4-(2-methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid



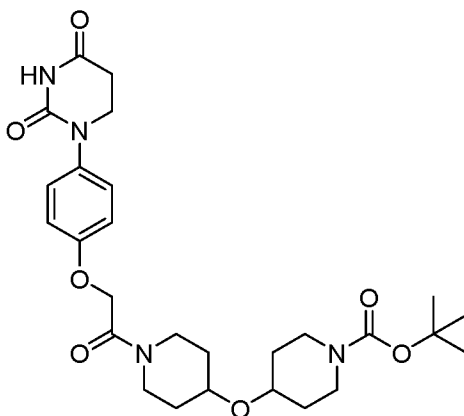
To a 100 mL round bottom flask were added methyl 2-(4-aminophenoxy)acetate (5.35 g, 25.7 mmol), acrylic acid (11 mL, 160 mmol) and water (5 mL). The RM was stirred at 70 °C for 1.5 h. The RM was cooled to RT, adsorbed on Isolute[®] and purified by chromatography on silica gel eluting with a mixture (4:1) of DCM and iPrOH (from 0% to 50%) in DCM, yielding the title compound as a solid (8.24 g). Method LCMS1: Rt = 0.47 min; [M+H]⁺ = 326.

Step 4: 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid



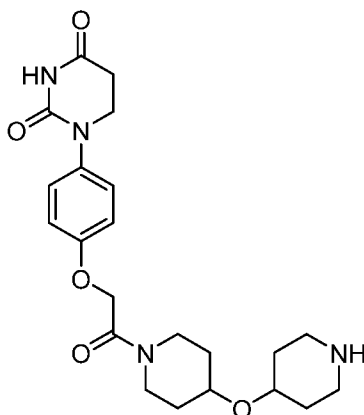
To a 250 mL round bottom flask were added 3,3'-((4-(2-methoxy-2-oxoethoxy)phenyl)azanediyl)dipropionic acid (8.24 g, 25.09 mmol), urea (2.26 g, 37.6 mmol) and HOAc (60 mL). The RM was stirred at 120 °C overnight, an aq. solution of HCl (4 M, 80 mL) was added and the RM was stirred at 120 °C for 45 min. The RM was cooled to 0 °C and filtered, yielding the title compound as a solid (4.93 g). Method LCMS1: Rt = 0.75 min; [M+H]⁺ = 265.

Step 5: *tert*-Butyl 4-((1-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetyl)piperidin-4-yl)oxy)piperidine-1-carboxylate



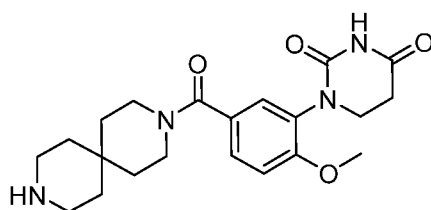
To a 50 mL round bottom flask were added *tert*-butyl 4-(piperidin-4-yloxy)piperidine-1-carboxylate (intermediate A, 538 mg, 1.892 mmol), 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (500 mg, 1.892 mmol), HATU (863 mg, 2.271 mmol), TEA (0.800 mL, 5.74 mmol) and DMF (8 mL). The RM was stirred at RT for 6 h. The mixture was diluted with EtOAc and water, the aqueous layer was extracted with EtOAc, the combined organic phases were washed with brine and dried over MgSO₄, yielding the title compound as a solid (795 mg), which was directly used for next step without further purification. Method LCMS1: Rt = 0.90 min; [M+H]⁺ = 531.

Step 6: 1-(4-(2-oxo-2-(4-(piperidin-4-yloxy)piperidin-1-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



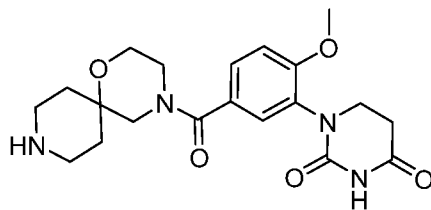
- 5 To a 25 mL round bottom flask were added *tert*-butyl 4-((1-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (795 mg, 1.423 mmol), a solution of HCl (4 M) in 1,4-dioxane (10 mL, 40.0 mmol), MeOH (5 mL), and DCM (5 mL). The RM was stirred at RT for 1 h, concentrated, diluted with water and freeze dried, yielding the corresponding HCl salt of the title compound as a solid (785 mg). Method LCMS1: Rt = 0.43 min;
10 $[M+H]^+ = 431$.

ILB-56: **1-(2-methoxy-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

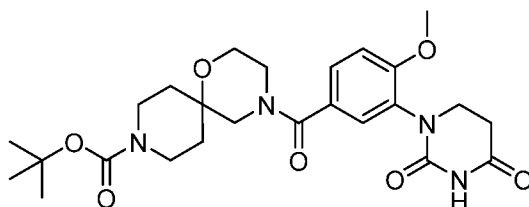


- 15 This compound was prepared as described in PCT/IB2019/052346 intermediate 21.

ILB-57: **1-(2-methoxy-5-(1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

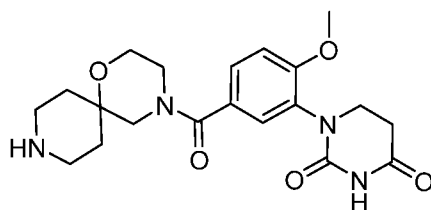


Step 1: *tert*-Butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



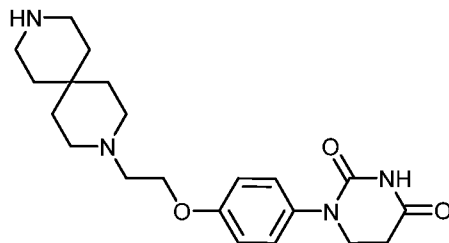
5 A mixture of *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (CAS No. [930785-40-3], 256 mg, 1 mmol), 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid (ILB-26, 264 mg, 1 mmol) and K_2CO_3 (276 mg, 2 mmol) in DMF (6 mL) was stirred at RT, then HATU (570 mg, 1.5 mmol) was added and the mixture was stirred at RT for 2 h. After filtration, the mixture was purified by reverse phase chromatography using Method PA on a Xtimate[®] C18
10 column eluting with ACN in an aq. solution of TFA (0.1%) to afford the title compound as a yellow solid (450 mg). Method XF: $R_t = 1.16$ min; $[M-Boc+H]^+ = 403$.

Step 2: 1-(2-methoxy-5-(1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)phenyl) dihydropyrimidine-2,4(1H,3H)-dione

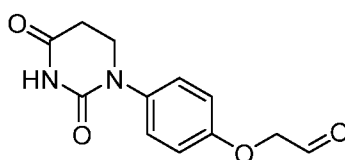


15 A mixture of *tert*-butyl 4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (450 mg, 0.9 mmol) in DCM (3 mL) was stirred at RT. Then, TFA (3 mL) was added and the mixture was stirred at RT for 16 h. The solvent was removed *in vacuo* to afford the title compound as a yellow solid TFA salt (760 mg). Method XF: $R_t = 0.72$
20 min; $[M+H]^+ = 403$.

ILB-58: 1-(4-(2-(3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

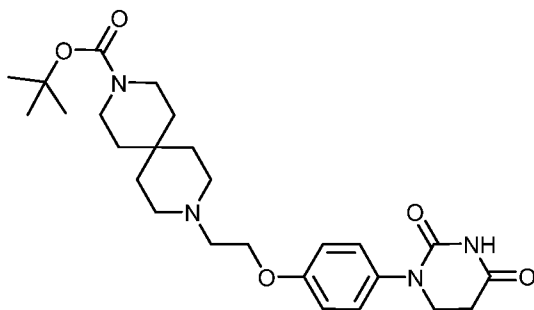


Step 1: 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde



5 To a solution of 1-(4-(2,2-dimethoxyethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-21, 190 mg, 0.646 mmol) in acetone (2 mL) was added 2M HCl (1.6 mL, 3.23 mmol). The RM was stirred at 50°C for 18 h. The precipitate was collected by filtration and dried under high vacuum for 18h to afford the title compound (91 mg). Method XP-A: Rt = 046 min; [M+H]⁺ = 249.2.

Step 2: *tert*-Butyl 9-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

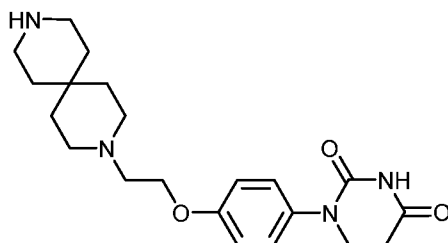


15 To a white mixture of 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde (100 mg, 0.403 mmol) and *tert*-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (CAS No. [173405-78-2], 113 mg, 0.443 mmol) in MeOH (8 mL) was added ZnCl₂ 0.5 M in THF (0.886 mL, 0.443 mmol). The resulting white mixture was flushed with N₂ and stirred at RT for 4.5 h. Then, NaBH₃CN (40 mg, 0.604 mmol) was added, the RM was stirred at RT for 18 h, diluted with ACN and concentrated to afford a white resin. The resin was dissolved in MeOH/ACN, adsorbed on

20

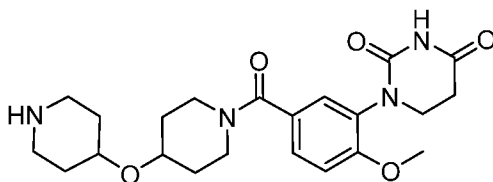
Isolute[®], concentrated, and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound as a white solid TFA salt (229 mg). Method LCMS1: Rt = 0.69 min; [M+H]⁺ = 487.4.

- 5 **Step 3:** 1-(4-(2-(3,9-diazaspiro[5.5]undecan-3-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



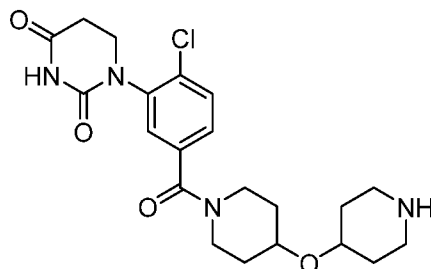
- 10 To a colorless solution of *tert*-butyl 9-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (228 mg, 0.380 mmol) in DCM (5.4 mL) was added TFA (877 μ L, 11.39 mmol). The resulting solution was stirred at RT for 1 h, diluted with DCM, concentrated until dryness, then co-evaporated with DCM, dried under HV pump and freeze dried to afford the title compound as an off-white solid TFA salt (266 mg). Method LCMS1: Rt = 0.19 min; [M+H]⁺ = 387.3.

- 15 **ILB-59: 1-(2-methoxy-5-(4-(piperidin-4-yloxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**

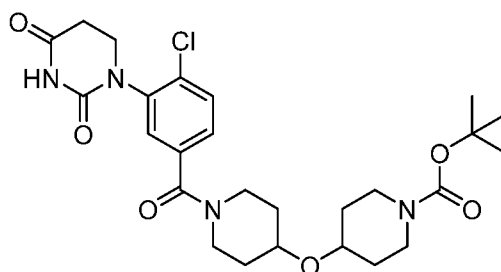


This compound was prepared as described in PCT/IB2019/052346 compound 32, step 2.

- 20 **ILB-60: 1-(2-Chloro-5-(4-(piperidin-4-yloxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione**



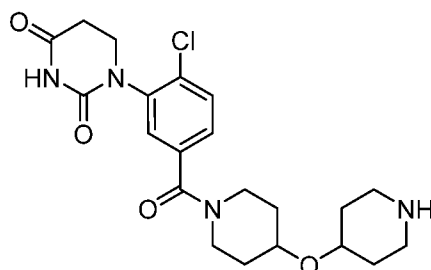
Step 1: *tert*-Butyl 4-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)piperidin-4-yl)oxy)piperidine-1-carboxylate



- 5 To a 50 mL round bottom flask were added HATU (849 mg, 2.233 mmol), 4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoic acid (ILB-25, 500 mg, 1.861 mmol), DIPEA (1 mL, 5.73 mmol) and DMF (10 mL). The RM was stirred at RT for 30 min, solid *tert*-butyl 4-(piperidin-4-yloxy)piperidine-1-carboxylate (CAS No. [845305-83-1], 529 mg, 1.861 mmol) was added and the RM was stirred at RT for 1.5h. The solvent was removed and the residue was purified by
- 10 reversed phase chromatography on a RediSep[®] Gold HP C18 column (50 g) eluting with ACN (from 2% to 100%) in an aq. solution of TFA (0.1%), yielding the title compound as a solid (1.07 g). Method LCMS1: Rt = 0.98 min; [M+H]⁺ = 535.

Step 2: 1-(2-chloro-5-(4-(piperidin-4-yloxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

15

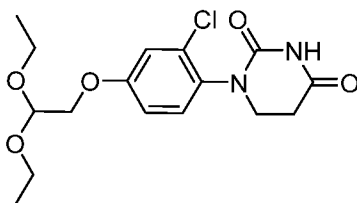


To a 25 mL round bottom flask were added *tert*-butyl 4-((1-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)benzoyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (1.07 g,

1.820 mmol), a solution of HCl (4 M) in 1,4-dioxane (9 mL) and 1,4-dioxane (9 mL). The RM was stirred at RT for 3 h, the solvents were removed, the residue was redissolved in a mixture of water and ACN and freeze dried, yielding the corresponding hydrochloride salt of the title compound as a solid (884 mg). Method LCMS1: Rt = 0.47 min; $[M+H]^+ = 435$.

5

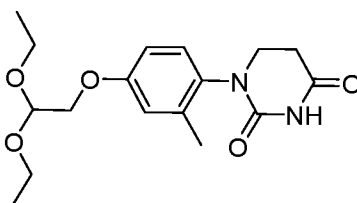
ILB-61: 1-(2-chloro-4-(2,2-diethoxyethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



To a mixture of 1-(2-chloro-4-hydroxyphenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-12, 1.69 g, 7.02 mmol) in DMF (18 mL) was added potassium carbonate (4.37 g, 31.6 mmol) and potassium iodide (0.583 g, 3.51 mmol) at RT. The RM was stirred for 0.5 h at RT. Afterwards 2-bromo-1,1-diethoxyethane (1.091 mL, 7.02 mmol) was added and the RM was heated overnight at 80 °C. UPLC-MS next morning showed the reaction was incomplete. Again 2-bromo-1,1-diethoxyethane (1.091 mL, 7.02 mmol) was added and stirred overnight at 80 °C then standing over the weekend at room temperature. The reaction was stopped. The RM was diluted with AcOEt. The organic phase was washed with water and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to obtain the crude material: brown oil. The crude material was purified by flash chromatography on a silica flash column 24 g eluting with DCM/MeOH to afford the title compound (0.99 g). Method LCMS1: Rt = 0.87 min; $[M+NH_3]^+ = 374.2$.

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ILB-62: 1-(4-(2,2-diethoxyethoxy)-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione

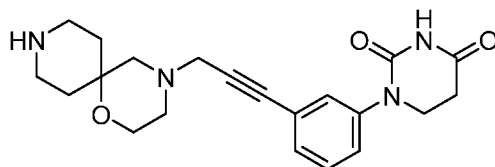


To a mixture of 1-(4-hydroxy-2-methylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-13, 0.95 g, 4.31 mmol) in DMF (10 mL) was added potassium carbonate (2.68 g, 19.41 mmol) and potassium iodide (0.358 g, 2.157 mmol) at room temperature. The RM was stirred for 0.5 h at RT.

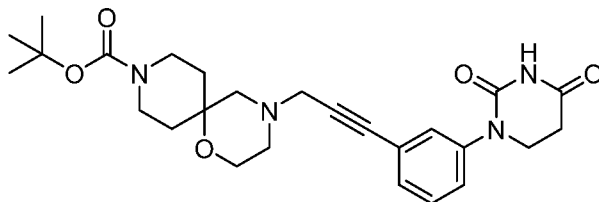
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Afterwards 2-bromo-1,1-diethoxyethane (0.670 mL, 4.31 mmol) was added and the RM was heated overnight at 80 °C. Again 2-bromo-1,1-diethoxyethane (0.670 mL, 4.31 mmol) was added and stirred overnight at 80 °C. The RM was diluted with AcOEt. The organic phase was washed with water and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated *in vacuo* to obtain the crude material: 1.68 g brown oil. The RM was concentrated and absorbed on silica gel and purified by flash chromatography on a silica flash column 24 g eluting with DCM/MeOH to afford the title compound (0.52 g). Method LCMS1: Rt = 0.83 min; [M+H₂O]⁺ = 354.2.

10 ILB-63: 1-(3-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

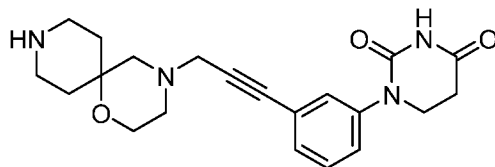


15 **Step 1:** *tert*-butyl 4-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate



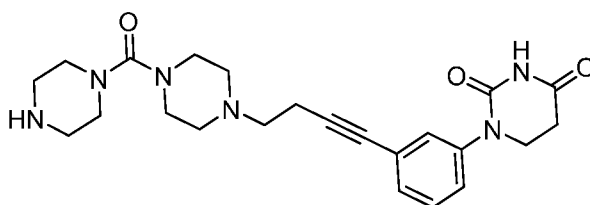
A mixture of Intermediate EE (500 mg, 1.58 mmol), Intermediate DD (559 mg, 1.90 mmol), Pd(PPh₃)₂Cl₂ (56 mg, 0.08 mmol), CuI (30 mg, 0.16 mmol), and Et₃N (0.7 mL, 4.75 mmol) in DMF (5 mL) was stirred at 60 °C for 16 h. The reaction mixture was poured into 50 mL H₂O, extracted with EtOAc (2 × 50 mL), washed with water, brine, dried, and concentrated. The crude residue was purified by silica gel column chromatography (0% to 60% EtOAc in PE) to give the desired product as light yellow solid (500 mg). Method G: Rt = 1.86 min, [M-Boc+H]⁺ = 383.

25 **Step 2:** 1-(3-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

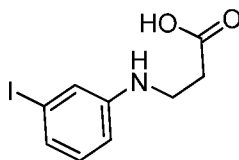


tert-Butyl 4-(3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (Step 1, 500 mg, 1.04 mmol) was dissolved in TFA/DCM (3 mL/1 mL) at RT and the mixture was stirred at RT for 16 h. The mixture was concentrated to give 500 mg of the desired product as dark brown gummy oil. Method G: $R_t = 1.41$ min, $[M+H]^+ = 383$

ILB-64: 1-(3-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

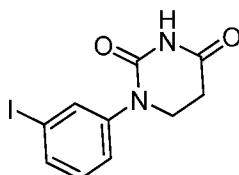


Step 1: 3-((3-iodophenyl)amino)propanoic acid



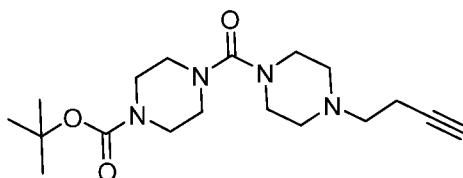
To a solution of 3-iodoaniline (10 g, 45.66 mmol) in toluene (131 mL) was added acrylic acid (4.28 g, 59.36 mmol). The mixture was stirred at 115 °C for 48 h. The solvent was removed to obtain the title compound as an orange oil (15 g, crude). Method H: $R_t = 1.36$ min; $[M+H]^+ = 291.9$.

Step 2: 1-(3-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione



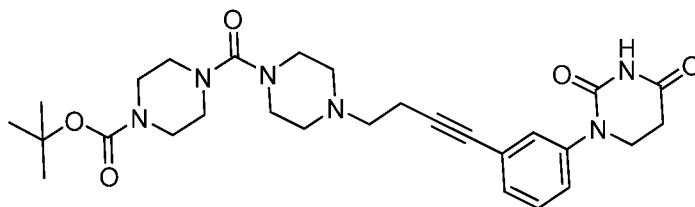
To a solution of 3-((3-iodophenyl)amino)propanoic acid (15 g, 51.5 mmol) in AcOH (125 mL) was added urea (9.284 g, 154.6 mmol). The mixture was stirred at 120 °C for 16 h. The solvent was removed and water (200 mL) was added. The mixture was filtered. The filter cake was washed with water (2 × 20 mL) and dried under vacuum. The solid was suspended in EtOAc (60 mL),
 5 trituated for 16 h at RT. The mixture was filtered. The filter cake was washed with EtOAc (2 × 5 mL) and dried to afford the title compound as a pale solid (7.9 g). Method E: Rt = 1.43 min; [M+H]⁺ = 317.0.

Step 3: *tert*-Butyl 4-(4-(but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate



To a suspension of 1-(but-3-yn-1-yl)piperazine dihydrochloride (3.86 g, 17.36 mmol) in DCM (54 mL) flushed with argon was added, at RT, TEA (9.82 mL, 70.5 mmol). Then, a solution of 4-Boc-1-piperazinecarbonyl chloride in DMF (18 mL) was added slowly (exothermic), and the light brown RM was stirred at RT for 2 days. The RM was diluted with DCM (25–30 mL) and water
 15 (90 mL) and the layers were separated. The aq. layer was extracted with EtOAc (60 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under HV to give the title compound as a yellow-beige solid (6.23 g). Method LCMS1: Rt = 0.59 min; [M+H]⁺ = 351.1.

Step 4: *tert*-Butyl 4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate

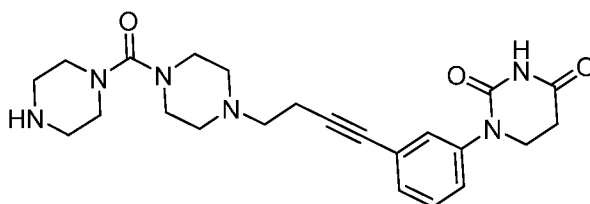


To a solution of *tert*-butyl 4-(4-(but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate (420 mg, 1.2 mmol) in DMF (3 mL) was added 1-(3-iodophenyl)dihydropyrimidine-2,4(1H,3H)-dione (316 mg, 1 mmol), CuI (38 mg, 0.2 mmol) and TEA (607 mg, 6 mmol) at RT. The RM was
 25 degassed by bubbling N₂ through the mixture for 5 min then Pd(PPh₃)₂Cl₂ (70 mg, 0.1 mmol) was

added. The RM was stirred at 45 °C for 1 h. The RM was poured into 100 mL water and filtered. The crude filter cake was dried then purified by chromatography on a 25 g silica gel Biotage[®] column eluting with MeOH in DCM (from 0 to 10%) over 30 min to afford the title compound as a grey foam (350 mg). Method H: Rt = 1.76 min; [M+H]⁺ = 539.

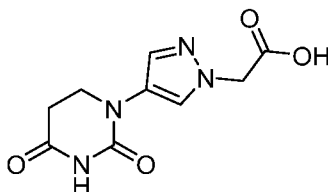
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Step 5: 1-(3-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

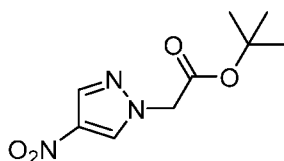


A solution of *tert*-butyl 4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazine-1-carboxylate (265 mg, 0.492 mmol) in DCM (5 mL) and TFA (1 mL) was stirred at RT for 3 h. The solvent was removed. MTBE (10 mL) was added and the mixture concentrated (repeated 3 times) to obtain the title compound as a grey semi-solid TFA salt (300 mg, crude). Method H: Rt = 1.357 min; [M+H]⁺ = 439.

15 **ILB-65: 2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)acetic acid**



Step 1: *tert*-Butyl 2-(4-nitro-1H-pyrazol-1-yl)acetate

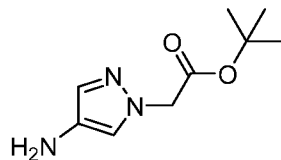


To a solution of 4-nitro-1H-pyrazole (10 g, 88.4 mmol) in ACN (100 mL) at 25 °C was added cesium carbonate (8 mL, 8 mmol) and *tert*-butyl 2-bromoacetate (14.3 mL, 17.3 g, 88.4 mmol) and the reaction mixture was heated at 80 °C for 5 h. The RM was poured into water and extracted with EtOAc (4 x 50 mL). The organic phase was washed brine (2 x 50 mL), dried over Na₂SO₄ and concentrated in vacuo to give crude *tert*-butyl 2-(4-nitro-1H-pyrazol-1-yl)acetate as a brown

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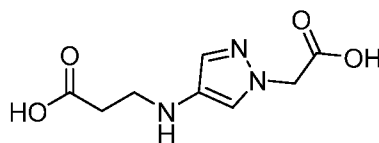
solid (21 g) which was used directly in step 2 without further purification. LCMS10: $R_t = 1.006$ min; $[M+H-56]^+ = 172$.

Step 2: tert-Butyl 2-(4-amino-1H-pyrazol-1-yl)acetate



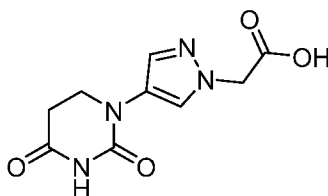
- 5 To a solution of crude tert-butyl 2-(4-nitro-1H-pyrazol-1-yl)acetate (21 g) in MeOH (100 mL) at 25 °C was added iron (51.6 g, 924 mmol) and a saturated solution of ammonium chloride in water (100 mL). The reaction mixture was heated at 80 °C for 2 h. The RM was cooled to RT, filtered through a pad of Celite® and the cake was washed with EtOAc (5 x 70 mL). The filtrate was washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated in vacuo to give a crude oil
- 10 (12 g). The crude was purified by flash chromatography on silica gel eluting with 50–66% EtOAc in PE to afford tert-butyl 2-(4-amino-1H-pyrazol-1-yl)acetate as a black oil (7 g). LCMS10: $R_t = 0.329$ min; $[M+H-56]^+ = 142$.

Step 3: 3-((1-(Carboxymethyl)-1H-pyrazol-4-yl)amino)propanoic acid



- 15 To a solution of tert-butyl 2-(4-amino-1H-pyrazol-1-yl)acetate (5 g, 25.4 mmol) in H₂O (50 mL) at 25 °C was added acrylic acid (2.26 mL, 33.0 mmol). The reaction mixture was heated at 70 °C for 4 h then cooled to RT. The RM was concentrated in vacuo to give crude 3-((1-(carboxymethyl)-1H-pyrazol-4-yl)amino)propanoic acid as a black solid (6.8 g) which was used directly for step 4 without further purification. LCMS10: $R_t = 0.141$ min; $[M+H]^+ = 214$.

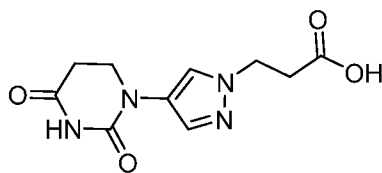
- 20 **Step 4:** 2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)acetic acid



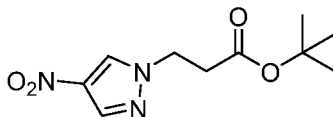
To a solution of crude 3-((1-(carboxymethyl)-1H-pyrazol-4-yl)amino)propanoic acid (6.8 g) in AcOH (50 mL) at 25 °C was added urea (4.55 g, 75.8 mmol). The reaction mixture was heated at 100 °C for 12 h, then cooled to RT. The RM was concentrated in vacuo. EtOH (10 ml) and PE (10

ml) were then added and the mixture stirred at RT. The solid was collected by filtration and washed with cooled PE to afford a crude batch (3 g) which was combined with an additional batch (2.1 g), made under similar conditions, prior to further purification. Thus, the combined filter cake was triturated in MeOH and the solid again collected by filtration. To the black filter cake (2.3 g) was added EtOH (5 mL) and the RM was heated at 80 °C for 2 h. The hot RM was filtered and the filter cake was dried in vacuo providing solid material (1.7 g). An aliquot of this material (300 mg) was purified by reverse phase chromatography on a Water Atlantis[®] T3C column eluting with ACN in an aq. solution of TFA (0.1%) (from 1% to 25%) **Method PA3** to afford 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)acetic acid as a white solid (127 mg). LCMS13: Rt = 2.558 min; [M+H]⁺ = 239. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.39 (s, 1H), 7.95 (s, 1H), 7.61 (s, 1H), 4.92 (s, 2H), 3.77 (t, J = 6.8 Hz, 2H), 2.73 - 2.67(m, 2H).

ILB-66: 3-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)propanoic acid

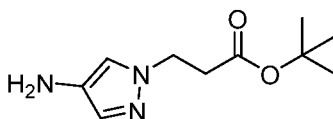


Step 1: tert-Butyl 3-(4-nitro-1H-pyrazol-1-yl)propanoate



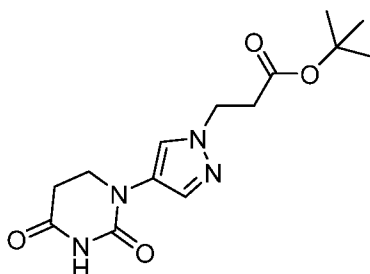
To a solution of 4-nitro-1H-pyrazole (5 g, 44.2 mmol) in DMF (50 mL) at 25 °C was added tert-butyl acrylate (5.67 g, 44.2 mmol) and DBU (10.09 g, 9.9 mL, 66.33 mmol). The reaction mixture was heated at 50 °C for 12 h, then cooled to RT. The RM was poured into water (300 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the desired product (11 g) as a black oil, which was used directly in Step 2 without further purification. LCMS10: Rt=1.05 min, (M+H-56)⁺ = 186.0

Step 2: tert-Butyl 3-(4-amino-1H-pyrazol-1-yl)propanoate



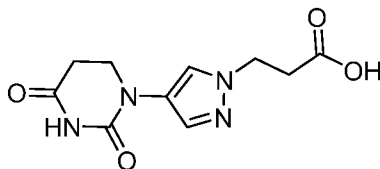
To a solution of tert-butyl 3-(4-nitro-1H-pyrazol-1-yl)propanoate (11 g) in methanol (80 mL), was added iron powder (25.46 g, 456 mmol) and saturated aqueous NH_4Cl (80 mL) at 25 °C. The reaction mixture was then heated and stirred at 80 °C for 2 hrs. The mixture was cooled to RT, filtered through a pad of Celite and the cake was washed with ethyl acetate (4 x 100 mL). The combined organic phase was washed with brine (2 x 50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated to afford the crude product (10 g) as black oil which was used directly in the next step. LCMS10: $R_t=0.628$ min, $(M+H-56)^+ = 156.0$

Step 3: tert-Butyl 3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)propanoate



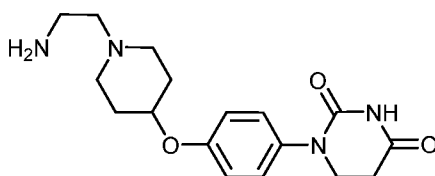
To a solution of tert-butyl 3-(4-amino-1H-pyrazol-1-yl)propanoate (10 g) in water (100 mL) was added acrylic acid 3.41 g, 47.3 mmol). The reaction mixture was heated to 70 °C for 4 h, then cooled to RT. The mixture was concentrated under vacuum to afford a black oil (12.5 g), which was then dissolved in acetic acid (100 mL). Urea (7.95 g, 132 mmol) was added and the reaction mixture was heated to 100 °C for 12 h, then cooled and concentrated under vacuum to remove the acetic acid. The residue was purified by flash column chromatography to provide tert-butyl 3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)propanoate (1.8 g) as a black solid. LCMS10: $R_t=0.942$ min, $(M+H-56)^+ = 253.1$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) ppm = 10.36 (s, 1H), 7.91 (s, 1H), 7.58 (s, 1H), 4.37 - 4.20 (m, 2H), 3.74 (t, $J = 6.8$ Hz, 2H), 2.80 - 2.65 (m, 4H), 1.42 - 1.33 (m, 9H).

Step 4: 3-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)propanoic acid

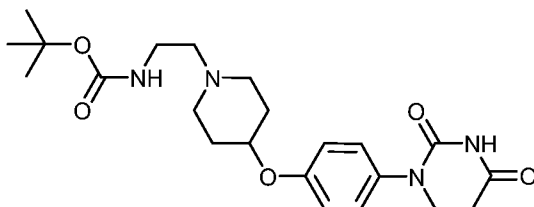


tert-Butyl 3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-1H-pyrazol-1-yl)propanoate (1.8 g, 5.6 mmol) was dissolved in DCM (10 mL) and TFA (2 mL) was added. The reaction mixture was stirred at RT for 4 h, then concentrated under vacuum. The solid residue was purified using reverse phase preparative HPLC eluting with ACN in an aq. solution of $\text{NH}_4\text{CO}_3\text{H}$ (10 mM) to give the title compound as a white solid (125 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 7.88 (s, 1H), 7.54 (s, 1H), 4.21 (t, J = 7.2 Hz, 2H), 3.73 (t, J = 6.8 Hz, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.55-2.40 (m, 2H). LCMS Method LCMS10: R_t =0.325 min, $(\text{M}+\text{H})^+=253$

ILB-68: 1-(4-((1-(2-aminoethyl)piperidin-4-yl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



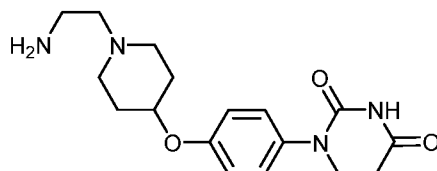
Step 1: tert-Butyl (2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)carbamate



To a colorless solution of 1-(4-(piperidin-4-yloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-36, 200 mg, 0.496 mmol), N-Boc-aminoacetaldehyde (CAS No. [89711-08-8], 91 mg, 0.545 mmol), and TEA (69 μL , 0.496 mmol) in MeOH (10 mL) was added ZnCl_2 0.5 M in THF (1.091 mL, 0.545 mmol). The resulting cloudy solution was flushed with N_2 and stirred at RT. After 3 h at RT, NaBH_3CN (49.2 mg, 0.744 mmol) was added and the RM was stirred at RT for 18 h. More N-Boc-aminoacetaldehyde (25 mg, 0.150 mmol) in MeOH (0.2 mL), followed by more ZnCl_2 0.5 M in THF (300 μL , 0.150 mmol) were added, the RM was stirred at RT for 2 h, before more NaBH_3CN (23 mg, 0.348 mmol) was added. The resulting RM was then stirred at RT for overnight. The RM was diluted with ACN, concentrated until dryness to give a white resin, that was then redissolved in MeOH/ACN, adsorbed on Isolute[®], concentrated until dryness and purified by

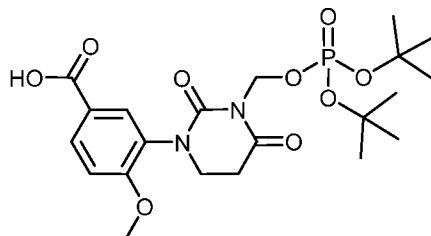
reverse phase chromatography on a Redise[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound as a white solid TFA salt (169 mg). Method LCMS1: $R_t = 0.60$ min; $[M+H]^+ = 433.3$.

5 **Step 2:** 1-(4-((1-(2-aminoethyl)piperidin-4-yl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

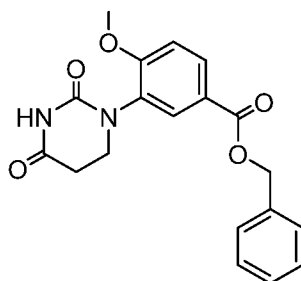


To a colorless solution of *tert*-butyl (2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)carbamate (166 mg, 0.304 mmol) in DCM (4.35 mL) was added TFA (702 μ L, 9.11 mmol). The resulting solution was stirred at RT for 1 h. The RM was diluted
10 with DCM, concentrated until dryness, co-evaporated with DCM (1 $\times$), then dried under HV pump and freeze dried to afford the title compound as a white resin TFA salt (188 mg). Method LCMS1: $R_t = 0.19$ min; $[M+H]^+ = 333.2$.

15 **ILB-69: 3-(3-(((di-*tert*-butoxyphosphoryl)oxy)methyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid**

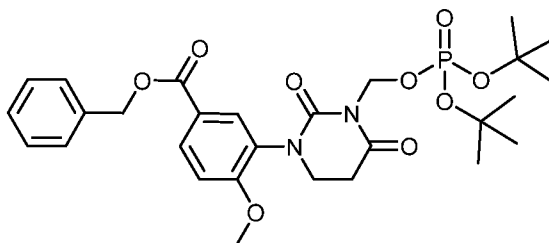


Step 1: Benzyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoate



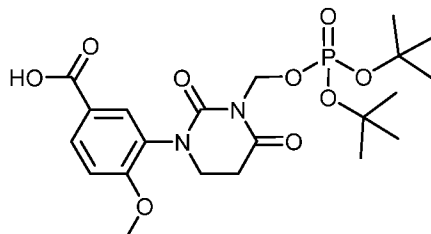
To a solution of 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid (ILB-26, 800 mg, 3.03 mmol) in DMF (25 mL) under N₂ at RT were added 4-(dimethylamino)pyridine (CAS No. [1122-58-3], 407 mg, 3.33 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (CAS No. [25952-53-8], 638 mg, 3.33 mmol) and benzyl alcohol (CAS No. [100-51-6], 0.345 mL, 3.33 mmol). The RM was stirred at RT overnight, then concentrated under vacuum. The residue was purified by flash chromatography on silica gel eluting with 0–100% EtOAc in heptane to afford the title compound as a white powder (730 mg). Method LCMS1: Rt = 0.89 min; [M+H]⁺ = 355.3.

Step 2: Benzyl 3-(3-(((di-*tert*-butoxyphosphoryl)oxy)methyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoate



A mixture of benzyl 3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoate (100 mg, 0.282 mmol), di-*tert*-butyl(chloromethyl) phosphate (CAS No. [229625-50-7]) (0.144 mL, 0.621 mmol), Cs₂CO₃ (276 mg, 0.847 mmol) and KI (94 mg, 0.564 mmol) in dry ACN (1 mL) was flushed with N₂ and stirred at RT for 3 nights. The RM was diluted with EtOAc (5 mL), filtered through a frit, rinsed with EtOAc (2×), then the filtrate was concentrated at 35 °C and dried overnight under HV to afford a crude yellow oil. The oil was purified by flash chromatography on silica gel eluting with 30–100% (CHX/acetone 1/1) in CHX to afford the title compound as a white solid (48 mg). Method LCMS1: Rt = 1.21 min; [M+H]⁺ = 577.2.

Step 3: 3-(3-(((di-*tert*-butoxyphosphoryl)oxy)methyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoic acid



A colorless solution of benzyl 3-(3-(((di-*tert*-butoxyphosphoryl)oxy)methyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoate (46 mg, 0.077 mmol) in a mixture of EtOAc (1.28 mL) and EtOH (0.64 mL) was treated with 10% palladium on activated charcoal (CAS No. [7440-05-3]) (8.2 mg, 7.7 μ mol) and the resulting black RM was stirred at RT under H₂ atmosphere for 1 h. Then, the RM was diluted with EtOAc/EtOH 2/1 (2 mL), then filtered through Hyflo[®] and rinsed with EtOAc/EtOH 2/1 (3 $\times$ 2 mL). The filtrate was then concentrated until dryness to afford the title compound as a white solid (40 mg). Method LCMS1: Rt = 0.88 min; [M+H]⁺ = 487.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.41 (s, 18 H) 2.79 - 3.02 (m, 2 H) 3.62 (br t, J = 6.28 Hz, 2 H) 3.87 (s, 3 H) 5.47 (br d, J = 5.53 Hz, 2 H) 7.22 (d, J = 8.83 Hz, 1 H) 7.86 (d, J = 1.80 Hz, 1 H) 7.93 (dd, J = 8.60, 2.02 Hz, 1 H) 12.83 (s, 1 H).

ILB-71: Ethyl 2-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyridin-3-yl)acetate

ILB-72: Methyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate

15 ILB-73: 1-(5-Chloropyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-74: 1-(5-(Prop-1-en-2-yl)pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-75: 1-(6-(1-Hydroxyethyl)pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-76: 1-(5-Bromopyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-77: 1-(5-Hydroxypyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

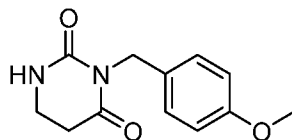
20 ILB-78: Ethyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate

ILB-79: 1-(1H-Pyrazol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione

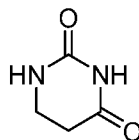
ILB-80: 1-(5-Bromopyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

Compounds ILB-71 to ILB-80 were prepared in a parallel synthesis format requiring the synthetic intermediates PMB-DHU and DMB-DHU:

3-(4-Methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione



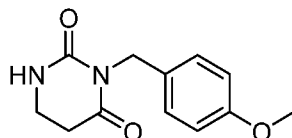
Step 1: Dihydropyrimidine-2,4(1H,3H)-dione



5 Eight parallel reactions: A mixture of pyrimidine-2,4-diol (25.0 g, 223 mmol) and Rh/C (10.0 g) in H₂O (1.5 L) was degassed under vacuum and purged with H₂ several times. The mixture was stirred at 80 °C for 32 h under H₂ (30 psi). Eight parallel reactions were combined and filtered. The filtrate was concentrated to give crude product which was washed with MeOH (2 × 200 mL) to give dihydropyrimidine-2,4(1H,3H)-dione (192 g) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 9.93 (br s, 1H), 7.49 (br s, 1H), 3.20 (dt, *J* = 2.1, 6.7 Hz, 2H), 2.43 (t, *J* = 6.7 Hz, 2H).

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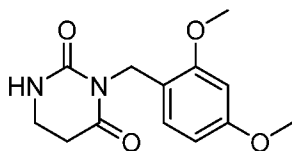
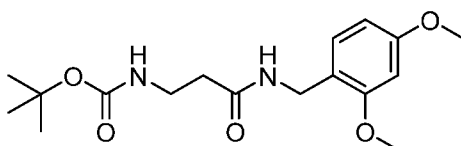
Step 2: 3-(4-Methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione



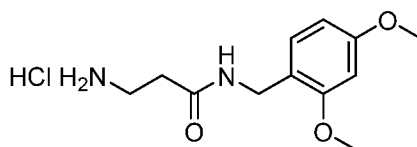
Three parallel reactions: To a mixture of dihydropyrimidine-2,4(1H,3H)-dione (60.0 g, 525 mmol) and Cs₂CO₃ (257 g, 789 mmol) in DMSO (1.2 L) was added a solution of PMBCl (82.4 g, 526 mmol) in CH₂Cl₂ (500 mL) at 20 °C. The mixture was stirred at 20 °C for 15 h. Three parallel reactions were combined and filtered. After addition of brine (6.0 L) to the filtrate, a white precipitate was formed. The solid was collected by filtration and washed with EtOAc (2 × 300 mL). The aqueous filtrate was then extracted with EtOAc (3 × 1 L). The combined organic phases were dried over Na₂SO₄, filtered and concentrated to give the crude product which was washed with EtOAc (2 × 150 mL) to give a white solid. The solid crops were combined and dried to give 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (195 g) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.86 - 7.77 (m, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.71 (s, 2H), 3.71 (s, 3H), 3.27 - 3.14 (m, 2H), 2.62 (t, *J* = 6.8 Hz, 2H).

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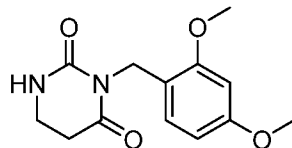
3-(2,4-Dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione**Step 1: *tert*-Butyl (3-((2,4-dimethoxybenzyl)amino)-3-oxopropyl)carbamate**

To a mixture of 3-((*tert*-butoxycarbonyl)amino)propanoic acid (400 g, 2.11 mol) in CH₂Cl₂ (2.4 L) was added a suspension of CDI (360 g, 2.22 mol) in CH₂Cl₂ (0.8 L) at 0 °C. The mixture was stirred at 0 °C for 30 min. DMBNH₂ (424 g, 2.53 mol) was added to the mixture at 0 °C. The mixture was stirred at 25 °C for 1.5 h. The mixture was washed with water (800 mL), sat. aq. Na₂CO₃ (2 × 800 mL), HCl aq. (2 × 800 mL) and brine (500 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give *tert*-butyl (3-((3,4-dimethoxyphenyl)amino)-3-oxopropyl)carbamate (540 g) as a white solid which was used directly for step 2 without further purification. [M+H]⁺ = 339.1.

Step 2: 3-Amino-N-(2,4-dimethoxybenzyl)propanamide hydrochloride

To the mixture of 3-((3,4-dimethoxyphenyl)amino)-3-oxopropyl)carbamate (step 1, 540 g, 1.6 mol) in EtOAc (4 L) was added a solution of HCl in EtOAc (4 mol/L, 1.6 L). The mixture was stirred at 25 °C for 16 h. The mixture was filtrated and the solid was dried under vacuum to give 3-amino-N-(2,4-dimethoxybenzyl)propanamide hydrochloride (430 g) as a white solid which was used directly for step 3 without further purification. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.41 (br t, J = 5.3 Hz, 1H), 8.29 - 8.05 (m, 3H), 7.13 - 7.03 (m, 1H), 6.52 (s, 1H), 6.48 - 6.43 (m, 1H), 6.40 - 6.27 (m, 4H), 4.21 - 4.10 (m, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.04 - 2.88 (m, 2H), 2.58 (s, 2H).

Step 3: 3-(2,4-Dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione



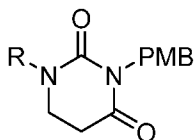
To a mixture of 3-amino-N-(2,4-dimethoxybenzyl)propanamide hydrochloride (step 2, 215 g, 0.78 mol) in DCE (2 L) was added DIEA (299 g, 1.56 mol) at 0 °C. The mixture was stirred at 0 °C for 0.5 h. Then the mixture was added to a suspension of CDI (152 g, 0.94 mol) in DCE (2 L) and stirred at 25 °C for 16 h. The mixture was warmed to 100 °C and stirred at 100 °C for another 4 h. The mixture was washed with aq. citric acid solution (2 × 800 mL) and brine (500 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (170 g, 0.64 mmol) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 7.83 (br s, 1H), 6.83 - 6.68 (m, 1H), 6.58 - 6.50 (m, 1H), 6.47 - 6.34 (m, 1H), 4.74 - 4.63 (m, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 3.32 - 3.24 (m, 2H), 2.73 - 2.62 (m, 2H).

Compounds ILB-71 to ILB-80 were prepared in two steps from either 3-(4-Methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or 3-(2,4-Dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione in a parallel synthesis format:

Step 1: PMB-ILB-76: 1-(5-bromopyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

PMB-ILB-80: 1-(4-bromothiophen-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

PMB-ILB-79: 3-(4-methoxybenzyl)-1-(1H-pyrazol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione

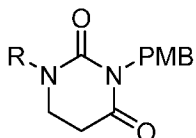


To a mixture of 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (150 mg, 0.64 mmol), heteroaryl bromide (0.83 mmol, 1.3 eq.), K₂CO₃ (266 mg, 3.0 eq.) and DMEDA (6 mg, 0.1 eq.) in DMF (5 mL) was added CuI (12 mg, 0.1 eq.) under N₂. The mixture was stirred at 100 °C for 16 h. To the solution was added thiol resin (500 mg, LS-2000) and the suspension was stirred at RT

for 2 h. The suspension was filtered and concentrated to obtain the crude product without Cu catalyst. The crude product was purified by prep-HPLC (HCOOH) to give the desired products.

PMB-ILB-73: 1-(5-chloropyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

PMB-ILB-78: Ethyl 5-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate

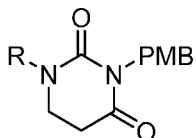


To the mixture of 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (150 mg, 0.64 mmol), heteroaryl bromide (0.83 mol, 1.3 eq.) and K₂CO₃ (266 mg, 1.92 mmol) in DMF (4 mL) was added DMEDA (6 mg, 0.06 mmol) and CuI (12 mg, 0.06 mmol) at 20 °C under N₂. The mixture was stirred at 120 °C for 16 h. To the solution was added thiol resin (500 mg, LS-2000) and the suspension was stirred at 25 °C for 2 h. The suspension was filtered and concentrated to obtain the crude product without Cu catalyst. The crude product was purified by prep-HPLC (HCl or HCOOH) to give the desired products.

PMB-ILB-77: 1-(5-hydroxypyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

1-(5-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione

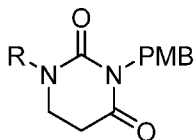
PMB-ILB-75: 1-(6-(1-hydroxyethyl)pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione



To the mixture of 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 0.21 mmol), heteroaryl bromide (0.19 mol, 0.9 eq.) and K₂CO₃ (89 mg, 0.64 mmol) in DMF (2 mL) was added DMEDA (2 mg, 0.02 mmol) and CuI (4 mg, 0.02 mmol) at 20 °C under N₂. The mixture was stirred at 100 °C for 16 h. To the solution was added thiol resin (500 mg, LS-2000) and the suspension was stirred at 25 °C for 2 h. The suspension was filtered and concentrated to obtain the

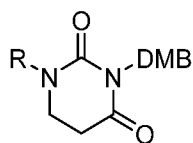
crude product without Cu catalyst. The crude product was purified by prep-HPLC (HCl or HCOOH) to give the desired products.

PMB-ILB-72: methyl 5-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate



5 To the mixture of 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 0.21 mmol), heteroaryl bromide (0.19 mmol, 0.9 eq.), KI (43 mg, 1.2 eq.) and K₂CO₃ (89 mg, 0.64 mmol) in DMF (2 mL) was added DMEDA (2 mg, 0.02 mmol) and CuI (4 mg, 0.02 mmol) at 20 °C under N₂. The mixture was stirred at 110 °C for 16 h. To the solution was added thiol resin (500 mg, LS-
10 2000) and the suspension was stirred at 25 °C for 2 h. The suspension was filtered and concentrated to obtain the crude product without Cu catalyst. The crude product was purified by prep-HPLC (HCl or HCOOH) to give the desired product.

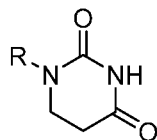
15 DMB-ILB-71: Ethyl 2-(5-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyridin-3-yl)acetate



20 To the mixture of 3-(2,4-dimethoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (50 mg, 0.19 mmol), heteroaryl bromide (0.17 mmol, 0.9 eq.), KI (38 mg, 1.2 eq.) and K₂CO₃ (78 mg, 0.58 mmol) in DMF (1 mL) was added DMEDA (2 mg, 0.02 mmol) and CuI (4 mg, 0.02 mmol) at 20 °C under N₂. The mixture was stirred at 100 °C for 16 h. To the solution was added thiol resin (200 mg, LS-2000) and the suspension was stirred at 25 °C for 2 h. The suspension was filtered and concentrated to obtain the crude product without Cu catalyst. The crude product was purified by prep-HPLC (HCl or HCOOH) to give the desired product.

25 **Step 2: ILB-76: 1-(5-Bromopyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

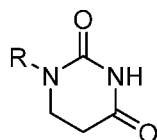
ILB-80: 1-(5-Bromopyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione



A mixture of either 1-(5-bromopyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or 1-(4-bromothiophen-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (1.0 eq., 0.32 mmol) in TFA/TfOH (1/1, 2 mL) was stirred at 20 °C for 2 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (HCOOH) to give the desired product. ILB-76 $[M+H]^+ = 270.0 / 272.0$. ILB-80 $[M+H]^+ = 275.0 / 277.0$.

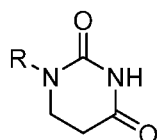
ILB-73: 1-(5-Chloropyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-78: Ethyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate



A mixture of 1-(5-chloropyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or ethyl 5-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate (1.0 eq., 0.20 mmol) in TFA/TfOH (1/1, 2 mL) was stirred at 20 °C for 16 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (HCOOH or HCl) to give the desired product. ILB-73 $[M+H]^+ = 226.1$. ILB-78 $[M+H]^+ = 264.1$.

ILB-79: 1-(1H-pyrazol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione



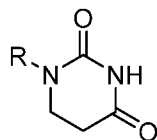
A mixture of 3-(4-methoxybenzyl)-1-(1H-pyrazol-4-yl)dihydropyrimidine-2,4(1H,3H)-dione (0.12 mmol) in TFA/TfOH (5/1, 1 mL) was stirred at 80 °C for 1 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (HCl) to give ILB-79. ILB-79 $[M+H]^+ = 181.0$.

ILB-77: 1-(5-Hydroxypyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-74: **1-(5-(Prop-1-en-2-yl)pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

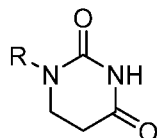
ILB-75: **1-(6-(1-Hydroxyethyl)pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione**

ILB-72: **Methyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate**



5 A mixture of either 1-(5-hydroxypyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or 1-(5-(2-hydroxypropan-2-yl)pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or 1-(6-(1-hydroxyethyl)pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione or methyl 5-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)nicotinate (1.0 eq., 0.10 mmol) in TFA/TfOH (5/1, 1 mL) was
 10 stirred at 60 °C for 2 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (HCOOH) to give the desired product. ILB-77 [M+H]⁺ = 208.1. ILB-74 [M+H]⁺ = 232.1. ILB-75 [M+H]⁺ = 236.1. ILB-72 [M+H]⁺ = 250.0.

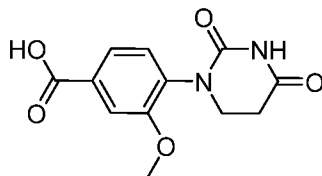
ILB-71: **Ethyl 2-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyridin-3-yl)acetate**



15 A mixture of ethyl 2-(5-(3-(2,4-dimethoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)pyridin-3-yl)acetate (1.0 eq., 0.10 mmol) in TFA (1 mL) was stirred at 80 °C for 48 h. The mixture was concentrated to give a crude product. The crude product was purified by prep-HPLC (HCOOH) to give the desired product. ILB-71 [M+H]⁺ = 278.1.

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ILB-81: **4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzoic acid**



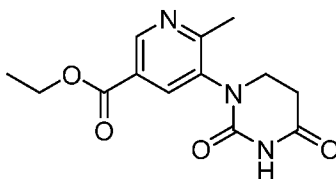
4-amino-3-methoxybenzoic acid (6 g, 35.9 mmol) and acrylic acid (7.5 mL, 108 mmol) were dissolved in acetic acid (23 mL) at RT. H₂SO₄ (11 drops) were added and the resulting brown

suspension was stirred at 100 °C overnight. To the RM was added urea (10.8 g, 180 mmol). The resulting brown suspension was stirred at 120 °C for 2 days. The reaction was concentrated to dryness. The crude material was suspended in 10% aqueous HCl, cooled to 0 °C and filtered. The resultant solid was triturated with MBTE and filtered to afford the title compound (541 mg).

5 Method LCMS2: Rt = 0.80 min; $[M+H]^+ = 265.1$.

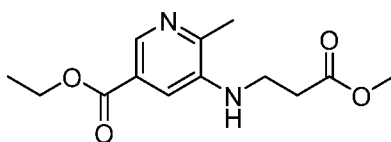
Further material was isolated from the filtrate. The mother liquors were concentrated to dryness and purified by reverse phase chromatography on a RediSep® C18 column eluting with ACN in an aqueous solution of TFA (0.1%) (from 2% to 100%). The appropriate fractions were combined, 10 concentrated to dryness and treated with acetone, observing precipitation. Suspension was filtered and the solid washed with water to afford the title compound as a solid (4.67 g). Method LCMS2: Rt = 0.80 min; $[M+H]^+ = 265.2$.

ILB-82: Ethyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-6-methylnicotinate



15

Step 1: Ethyl 5-((3-methoxy-3-oxopropyl)amino)-6-methylnicotinate

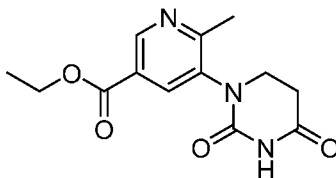


20

A mixture of ethyl 5-amino-6-methylnicotinate (CAS [1008138-73-5]) (700 mg, 3.88 mmol), methyl acrylate (CAS No. [96-33-3], 1.75 mL, 19.42 mmol) in DMF (1.7 mL) and AcOH (170 20 μ L) was heated in a capped vial at 100 °C for 7 days. The RM was diluted with EtOAc, washed with water (3 $\times$) and brine (1 $\times$). The organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with 20–100% EtOAc in DCM to afford the title compound as a yellow solid (420 mg). Method XO: Rt = 1.34 min; $[M+H]^+ = 267.2$.

25

Step 2: Ethyl 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-6-methylnicotinate



A 300 mL round bottom flask containing ethyl 5-((3-methoxy-3-oxopropyl)amino)-6-methylnicotinate (600 mg, 2.253 mmol) and a stirring bar was capped and purged with N₂. Then, THF (20 mL) was added, the flask was cooled in an ice bath, and triphosgene (334 mg, 1.127 mmol) was added. To the flask was then added DIPEA (590 µL, 3.38 mmol) portionwise over 5 min. The mixture was stirred at 0 °C, then slowly warmed to RT and stirred for 2 h. The flask was cooled in an ice bath, NH₃ 7 N in MeOH (22.53 mL, 158 mmol) was added dropwise, and the mixture was slowly warmed to RT and stirred for overnight. The RM was transferred to a sealed pressure tube and heated overnight at 90 °C, then at 100 °C for 24 h. The RM was concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with 5–15% MeOH in DCM to afford a mixture of the title compound and its corresponding methyl ester (500 mg). The mixture was then purified by reverse phase chromatography on a Redise[®] C18 column eluting with ACN in an aq. solution of NH₄OH (0.1%) (from 5% to 80%) to afford, after recrystallization from EtOH, the title compound as colorless crystals (80 mg). Method XP: Rt = 0.99 min; [M+H]⁺ = 278.1

ILB-83: 1-((3-bromothiophen-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-84: 1-((5-(trifluoromethyl)-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-85: 1-((4-bromo-1-methyl-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-87: 2-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)thiazole-4-carboxylic acid

ILB-88: 1-((4-bromo-1H-pyrazol-5-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-89: 1-((3-bromopyridin-4-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-90: 1-((5-bromopyrimidin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

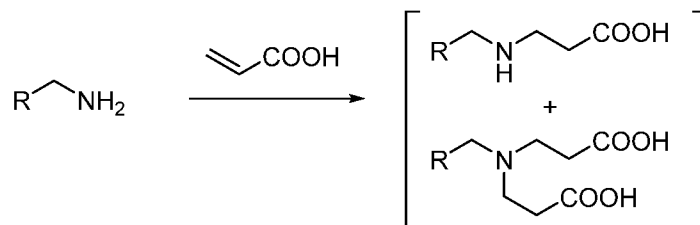
ILB-91: 1-((4-chloropyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-92: 1-((4-bromopyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

ILB-93: 1-((2-amino-5-bromopyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

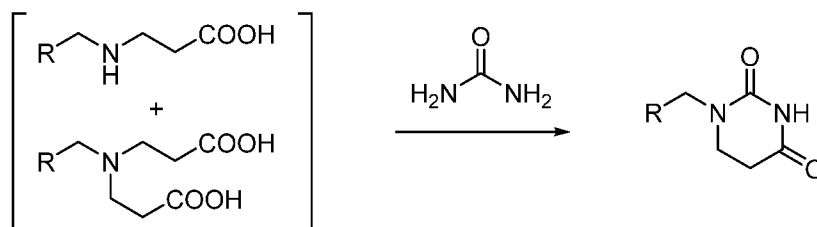
Compounds ILB-83 to ILB-93 were prepared in a parallel synthesis format according to a general procedure:

5 Step 1: Mixture of carboxyethyl-R-methanamines and bis(carboxyethyl)-R-methanamines



To a solution of amine or its salt (1.0 equiv.) in ACN (2.0 mL), acrylic acid (1.1 or 2.0 equiv.) and TEA (1.1 or 4.0 equiv. per each acid equiv. if amine salt used) were added. The resulting mixture was stirred at 80 °C for 4 h. After the completion of the reaction, the resulting mixture was concentrated under reduced pressure. The obtained crude solid was used in the next step without an additional work-up.

15 **Step 2:** 1-R-methandihydropyrimidine-2,4(1H,3H)-diones



The crude product from step 1 (1.0 equiv.) was dissolved in AcOH (2.0 mL) and urea (3.0 equiv.) was added. After stirring the reaction mixture at 130 °C for 16 h, the solvent was removed *in vacuo* and the residue was purified by HPLC (C18 column; MeOH-H₂O mobile phase, gradient is given in the tabulated data, run time 5 min) to afford pure product.

ILB-83: 1-((3-bromothiophen-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

From (3-bromothiophen-2-yl)methanamine (100.1 mg, 0.52 mmol), acrylic acid (75.1 mg, 1.04 mmol) and urea (93.9 mg, 1.56 mmol); after purification (H₂O, 15–65% MeOH gradient) was

obtained 50.6 mg 1-((3-bromothiophen-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as yellow solid. $[M+H]^+ = 291$.

ILB-84: **1-((5-(trifluoromethyl)-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione**

From (5-(trifluoromethyl)-1H-pyrazol-3-yl)methanamine dihydrochloride (90.8 mg, 0.38 mmol), acrylic acid (30.2 mg, 0.42 mmol), urea (68.7 mg, 1.14 mmol) and TEA (84.9 mg, 0.84 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 2.7 mg 1-((5-(trifluoromethyl)-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as white solid. $[M+H]^+ = 263$.

ILB-85: **1-((4-bromo-1-methyl-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione**

From (4-bromo-1-methyl-1H-pyrazol-3-yl)methanamine (99.7 mg, 0.52 mmol), acrylic acid (75.6 mg, 1.05 mmol) and urea (94.5 mg, 1.57 mmol); after purification (H₂O, 5–50% MeOH gradient) was obtained 75.2 mg 1-((4-bromo-1-methyl-1H-pyrazol-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as beige solid. $[M+H]^+ = 287$.

ILB-87: **2-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)thiazole-4-carboxylic acid**

From 2-(aminomethyl)thiazole-4-carboxylic acid hydrochloride (76.3 mg, 0.39 mmol), acrylic acid (56.5 mg, 0.78 mmol), urea (70.6 mg, 1.18 mmol) and TEA (158.6 mg, 1.57 mmol); after purification (H₂O, 0–25% ACN gradient) was obtained 2.6 mg 2-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)thiazole-4-carboxylic acid as yellow solid. $[M+H]^+ = 256$.

ILB-88: **1-((4-bromo-1H-pyrazol-5-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione**

From (4-bromo-1H-pyrazol-5-yl)methanamine hydrobromide (94.1 mg, 0.37 mmol), acrylic acid (29.0 mg, 0.40 mmol), urea (66.0 mg, 1.10 mmol) and TEA (40.8 mg, 0.40 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 2.8 mg 1-((4-bromo-1H-pyrazol-5-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as white solid. $[M+H]^+ = 287$.

ILB-89: **1-((3-bromopyridin-4-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione**

From (3-bromopyridin-4-yl)methanamine dihydrochloride (137.8 mg, 0.53 mmol), acrylic acid (76.4 mg, 1.06 mmol), urea (95.5 mg, 1.59 mmol) and TEA (118 mg, 1.17 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 55.7 mg 1-((3-bromopyridin-4-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as yellow solid. $[M+H]^+ = 284/286$.

5

ILB-90: 1-((5-bromopyrimidin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

From (5-bromopyrimidin-2-yl)methanamine hydrochloride (118.1 mg, 0.53 mmol), acrylic acid (75.8 mg, 1.05 mmol), urea (94.8 mg, 1.58 mmol) and TEA (58.6 mg, 0.58 mmol); after purification (H₂O, 5–55% MeOH gradient) was obtained 8.7 mg 1-((5-bromopyrimidin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as brown solid. $[M+H]^+ = 285/287$.

10

ILB-91: 1-((4-chloropyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

From (4-chloropyridin-2-yl)methanamine (89.2 mg, 0.63 mmol), acrylic acid (90.2 mg, 1.25 mmol) and urea (112.8 mg, 1.88 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 2.4 mg 1-((4-chloropyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as yellow solid. $[M+H]^+ = 240$.

15

ILB-92: 1-((4-bromopyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

From (4-bromopyridin-2-yl)methanamine (98.7 mg, 0.53 mmol), acrylic acid (76.1 mg, 1.04 mmol) and urea (95.1 mg, 1.58 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 2.9 mg 1-((4-bromopyridin-2-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as yellow solid. $[M+H]^+ = 284/286$.

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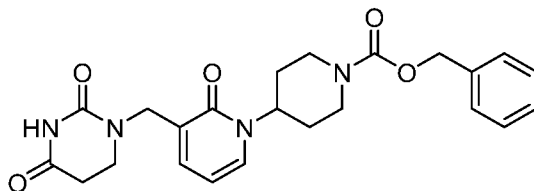
ILB-93: 1-((2-amino-5-bromopyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione

From 3-(aminomethyl)-5-bromopyridin-2-amine (76.5 mg, 0.33 mmol), acrylic acid (26.5 mg, 0.37 mmol) and urea (60.2 mg, 1.0 mmol); after purification (H₂O, 10–60% MeOH gradient) was obtained 9.1 mg 1-((2-amino-5-bromopyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione as yellow solid. $[M+H]^+ = 299/301$.

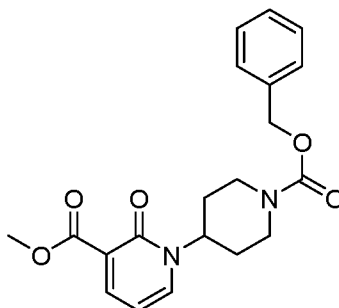
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ILB-94: Benzyl-4-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate

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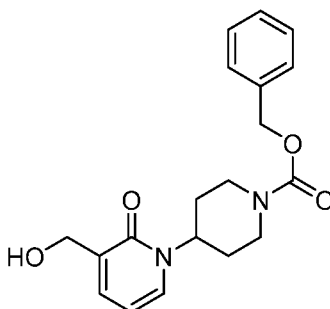


Step 1: Methyl 1-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate



5 This compound was prepared according to a procedure published in WO 2015/89143 A1.

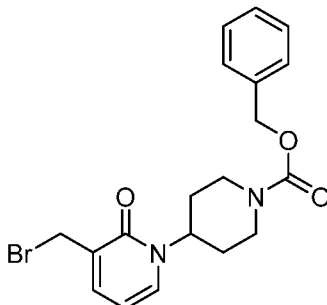
Step 2: Benzyl 4-(3-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate



To a solution of methyl 1-(1-((benzyloxy)carbonyl)piperidin-4-yl)-2-oxo-1,2-dihydropyridine-3-carboxylate (1 g, 2.295 mmol) in dry THF (23 mL) under Ar, was added at -4°C (internal temperature) DIBAL-H, 1 M in toluene (5.05 mL, 5.05 mmol) portion wise in order not to exceed -1°C . Upon completion of the addition, the reaction was allowed to warm and was kept stirring between 0°C and 5°C for 120 min after which time additional DIBAL-H, 1 M in toluene (2 mL, 2 mmol) was added at 0°C . After 3 h at 0°C , the reaction was quenched with the portion wise addition of MeOH (1.3 mL), water (1.3 mL), 15% aq. NaOH (1.3 mL) and water (2.6 mL). The reaction was filtered on a pre-packed Celite[®] filter and the filtrate was concentrated *in vacuo*. The crude was purified by chromatography on a 40 g silica gel column eluting with MeOH in DCM (0

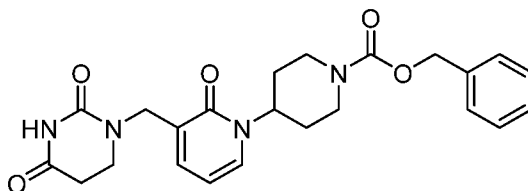
to 20%) over 21 min to afford the title compound as a yellow/orange solid (450 mg). Method LCMS9: Rt = 0.75 min; $[M+H]^+ = 343.3$.

Step 3: Benzyl 4-(3-(bromomethyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate



To a solution of benzyl 4-(3-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate (450 mg, 1.235 mmol) in dry ACN (5 mL) at 0 °C, under Ar, was added $CBBr_4$ (574 mg, 1.730 mmol). PPh_3 (421 mg, 1.606 mmol) dissolved in dry ACN (6.5 mL) was added dropwise over 10 min. Upon completion of the addition, the reaction was further stirred at 0 °C for 2 h. The reaction was concentrated under reduced pressure to leave an oil which was purified by chromatography on a 24 g silica gel column eluting with EtOAc in cyclohexane (0 to 100%) over 23.5 min to afford the title compound as a white foam (330 mg). ^1H NMR (400 MHz, Chloroform-*d*) δ 7.48 (dd, $J = 6.8, 2.0$ Hz, 1H), 7.41–7.31 (m, 5H), 7.30–7.22 (m, 1H), 6.23 (t, $J = 6.9$ Hz, 1H), 5.26–5.07 (m, 3H), 4.47 (s, 2H), 4.45–4.27 (m, 2H), 3.13–2.87 (m, 2H), 1.99–1.87 (m, 2H), 1.78–1.59 (m, 2H).

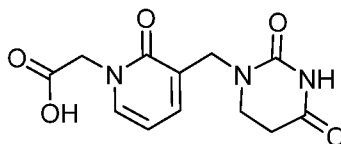
Step4: Benzyl 4-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate



To a solution of intermediate GG (3-((2-(trimethylsilyl)ethoxy)methyl)dihydropyrimidine-2,4(1H,3H)-dione (180 mg, 0.737 mmol) in dry DMF (5 mL) at RT, under Ar, was added NaH, 60% dispersion in mineral oil (58.9 mg, 1.473 mmol). After 5 min, benzyl 4-(3-(bromomethyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate (320 mg, 0.790 mmol) in dry DMF (3 mL) was

- added dropwise to give a clear yellow solution. The reaction was stirred at RT for 50 min. At RT, the RM was poured portionwise in a sat. aq. NH_4Cl solution. EtOAc and water were added. The 2 layers were separated. The aqueous layer was extracted once with EtOAc. The combined organic layers were washed once with aq. 0.1M LiBr sol., once with a 1:1 mixture of a sat. aq. NaCl sol. and water, once with a sat. aq. NaCl sol., dried over MgSO_4 , filtered, and evaporated to give a mixture of benzyl 4-(3-((2,4-dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)tetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate and benzyl 4-(3-((3-(hydroxymethyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate. Chromatography on a 12 g silica gel column eluting with EtOAc in cyclohexane (20% to 100%) then MeOH in DCM (0% to 20%) over 26.4 min provided the pure benzyl 4-(3-((2,4-dioxo-3-((2-(trimethylsilyl)ethoxy)methyl)tetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)piperidine-1-carboxylate (91 mg). Method LCMS9: $R_t = 1.24$ min; $[\text{M}+\text{H}]^+ = 569.5$.
- The remaining mixture (140 mg) was dissolved in DCM (2 mL) and TFA (1 mL) and stirred at RT for 15 min. The RM was evaporated to dryness, taken up in THF (1 mL) and a 5% NH_4OH sol. (1 mL) and stirred for 1 h. The RM was adsorbed on Isolute[®] HM-N and purified by reverse phase chromatography on a 15.5 g C18 column eluting with ACN (2–100%) in an aq. solution of TFA (0.1%) over 14.2 min. The obtained product was dissolved in MeOH (1.4 mL) and further purified by SFC using method XU (250 $\times$ 3 0 Reprospher PEI 100A 5 μm , MeOH/ CO_2 14–22% in 9.3 min, total: 13 min) to afford the title compound as a white solid (3.5 mg). Method LCMS9: $R_t = 0.69$ min; $[\text{M}+\text{H}]^+ = 439.4$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.15 (s, 1H), 7.70 (d, $J = 6.7$ Hz, 1H), 7.41–7.37 (m, 4H), 7.36–7.29 (m, 1H), 7.26 (d, $J = 6.8$ Hz, 1H), 6.25 (t, $J = 6.9$ Hz, 1H), 5.10 (s, 2H), 5.02–4.84 (m, 1H), 4.27 (s, 2H), 4.17 (d, $J = 13.8$ Hz, 2H), 3.42 (t, $J = 6.8$ Hz, 2H), 3.12–2.85 (m, 2H), 2.57 (t, $J = 6.9$ Hz, 2H), 1.82–1.71 (m, 4H).

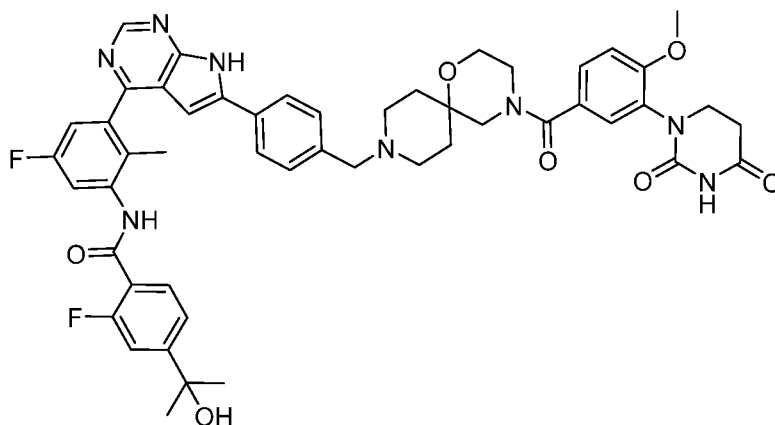
ILB-95: **2-(3-((2,4-Dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)acetic acid**



To a stirred solution of 2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)acetaldehyde (ILB-2, 60 mg, 0.228 mmol) in 3 mL of acetone at RT under argon was added KMnO₄ (72.0 mg, 0.456 mmol). The resulting purple RM was stirred at RT for 2 h. The RM was diluted with a 0.1% aq. solution of TFA and ACN, adsorbed on Isolute[®] and purified by reverse phase chromatography on a 5.5g Redisep[®] C18 Gold column eluting with ACN (from 1 to 100%) in a 0.1% aq. solution of TFA to afford the title compound as an oil (15 mg). Method LCMS12: Rt = 0.14 min; [M+H]⁺ = 280.1.

Example 6: Bifunctional Degradar Synthesis

Compound 01: N-(3-(6-(4-((4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

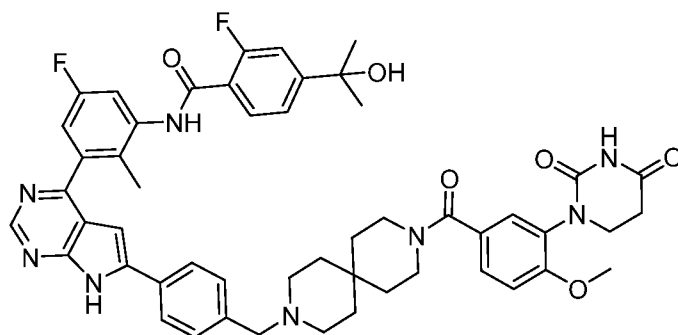


A mixture of 1-(2-methoxy-5-(1-oxa-4,9-diazaspiro[5.5]undecane-4-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-57, 380 mg, 0.45 mmol) and K₂CO₃ (124 mg, 0.9 mmol) in DMSO (4 mL) was stirred at RT for 30 min. Then, 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 236 mg, 0.5 mmol) and ZnCl₂ 1 M in THF (0.5 mL, 0.5 mmol) were added. The resulting mixture was stirred at RT for 1 h. Then, NaBH₃CN (126 mg, 2 mmol) and MeOH (4 mL) were added. The mixture was stirred at RT for 16 h, then purified by reverse phase chromatography using Method PB on a Xtimate[®] C18 column eluting with ACN in an aq. solution of NH₄HCO₃ (10 mM) to afford the title compound as a yellow solid (120 mg). Method XI: Rt = 0.96 min; [M+H]⁺ = 913. ¹H NMR (400 MHz,

DMSO-*d*₆) δ 12.78 (s, 1 H) 10.35 (s, 1 H) 9.95 (s, 1 H) 8.85 (s, 1 H) 7.94 (s, 2 H) 7.73 (t, *J* = 8.0 Hz, 1 H) 7.66 (d, *J* = 9.6 Hz, 1 H) 7.44–7.35 (m, 5 H) 7.24 (d, *J* = 8.9 Hz, 1 H) 7.16 (d, *J* = 8.9 Hz, 1 H) 6.84 (s, 1 H) 5.31 (s, 1 H) 3.84 (s, 3 H) 3.60–3.48 (m, 9 H) 3.33–3.30 (m, 2 H) 2.67 (s, 2 H) 2.48–2.36 (m, 6 H) 2.18 (s, 3 H) 1.74 (s, 2 H) 1.45 (s, 6 H).

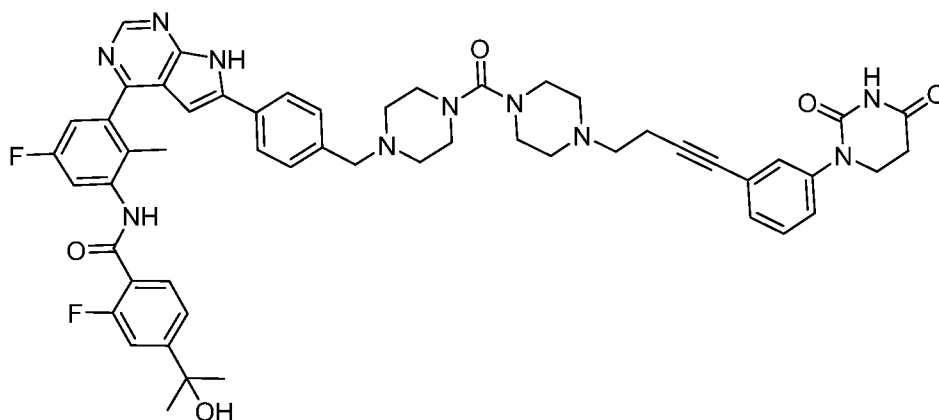
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Compound 02: N-(3-(6-(4-((9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



10 This compound was prepared as described in PCT/IB2019/052346 compound 9.

Compound 03: N-(3-(6-(4-((4-(4-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

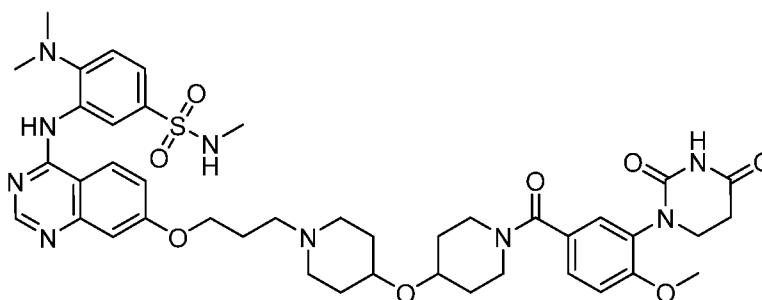


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To a solution of 1-(3-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (300 mg, 0.49 mmol) in DMSO (5 mL) was added K₂CO₃ (204 mg, 1.48 mmol). The solution was stirred for 30 min then 2-fluoro-N-(5-fluoro-3-(6-

(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 216 mg, 0.41 mmol) and ZnCl₂ (0.54 mL, 1 N in THF) were added. After 30 min, NaBH₃CN (46 mg, 0.74 mmol) was added. The reaction mixture was stirred at RT for 16 h. The solution was purified by reverse phase chromatography on a 120 g C18 Biotage[®] column eluting with ACN (0–60%) in an aq. solution of NH₄HCO₃ (0.1%) over 1 h to afford the title compound as a white solid (114 mg). Method G: Rt = 1.77 min; [M+H]⁺ = 949. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.86–12.68 (m, 1H), 10.39 (s, 1H), 9.94 (d, *J* = 2.6 Hz, 1H), 8.85 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.70–7.63 (m, 1H), 7.46–7.37 (m, 4H), 7.36–7.32 (m, 2H), 7.32–7.28 (m, 1H), 7.26–7.20 (m, 2H), 6.84 (d, *J* = 1.7 Hz, 1H), 5.30 (s, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.52 (s, 2H), 3.21–3.09 (m, 8H), 2.69 (t, *J* = 6.6 Hz, 2H), 2.58 (s, 4H), 2.46–2.39 (m, 4H), 2.39–2.32 (m, 4H), 2.18 (s, 3H), 1.45 (s, 6H).

Compound 04: **4-(dimethylamino)-3-((7-(3-(4-((1-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)propoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide**

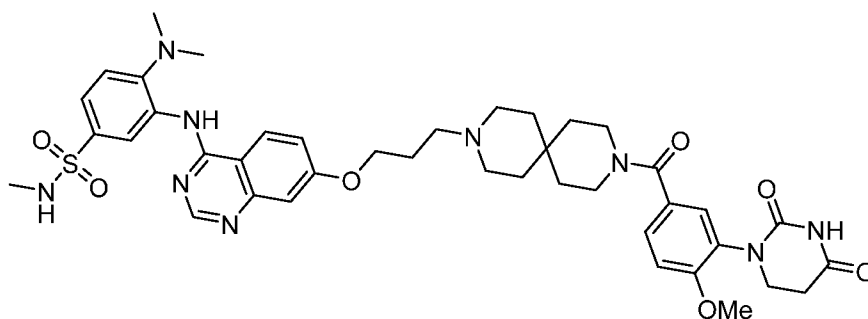


To a suspension of 3-((7-(3-chloropropoxy)quinazolin-4-yl)amino)-4-(dimethylamino)-N-methylbenzenesulfonamide (Intermediate CC, 21.74 mg, 0.048 mmol) and 1-(2-methoxy-5-(4-(piperidin-4-yloxy)piperidine-1-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-59, 20.8 mg, 0.048 mmol) in DMA (483 μL) was added potassium iodide (16.04 mg, 0.097 mmol) and DIPEA (50.6 μL, 0.290 mmol). The resulting solution was stirred at 80 °C for 90 min, then at 60 °C for 18 h. The reaction mixture was diluted with ACN and DMSO and purified via preparative HPLC (XBridge 30 × 50 mm 10–30% MeCN/H₂O (0.1% formic acid) to afford, after filtration of the fractions containing the pure target compound through PL-HCO₃ MP SPE cartridges and freeze drying, the title compound as a white powder (20 mg). Method XR: Rt = 2.04 min; [M+H]⁺ = 844.6. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.33 (s, 1H), 9.43 (s, 1H), 8.43 (s, 1H), 8.36 (d, *J* = 9.2

Hz, 1H), 7.91 (d, $J = 2.3$ Hz, 1H), 7.54 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.43–7.31 (m, 2H), 7.31–7.12 (m, 5H), 4.19 (t, $J = 6.2$ Hz, 2H), 3.84 (s, 3H), 3.69 (s, 2H), 3.59 (t, $J = 6.6$ Hz, 2H), 3.50 (s, 1H), 3.26–3.16 (m, 3H), 2.82 (s, 2H), 2.76 (s, 6H), 2.73–2.63 (m, 3H), 2.57 (d, $J = 13.5$ Hz, 2H), 2.42 (d, $J = 5.2$ Hz, 3H), 2.33 (q, $J = 1.8$ Hz, 1H), 1.97 (s, 2H), 1.82 (s, 4H), 1.43 (s, 4H).

5

Compound 05: **4-(dimethylamino)-3-((7-(3-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)propoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide**



10 To a suspension of 3-((7-(3-chloropropoxy)quinazolin-4-yl)amino)-4-(dimethylamino)-N-methylbenzenesulfonamide (Intermediate CC, 45.0 mg, 0.100 mmol) and 1-(2-methoxy-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-56, 51.4 mg, 0.100 mmol) in DMA (1.0 mL) was added potassium iodide (16.60 mg, 0.100 mmol) and DIPEA (105 μ L, 0.600 mmol). The resulting solution was stirred at 80 $^{\circ}$ C for 72 h. The RM was

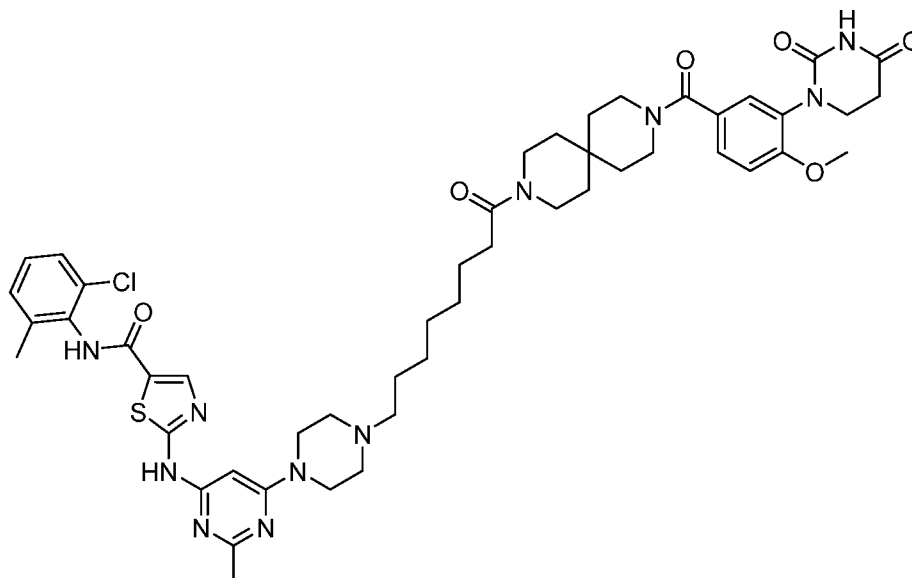
15 concentrated and the residue was purified via flash chromatography (0–40% MeOH / DCM) and then further via preparative HPLC (XBridge 30 $\times$ 50 mm 5–20% MeCN/H₂O (0.1% formic acid) to afford, after filtration of the fractions containing the pure target compound through PL-HCO₃ MP SPE cartridges and freeze drying, the title compound as a white powder (23 mg, 0.028 mmol).

Method XR: Rt = 2.07 min; $[M+H]^+ = 814.7$. ¹H NMR (400 MHz, DMSO-d₆) δ 10.33 (s, 1H),

20 9.42 (s, 1H), 8.43 (s, 1H), 8.35 (d, $J = 9.2$ Hz, 1H), 7.91 (d, $J = 2.4$ Hz, 1H), 7.54 (dd, $J = 8.6, 2.2$ Hz, 1H), 7.37 (dd, $J = 8.5, 2.2$ Hz, 1H), 7.32 (d, $J = 2.1$ Hz, 1H), 7.27 (q, $J = 5.0$ Hz, 1H), 7.25–7.13 (m, 4H), 4.17 (t, $J = 6.2$ Hz, 2H), 3.84 (s, 3H), 3.60 (t, $J = 6.6$ Hz, 2H), 3.45 (d, $J = 23.4$ Hz, 4H), 2.76 (s, 6H), 2.68 (t, $J = 6.6$ Hz, 2H), 2.46–2.41 (m, 5H), 2.41–2.31 (m, 4H), 2.00–1.88 (m, 2H), 1.51 (d, $J = 6.9$ Hz, 4H), 1.42 (s, 4H).

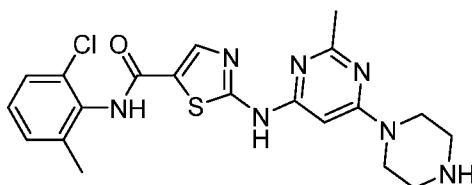
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Compound 06: N-(2-chloro-6-methylphenyl)-2-((6-(4-(8-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (as TFA salt)



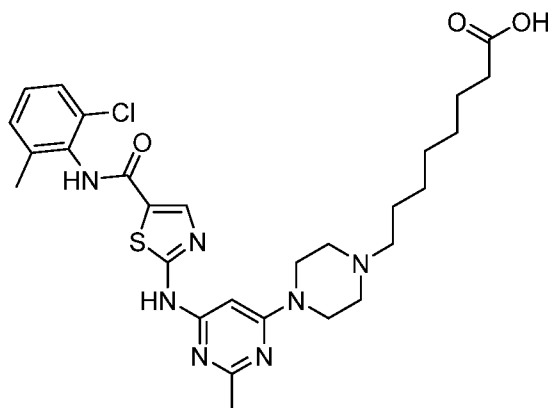
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Step 1: N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide



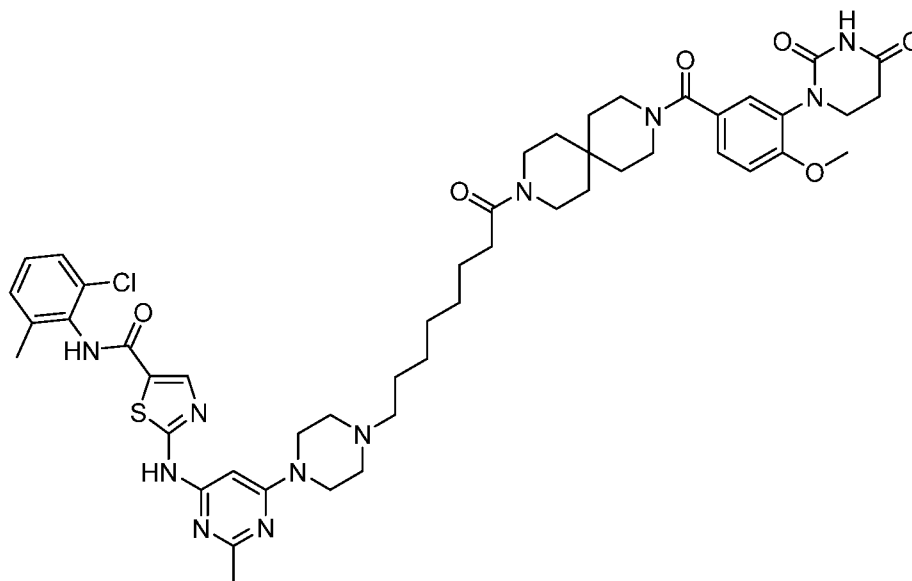
- 10 To a suspension of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (CAS No. [302964-08-5], 1 g, 2.54 mmol) in 1,4-Dioxane (30 mL) piperazine (CAS No. [110-85-0], 2.185 g, 25.4 mmol) and DIPEA (0.886 mL, 5.07 mmol) were added. The RM was heated at 100 °C under stirring for 2 h. Next it was allowed to reach RT and it was stirred for 5 days. The solvent was evaporated under reduced pressure to
- 15 obtain a residue which was triturated sequentially in MeOH/H₂O/, Et₂O/H₂O, and Et₂O to obtain the title compound as a white solid (1.1 g). Method LCMS1: Rt = 0.70 min. [M+H]⁺ = 444.1.

Step 2: 8-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)octanoic acid



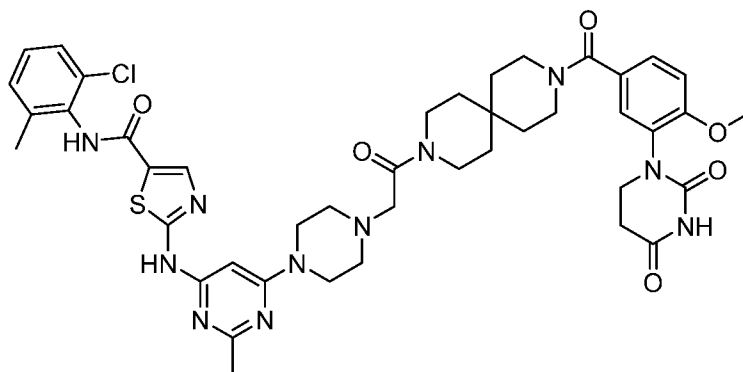
To a suspension of N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (CAS No. [910297-51-7] prepared according to *J. Med. Chem.* 50:5853-5857 (2007), 100 mg, 0.225 mmol) in 1,4-dioxane (1 mL) 8-bromooctanoic acid (CAS No. [17696-11-6], 50.0 mg, 0.225 mmol) and DIPEA (79 μ L, 0.452 mmol) were added. The RM was heated to 100 °C and stirred for 3 days and subsequently stirred at RT for 2 days. The reaction mixture was diluted with DCM (10 mL) and washed with NaHCO₃ saturated aqueous solution (5 mL) and brine (5 mL). The combined organic layers were evaporated to dryness to obtain the solid crude material. The solid was dissolved in water and TFA was added until pH 1. This water solution was extracted with DCM:Isopropanol (7:3) and the organic phase was evaporated to obtain the crude material as a solid. Finally, the crude material was purified via preparative HPLC using the method XX (eluting with ACN in aq. TFA (0.1%) from 5% to 40%) to obtain, after freeze drying, the title compound as a TFA salt (150 mg). Method LCMS1: Rt = 0.79 min; [M+H]⁺ = 586.3.

Step 3: N-(2-chloro-6-methylphenyl)-2-((6-(4-(8-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-8-oxooctyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide

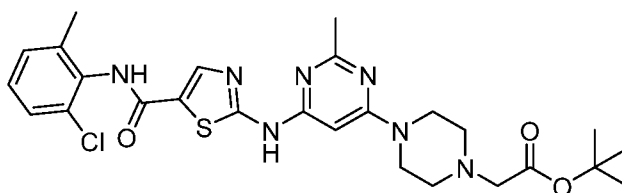


TEA (0.023 mL, 0.166 mmol) was added to a mixture of 8-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)octanoic acid as TFA salt (27 mg, 0.017 mmol) and HBTU (12.59 mg, 0.033 mmol) in DMF (0.5 mL). The resulting RM was stirred at RT for 20 min. A solution of 1-(2-methoxy-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione as HCl salt (ILB-56, 12.81 mg, 0.025 mmol) in DMF (0.2 mL) was added. The resulting mixture was stirred at RT overnight. The reaction mixture was directly purified via preparative HPLC Method XX (eluting with ACN in aq. TFA (0.1%) from 5% to 50%) to afford, after freeze drying, the title compound as a white solid TFA salt (16 mg). Method LCMS1: $R_t = 0.84$ min; $[M+H]^+ = 968.6$ and $[M-H]^- = 966.6$. ^1H NMR (400 MHz, $DMSO-d_6$) δ 11.63 (s, 1H), 10.33 (s, 1H), 9.90 (s, 1H), 9.60 (s, 1H), 8.24 (s, 1H), 7.43–7.20 (m, 5H), 7.15 (d, $J = 8.6$ Hz, 1H), 6.15 (s, 1H), 4.36 (d, $J = 12.7$ Hz, 2H), 3.84 (s, 3H), 3.63–3.54 (m, 3H), 3.39 (s, 4H), 3.20 (dd, $J = 22.1, 9.5$ Hz, 4H), 3.11 (s, 2H), 3.04 (d, $J = 9.5$ Hz, 2H), 2.68 (t, $J = 6.4$ Hz, 2H), 2.45 (s, 3H), 2.26 (d, $J = 17.5$ Hz, 5H), 1.65 (s, 2H), 1.43 (d, $J = 28.4$ Hz, 10H), 1.30 (s, 8H).

Compound 07: **N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide**



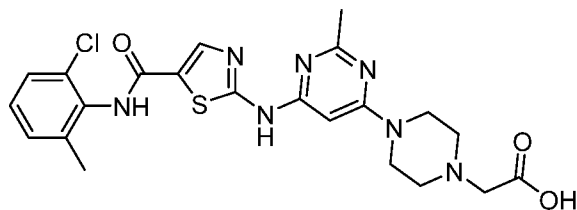
Step 1: *tert*-Butyl 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetate



- 5 DIPEA (2 mL, 11.45 mmol) was added to a mixture of 2-((6-chloro-2-methylpyrimidin-4-yl)amino)-N-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (CAS No. [302964-08-5], 500 mg, 1.268 mmol) and *tert*-butyl 2-(piperazin-1-yl)acetate (CAS No. [827614-56-2], 2000 mg, 9.99 mmol) in DMF (18 mL). The RM was heated in a sealed vial at 110 °C overnight. The RM was cooled to RT and then, it was diluted in EtOAc (100 mL). The obtained solution was washed with
- 10 H₂O (100 mL × 2), brine (100 mL × 2), dried with MgSO₄, and evaporated to dryness. The crude material was purified by flash chromatography on a CombiFlash RF200 equipped with a RediSep[®] Column (silica 40 g), eluting with a gradient from 0% to 10% MeOH in DCM to afford after evaporation under reduced pressure a solid material. This was triturated in EtOAc (40 mL) to afford the title compound as a white solid (532 mg). Method LCMS1: Rt = 0.61 min; [M+H]⁺ =
- 15 558.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 11.47 (s, 1H), 9.87 (s, 1H), 8.21 (s, 1H), 7.40 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 10.1 Hz, 2H), 6.05 (s, 1H), 3.52 (s, 4H), 3.17 (s, 2H), 2.58 (s, 4H), 2.41 (s, 3H), 2.24 (s, 3H), 1.42 (s, 9H).

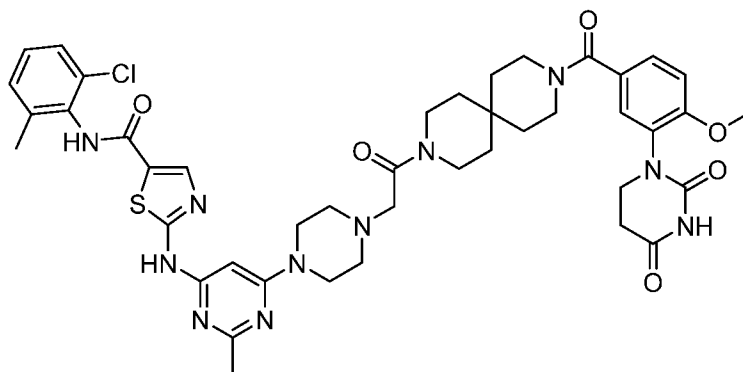
Step 2: 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetic acid

20



HCl in dioxane (4 M) (20 mL, 80 mmol) was added to a suspension of *tert*-butyl 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetate (532 mg, 0.953 mmol) in 50% dioxane/Water (10 mL). The RM was stirred at RT for 14 h. The solvent was removed under reduced pressure and the obtained solid was triturated in n-hexane to afford the title compound as a white solid HCl salt (580 mg). Method LCMS1: $R_t = 0.70$ min; $[M+H]^+ = 502.2$.

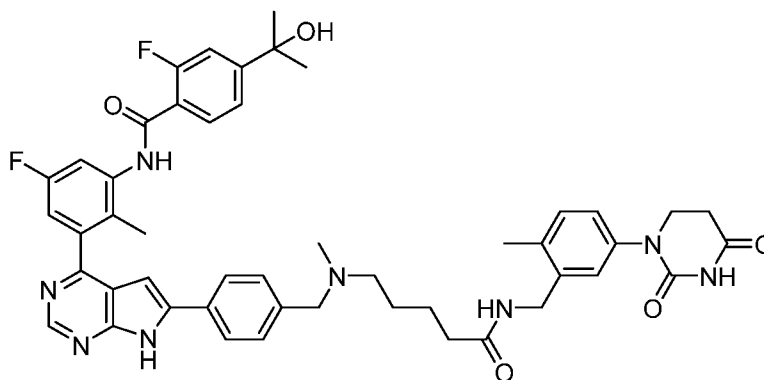
Step 3: N-(2-chloro-6-methylphenyl)-2-((6-(4-(2-(9-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methoxybenzoyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide



TEA (0.045 mL, 0.324 mmol) was added to a mixture of 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetic acid (31 mg, 0.054 mmol) and HBTU (30.7 mg, 0.081 mmol) in DMF (1 mL). The RM was stirred at RT for 30 min. Next 1-(2-methoxy-5-(3,9-diazaspiro[5.5]undecane-3-carbonyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (28.3 mg, 0.065 mmol) was added and the reaction was stirred at RT overnight. Finally, the RM was purified via preparative HPLC Method XX (eluting with ACN in aq. TFA (0.1%) from 5% to 70%) to afford, after freeze drying, the title compound as a white solid TFA salt (27 mg). Method LCMS1: $R_t = 0.80$ min; $[M+H]^+ = 884.5$. ^1H NMR (400 MHz, DMSO- d_6) δ 11.65 (s, 1H), 10.33 (s, 1H), 10.06 (s, 1H), 9.90 (s, 1H), 8.24 (s,

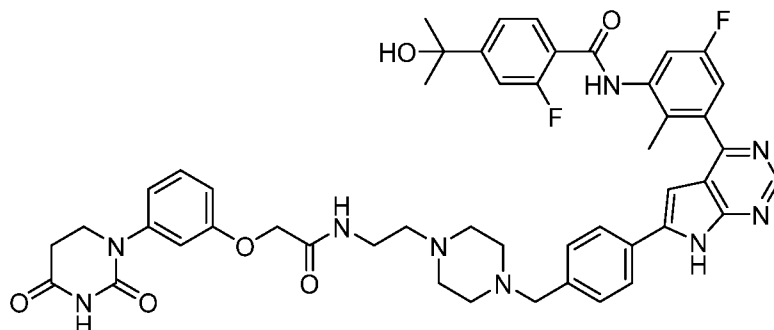
1H), 7.32 (m, 5H), 7.16 (d, $J = 8.6$ Hz, 1H), 6.14 (s, 1H), 4.35 (s, 2H), 4.27 (s, 1H), 3.85 (s, 4H), 3.64 - 3.51 (m, 8H), 3.42 (s, 3H), 3.31 (s, 2H), 3.15 (d, $J = 16.7$ Hz, 2H), 2.69 (d, $J = 6.6$ Hz, 2H), 2.45 (s, 3H), 2.24 (s, 3H), 1.51 (d, $J = 20.8$ Hz, 8H).

- 5 Compound 08: **N-(3-(6-(4-(((5-((5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)amino)-5-oxopentyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**

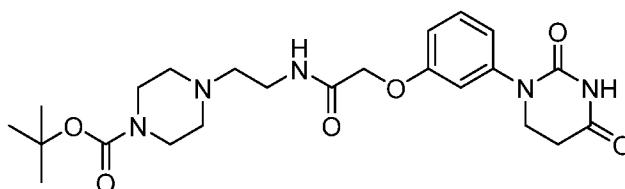


- N-(5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-2-methylbenzyl)-5-(methylamino)pentanamide
 10 (200 mg, 0.38 mmol) in DMSO (2 mL) was added to a mixture of K_2CO_3 (200 mg) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 145 mg, 0.42 mmol) in DMSO (3 mL), followed by the addition of $ZnCl_2$ 1 M (0.4 mL, 0.42 mmol). The RM was stirred at RT for 30 min. $NaBH_3CN$ (48 mg, 0.76 mmol) was added to the RT. The RM was stirred at RT
 15 for an additional 30 min. MeOH (1 mL) was added to the mixture. The RM was stirred at RT for 16 h. The RM was concentrated and filtered to give the crude product as a brown liquid. The crude product was purified by reverse phase HPLC (5% to 95% ACN in H_2O , 0.1% NH_4HCO_3) using method PB to afford the title compound as a white solid (38 mg). Method G: $R_t = 1.77$ min; $[M+H]^+ = 857$. ^1H NMR (500 MHz, $DMSO-d_6$) δ 12.77 (s, 1H), 10.34 (s, 1H), 9.96 (s, 1H), 8.85 (s, 1H), 8.30 (t, $J = 5.7$ Hz, 1H), 7.94 (d, $J = 7.8$ Hz, 2H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.66-7.64 (m, 1H), 7.45-7.35 (m, 4H), 7.24 (dd, $J = 9.0$, 2.8 Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.13-7.07 (m, 2H), 6.84 (s, 1H), 5.31 (s, 1H), 4.22 (d, $J = 5.9$ Hz, 2H), 3.72-3.69 (m, 1H), 3.52-3.43 (m, 3H), 2.80-2.70 (m, 1H), 2.68-2.61 (m, 1H), 2.33 (t, $J = 7.2$ Hz, 2H), 2.18 (s, 3H), 2.16-2.11 (m, 5H), 2.09 (s, 3H), 1.59-1.50 (m, 2H), 1.45 (s, 8H).

Compound 09: N-(3-(6-(4-((4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

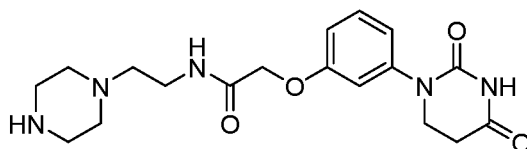


5 **Step 1:** *tert*-Butyl 4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperazine-1-carboxylate



To a mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (ILB-16, 100 mg, 0.378 mmol) in DMF (2 mL) under argon was added NMM (0.208 mL, 1.892 mmol). The mixture was stirred at RT for 5 min. HATU (201 mg, 0.530 mmol) was added and the mixture was stirred at RT for 5 min. *tert*-Butyl 4-(2-aminoethyl)piperazine-1-carboxylate (174 mg, 0.757 mmol) was added and the RM was stirred at RT for 3 h. The RM was partially concentrated, adsorbed on Isolute[®] and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%), to afford the title compound as a TFA salt (185 mg). Method LCMS1: Rt = 0.58 min; [M+H]⁺ = 476.3.

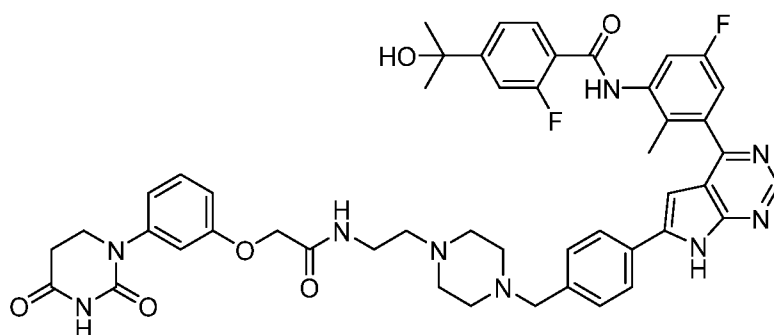
Step 2: 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-N-(2-(piperazin-1-yl)ethyl)acetamide



20 To a solution of *tert*-butyl 4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperazine-1-carboxylate TFA salt (185 mg, 0.389 mmol) in DMF

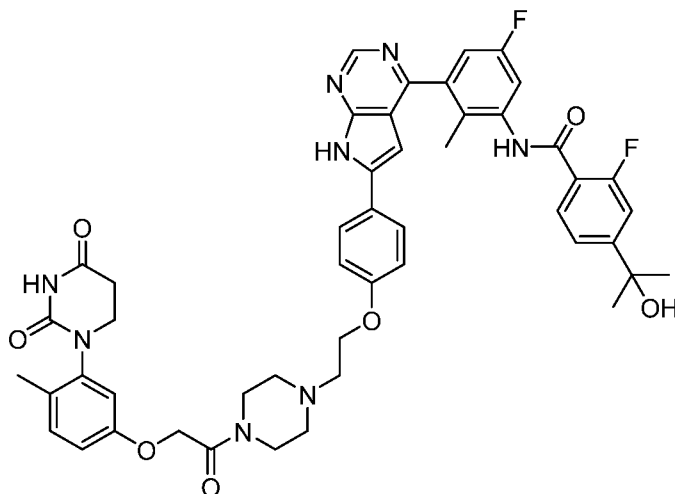
(2 mL) at 0 °C under argon was added a solution of HCl 4M in dioxane (5 mL, 20.0 mmol). The RM was stirred at RT for 45 min and concentrated. The resin was redissolved in a mixture of ACN and water and freeze dried to afford the HCl salt of the title compound as a white powder (145 mg). Method LCMS1: Rt = 0.38 min; $[M+H]^+ = 376.3$.

5
Step 3: N-(3-(6-(4-((4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

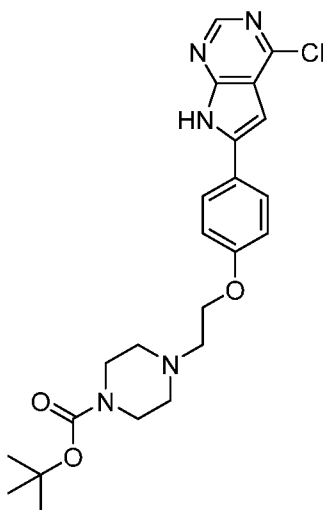


10 To a mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-N-(2-(piperazin-1-yl)ethyl)acetamide HCl salt (120 mg, 0.291 mmol), 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 as described in PCT/IB2019/052346 184 mg, 0.350 mmol) were added TEA (0.081
 15 mL, 0.583 mmol) and MeOH (0.5 mL) at RT under argon. The resulting mixture was stirred at RT for 5 min. A solution of ZnCl₂ 0.5 M in THF (0.699 mL, 0.350 mmol) was added and the RM was stirred at RT for 7.5 h. NaBH₃CN (27.5 mg, 0.437 mmol) was added and the RM was stirred at RT overnight. The RM was partially concentrated, adsorbed on Isolute® and purified by reverse
 20 phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of formic acid (0.5%) (from 5% to 100%), to afford the title compound as a formic acid salt (105 mg). Method LCMS1: Rt = 0.78 min; $[M+H]^+ = 886.6$. ¹H NMR (600 MHz, DMSO-*d*₆) δ 13.66 (m, 1H), 10.40 (s, 1H), 10.08 (d, *J* = 2.5 Hz, 1H), 9.15 (s, 1H), 8.39 (t, *J* = 5.9 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 2H), 7.84–7.77 (m, 1H), 7.74 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.47–7.41 (m, 2H), 7.38 (m, 1H), 7.32 (m, 1H), 7.24 (s, 1H), 6.99 (m, 1H), 6.96 (m, 1H), 6.86 (m, 1H), 4.53 (s, 2H), 4.33
 25 (s, 2H), 3.80–3.07 (m, 14H), 2.70 (t, *J* = 6.6 Hz, 2H), 2.20 (s, 3H), 1.46 (s, 6H).

Compound 10: **N-(3-(6-(4-(2-(4-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetyl)piperazin-1-yl)ethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**



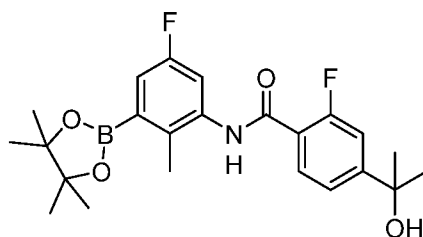
5 **Step 1:** *tert*-Butyl 4-(2-(4-(4-Chloro-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)ethyl)piperazine-1-carboxylate



10 A solution of 4-Chloro-6-iodo-7H-pyrrolo[2,3-d]pyrimidine (CAS No. [876343-10-1], 733 mg, 2.493 mmol), *tert*-butyl 4-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)ethyl)piperazine-1-carboxylate (CAS No. [1310404-00-2], 1100 mg, 2.493 mmol) and cesium carbonate (2031 mg, 6.23 mmol) in 1,4-dioxane (7.5 mL) and water (7.5 mL) was degassed with argon. Pd(dppf)Cl₂ (200 mg, 0.245 mmol) was added and the RM was stirred at 100 °C for 1.5 h. The RM was partitioned between EtOAc and water and extracted. The organic phase was washed with brine, dried over MgSO₄, and concentrated. The crude was purified by

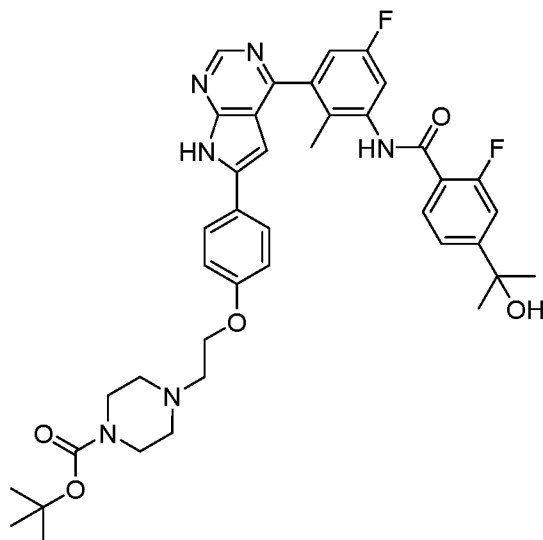
chromatography on silica gel eluting with MeOH in DCM (from 0% to 12.5%) to afford the title compound as a beige solid (1183 mg). Method LCMS1: $R_t = 0.85$ min; $[M+H]^+ = 458.3$.

Step 2: 2-Fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide



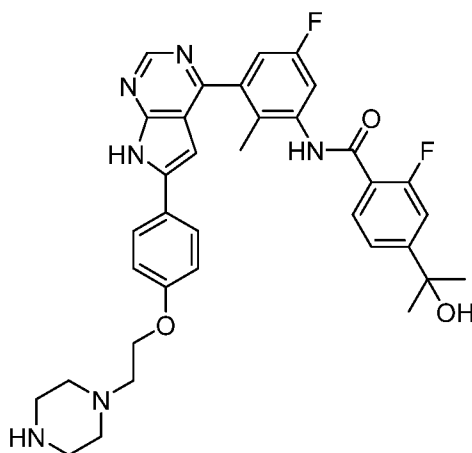
A mixture of 2-fluoro-4-(2-hydroxypropan-2-yl)benzoic acid (6.35 g, 32.0 mmol), HATU (17.06 g, 44.9 mmol) and DIPEA (16.79 mL, 96 mmol) in DMF (100 mL) was stirred at RT for 30 min. Then, 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (can be prepared according to the procedure described in published patent application WO2013/008095 A1, page 37, intermediate 5) (8.47 g, 32.0 mmol) was added and the RM was stirred at 50°C overnight. The RM was diluted with EtOAc and the organic phase was washed with a sat. aq. solution of NaHCO_3 and brine. The combined aqueous phases were extracted again with EtOAc and the combined organic phases were dried over Na_2SO_4 , filtered, concentrated, and purified by chromatography on silica gel eluting with MeOH in DCM (from 0 to 10%). The resulting solid was triturated with Et_2O , filtered, the solids were washed with diisopropyl ether and dried to afford the title compound as a solid (9.28 g). Method A: $R_t = 1.28$ min; $[M+H]^+ = 432.3$. Note: An alternative preparation of intermediate 2 is described in WO2013/008095 A1, page 81, intermediate 35.

Step 3: *tert*-butyl 4-(2-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)ethyl)piperazine-1-carboxylate



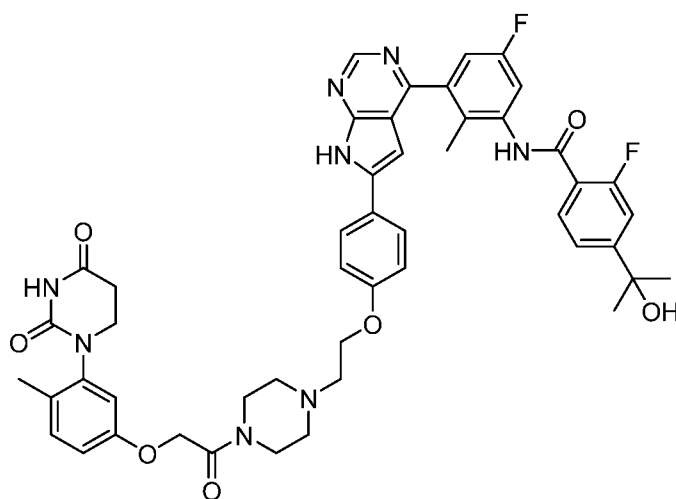
A solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide, 535 mg, 1.178 mmol), *tert*-butyl 4-(2-(4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)ethyl)piperazine-1-carboxylate (535 mg, 0.946 mmol) and K₂CO₃ (330 mg, 2.366 mmol) in 1,4-dioxane (4 mL) and water (4 mL) was degassed with argon. Pd(dppf)Cl₂ (77 mg, 0.095 mmol) was added and the RM was stirred at 100 °C for 1.5 h. The RM was partitioned between EtOAc and water and extracted. The organic phase was washed with brine, dried over MgSO₄, and concentrated. The crude was purified by flash chromatography on silica gel eluting with MeOH in DCM (from 0% to 15%) to afford the title compound as an orange residue (561 mg). Method LCMS1: Rt = 0.97 min; [M+H]⁺ = 727.4.

Step 4: 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(4-(2-(piperazin-1-yl)ethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide



A solution of *tert*-butyl 4-(2-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)phenoxy)ethyl)piperazine-1-carboxylate (561 mg, 0.633 mmol) and TFA (1 mL, 12.98 mmol) in DCM (5 mL) was stirred at RT for 1.5 h. The RM was concentrated and purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%), to afford the TFA salt of the title compound as yellow solid (477 mg). Method LCMS1: Rt = 0.76 min; [M+H]⁺ = 627.5.

Step 5: N-(3-(6-(4-(2-(4-(2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetyl)piperazin-1-yl)ethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

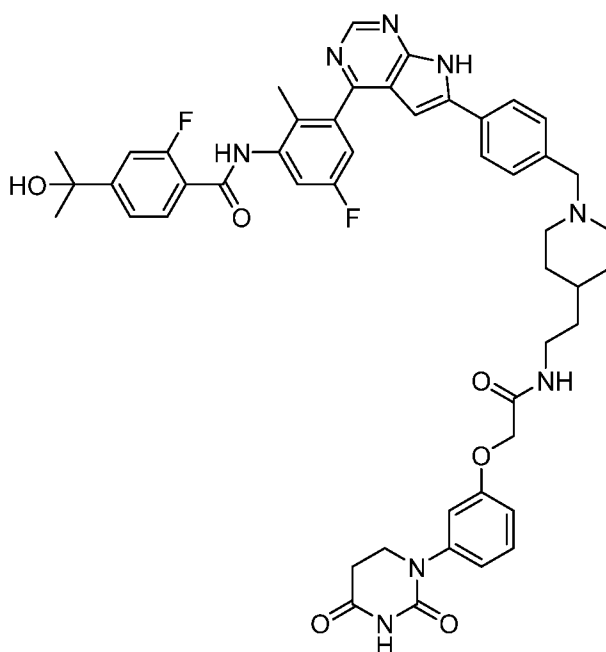


To a mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenoxy)acetic acid (ILB-20, 85 mg, 0.117 mmol) in DMF (2 mL) was added NMM (0.050 mL, 0.455 mmol). HATU (106 mg, 0.279 mmol) was added and the mixture was stirred at RT for 30 min. A solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(4-(2-(piperazin-1-yl)ethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide TFA salt (185 mg, 0.214 mmol) and NMM (0.050 mL, 0.455 mmol) was added and the RM was stirred at RT for 2.5 hr. The RM was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%). Fractions containing pure target compound were filtered through PL-HCO₃ MP SPE cartridges and freeze dried to afford crude material. The material was purified further by SFC Method XU on a Princeton PPU column (250 × 30 mm, 100A, 5 μm) eluting with MeOH from 5% to 55%, to afford the title compound (36 mg). Method LCMS5: Rt = 3.83 min; [M+H]⁺ = 887.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.92 (m, 2H), 8.74 (s,

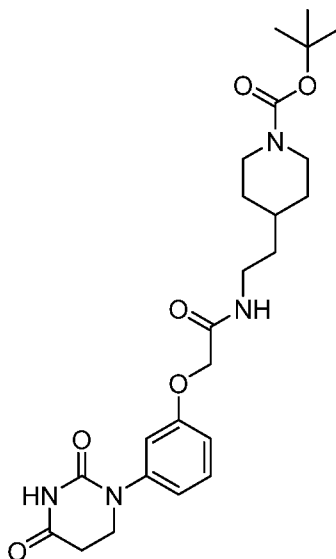
1H), 7.91 (d, $J = 8.3$ Hz, 2H), 7.72 (m, 1H), 7.61 (m, 1H), 7.48–7.34 (m, 2H), 7.25–7.17 (m, 1H), 7.14 (m, 1H), 7.01 (d, $J = 8.4$ Hz, 2H), 6.87 (m, 1H), 6.79 (m, 1H), 6.65 (s, 1H), 5.29 (m, 1H), 4.75 (s, 2H), 4.14 (t, $J = 5.7$ Hz, 2H), 3.74 (m, 1H), 3.51–3.40 (m, 7H), 2.82–2.58 (m, 6H), 2.16 (s, 3H), 2.07 (s, 3H), 1.44 (s, 6H).

5

Compound 11: N-(3-(6-(4-((4-(2-(2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

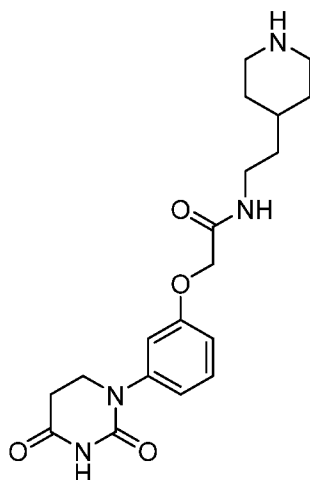


10 **Step 1:** *tert*-Butyl 4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-
yl)phenoxy)acetamido)ethyl)piperidine-1-carboxylate



A mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (ILB-16, 100 mg, 0.375 mmol), *tert*-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (90 mg, 0.394 mmol), NMM (0.050 mL, 0.455 mmol) and HATU (142 mg, 0.375 mmol) in DMF (2 mL) was stirred at RT for 3 h. The RM was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%), to afford the title compound as a white powder (150 mg). Method LCMS1: Rt = 0.91 min; [M+H]⁺ = 475.3.

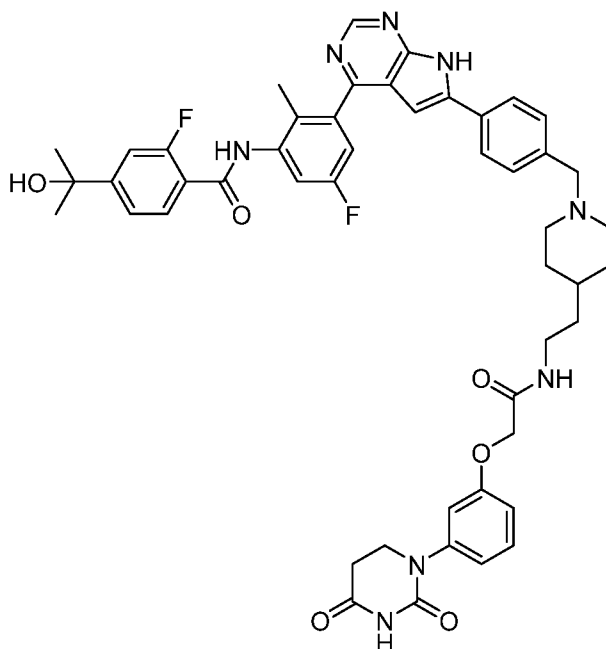
Step 2: 2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-N-(2-(piperidin-4-yl)ethyl)acetamide



To a solution of *tert*-butyl 4-(2-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperidine-1-carboxylate (143.5 mg, 0.302 mmol) in MeOH (2 mL)

was added a solution of HCl 4 M in dioxane (1.5 mL, 6.0 mmol). The RM was stirred at RT for 1.5 h and concentrated to dryness, yielding the HCl salt of the title compound used in next step without further purification (131 mg). Method LCMS2: Rt = 0.80 min; $[M+H]^+ = 375.3$.

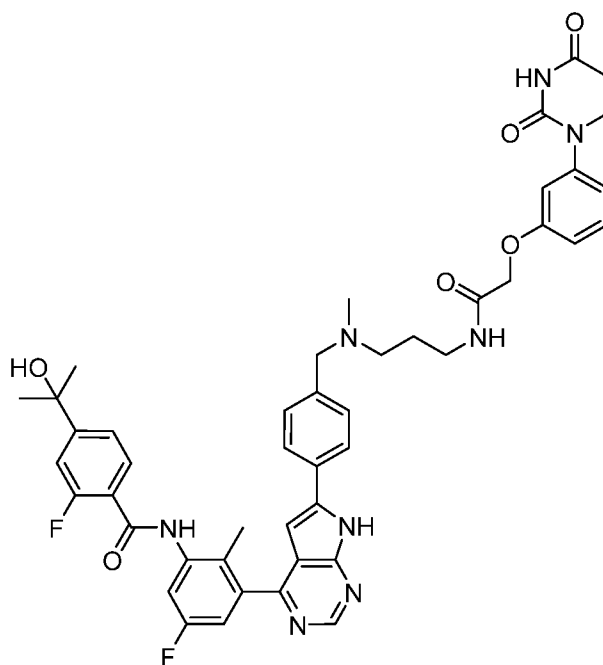
- 5 **Step** **3:** N-(3-(6-(4-((4-(2-(2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



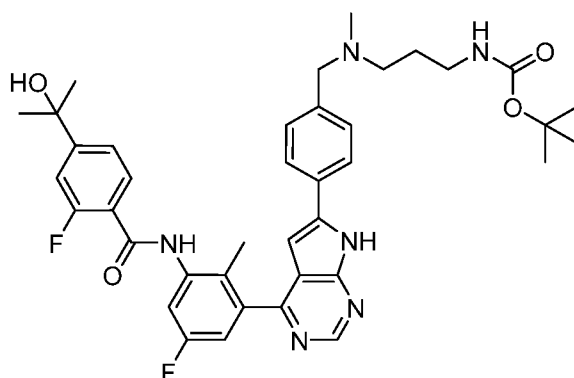
- To a mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-N-(2-(piperidin-4-yl)ethyl)acetamide HCl salt (130 mg, 0.302 mmol), and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 as described in PCT/IB2019/052346 162 mg, 0.302 mmol) were added TEA (0.100 mL, 0.717 mmol) and MeOH (2 mL) at RT. A solution of $ZnCl_2$ 0.5 M in THF (0.700 mL, 0.350 mmol) was added and the RM was stirred at RT for 3 h. $NaBH_3CN$ (22 mg, 0.350 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated and purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2% to 100%). Fractions containing pure target compound were filtered through PL- HCO_3 MP SPE cartridges and freeze dried to afford crude material. The material was purified further by SFC (Method XU) on a Reprospher PEI column (250 × 30 mm, 100 Å, 5 μm) eluting with MeOH from 22% to 54%, yielding the title compound (118 mg). Method

LCMS5: Rt = 3.73 min; $[M+H]^+ = 885.4$. ^1H NMR (400 MHz, DMSO- d_6) δ 12.75 (s, 1H), 10.36 (s, 1H), 9.93 (s, 1H), 8.84 (d, $J = 2.7$ Hz, 1H), 8.04 (m, 1H), 7.93 (d, $J = 7.7$ Hz, 2H), 7.72 (m, 1H), 7.64 (m, 1H), 7.39 (m, 4H), 7.32–7.18 (m, 2H), 6.94 (m, 2H), 6.82 (m, 2H), 5.28 (s, 1H), 4.52–4.36 (s, 2H), 3.75 (m, 2H), 3.49 (m, 2H), 3.15 (m, 2H), 2.79 (m, 2H), 2.68 (m, 2H), 2.16 (s, 3H), 1.91 (m, 2H), 1.61 (s, 2H), 1.51–1.30 (m, 9H), 1.15 (m, 2H).

Compound 12: **N-(3-(6-(4-(((3-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)propyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**

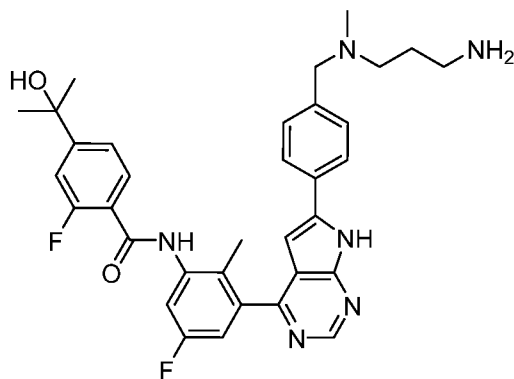


Step 1: *tert*-Butyl (3-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)(methyl)amino)propyl)carbamate



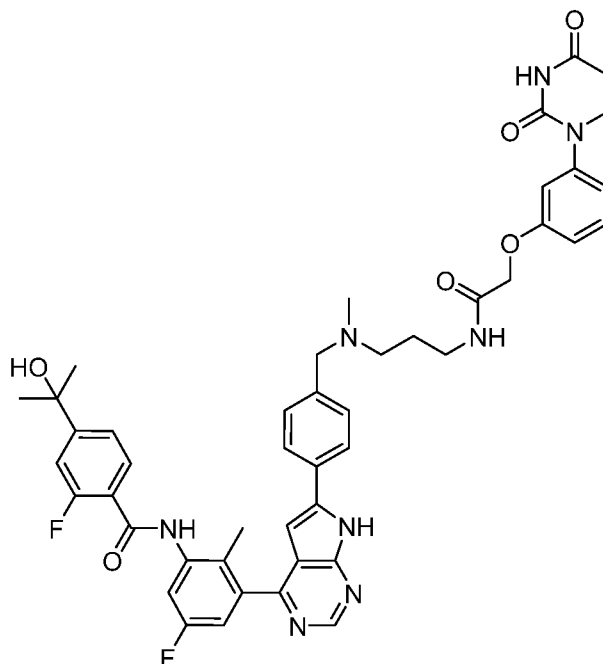
To a mixture of 3-(methylaminopropyl)carbamic acid *tert*-butyl ester (129 mg, 0.684 mmol), 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 300 mg, 0.570 mmol) in MeOH (5 mL) at RT was added a solution of ZnCl₂ 0.5 M in THF (1.4 mL, 0.700 mmol) and the RM was stirred at RT for 2 days. NaBH₃CN (40 mg, 0.637 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated and purified by chromatography on silica gel eluting with MeOH in DCM (from 0% to 50%) yielding the title compound (400 mg). Method LCMS1: Rt = 0.87 min; [M+H]⁺ = 699.4.

Step 2: N-(3-(6-(4-(((3-aminopropyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



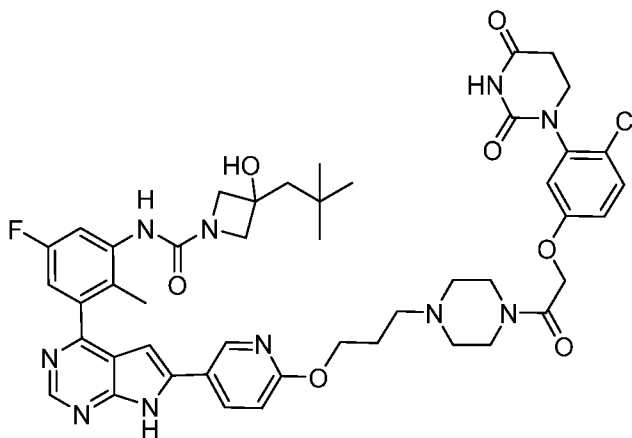
To a solution of *tert*-butyl (3-(((4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)(methyl)amino)propyl)carbamate (400 mg, 0.561 mmol) in MeOH (2 mL) was added a solution of HCl 4 M in dioxane (2 mL, 8.0 mmol). The RM was stirred at RT for 1 h and concentrated, yielding the HCl salt of the title compound as a yellow solid (395 mg). Method LCMS1: Rt = 0.67 min; [M+H]⁺ = 599.4.

Step 3: N-(3-(6-(4-(((3-(2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)propyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



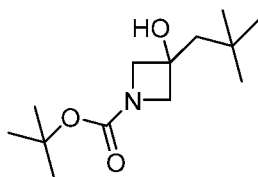
To a mixture of 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (ILB-16, 42 mg, 0.153 mmol) in DMF (0.5 mL) was added NMM (0.020 mL, 0.182 mmol). HATU (60 mg, 0.158 mmol) was added and the mixture was stirred at RT for 30 min. A solution of N-(3-(6-(4-
 5 (((3-aminopropyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide HCl salt (95 mg, 0.151 mmol) and NMM (0.020 mL, 0.182 mmol) in DMF (1 mL) was added and the RM was stirred at RT for 1.5 h. The RM was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 5% to 100%). Fractions containing pure target
 10 compound were filtered through PL-HCO₃ MP SPE cartridges and freeze dried to afford crude material. The material was purified further by SFC Method XU on a Princeton PPU column (250 × 30 mm, 100 Å, 5 µm) eluting with MeOH from 5% to 55%, yielding the title compound (24 mg). Method LCMS5: Rt = 3.46 min; [M+H]⁺ = 845.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.81 (m, 2H), 10.35 (s, 1H), 9.94 (s, 1H), 8.86 (s, 1H), 8.04 (m, 3H), 7.78–7.34 (m, 6H), 7.24 (m, 2H),
 15 7.08–6.74 (m, 4H), 5.29 (s, 1H), 4.45 (s, 2H), 3.74 (m, 4H), 3.49 (m, 4H), 2.66 (m, 2H), 2.50 (s, 3H), 2.16 (s, 3H), 1.44 (s, 6H), 1.22 (m, 2H).

Compound 13: **N-(3-(6-(6-(3-(4-(2-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetyl)piperazin-1-yl)propoxy)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide**



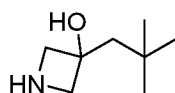
5

Step 1: *tert*-Butyl 3-hydroxy-3-neopentylazetidine-1-carboxylate



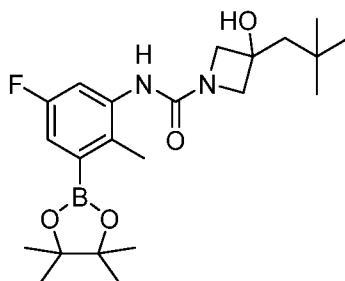
1-Boc-3-azetidinone (5 g, 29.2 mmol) was dissolved in a solution of lanthanum(III)chloride bis(lithium chloride) 0.6M in THF (48.7 mL, 29.2 mmol) and stirred for 1 h at RT. The mixture was cooled at 0 °C. A solution of 2,2-dimethylpropylmagnesium chloride 1.0 M in Et₂O (30.7 mL, 30.7 mmol) was added dropwise. The RM was stirred at 0 °C for 1 h, quenched with aq. sat. NH₄Cl sol. (29 mL) and H₂O (29 mL), filtered over Hyflo[®] and rinsed with Et₂O. The aqueous layer of the filtrate was extracted twice with Et₂O. The organic phase was dried over Na₂SO₄ and evaporated to dryness, yielding the title compound as a beige solid (6.6 g). ¹H NMR (400 MHz, chloroform-*d*) δ 1.02 (s, 9 H) 1.43 (s, 9 H) 1.73 (s, 2 H) 3.78 (d, J = 9.35 Hz, 2 H) 3.94 (d, J = 9.35 Hz, 2 H).

Step 2: 3-Neopentylazetidin-3-ol



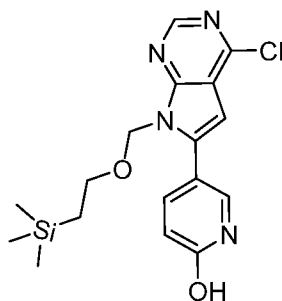
To a mixture of *tert*-butyl 3-hydroxy-3-neopentylazetidine-1-carboxylate (1.6 g, 6.58 mmol) in DCM (60 mL) was added TFA (5.07 mL, 65.8 mmol) at RT. The RM was stirred at RT for 4 h and concentrated to dryness to afford the TFA salt of the title compound as a brown oil (2.6 g). ¹H NMR (400 MHz, chloroform-*d*) δ 1.02 (s, 9 H), 1.80 (s, 2 H) 4.12 (m, 2 H) 4.26 (m, 2 H), 8.08 (m, 1 H), 8.76 (m, 1 H).

Step 3: N-(5-Fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide



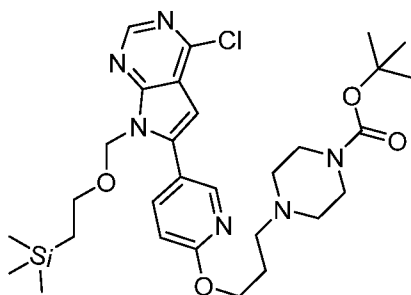
To a solution of 5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (CAS [1418128-33-2], 3.6 g, 14.34 mmol) and DIPEA (10.02 mL, 57.3 mmol) in DCM (40 mL) was slowly added a solution of phosgene 20% in toluene (9.05 mL, 17.20 mmol) at 0 °C. The resulting solution was stirred at 0 °C for 10 min, then transferred to a stirring solution of 3-neopentylazetidin-3-ol TFA salt (4.06 g, 15.77 mmol) in DCM (40.0 mL) at 0 °C. The RM was stirred at 0 °C for 1 h. The RM was concentrated, then poured into water and extracted three times with EtOAc. The organic phase was washed with H₂O and brine, dried with MgSO₄, and concentrated. The crude product was triturated in DCM/MTBE (1:5), then filtered off and dried under HV yielding the title compound as white crystals (4 g). The filtrate was concentrated and crystallized again in TBME to afford the title compound as white crystals (1 g). Method LCMS1: Rt = 1.26 min; [M+H]⁺ = 421.4.

Step 4: 5-(4-Chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-ol



To a solution of 4-chloro-6-iodo-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidine (intermediate 15 in PCT/IB2019/052346 3 g, 7.32 mmol), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol (1800 mg, 8.14 mmol) and a solution of tripotassium phosphate 2M in H₂O (8 mL, 216.00 mmol) in degassed 1,4-dioxane (30 mL) was added Pd(dppf)Cl₂ (540 mg, 0.738 mmol). The RM was stirred at 90 °C for 1 h. 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-ol (900 mg, 4.39 mmol) was added and the RM was stirred at 90 °C for 2 h. The RM was partitioned between EtOAc and water and extracted. The organic phase was washed twice with H₂O and once with brine, dried over Na₂SO₄, and evaporated. The crude was purified by chromatography on silica gel eluting with EtOAc in hexane (from 0% to 100%) yielding the title compound as a yellow residue (270 mg). Method LCMS1: Rt = 1.09 min; [M+H]⁺ = 377.2.

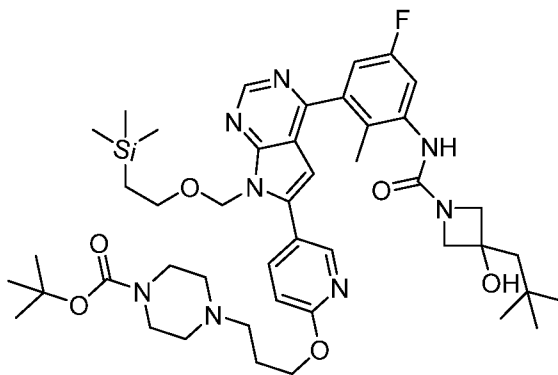
Step 5: *tert*-Butyl 4-(3-((5-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate



To a mixture of 5-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-ol (270 mg, 0.609 mmol), *tert*-butyl 4-(3-hydroxypropyl)piperazine-1-carboxylate (298 mg, 1.218 mmol), PPh₃ (399 mg, 1.522 mmol) and anhydrous THF (5 mL) was added dropwise DIAD (0.296 mL, 1.522 mmol) at 0 °C and the RM was stirred at 0 °C for 20 min. The RM was evaporated and purified by chromatography on silica gel eluting with EtOAc in hexane

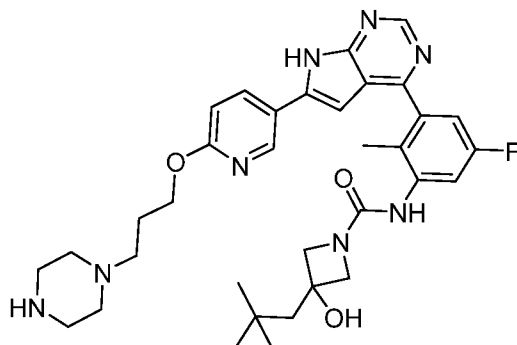
yielding the title compound as a yellow residue (218 mg). Method LCMS5: Rt = 5.95 min; $[M+H]^+$ = 603.4.

Step 6: *tert*-Butyl 4-(3-((5-(4-(5-fluoro-3-(3-hydroxy-3-neopentylazetidine-1-carboxamido)-2-methylphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate



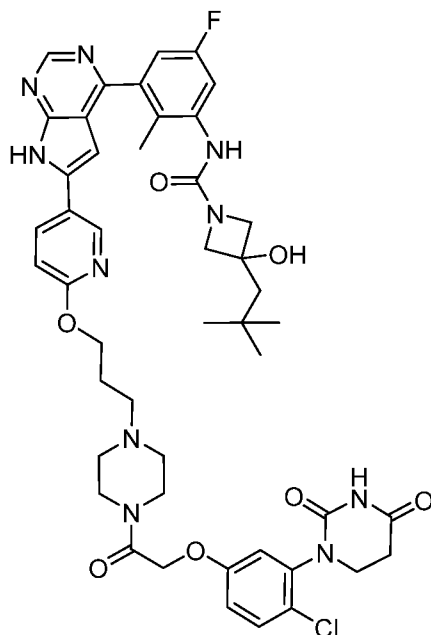
To a solution of *tert*-butyl 4-(3-((5-(4-chloro-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate (215 mg, 0.356 mmol), N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide (225 mg, 0.535 mmol) and a solution of tripotassium phosphate 2 M in H₂O (0.446 mL, 0.891 mmol) in degassed 1,4-dioxane (2.5 mL) was added [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium (II) (23.23 mg, 0.036 mmol). The RM was stirred at RT for 5 min. The RM was partitioned between EtOAc and water and extracted. The organic phase was washed with H₂O and with brine, dried over Na₂SO₄, and evaporated. The crude was purified by chromatography on silica gel eluting with EtOAc / EtOH (95:5) in hexane yielding the title compound as a yellow residue (270 mg). Method LCMS5: Rt = 6.27 min; $[M+H]^+$ = 861.6.

Step 7: N-(5-Fluoro-2-methyl-3-(6-(6-(3-(piperazin-1-yl)propoxy)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide



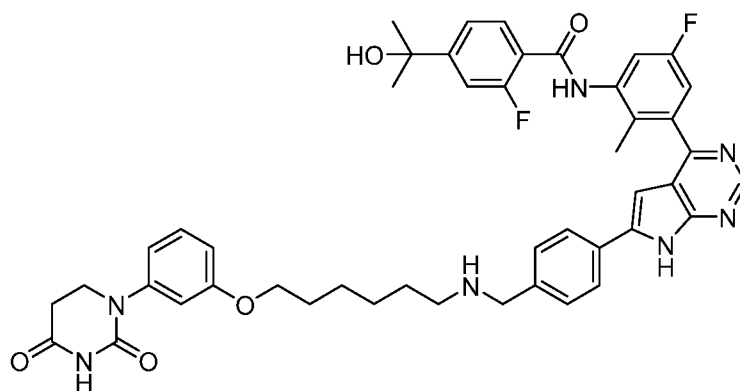
To a mixture of *tert*-butyl 4-(3-((5-(4-(5-fluoro-3-(3-hydroxy-3-neopentylazetidine-1-carboxamido)-2-methylphenyl)-7-((2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)pyridin-2-yl)oxy)propyl)piperazine-1-carboxylate (168 mg, 0.195 mmol) in DCM (2 mL) was added TFA (0.750 mL) at RT. The RM was stirred at RT for 3 h. TFA (0.300 mL) was added and the RM was stirred at RT overnight. The crude was diluted with MeOH (1 mL) and filtered through a PoraPak cartridge (20 mL, 2 g), yielding the title compound as a yellow residue (120 mg). Method LCMS1: Rt = 0.73 min; $[M+H]^+ = 631.5$.

Step 8: N-(3-(6-(6-(3-(4-(2-(4-Chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetyl)piperazin-1-yl)propoxy)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide



To a mixture of 2-(4-chloro-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (20.27 mg, 0.061 mmol), TEA (0.020, 0.141 mmol) and HATU (30.4 mg, 0.080 mmol) in DMF (0.5 mL). The mixture was stirred at RT for 10 min and poured into a solution of N-(5-fluoro-2-methyl-3-(6-(6-(3-(piperazin-1-yl)propoxy)pyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-3-hydroxy-3-neopentylazetidine-1-carboxamide (39 mg, 0.047 mmol) in DMF (0.5 mL). The RM was stirred at RT for 20 min and poured into a mixture of EtOAc and H₂O. The aqueous layer was back-extracted with EtOAc/THF. Combined organic layers were washed with H₂O and with brine, dried over Na₂SO₄ and evaporated. The RM was purified by prep-TLC (Merck: PLC Silica gel 60 F₂₅₄, 0.5 mm, mobile phase: DCM:MeOH, 9:1), yielding the title compound (13 mg). Method LCMS5: Rt = 3.85 min; [M+H]⁺ = 911.6. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.80 (d, *J* = 2.2 Hz, 1H), 10.49 (s, 1H), 8.85 (s, 1H), 8.79 (d, *J* = 2.5 Hz, 1H), 8.29 (m, 1H), 7.92 (s, 1H), 7.49–7.44 (m, 2H), 7.13 (d, *J* = 3.0 Hz, 1H), 7.07 (m, 1H), 6.99–6.87 (m, 2H), 6.81 (d, *J* = 2.0 Hz, 1H), 5.52 (s, 1H), 4.87 (s, 2H), 4.36 (t, *J* = 6.6 Hz, 2H), 3.96 (m, 2H), 3.84 (m, 2H), 3.65 (m, 2H), 3.46 (m, 4H), 2.73 (m, 2H), 2.50–2.31 (m, 6H), 2.09 (s, 3H), 1.96–1.88 (m, 2H), 1.67 (s, 2H), 0.99 (s, 9H).

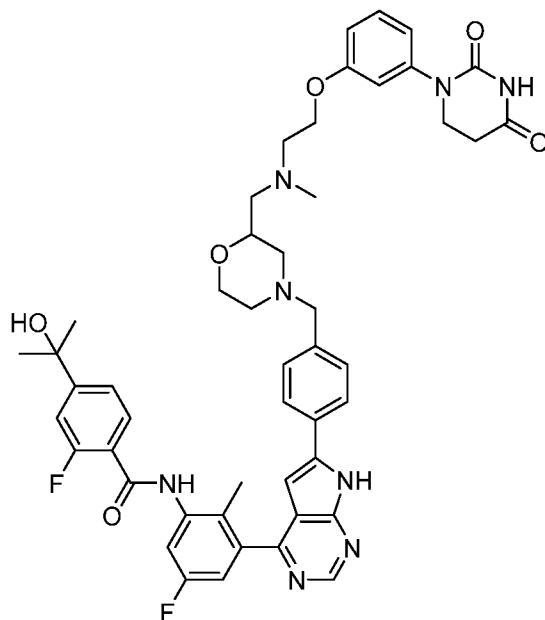
Compound 14: N-(3-(6-(4-(((6-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



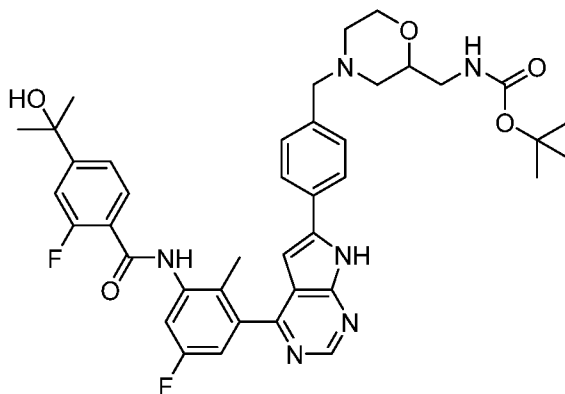
To a mixture of 1-(3-(((6-aminohexyl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-37, 85 mg, 0.244 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-

d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 154 mg, 0.292 mmol) was added at RT under argon THF (0.5 mL), MeOH (0.5 mL) and TEA (0.068 mL, 0.487 mmol). After stirring the mixture for 5 min at RT, a solution of zinc chloride (0.5 M) in THF (0.731 mL, 0.366 mmol) was added dropwise and stirring was continued at RT. After stirring for 5.5 h at RT, NaBH₃CN (16.85 mg, 0.268 mmol) was added in one portion and stirring was continued at RT overnight. Solvent was partially evaporated and then adsorbed on Isolute[®] and purified by reverse phase chromatography on a Redisep[®] Rf Gold 50 g HP C18 column eluting with ACN in an aq. solution of AcOH (0.5%) (from 2 to 100%) to afford, after filtration of the fraction 10 containing the pure target compound through PL-HCO₃ MP SPE cartridges and freeze drying, the title compound as a solid (41 mg). The fraction 11 also containing the expected compound (but not pure) was freeze dried yielding 27 mg of a slightly yellow solid which was then purified further by SFC Method XU on a Princeton PPU column (250 × 30 mm, 100A, 5μm) eluting with methanol from 20% to 52% to afford the title compound (15 mg). Method LCMS1: Rt = 0.86 min; [M+H]⁺ = 816.5. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.71 (s, 1H), 10.33 (s, 1H), 9.93 (s, 1H), 8.84 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.73 (t, J = 7.9 Hz, 1H), 7.66 (d, J = 9.9 Hz, 1H), 7.45 - 7.34 (m, 4H), 7.28 - 7.18 (m, 2H), 6.92 - 6.72 (m, 4H), 5.29 (s, 1H), 3.94 (t, J = 6.3 Hz, 2H), 3.78 - 3.66 (m, 4H), 2.66 (t, J = 6.6 Hz, 3H), 2.16 (s, 3H), 1.69 (q, J = 7.0 Hz, 2H), 1.50 - 1.30 (m, 14H).

Compound 15: **N-(3-(6-(4-(((2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)(methyl)amino)methyl)morpholino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**

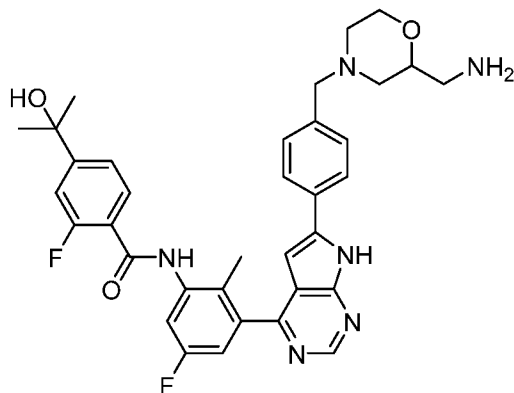


Step 1: *tert*-Butyl ((4-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)morpholin-2-yl)methyl)carbamate



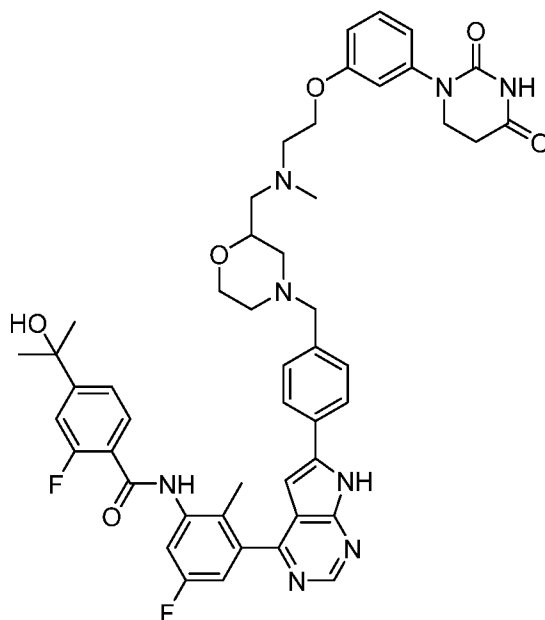
- 5 To a mixture of *tert*-butyl (morpholin-2-ylmethyl)carbamate (CAS No. [173341-02-1], 140 mg, 0.641 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 300 mg, 0.558 mmol) was added MeOH (5 mL) at RT under argon. After stirring the mixture for 5 min at RT, a solution of zinc chloride (0.5 M) in THF (1.3 mL, 0.650 mmol) was added and
- 10 stirring was continued at RT. After stirring 6 h at RT, NaBH₃CN (40 mg, 0.637 mmol) was added in one portion and stirring was continued at RT overnight. Solvent was evaporated and the residue was purified by flash chromatography eluting with MeOH in DCM (from 0 to 18%) to afford the title compound as a yellow solid (406 mg). Method LCMS1: Rt = 0.90 min; [M+H]⁺ = 727.4.

Step 2: N-(3-(6-(4-((2-(Aminomethyl)morpholino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



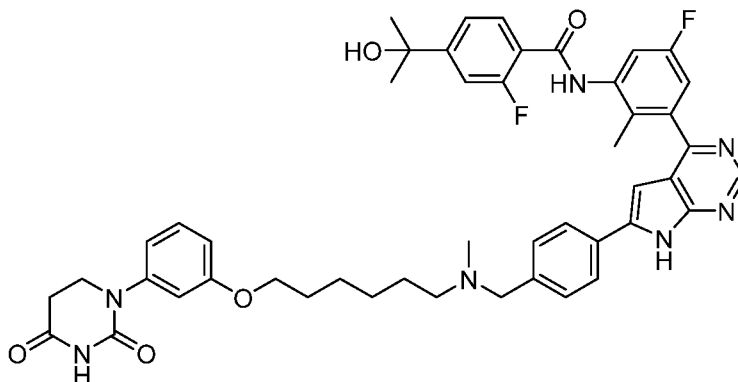
To *tert*-butyl ((4-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)morpholin-2-yl)methyl)carbamate (406 mg, 0.547 mmol) was added HCl (4.0 M) in dioxane (2.0 mL, 8.00 mmol). The resulting solution was stirred at RT for 2 h, then evaporated to dryness and further dried under HV overnight to afford the title compound as an HCl salt (409 mg). Method LCMS1: Rt = 0.70 min; [M+H]⁺ = 627.4.

Step 3: N-(3-(6-(4-(((2-((2-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)(methyl)amino)methyl)morpholino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

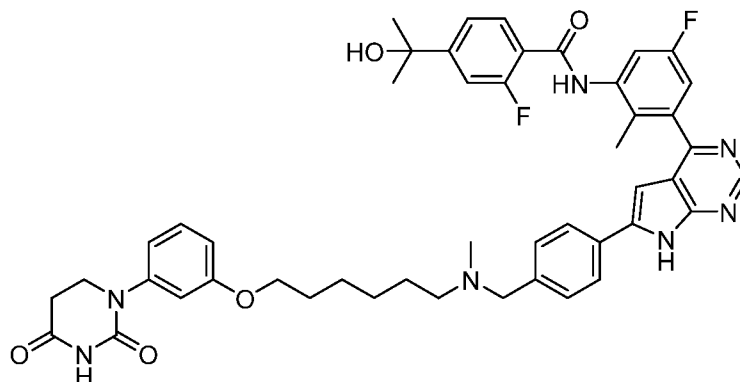


N-(3-(6-(4-((2-(Aminomethyl)morpholino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide (116 mg, 0.156 mmol), TEA (0.050 mL, 0.359 mmol) and 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde (ILB-18, 38.7 mg, 0.156 mmol) were dissolved in MeOH (1.5 mL) at RT. Zinc chloride (0.5 M) in THF (0.350 mL, 0.175 mmol) was added and the RM was stirred overnight at RT. Then NaBH₃CN (12 mg, 0.191 mmol) was added and the RM was stirred overnight at RT. More 2-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde (ILB-13, 38.7 mg, 0.156 mmol) in THF (0.5 mL) was then added and the RM was stirred for 3 days at RT. The crude was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2 to 90%) to afford, after filtration of the fractions containing the target compound through PL-HCO₃ MP SPE cartridges and freeze drying, 19 mg of the title compound (Purity 65%). It was then purified further by SFC using Method XU on a Torus 2PIC column (250 × 30 mm, 130 Å, 5µm) eluting with methanol from 22% to 48% to afford the title compound as a white powder (3.4 mg). Method LCMS1: Rt = 0.84 min; [M+H]⁺ = 873.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.73 (s, 1H), 10.31 (s, 1H), 9.92 (s, 1H), 8.83 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.72 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 9.9 Hz, 1H), 7.44 - 7.34 (m, 4H), 7.24 - 7.18 (m, 2H), 6.91 - 6.78 (m, 3H), 6.75 (d, J = 8.4 Hz, 1H), 5.28 (s, 1H), 3.97 (t, J = 6.3 Hz, 2H), 3.78 - 3.68 (m, 3H), 3.55 (m, 3H), 3.47 (m, 3H), 2.82 - 2.58 (m, 6H), 2.42 (m, 2H), 2.24 (s, 3H), 2.16 (s, 3H), 1.44 (s, 6H).

Compound 16: N-(3-(6-(4-(((6-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

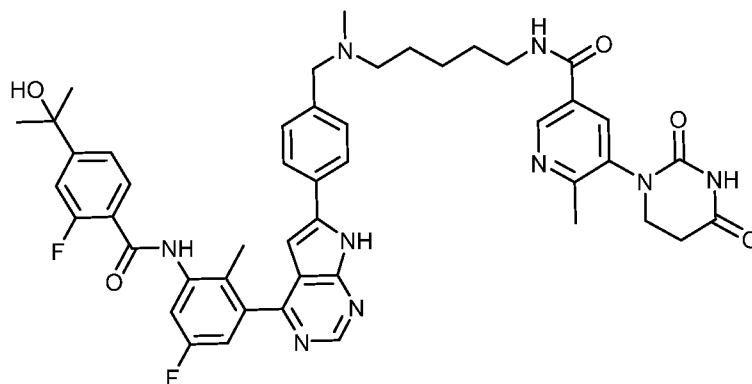


Step 1: N-(3-(6-(4-(((6-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)hexyl)(methylamino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

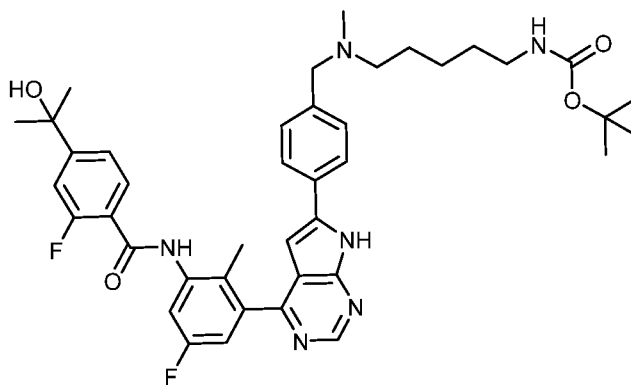


- 5 To a mixture of 1-(3-(((6-(methylamino)hexyl)oxy)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (ILB-54, 85 mg, 0.239 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 151 mg, 0.287 mmol) was added at RT under argon THF (0.5 mL), MeOH (0.5 mL) and TEA (0.067 mL, 0.478 mmol). After stirring the mixture for 5 min at RT, a solution of zinc chloride (0.5 M) in THF (0.717 mL, 0.358 mmol) was added dropwise and stirring was continued at RT. After stirring for 5.5 h at RT, NaBH₃CN (16.51 mg, 0.263 mmol) was added in one portion and stirring was continued at RT overnight. Solvent was partially evaporated and then adsorbed on Isolute[®] and purified by reverse phase chromatography on a Redisep[®] Rf Gold 50 g HP C18 column eluting with ACN in an aq. solution of AcOH (0.5%) (from 2 to 100% ACN) to afford, after freeze drying, the title compound as a acetic acid salt (123 mg). Method LCMS1: Rt = 0.85 min; [M+H]⁺ = 830.5. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.74 (s, 1H), 10.32 (s, 1H), 9.92 (s, 1H), 8.84 (s, 1H), 7.93 (d, J = 7.8 Hz, 2H), 7.72 (t, J = 7.9 Hz, 1H), 7.65 (d, J = 10.1 Hz, 1H), 7.47 - 7.33 (m, 4H), 7.27 - 7.18 (m, 2H), 6.92 - 6.80 (m, 3H), 6.77 (dd, J = 8.3, 2.2 Hz, 1H), 5.28 (s, 1H), 3.93 (t, J = 6.4 Hz, 2H), 3.74 (t, J = 6.6 Hz, 2H), 3.48 (s, 2H), 2.66 (t, J = 6.6 Hz, 2H), 2.33 (m, 2H), 2.23 - 2.02 (m, 6H), 1.77 - 1.62 (m, 2H), 1.57 - 1.27 (m, 13H).

Compound 17: 5-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-N-(5-(((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)(methylamino)pentyl)-6-methylnicotinamide



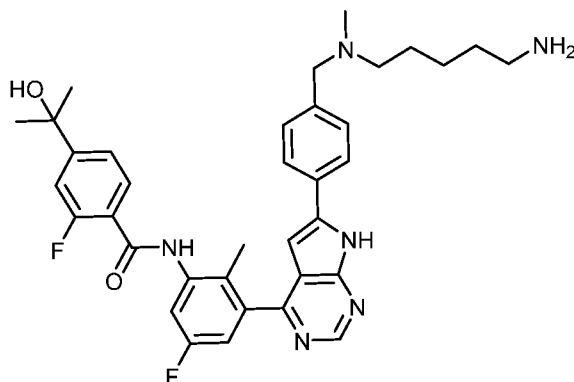
Step 1: *tert*-Butyl (5-((4-(4-(5-Fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)(methylamino)pentyl)carbamate



- 5 To a mixture of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 300 mg, 0.570 mmol) and 5-(methylamino)-N-Boc-pentanamine (CAS [1311458-36-2], 140 mg, 0.627 mmol) in MeOH (12 mL) was added ZnCl₂ 0.5 M in THF (1.253 mL, 0.627 mmol). The resulting yellow mixture was flushed with N₂ and stirred at RT for 3 h. Then, NaBH₃CN (41.5 mg, 0.627 mmol) was added, and it was stirred at RT for 18 h. More 5-(methylamino)-N-Boc-pentanamine (25 mg, 0.112 mmol) in MeOH (1 mL), followed by more ZnCl₂ 0.5 M in THF (228 μL, 0.114 mmol) were added and the RM was stirred at RT. After 6 h, more NaBH₃CN (37 mg, 0.559 mmol) was added and the RM was stirred at RT for overnight. Then, more NaBH₃CN (19 mg, 0.287 mmol) was added, and it was stirred at RT for 6 h. Then, more 5-(methylamino)-N-Boc-pentanamine (64 mg, 0.287 mmol), followed by more ZnCl₂ 0.5 M in THF (570 μL, 0.285 mmol) were added and the RM was stirred at RT for overnight. The RM was concentrated until dryness and purified by flash chromatography on silica gel eluting with 10–70% (DCM/MeOH 80/20) in
- 10
- 15

DCM to afford the title compound as a yellow solid (366 mg). Method LCMS1: Rt = 0.92 min; $[M+H]^+ = 727.5$.

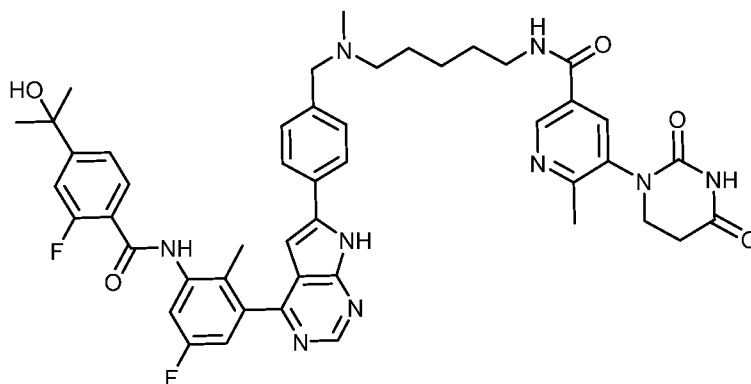
Step 2: N-(3-(6-(4-(((5-Aminopentyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



To a yellow mixture of *tert*-butyl (5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-

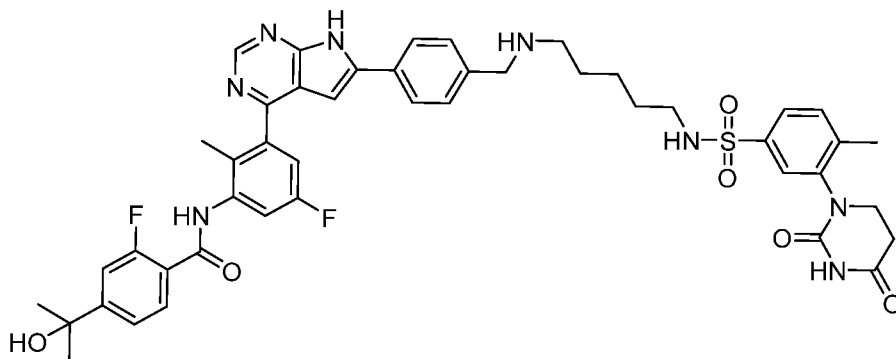
yl)benzyl)(methyl)amino)pentyl)carbamate (366 mg, 0.493 mmol) in dioxane (10 mL) was added HCl 4 M in dioxane (1.851 mL, 7.40 mmol). The resulting yellow mixture was then stirred at RT for 2.5 h, the RM was concentrated until dryness and dried under HV to afford the title compound as a yellow solid HCl salt (431 mg). Method LCMS1: Rt = 0.66 min; $[M+H]^+ = 627.4$.

Step 3: 5-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-N-(5-((4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)(methyl)amino)pentyl)-6-methylnicotinamide



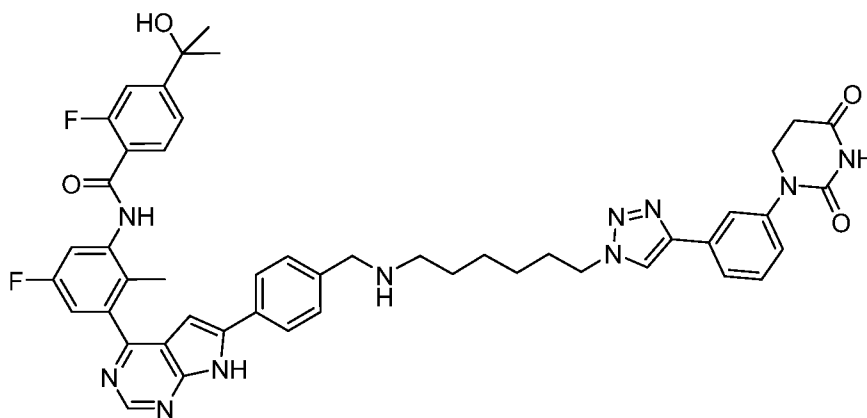
To a yellow solution of N-(3-(6-(4-(((5-aminopentyl)(methyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide (36 mg, 0.049 mmol), 5-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-6-methylnicotinic acid (ILB-30, 19.54 mg, 0.054 mmol) and HBTU (20.82 mg, 0.054 mmol) in dry DMF (1.2 mL) flushed with N₂ was added DIPEA (68 µL, 0.391 mmol). The resulting RM was stirred at RT for 1 h. The RM was stored in the freezer for overnight, then diluted with ACN, adsorbed on Isolute[®], concentrated until dryness and dried under HV pump. It was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 10% to 100%) to afford, after filtration of the fractions containing the target compound through PL-HCO₃ MP SPE cartridges and freeze drying, a non-pure off-white solid. The solid was then purified by SFC Method XU (column: Princeton PPU 250 × 30 mm, 100 Å, 5 µM) eluting with 30–45% CO₂ in MeOH to afford the title compound as a white solid (5 mg). Method LCMS1: Rt = 0.75 min; [M+H]⁺ = 858.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.32 - 1.40 (m, 2 H) 1.47 (s, 6 H) 1.49 - 1.63 (m, 4 H) 1.97 - 2.35 (m, 6 H) 2.43 (s, 3 H) 2.45 - 2.49 (m, 2 H) 2.71 - 2.75 (m, 1 H) 2.79 - 2.84 (m, 1 H) 3.22 - 3.28 (m, 2 H) 3.51 (m, J = 10.00 Hz, 2 H) 3.58 - 3.64 (m, 1 H) 3.80 - 3.89 (m, 1 H) 5.32 (s, 1 H) 6.86 (br s, 1 H) 7.26 (dd, J = 8.74, 2.75 Hz, 1 H) 7.32 - 7.49 (m, 4 H) 7.67 (br d, J = 10.15 Hz, 1 H) 7.72 - 7.77 (m, 1 H) 7.86 - 8.07 (m, 2 H) 8.10 (d, J = 1.83 Hz, 1 H) 8.64 (t, J = 1.00 Hz, 1 H) 8.82 - 8.89 (m, 2 H) 9.96 (s, 1 H) 10.52 (s, 1 H) 12.78 (br s, 1 H).

Compound 18: N-(3-(6-(4-(((5-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylphenylsulfonamido)pentyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

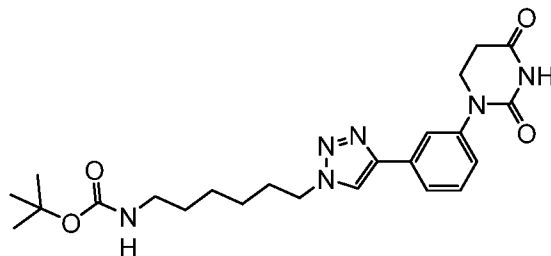


N-(5-aminopentyl)-3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-4-methylbenzenesulfonamide TFA salt (ILB-53, 228 mg, 0.392 mmol), TEA (0.150 mL, 1.076 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 220 mg, 0.418 mmol) were dissolved in MeOH (3 mL). A solution of ZnCl₂ 0.5M in THF (1 mL, 0.500 mmol) was added and the RM was stirred at RT overnight. NaBH₃CN (30 mg, 0.477 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated to dryness. The crude material was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aqueous solution of TFA (0.1%) (from 2% to 100%). Fractions containing pure target compound were filtered through PL-HCO₃ MP SPE cartridges and freeze dried to afford crude material. The material was purified further by SFC Method XU on a Princeton PPU column (250 × 30 mm, 100 Å, 5 μm) eluting with MeOH from 35% to 52%, yielding the title compound (36 mg). Method LCMS1: Rt = 0.79 min; [M+H]⁺ = 879.5.

Compound 19: N-(3-(6-(4-(((6-(4-(3-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)hexyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

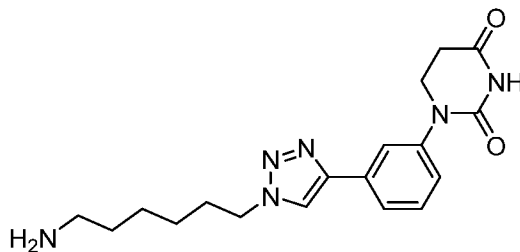


Step 1: *tert*-Butyl (6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)hexyl)carbamate



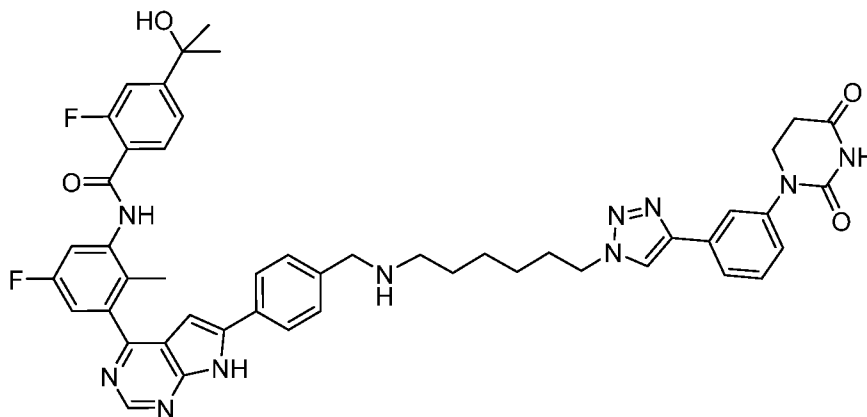
To a suspension of 1-(3-ethynylphenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-33, 0.19 g, 0.579 mmol) and *tert*-butyl (6-azidohexyl)carbamate (CAS [129392-87-6], 0.154 g, 0.637 mmol) in THF (4 mL) and water (2 mL) was added sodium L-ascorbate (0.3M, 0.965 mL, 0.289 mmol) followed by Copper(II) sulfate pentahydrate (1M, 0.058 mL, 0.058 mmol). The reaction mixture was stirred at RT over 3 days. The reaction mixture was diluted with EtOAc and the organic phase was washed with aqueous NH₄OH solution and brine. The organic phase was dried over Na₂SO₄, filtered, and concentrated to dryness to afford the title compound as an oil (0.18 g). Method LCMS1: Rt = 0.89 min; [M+H]⁺ = 457.3.

Step 2: 1-(3-(1-(6-Aminoethyl)-1H-1,2,3-triazol-4-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



To a solution of *tert*-butyl (6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)hexyl)carbamate (0.18 g, 0.359 mmol) in DCM (3 mL) was added TFA (0.829 mL, 10.76 mmol). The reaction mixture was stirred at RT for 45 minutes. The reaction mixture was concentrated to dryness. The crude mixture purified by reverse phase preparative HPLC to afford the title compound as a TFA salt (0.04 g). Method LCMS1: Rt = 0.46 min; [M+H]⁺ = 357.3.

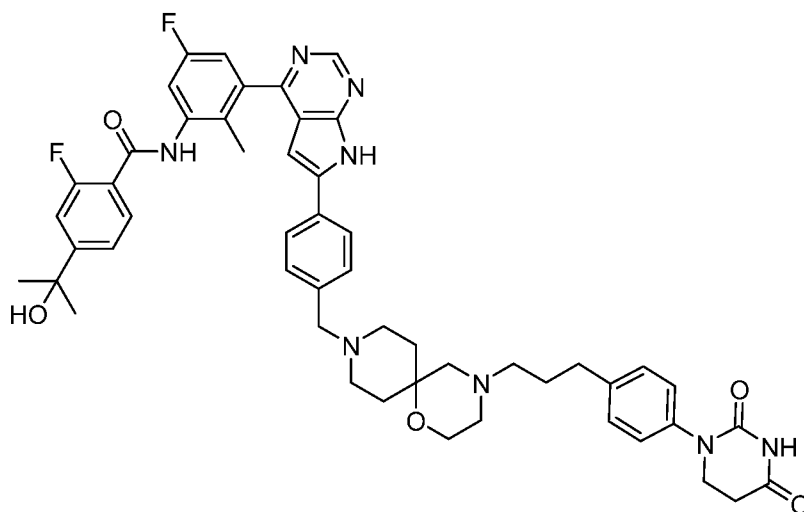
Step 3: N-(3-(6-(4-(((6-(4-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)-1H-1,2,3-triazol-1-yl)hexyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



To a mixture of 1-(3-(1-(6-aminohexyl)-1H-1,2,3-triazol-4-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (0.041 g, 0.088 mmol), 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide

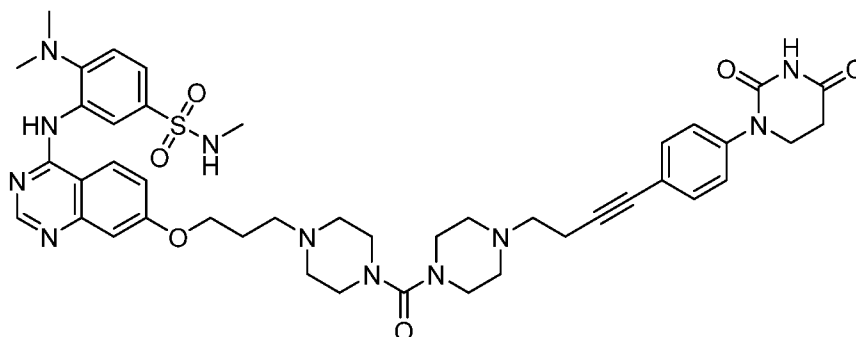
(intermediate 3 in PCT/IB2019/052346 0.06 g, 0.114 mmol) in MeOH (2 mL) and THF (1 mL, Ratio: 1.000) was added AcOH (0.015 mL, 0.263 mmol). The reaction mixture was stirred at room temperature for 7 h. NaBH₃CN (0.017 g, 0.263 mmol) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated to dryness. The residue dissolved in MeOH/TFA and purified by reverse phase preparative HPLC (Method XN) to afford the title compound as a solid TFA salt. Method LCMS1: Rt = 0.82 min; [M+H]⁺ = 867.6. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.88 (s, 1H), 10.44 (s, 1H), 9.99 (d, *J* = 2.4 Hz, 1H), 8.90 (s, 1H), 8.70 (s, 2H), 8.63 (s, 1H), 8.08 (d, *J* = 8.2 Hz, 2H), 7.82 (t, *J* = 1.9 Hz, 1H), 7.72 (dt, *J* = 24.5, 7.1 Hz, 3H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.53–7.36 (m, 2H), 7.34–7.22 (m, 1H), 6.97 (d, *J* = 2.1 Hz, 1H), 5.33 (br s, 1H), 4.42 (t, *J* = 6.9 Hz, 2H), 3.85 (t, *J* = 6.7 Hz, 2H), 2.94 (d, *J* = 14.3 Hz, 2H), 2.74 (t, *J* = 6.6 Hz, 2H), 2.54–2.49 (m, 2H), 2.18 (s, 3H), 1.88 (t, *J* = 7.4 Hz, 2H), 1.61 (s, 2H), 1.46 (s, 6H), 1.40–1.20 (m, 4H).

Compound 20: N-(3-(6-(4-((4-(3-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenyl)propyl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

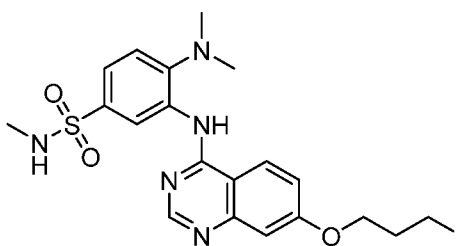


To a mixture of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 135 mg, 0.26 mmol), 1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)propyl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-47, 90 mg, 0.23 mmol) in DMSO (3 mL) was added a solution of ZnCl₂ in THF (1 M, 0.35 mL, 0.35 mmol). The RM was stirred at 25 °C for 1 h then NaBH₃CN (147 mg, 2.33 mmol) and MeOH (1 mL) were added. The mixture was stirred at 40 °C for 6 h. The mixture was concentrated *in vacuo*. To the residue was added water (10 mL). A light yellow solid precipitated. The solid was filtered, dissolved in DCM/MeOH (1:1) and silica gel (100–200 mesh) was added. The mixture was concentrated *in vacuo* and purified by chromatography on a 12 g silica Biotage[®] column eluting with a methanolic ammonia solution (1N) in DCM (5–10%), 20 mL/min, to afford a crude product. The product was further purified by prep-TLC (silica, ammonia in MeOH (0.7 N)/DCM 1:8) to afford a white solid (40 mg). The crude product was purified by flash chromatography on a C18 column eluting with MeOH (10–80%) in an aq. solution of NH₄HCO₃ (10 mM) to afford the title compound as a white solid (31 mg). Method G: Rt = 1.89 min; [M+H]⁺ = 897.4. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 10.33 (s, 1H), 9.94 (s, 1H), 8.85 (s, 1H), 7.94 (d, J = 8.0 Hz, 2H), 7.73 (t, J = 7.9 Hz, 1H), 7.66 (d, J = 9.5 Hz, 1H), 7.46–7.33 (m, 4H), 7.26–7.16 (m, 5H), 6.83 (s, 1H), 5.30 (s, 1H), 3.75 (t, J = 6.7 Hz, 2H), 3.66–3.54 (m, 2H), 3.49 (s, 2H), 2.69 (t, J = 6.7 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 2.46–2.38 (m, 2H), 2.35–2.24 (m, 4H), 2.24–2.10 (m, 7H), 1.90–1.76 (m, 2H), 1.74–1.66 (m, 2H), 1.58–1.48 (m, 2H), 1.45 (s, 6H).

Compound 21: 4-(dimethylamino)-3-((7-(3-(4-(4-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazin-1-yl)propoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide

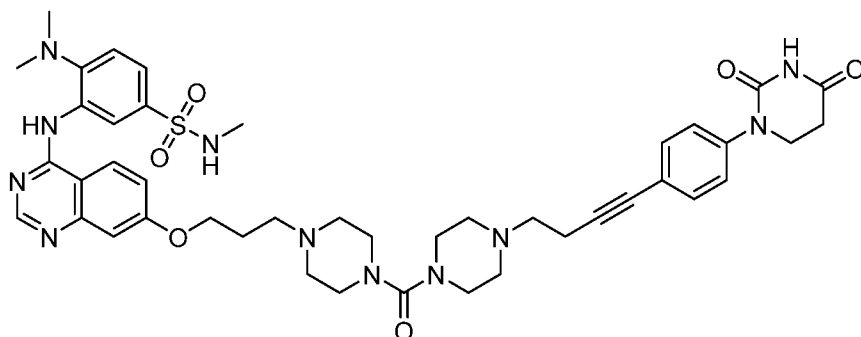


5 **Step 1:** 4-(dimethylamino)-3-((7-(3-iodopropoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide



3-((7-(3-chloropropoxy)quinazolin-4-yl)amino)-4-(dimethylamino)-N-methylbenzenesulfonamide (intermediate CC, 1.00 g, 2.222 mmol) and NaI (0.666 g, 4.44 mmol) were suspended in acetone (20 mL) and refluxed for 72 hours. Upon heating, the reactants dissolve completely. The reaction mixture was cooled to RT and concentrated. The resulting solid was suspended in acetone (5 mL) and filtered, collecting the solid to afford the title compound as a yellow solid (1.20 g). Method XV: Rt = 1.04 min; [M+H]⁺ = 542.9.

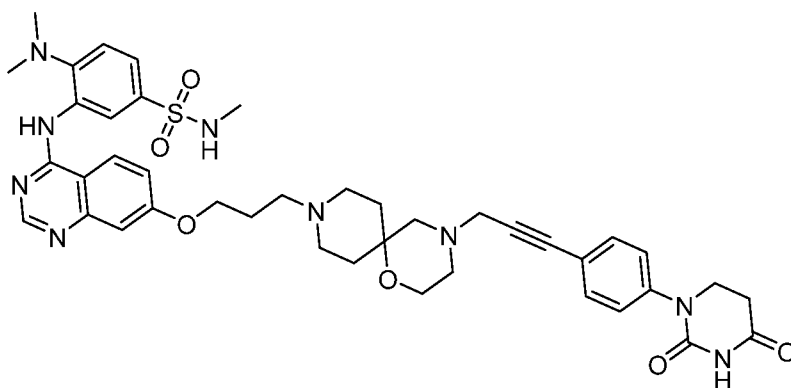
15 **Step 2:** 4-(dimethylamino)-3-((7-(3-(4-(4-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazin-1-yl)propoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide



To a suspension of 1-(4-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-41, 5 mg, 0.011 mmol) and 4-(dimethylamino)-3-((7-(3-iodopropoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide, 5 (6.79 mg, 0.013 mmol) in DMA (114 μ L) was added DIPEA (11.95 μ L, 0.068 mmol). The resulting solution was stirred at 70 $^{\circ}$ C for 18 h. The reaction mixture was then cooled to RT, diluted with ACN and DMSO and purified via preparative HPLC (XBridge 30x50 mm 25–50% MeCN/H₂O (5 mM NH₄OH)) to afford the title compound as a white powder (2.0 mg)

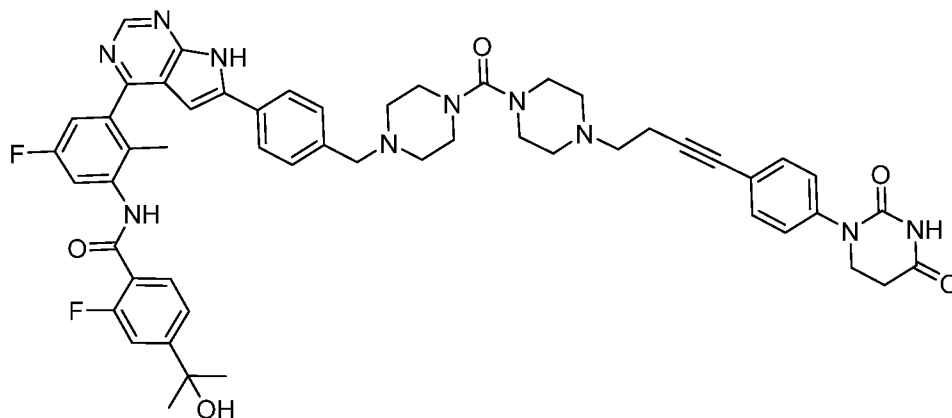
Method XR: Rt = 2.00 min; [M+H]⁺ = 853.5. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.41 (s, 1H), 9.42 (s, 1H), 8.43 (s, 1H), 8.36 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 6.7 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.36–7.14 (m, 6H), 4.19 (s, 2H), 3.79 (t, J = 6.5 Hz, 2H), 3.15 (s, 6H), 2.76 (s, 6H), 2.70 (s, 1H), 2.59 (s, 4H), 2.42 (d, J = 5.1 Hz, 4H), 2.39 (s, 4H), 2.11–2.03 (m, 4H), 1.95 (s, 2H), 1.24 (s, 4H).

15 Compound 22: 4-(dimethylamino)-3-((7-(3-(4-(3-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenyl)prop-2-yn-1-yl)-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)propoxy)quinazolin-4-yl)amino)-N-methylbenzenesulfonamide



To a suspension of 3-((7-(3-chloropropoxy)quinazolin-4-yl)amino)-4-(dimethylamino)-N-methylbenzenesulfonamide (intermediate CC, 34.4 mg, 0.076 mmol) and 1-(4-(3-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)prop-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-40, 32 mg, 0.076 mmol) in DMA (764 μ L) was added potassium iodide (25.4 mg, 0.153 mmol) and DIPEA (50.6 μ L, 0.290 mmol). The resulting solution was stirred at 80 °C for 72 h. The RM was diluted with ACN and DMSO and purified via preparative HPLC (XBridge 30 $\times$ 50 mm 10–30% MeCN/H₂O (0.1% formic acid) and further via preparative HPLC (XBridge 30 $\times$ 50 mm 25–50% MeCN/H₂O (5 mM NH₄OH) to afford the title compound as a white powder (15 mg). Method XR: Rt = 2.19 min; [M+H]⁺ = 796.4. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.42 (s, 1H), 9.42 (s, 1H), 8.43 (s, 1H), 8.35 (d, J = 9.3 Hz, 1H), 7.92 (d, J = 2.3 Hz, 1H), 7.53 (dd, J = 8.4, 2.4 Hz, 1H), 7.50–7.42 (m, 2H), 7.38–7.31 (m, 2H), 7.27 (q, J = 5.1 Hz, 1H), 7.25–7.14 (m, 3H), 4.18 (t, J = 6.3 Hz, 2H), 3.80 (t, J = 6.7 Hz, 2H), 3.65 (t, J = 4.7 Hz, 2H), 3.49 (s, 2H), 3.30–3.27 (m, 3H), 2.76 (s, 6H), 2.70 (t, J = 6.7 Hz, 2H), 2.42 (d, J = 5.2 Hz, 6H), 2.37 (s, 2H), 2.09 (s, 2H), 2.01–1.89 (m, 2H), 1.89–1.79 (m, 2H), 1.57 (d, J = 11.8 Hz, 2H).

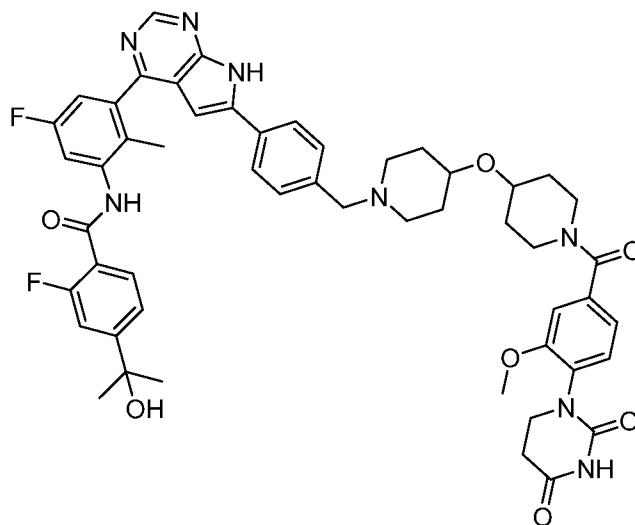
Compound 23: N-(3-(6-(4-((4-(4-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenyl)but-3-yn-1-yl)piperazine-1-carbonyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



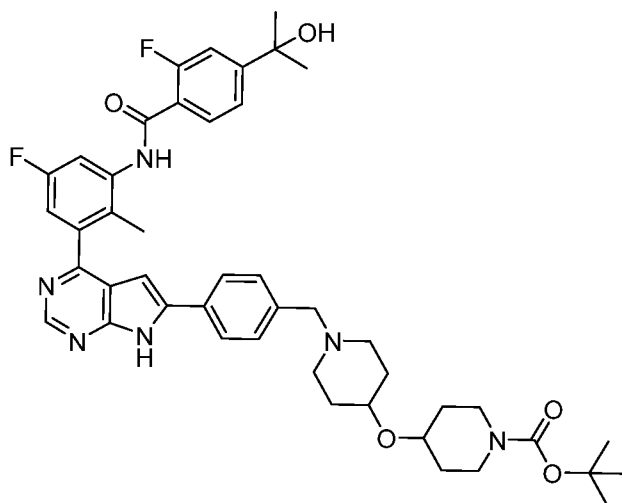
A solution of 1-(4-(4-(4-(piperazine-1-carbonyl)piperazin-1-yl)but-1-yn-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-41, 420 mg, 0.63 mmol) and DIPEA (215 mg, 1.66 mmol) in MeOH (8 mL) and DMSO (3 mL) was stirred at 12 °C for 5 min. A solution of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-

4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 216 mg, 0.41 mmol) in DMSO (5 mL) and ZnCl_2 (0.5 mL, 1 N in THF) was added at 12 °C. The mixture was stirred at 22 °C for 2 h then NaBH_3CN (40 mg, 0.636 mmol) was added. The RM was stirred at 22 °C for 2 h then NaBH_3CN (22 mg 0.35 mmol) was added. The RM was stirred at 22 °C for 18 h. The RM (combined with the RM of a trial reaction) was concentrated under vacuum to give a DMSO solution which was purified by reverse phase chromatography eluting with ACN in an aq. solution of NH_4HCO_3 (10 mM) to give a crude product. Further purifications by reverse phase column chromatography eluting with ACN in an aq. solution of TFA (0.01%) and prep-HPLC using method PB (ACN in an aq. solution of NH_4HCO_3 (10 mM)) afforded the title product as a white solid (36 mg). Method H: $R_t = 1.893$ min; $[\text{M}+\text{H}]^+ = 949$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.79 (s, 1H), 10.43 (s, 1H), 9.97 (s, 1H), 8.86 (s, 1H), 7.96 (d, $J = 8.2$ Hz, 2H), 7.73 (t, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 8.3$ Hz, 1H), 7.45-7.36 (m, 6H), 7.30 (d, $J = 8.5$ Hz, 2H), 7.24 (dd, $J = 8.8, 2.5$ Hz, 1H), 6.85 (s, 1H), 5.31 (s, 1H), 3.79 (t, $J = 6.6$ Hz, 2H), 3.52 (s, 2H), 3.14 (s, 8H), 2.69 (t, $J = 6.6$ Hz, 2H), 2.58 (s, 4H), 2.45-2.33 (m, 8H), 2.18 (s, 3H), 1.45 (s, 6H).

Compound 24: N-(3-(6-(4-((4-((1-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

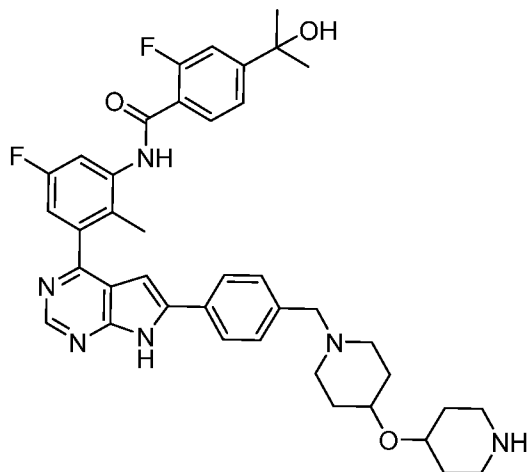


Step 1: *tert*-Butyl 4-((1-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperidin-4-yl)oxy)piperidine-1-carboxylate



tert-Butyl 4-(piperidin-4-yloxy)piperidine-1-carboxylate (CAS No. [845305-83-1], 106.5 mg, 0.374 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 190 mg, 0.361 mmol) were dissolved in MeOH (3 mL). A solution of ZnCl₂ 0.5M in THF (0.750 mL, 0.375 mmol) was added and the resulting solution was stirred at RT overnight. NaBH₃CN (24 mg, 0.382 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated to dryness and the crude material was purified by silica gel chromatography eluting with MeOH in DCM (from 0% to 50%) to afford the title compound (285 mg). Method LCMS1: Rt = 0.98 min; [M+H]⁺ = 795.5.

Step 2: 2-Fluoro-N-(5-fluoro-2-methyl-3-(6-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide

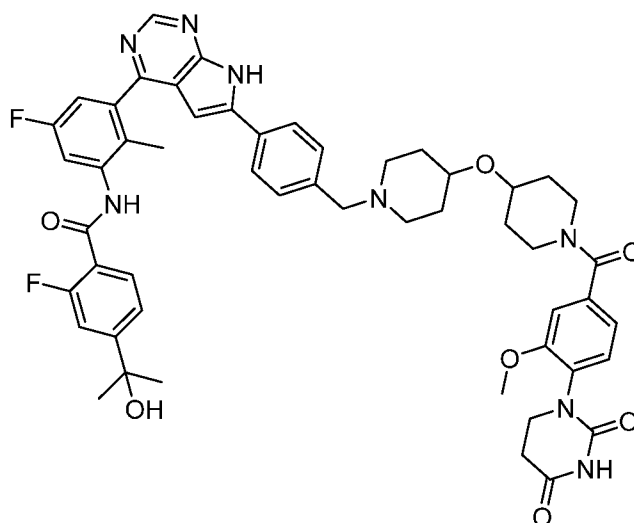


tert-Butyl 4-((1-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (269 mg, 0.332 mmol) was treated with HCl 4M in dioxane (1.5 mL, 6.00 mmol).

- 5 MeOH (2 mL) was added and the RM was stirred at RT for 90 min. The RM was concentrated to dryness to afford the HCl salt of the title compound as a yellow solid (304 mg). Method LCMS1: $R_t = 0.66$ min; $[M+H]^+ = 695.5$.

Step 3: N-(3-(6-(4-(((4-((1-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-3-

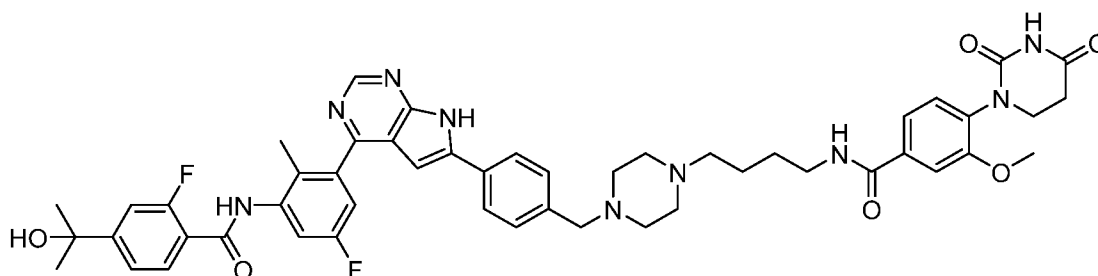
- 10 methoxybenzoyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxybenzoic acid (ILB-81, 32 mg, 0.105 mmol) was dissolved in DMF (0.5 mL) to which NMM (0.025 mL, 0.227 mmol) was added

followed by HATU (44 mg, 0.116 mmol). A solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(4-
 ((4-(piperidin-4-yloxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-
 4-(2-hydroxypropan-2-yl)benzamide HCl salt (90 mg, 0.100 mmol) and NMM (0.025 mL, 0.227
 5 mmol) in DMF (0.5 mL) was added dropwise. The RM was stirred at RT for 90 min. The crude
 RM was purified by reverse phase chromatography on a RediSep® C18 column eluting with ACN
 in an aqueous solution of TFA (0.1%) (from 5% to 100%). Fractions containing pure target
 compound were filtered through PL-HCO₃ MP SPE cartridges and freeze dried to afford the title
 compound (62 mg). Method LCMS5: Rt = 3.72 min; [M+H]⁺ = 941.4. ¹H NMR (400 MHz,
 DMSO-*d*₆) δ 12.73 (s, 1H), 10.32 (s, 1H), 9.92 (s, 1H), 8.84 (s, 1H), 7.92 (d, J = 7.9 Hz, 2H), 7.72
 10 (m, 1H), 7.64 (m, 1H), 7.44–7.34 (m, 4H), 7.28 (d, J = 7.9 Hz, 1H), 7.22 (d, J = 8.7 Hz, 1H), 7.07
 (s, 1H), 6.95 (d, J = 7.7 Hz, 1H), 6.81 (s, 1H), 5.28 (s, 1H), 3.80 (s, 3H), 3.72 - 3.63 (m, 1H), 3.58
 (t, J = 6.6 Hz, 2H), 3.53–3.39 (m, 3H), 2.66 (m, 6H), 2.16 (s, 3H), 2.08 (m, 4H), 1.90–1.68 (m,
 4H), 1.51–1.33 (m, 10H).

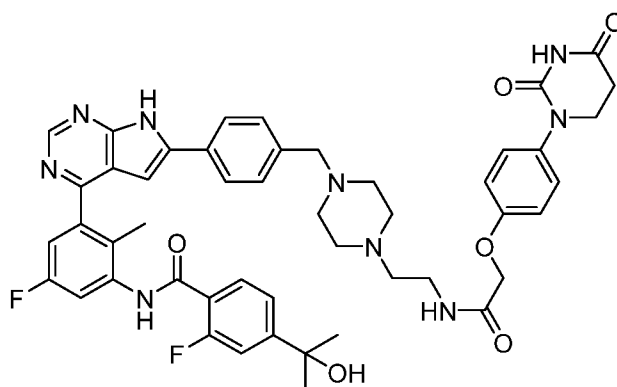
15 Compound 25: N-(3-(6-(4-((4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-
 methoxybenzamido)butyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-
 5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



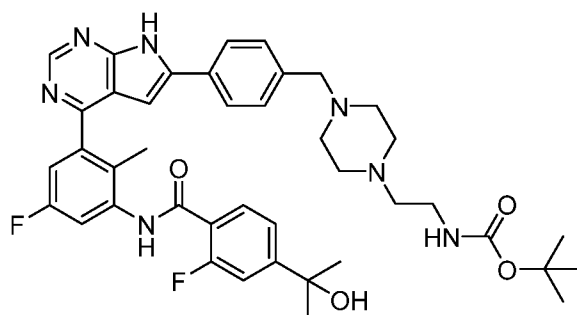
At RT, in a 10 mL round-bottomed flask, 4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methoxy-
 20 N-(4-(piperazin-1-yl)butyl)benzamide (intermediate FF, 103 mg, 0.205 mmol), TEA (0.050 mL,
 0.359 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-
 2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346
 110 mg, 0.205 mmol) were dissolved in MeOH (2 mL). ZnCl₂ 0.5M in THF (0.5 mL, 0.250 mmol)
 was added and the RM was stirred overnight at RT. Then NaBH₃CN (15 mg, 0.239 mmol) was
 25 added and RM was stirred overnight at RT. The reaction was evaporated. The crude product was
 loaded on a RediSep® C18 column and eluted from (water + 0.1% TFA)/ACN 98:2 to 1:9. The
 desired fractions were collected and filtered over a PL-HCO₃ MP SPE cartridge and lyophilized.

Further purification by SFC (250x30 Reprospher PEI 100A 5um, 33to50% in 10min), Method XU to afford the title compound (88 mg) as a white powder. Method LCMS6: Rt = 0.78min; [M+H]⁺ = 915. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.75 (s, 1H), 10.33 (s, 1H), 9.93 (m, 1H), 8.84 (m, 1H), 8.48 (m, 1H), 7.93 (m, 2H), 7.48 (m, 9H), 6.82 (s, 1H), 5.30 (s, 1H), 3.84 (m, 3H), 3.58 (m, 2H), 3.26 (m, 5H), 2.67 (m, 2H), 2.47 – 2.13 (m, 13H), 1.45 (m, 10H).

Compound 26: N-(3-(6-(4-((4-(2-(2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetamido)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



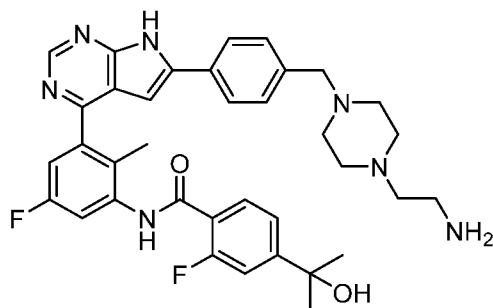
Step 1: *tert*-Butyl (2-(4-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethyl)carbamate



1-2-N-Boc-(2-aminoethyl)piperazine (103 mg, 0.450 mmol), TEA (0.100 mL, 0.717 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 220 mg, 0.409 mmol) were dissolved in MeOH (4 mL). A solution of ZnCl₂ 0.5M in THF (1 mL, 0.500 mmol) was added and the resulting RM was stirred at RT overnight. NaBH₃CN (30 mg, 0.477 mmol) was added and the RM was stirred at RT overnight. The RM was concentrated to dryness. The residue

was purified by chromatography on silica gel eluting with MeOH in DCM (from 0% to 50%) yielding the title compound (363 mg). Method LCMS1: Rt = 0.89 min; $[M+H]^+ = 740.6$.

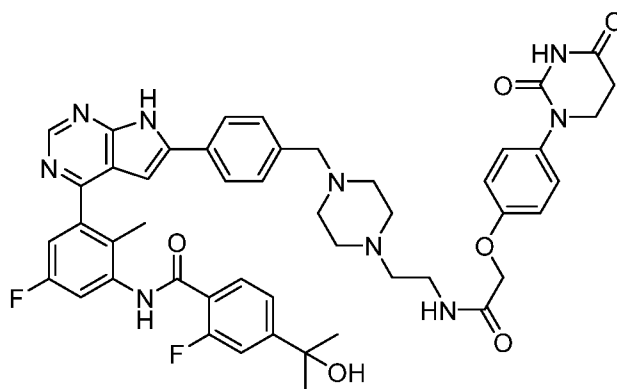
Step 2: N-(3-(6-(4-((4-(2-Aminoethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-
5 d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



To *tert*-butyl (2-(4-(4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperazin-1-yl)ethyl)carbamate (353 mg, 0.382 mmol) was added a solution of HCl 4M in dioxane (2 mL, 8.00 mmol) and MeOH (2 mL).

The RM was stirred at RT for 2 h and concentrated to dryness to afford the HCl salt of the title compound as a yellow solid (358 mg). Method LCMS1: Rt = 0.65 min; $[M+H]^+ = 640.4$.

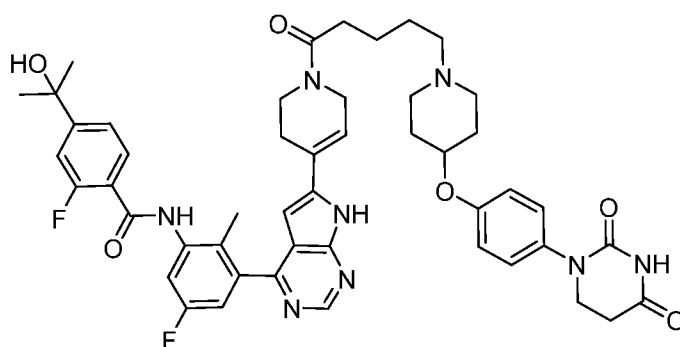
Step 3: N-(3-(6-(4-((4-(2-(2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-
yl)phenoxy)acetamido)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-
15 fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



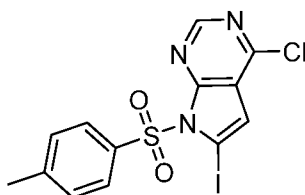
To a solution of 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetic acid (ILB-14, 33 mg, 0.124 mmol) in DMF (0.5 mL) was added NMM (0.025 mL, 0.227 mmol), then HATU (47 mg, 0.124 mmol). A solution of N-(3-(6-(4-((4-(2-aminoethyl)piperazin-1-yl)methyl)phenyl)-7H-

pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide HCl salt (100 mg, 0.112 mmol) and NMM (0.025 mL, 0.227 mmol) in DMF (0.5 mL) was added dropwise into the mixture. The RM was stirred at RT for 90 min. The crude RM was purified by reverse phase chromatography on a RediSep® C18 column eluting with ACN in an aqueous solution of TFA (0.1%) (from 2% to 100%). Fractions containing pure target compound were filtered through PL-HCO₃ MP SPE cartridges and freeze dried to afford the title compound (70 mg). Method LCMS5: Rt = 3.68 min; [M+H]⁺ = 886.5. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.79 (s, 1H), 10.33 (s, 1H), 9.97 (s, 1H), 8.87 (s, 1H), 8.01 – 7.86 (m, 3H), 7.75 (m, 1H), 7.67 (m, 1H), 7.49 – 7.34 (m, 4H), 7.27 – 7.18 (m, 3H), 6.98 (d, J = 8.5 Hz, 2H), 6.86 (s, 1H), 5.32 (s, 1H), 4.49 (s, 2H), 3.73 (t, J = 6.7 Hz, 2H), 3.60 – 3.42 (m, 2H), 3.31–2.81 (m, 8H), 2.70 (m, 2H), 2.46 – 2.25 (m, 4H), 2.19 (s, 3H), 1.47 (s, 6H).

Compound 27: N-(3-(6-(1-(5-(4-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoyl)-1,2,3,6-tetrahydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



Step 1: 4-chloro-6-iodo-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine

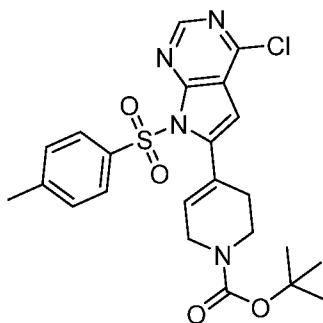


At RT, 4-chloro-6-iodo-7H-pyrrolo[2,3-d]pyrimidine (CAS [876343-10-1], 11 g, 37.4 mmol) was suspended in DMF (40 mL) to give a white suspension. At 0 °C, NaH 60% in mineral oil (1.795 g, 44.9 mmol) was added portionwise, resulting in a brown solution. After 15 min, *p*-toluenesulfonyl chloride (7.2 g, 37.4 mmol) was added portionwise, and the resulting red-brown

RM was stirred for 4h at RT. The RM was poured onto ice and water, then stirred overnight. The suspension was filtered, the solid was washed several times with a mixture of Et₂O/H₂O/ACN to afford the title compound as a beige solid (14.56 g). Method LCMS1: Rt = 1.23 min; [M+H]⁺ = 434.0.

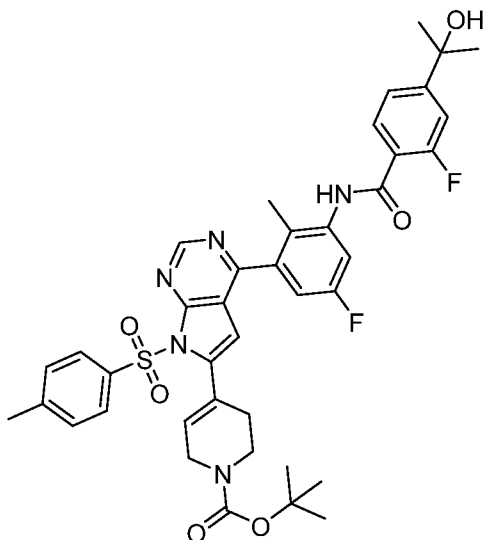
5

Step 2: *tert*-Butyl 4-(4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate



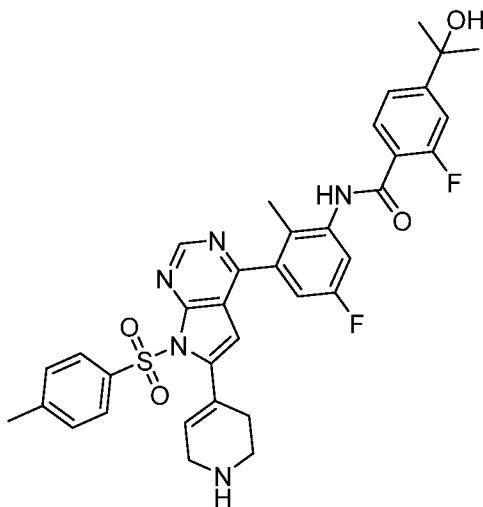
To a solution of 4-chloro-6-iodo-7-tosyl-7H-pyrrolo[2,3-d]pyrimidine (9.5 g, 21.47 mmol) and 3,6-dihydro-2H-pyridine-1-N-Boc-4-boronic acid pinacol ester (CAS No. [286961-14-6], 8 g, 25.4 mmol) in iPrOH (120 mL) was added aq. 2M Na₂CO₃ (43 mL, 86 mmol). The mixture was degassed with argon, then PdCl₂(PPh₃)₂ (1.5 g, 2.116 mmol) was added and the RM was heated at 75 °C for 2 h. The RM was cooled down to RT, filtered over Celite[®] filter aid and washed with EtOAc. The resulting filtrate was diluted with water and extracted. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 0 – 45 % EtOAc in CHX to afford an orange residue. The residue was triturated in Et₂O and filtered to afford the title compound as a beige powder (6.832 g). Method LCMS1: Rt = 1.38 min; [M+H]⁺ = 489.2.

Step 3: *tert*-Butyl 4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate



To a solution of *tert*-butyl 4-(4-chloro-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (7.915 g, 15.145 mmol) and 2-fluoro-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 2 in PCT/IB2019/052346 7.998 g, 18.174 mmol) in DME (150 mL) was added aq. 1M Na₂CO₃ (45.4 mL, 45.4 mmol). The mixture was degassed with argon, PdCl₂(PPh₃)₂ (1.074 g, 1.5145 mmol) was added and the RM was heated at 100 °C for 1 h. The RM was cooled down to RT, filtered over Celite[®] filter aid, and washed with EtOAc. The filtrate was diluted with water and extracted. The organic layer was washed with brine, dried over MgSO₄, and evaporated. The crude product was purified by flash chromatography on silica gel eluting with 0 – 65 % EtOAc in CHX to afford the title compound as an orange foam (13.52 g). Method LCMS1: Rt = 1.36 min; [M+H]⁺ = 758.4.

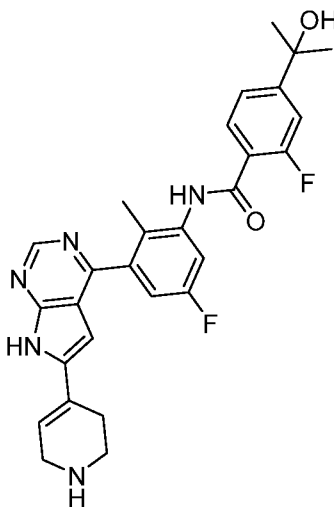
Step 4: 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(1,2,3,6-tetrahydropyridin-4-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide



To a solution of *tert*-butyl 4-(4-(5-fluoro-3-(2-fluoro-4-(2-hydroxypropan-2-yl)benzamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate (13.52 g, 14.99 mmol) in dioxane (50 mL) was added HCl 4 M in dioxane (25 mL, 100 mmol).

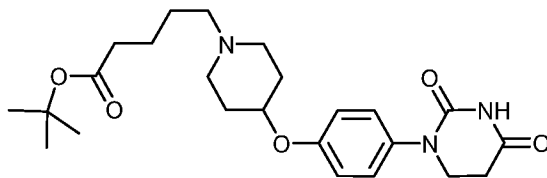
- 5 The orange solution was stirred overnight at RT, then the RM was evaporated to dryness. The resulting residue was diluted in EtOH, a few mL of cold MTBE were added and after trituration, the mixture was filtered. The crude product was purified by reverse phase chromatography on a Redisep® C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 10 to 100%). The fractions were evaporated, then partitioned between sat. aq. NaHCO₃ solution and DCM. After
- 10 extraction, the solution was evaporated and dried under HV to afford the title compound as a white solid (7.8 g). Method LCMS1: Rt = 0.88 min; [M+H]⁺ = 658.3.

Step 5: 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(1,2,3,6-tetrahydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide



To an orange solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(1,2,3,6-tetrahydropyridin-4-yl)-7-tosyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide (1.29 g, 1.961 mmol) in THF (19.5 mL) was added aq. 32% NaOH (363 μ L, 3.92 mmol) and the RM was stirred at RT. After 3 nights at RT, the RM was concentrated until dryness to afford an orange resin. The resin was diluted with ACN and water, then TFA (302 μ L, 3.92 mmol) was carefully added. The resulting solution was adsorbed on Isolute[®], concentrated until dryness, dried under HV and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after freeze drying, the title compound as a yellow solid TFA salt (830 mg). Method LCMS1: Rt = 0.67 min; [M+H]⁺ = 504.3.

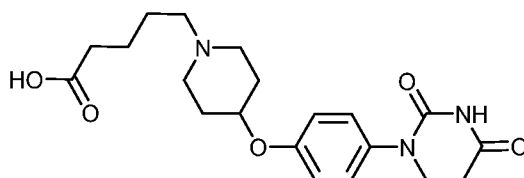
Step 6: *tert*-Butyl 5-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoate



To a colorless solution of 1-(4-(piperidin-4-yloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-36, 123 mg, 0.305 mmol), *tert*-butyl 5-oxopentanoate (CAS [192123-41-4], 60.8 mg, 0.335 mmol) and TEA (42 μ L, 0.305 mmol) in MeOH (6 mL) was added ZnCl₂ 0.5 M in THF (671 μ L, 0.335 mmol). The resulting mixture was flushed with N₂ and stirred at RT. After 3 h at RT, NaBH₃CN (21.1 mg, 0.335 mmol) was added, and the RM was stirred at RT for 18 h. Then more *tert*-butyl 5-oxopentanoate (17 mg, 0.094 mmol) in MeOH (0.2 mL), followed by more ZnCl₂ 0.5

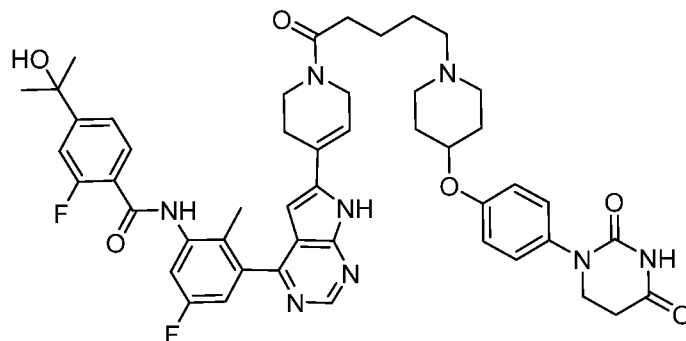
M in THF (183 μ L, 0.091 mmol) were added, the resulting RM was stirred at RT for 2 h, before more NaBH_3CN (14 mg, 0.222 mmol) was added. The resulting RM was then stirred at RT for overnight, diluted with ACN and concentrated until dryness to give a colorless resin. The crude product was diluted with a mixture of DCM/MeOH/ACN, adsorbed on Isolute[®], concentrated until dryness and purified by flash chromatography on silica gel eluting with 5 – 80 % (DCM/iPrOH 80/20) in DCM to afford the title compound as a colorless resin (118 mg). Method LCMS1: $R_t = 0.68$ min; $[\text{M}+\text{H}]^+ = 446.4$.

Step 7: 5-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoic acid



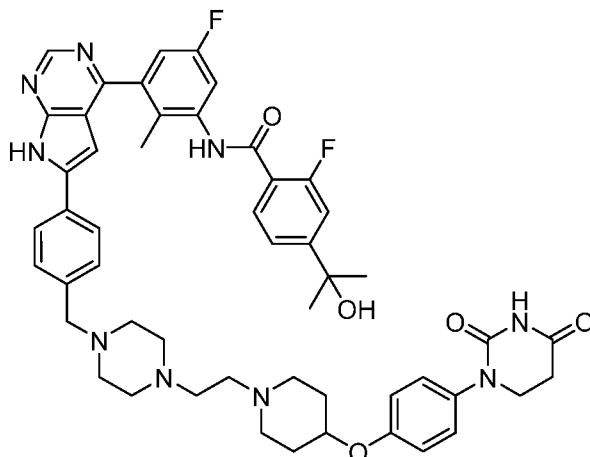
To a colorless solution of *tert*-butyl 5-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoate (117 mg, 0.197 mmol) in DCM (2.8 mL) was added TFA (455 μ L, 5.91 mmol). The resulting solution was stirred at RT for 1 h. The RM was diluted with DCM, concentrated until dryness, then co-evaporated with DCM (1x), and dried under HV pump to afford a colorless resin. The resin was freeze dried to afford an off-white solid. The solid was dissolved in ACN, adsorbed on Isolute[®], concentrated until dryness and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 2 to 100%) to afford the title compound as a white solid TFA salt (62 mg). Method LCMS1: $R_t = 0.42$ min; $[\text{M}+\text{H}]^+ = 390.3$.

Step 8: N-(3-(6-(1-(5-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoyl)-1,2,3,6-tetrahydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

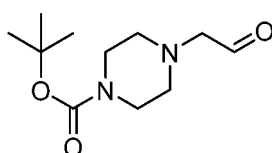


To a yellow solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(1,2,3,6-tetrahydropyridin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide (45 mg, 0.062 mmol), 5-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)pentanoic acid (34.1 mg, 0.068 mmol) and HBTU (26.2 mg, 0.068 mmol) in dry DMF (1.2 mL) flushed with N₂ was added DIPEA (75 μ L, 0.431 mmol). The resulting RM was stirred at RT for 1 h, diluted with ACN, adsorbed on Isolute[®], concentrated until dryness, then dried under HV and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1 %) (from 10 to 100 %) to afford, after filtration of the fractions containing the pure target compound through PL-HCO₃ MP SPE cartridges and freeze drying, the title compound as a white solid (38 mg). Method LCMS1: Rt = 0.77 min; [M+H]⁺ = 875.6. Method LCMS5: Rt = 3.64 min; [M+H]⁺ = 875.6. ¹H NMR (400 MHz, DMSO-*d*₆) δ 1.44 (s, 8 H) 1.48 - 1.62 (m, 4 H) 1.89 (br d, J = 10.64 Hz, 2 H) 2.10 - 2.18 (m, 5 H) 2.27 (br t, J = 6.72 Hz, 2 H) 2.33 - 2.41 (m, 2 H) 2.45 (br s, 1 H) 2.55 (br s, 1 H) 2.62 - 2.69 (m, 4 H) 3.60 - 3.71 (m, 4 H) 4.15 (br s, 1 H) 4.22 (br s, 1 H) 4.30 (br s, 1 H) 5.27 (s, 1 H) 6.33 (d, J = 3.91 Hz, 1 H) 6.59 (br s, 1 H) 6.90 (br dd, J = 8.74, 4.22 Hz, 2 H) 7.17 (br d, J = 7.82 Hz, 3 H) 7.37 - 7.43 (m, 2 H) 7.61 (br d, J = 10.15 Hz, 1 H) 7.71 (t, J = 7.89 Hz, 1 H) 8.81 (s, 1 H) 9.91 (br s, 1 H) 10.26 (s, 1 H) 12.43 (br s, 1 H).

Compound 28: N-(3-(6-(4-((4-(2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

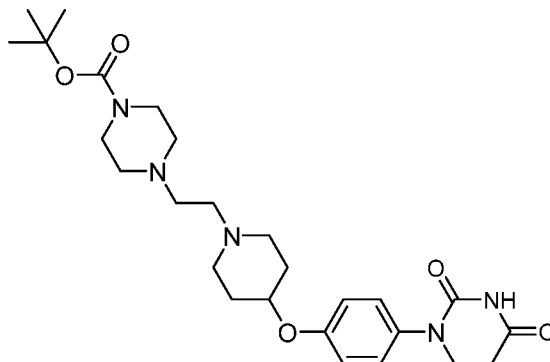


Step 1: *tert*-Butyl 4-(2-oxoethyl)piperazine-1-carboxylate



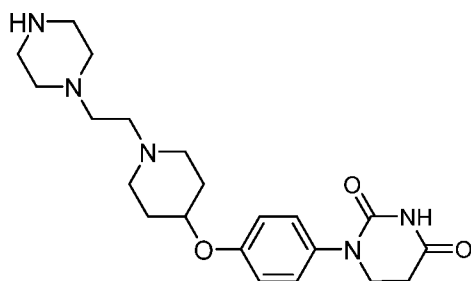
To a stirring solution of oxalyl chloride (380 μ L, 4.25 mmol) in anhydrous DCM (10 mL) cooled down to -78 $^{\circ}$ C was added DMSO (538 μ L, 7.58 mmol). The RM was stirred for 30 min, then 1-Boc-4-(2-hydroxyethyl)piperazine (CAS No. [77279-24-4]) (500 mg, 2.106 mmol) in DCM (10 mL) was added. The RM was stirred at the same temperature for 30 min, followed by the addition of TEA (2.4 mL, 17.22 mmol). The RM was then stirred for 1.5 h while allowing to reach RT, then quenched by sat. aq. NaHCO_3 solution and extracted with DCM (3x). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 0 – 30% EtOAc/MeOH 4/1 in EtOAc to afford the title compound as a pale yellow residue (371 mg). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.57 (d, J = 1.5 Hz, 1H), 3.31 (dd, J = 10.0, 5.0 Hz, 4H), 3.18 (d, J = 1.5 Hz, 2H), 2.38 (t, J = 5.1 Hz, 4H), 1.38 (s, 9H).

Step 2: *tert*-Butyl 4-(2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)piperazine-1-carboxylate



At RT, *tert*-butyl 4-(2-oxoethyl)piperazine-1-carboxylate (73 mg, 0.304 mmol), TEA (100 μ L, 0.717 mmol) and 1-(4-(piperidin-4-yloxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-36, 110 mg, 0.254 mmol) were dissolved in MeOH (2 mL). Then, ZnCl_2 0.7 M in THF (400 μ L, 0.280 mmol) was added and the RM was stirred overnight at RT under argon. Then, NaBH_3CN (19 mg, 0.302 mmol) was added and the RM was stirred overnight at RT. More *tert*-butyl 4-(2-oxoethyl)piperazine-1-carboxylate (73 mg, 0.304 mmol) was added and the RM was stirred for 3 days at RT under argon, then evaporated. The crude product was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1 %) (from 2 to 90%) to afford, after freeze drying, the title as a white powder TFA salt (130 mg). Method LCMS1: R_t = 0.66 min; $[\text{M}+\text{H}]^+$ 502.3.

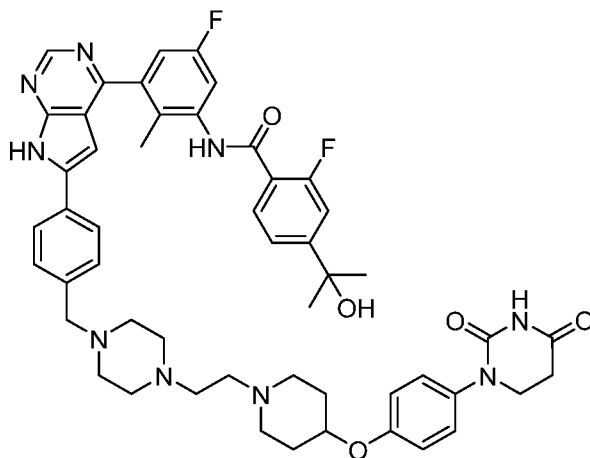
Step 3: 1-(4-((1-(2-(piperazin-1-yl)ethyl)piperidin-4-yl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione



A solution of *tert*-butyl 4-(2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)piperazine-1-carboxylate (130 mg, 0.192 mmol) and TFA (250 μ L, 3.24 mmol) in DCM (2 mL) was stirred for 2h at RT. The RM was concentrated to dryness, the crude product was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq.

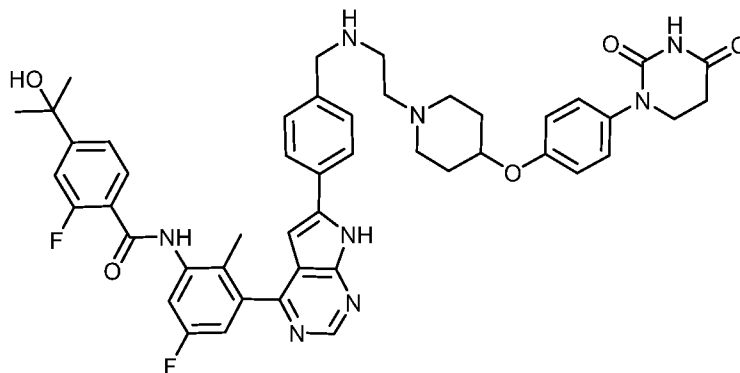
solution of TFA (0.1%) (from 2 to 100%) to afford, after freeze drying, the title compound as a white solid TFA salt (41 mg). Method LCMS2: $R_t = 0.65$ min; $[M+H]^+ = 402.3$.

Step 4: N-(3-(6-(4-((4-(2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



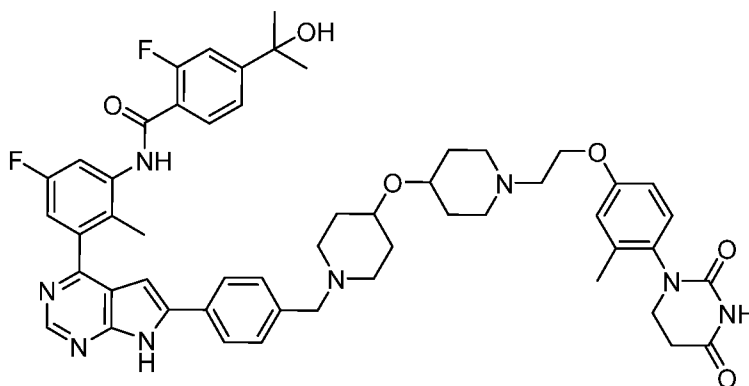
At RT, 1-(4-((1-(2-(piperazin-1-yl)ethyl)piperidin-4-yl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (41 mg, 0.040 mmol), TEA (50 μ L, 0.359 mmol) and 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 29 mg, 0.055 mmol) were dissolved in MeOH (500 μ L). Then, $ZnCl_2$ 0.7 M in THF (100 μ L, 0.070 mmol) was added and the RM was stirred overnight at RT under argon. Then $NaBH_3CN$ (5 mg, 0.080 mmol) was added and the RM was stirred overnight at RT, then evaporated. The crude product was purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of NH_4HCO_3 (0.1%) (from 2 to 90%) to afford, after partial evaporation, a cloudy white suspension. The suspension was cooled down to 0 $^{\circ}C$, filtered to afford a non-pure material, that was then purified by SFC using Method XU (column: Princeton PPU 250 x 30 mm, 100 A, 5 μ M) eluting with 35 – 50% CO_2 in MeOH to afford the title compound (10.3 mg). Method LCMS1: $R_t = 0.70$ min; $[M+H]^+ = 912.6$. Method LCMS5: $R_t = 3.14$ min; $[M+H]^+ = 912.6$.

Compound 29: N-(3-(6-(4-(((2-(4-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)piperidin-1-yl)ethyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

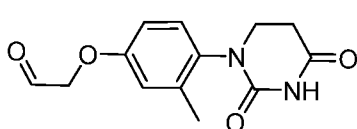


- 5 To a yellow-green mixture of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 60 mg, 0.114 mmol), 1-(4-((1-(2-aminoethyl)piperidin-4-yl)oxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-68, 78 mg, 0.125 mmol) and TEA (35 μ L, 0.251 mmol) in dry MeOH (2.3 mL) flushed with N₂ was added ZnCl₂ 0.5 M in THF (251 μ L, 0.125 mmol). The resulting RM was flushed with N₂ and stirred at RT for 4h. Then, NaBH₃CN (11.3 mg, 0.171 mmol) was added and it was stirred at RT for 18 h. The RM was diluted with ACN, adsorbed on Isolute[®], concentrated until dryness, dried under HV pump and purified by reverse phase chromatography on a Redisept[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) to afford, after filtration of the fractions containing the pure target compound through
- 15 PL-HCO₃ MP SPE cartridges and freeze drying, the title compound as an off-white solid (76 mg). Method LCMS1): Rt = 0.75 min; [M+H]⁺ = 843.5. Method LCMS5): Rt = 3.33 min; [M+H]⁺ = 843.4. ¹H NMR (400 MHz, DMSO-*d*₆): 1.45 (s, 6 H) 1.60 (q, J = 9.66 Hz, 2 H) 1.87 - 1.96 (m, 2 H) 2.15 - 2.23 (m, 5 H) 2.40 - 2.44 (m, 2 H) 2.56 - 2.61 (m, 2 H) 2.64 - 2.70 (m, 4 H) 3.65 - 3.77 (m, 4 H) 4.28 - 4.41 (m, 1 H) 5.29 (s, 1 H) 6.83 (s, 1 H) 6.94 (d, J = 8.93 Hz, 2 H) 7.17 - 7.26 (m, 3 H) 7.39 - 7.45 (m, 4 H) 7.66 (br d, J = 9.90 Hz, 1 H) 7.70 - 7.76 (m, 1 H) 7.94 (d, J = 8.19 Hz, 2 H) 8.84 (s, 1 H) 9.93 (s, 1 H) 10.28 (s, 1 H) 12.74 (br s, 1 H).
- 20

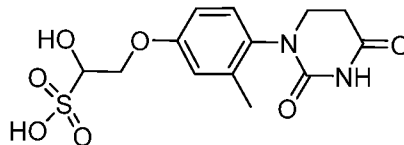
- Compound 30: N-(3-(6-(4-(((1-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methylphenoxy)ethyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide
- 25



Step 1: 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methylphenoxy)acetaldehyde, 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methylphenoxy)-1-hydroxyethanesulfonic acid



Intermediate compound A

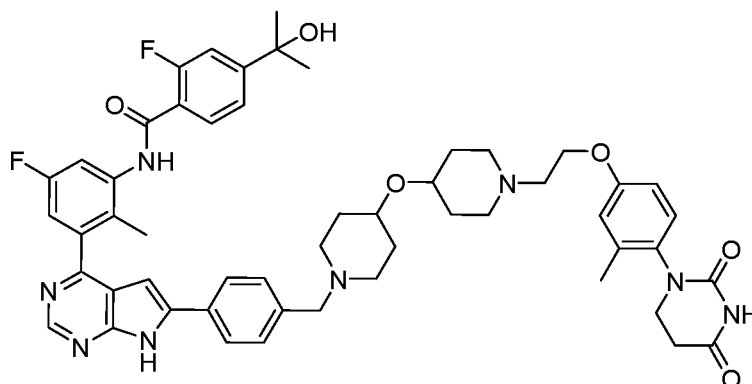


Title compound

- 5 **Formation of Intermediate compound A:** To a mixture of 1-(4-(2,2-diethoxyethoxy)-2-methylphenyl) dihydropyrimidine-2,4(1H,3H)-dione (0.49 g, 1.457 mmol) in THF (3.6 mL) was added HCl 2N (3.64 mL, 7.28 mmol). The RM was heated at 80 °C for 3 h. The yellow solution was immersed in an ice-bath. No precipitation after 0.5 h. Therefore the THF was evaporated off. The remaining aq. layer was freeze dried overnight. The crude material was evaporated and
- 10 absorbed on silica gel and purified by flash chromatography on a silica flash column 12 g eluting with DCM/MeOH to afford the intermediate compound A (0.52 g).

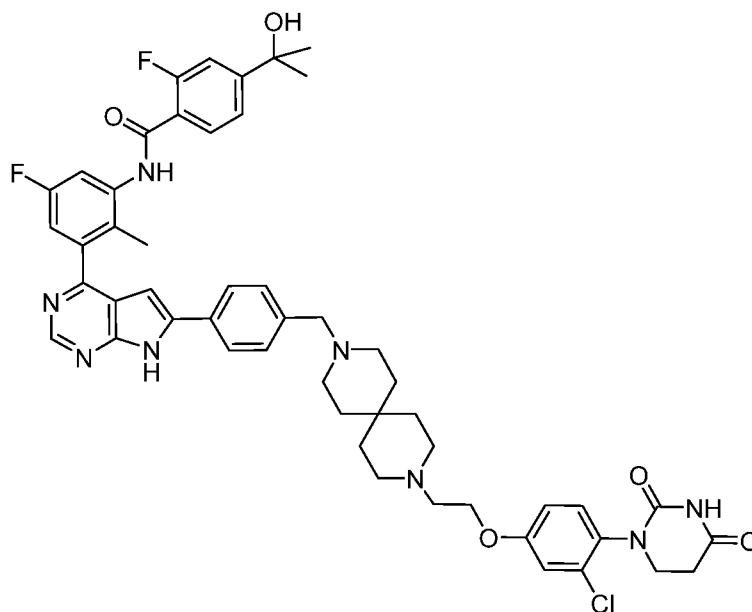
- Formation of title compound:** Intermediate compound A was dissolved in EtOH (2 mL, Ratio: 12.50) / Water (0.16 mL, Ratio: 1.0) then treated with sodium metabisulfite (0.388 g, 2.039 mmol)
- 15 - theoretical 0.7 eq / 1 eq aldehyde - and heated at 80 °C for 1.5 h. The suspension was cooled to RT, diluted with 2 mL EtOH then the precipitate was filtered off, washed with EtOH and dried overnight at 50 °C *in vacuo* to afford the title compound (51.6 mg). Method LCMS1: Rt = 0.33 min; [M-H]⁺ = 343.1.

Step 2: N-(3-(6-(4-((4-((1-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methylphenoxy)ethyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

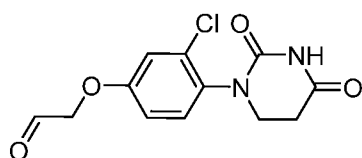


- 5 A solution of 2-fluoro-N-(5-fluoro-2-methyl-3-(6-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-4-(2-hydroxypropan-2-yl)benzamide HCl salt (compound 8 step 2 in PCT/IB2019/052346 30 mg, 0.043 mmol) in MeOH (Volume: 1.5 mL) was treated with NaOAc (17.71 mg, 0.216 mmol) and stirred at room temperature for 15 minutes. Afterwards 2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)-3-methylphenoxy)-1-hydroxyethanesulfonic acid (20.62 mg, 0.056 mmol) and picoline borane complex (5.43 mg, 0.043 mmol) was added. The RM was stirred overnight at RT. The slurry RM was diluted with MeOH then filtered through a disposal syringe filter. The filtrate was ready to inject in the prep. RP-HPLC with method XN. The crude compound was purified by prep. HPLC Method XN (reversed phase) on a Reprosil 100 C18 column eluting with ACN/aq. solution of TFA
- 15 0.1%. F54 was worked up (addition of NaHCO₃, extraction with AcOEt). The residue was dissolved in water / some drops of ACN and t-BuOH and freeze dried overnight to afford the title compound (3 mg) as a white solid. Method LCMS5: Rt = 3.12 min; [M+H]⁺ = 941.3. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.77 (s, 1H), 10.29 (s, 1H), 9.96 (s, 1H), 8.85 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.73 (t, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.24 (m, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 6.88 – 6.75 (m, 3H), 5.31 (s, 1H), 4.03 (s, 2H), 3.69 (m, 1H), 3.51 – 3.43 (m, 4H), 3.38 (s, 2H), 2.87 – 2.70 (m, 4H), 2.70 – 2.62 (m, 6H), 2.15 (m, 9H), 1.77 (s, 3H), 1.45 (m, 10H).
- 20

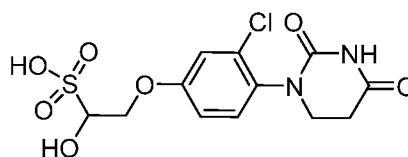
Compound 31: N-(3-(6-(4-((9-(2-(3-chloro-4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



Step 1: 2-(3-chloro-4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)acetaldehyde, 2-(3-chloro-4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-1-hydroxyethanesulfonic acid



Intermediate compound A



Title compound

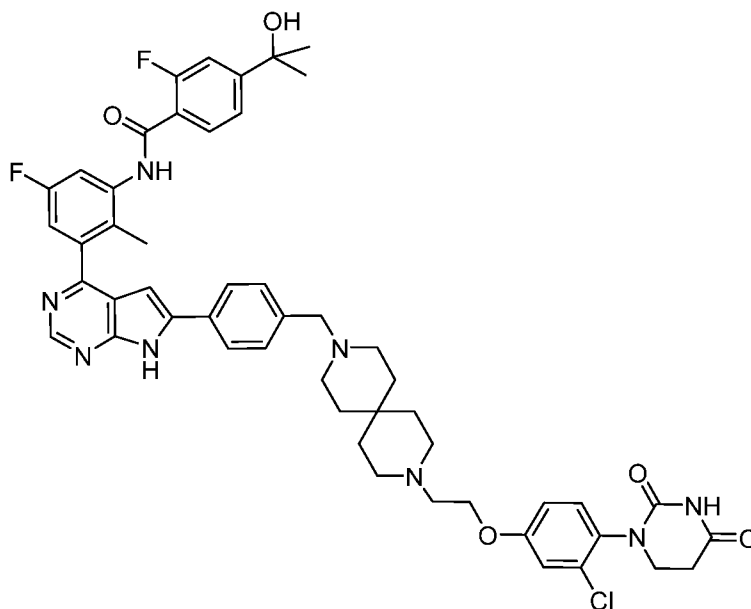
Formation of Intermediate compound A:

A mixture of 1-(2-chloro-4-(2,2-diethoxyethoxy)phenyl) dihydropyrimidine-2,4(1H,3H)-dione (0.49 g, 1.373 mmol) and HCl 2M aq. (0.034 mL, 0.069 mmol) in ACN (5 mL, Ratio: 31.3) was stirred at RT. After stirring overnight at RT, was added again HCl 2 M aq. (0.103 mL, 0.206 mmol). After stirring at RT, the RM was diluted with DCM and washed with water. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated *in vacuo* to obtain 0.34 g of the crude Intermediate compound A as a brown resin. The crude material was purified by flash chromatography on a silica flash column 4 g eluting with DCM/MeOH to afford the Intermediate compound A (0.24 g).

Formation of title compound:

Intermediate Compound A was dissolved in EtOH (2 mL, Ratio: 12.5) / Water (0.16 mL, Ratio: 1.0) then treated with sodium metabisulfite (0.091 g, 0.481 mmol) - theoretical 0.7 eq / 1 eq aldehyde - and heated at 80 °C for 1.5 h. The suspension was cooled to RT, diluted with 2 mL EtOH, then the precipitate was filtered off, washed with EtOH, and dried overnight at 50°C *in vacuo* to obtain the title compound as the sodium salt (265 mg). Method LCMS1: Rt = 0.35 min; [M-H]⁺ = 363.0.

Step 2: N-(3-(6-(4-((9-(2-(3-chloro-4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)-3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide

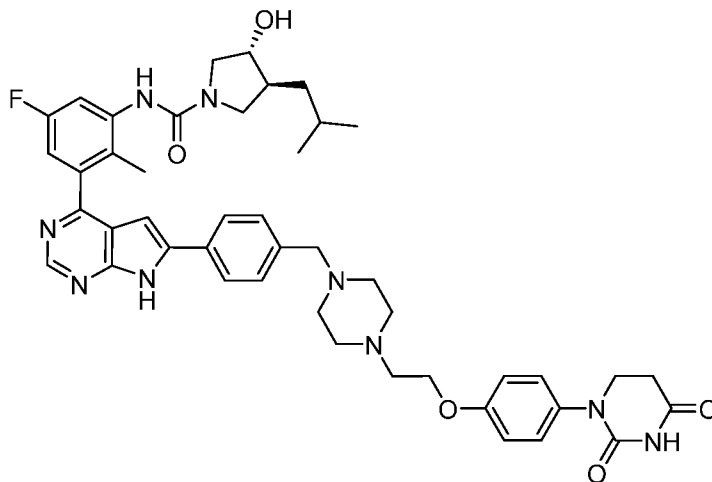


A solution of N-(3-(6-(4-(3,9-diazaspiro[5.5]undecan-3-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide (intermediate 6 in PCT/IB2019/052346 60 mg, 0.056 mmol) in MeOH (1.5 mL) was treated with NaOAc (22.96 mg, 0.280 mmol) and stirred at RT for 15 minutes. Afterwards 2-(3-chloro-4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)-1-hydroxyethanesulfonic acid (28.2 mg, 0.073 mmol) and picoline borane complex (7.04 mg, 0.056 mmol) was added. The RM was stirred overnight at RT. The slurry RM was diluted with MeOH then filtered through a disposal syringe filter. The filtrate was ready to inject in the prep. RP-HPLC. The crude compound was purified by

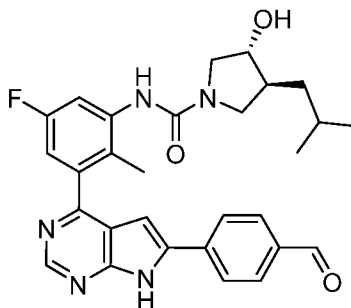
prep. HPLC (reversed phase) on a Reprosil® 100 C18 column eluting with ACN/aq. solution of TFA 0.1% using the method XN. Title compound was worked up (addition of NaHCO₃, extraction with AcOEt). The residue was dissolved in water and some drops of ACN and t-BuOH and freeze dried overnight to afford the title compound (16.9mg). Method LCMS5: Rt = 2.97 min; [M+H]⁺ = 932.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 10.41 (s, 1H), 9.94 (d, *J* = 2.5 Hz, 1H), 8.85 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 2H), 7.83 – 7.59 (m, 2H), 7.51 – 7.32 (m, 5H), 7.31 – 7.10 (m, 2H), 6.97 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.82 (s, 1H), 5.30 (s, 1H), 4.18 (s, 1H), 4.10 (m, 2H), 3.69 – 3.60 (m, 1H), 3.59 – 3.44 (m, 3H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.43 (m, 6H), 2.37 – 2.26 (m, 5H), 2.17 (s, 3H), 1.43 (m, *J* = 14.2 Hz, 14H).

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Compound 32: (3R,4S)-N-(3-(6-(4-((4-(2-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



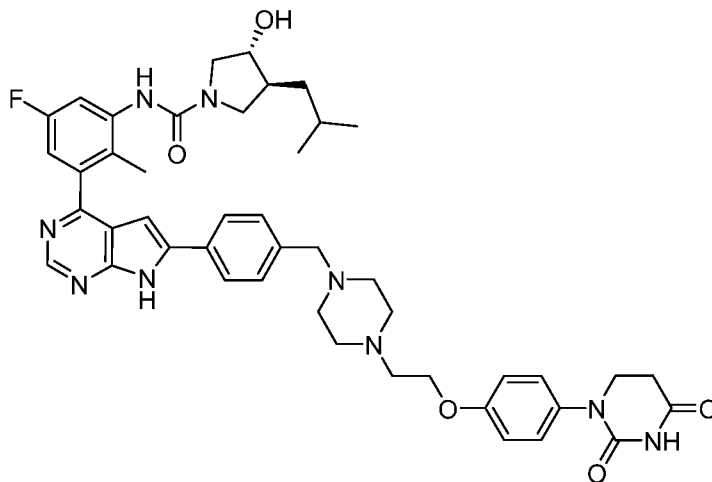
15 **Step 1:** (3R,4S)-N-(5-Fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



In a round-bottomed flask was added 4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzaldehyde (intermediate 3a in PCT/IB2019/052392, 150 mg, 0.582 mmol), (3R,4S)-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide (intermediate 7 in PCT/IB2019/052392, 269 mg, 0.640 mmol), and K₂CO₃ (201 mg, 1.455 mmol), PdCl₂(dppf) (42.6 mg, 0.058 mmol) was added. The reaction mixture was diluted with dioxane (3 mL, Ratio: 1.0) and with H₂O (3 mL, Ratio: 1.0). The RM was heated at 100 °C for 1.5 h. The RM was absorbed on silica and purified by flash chromatography on a 12 g column eluting DCM/MeOH to afford the title compound (90 mg). Method LCMS1: Rt = 0.95 min; [M+H]⁺ = 516.2.

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Step 2: (3R,4S)-N-(3-(6-(4-((4-(2-(4-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)phenoxy)ethyl)piperazin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide

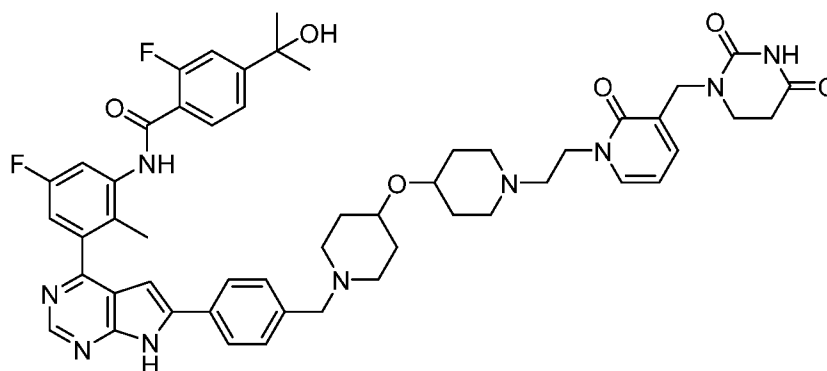


In a round-bottomed flask was added (3R,4S)-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide (103 mg, 0.200 mmol), 1-(4-(2-(piperazin-1-yl)ethoxy)phenyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-35, 131 mg, 0.240 mmol), and TEA (0.056 mL, 0.400 mmol) in MeOH (3 mL) to give a colorless solution. ZnCl₂ in solution in THF (0.420 mL, 0.210 mmol) was added. The RM was stirred 3 h under argon. After this time, NaBH₃CN (25.1 mg, 0.400 mmol) was added and the RM was stirred at RT overnight. The solution was diluted with CH₂Cl₂ and washed with Water and brine. The organic layer (suspension) was evaporated and purified by reverse phase. The crude compound was absorbed on Isolute and purified by reverse phase chromatography on a Redisep[®] C18 column

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eluting with ACN/aq. solution of TFA (0.1%). The most pure fractions were further purified by reverse phase prep HPLC using method XS (XBridge Prep C18 OBD 5 μ m 100 x 30 mm + 0.1%TFA 13-43% ACN in 15 min at 30 mL/min). Bond Elut SCX 2 mg/12 mL from Agilent was used to remove the TFA. The column was washed 2 times with 10 mL of MeOH and then the title compound was recovered from the cartridge by washing with ammonia in MeOH 7 N. The filtrate was evaporated to dryness to afford the title compound (33.6 mg). Method LCMS1: Rt = 0.84 min; [M-H]⁺ = 816.5. Method LCMS5: Rt = 3.49 min; [M-H]⁺ = 816.5. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.73 (s, 1H), 10.29 (s, 1H), 8.83 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.67 (s, 1H), 7.57-7.30 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.06 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.77 (s, 1H), 5.12 (d, *J* = 4.5 Hz, 1H), 4.06 (s, 2H), 3.94-3.82 (m, 1H), 3.75-3.59 (m, 5H), 3.50 (s, 2H), 3.30 (m, 1H), 3.19 (m, 1H), 3.14-3.01 (m, 1H), 2.68 (t, *J* = 6.6 Hz, 5H), 2.37 (m, 4H), 2.09 (m, 4H), 1.62 (m, 1H), 1.35 (m, 1H), 1.12 (m, 1H), 0.90 (m, 7H).

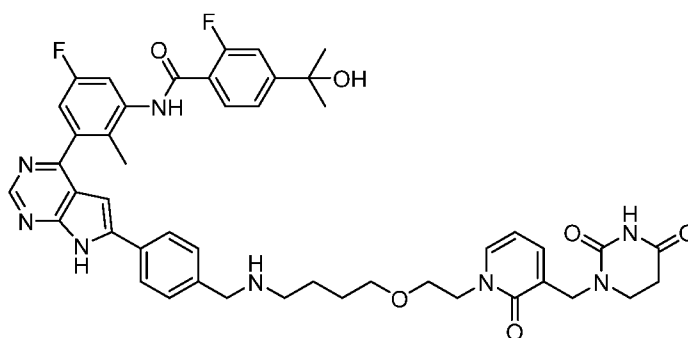
Compound 33: N-(3-(6-(4-((1-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



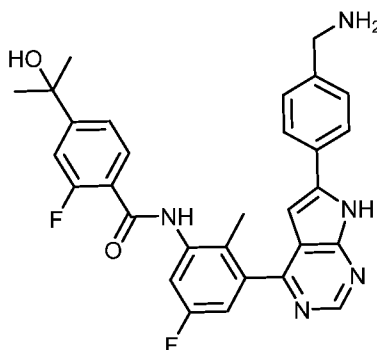
To a solution of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 56 mg, 0.13 mmol) and 1-((2-oxo-1-(2-(4-(piperidin-4-yloxy)piperidin-1-yl)ethyl)-1,2-dihydropyridin-3-yl)methyl)dihydropyrimidine-2,4(1H,3H)-dione (ILB-6, 89 mg, 0.169 mmol) in 1 mL DMSO was added ZnCl₂ (0.2 6mL 1M solution in THF, 0.26 mmol). The reaction mixture was stirred at 10°C for 2 h. To the mixture was added NaBH₃CN (26 mg, 0.416 mmol) and the mixture was stirred at RT for 18h. 2mL MeOH was added, the mixture was filtered and purified

by preparative HPLC (Xbridge C18, 21.2 x 250 mm, 10 μ m), eluting with 0.01M ammonium hydrogen carbonate buffer in H₂O/ACN yielding the target compound as light yellow solid (11 mg). Method LCMS XG: Rt = 1.99 min; (M+H)⁺ = 942. ¹H NMR (500 MHz, DMSO-d₆) δ 12.77 (br s, 1H), 10.16 (s, 1H), 9.95 (d, *J* = 2.0 Hz, 1H), 8.85 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.75-7.72 (m, 1H), 7.67-7.65 (m, 1H), 7.58-7.56 (m, 1H), 7.44-7.37 (m, 4H), 7.27-7.23 (m, 2H), 6.83 (s, 1H), 6.21-6.18 (m, 1H), 5.31 (s, 1H), 4.26 (s, 2H), 3.99-3.97 (m, 2H), 3.47 (s, 2H), 3.42-3.37 (m, 4H), 2.73-2.64 (m, 4H), 2.58-2.55 (m, 2H), 2.54-2.50 (m, 2H), 2.18 (s, 3H), 2.12-2.05 (m, 4H), 1.74-1.71 (m, 4H), 1.45 (s, 6H), 1.42-1.32 (m, 4H).

Compound 34: **N-(3-(6-(4-(((4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**



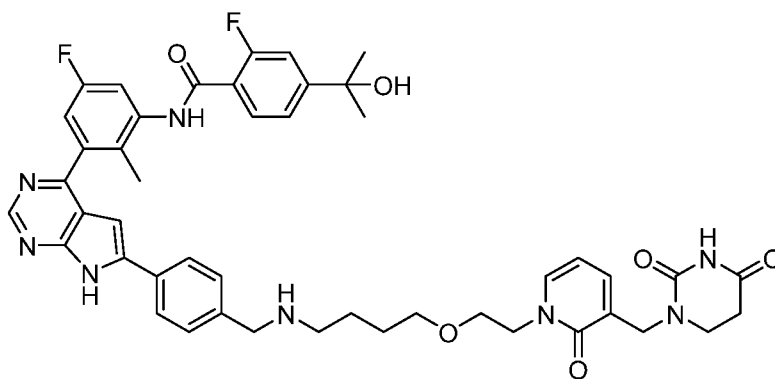
Step 1: **N-(3-(6-(4-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide**



A yellow mixture of 2-fluoro-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-4-(2-hydroxypropan-2-yl)benzamide (intermediate 3 in PCT/IB2019/052346 200 mg, 0.380 mmol), NH₃ 7 N in MeOH (5 mL, 35 mmol) and Raney-Nickel (Ra-Ni (EtOH) Degussa B113W) (100 mg) was shaken at RT under 3.5 bar of H₂ in a glass autoclave/hastelloy[®].

After 16.5 h at RT, the RM was diluted with more NH_3 7 N in MeOH (25 mL, 175 mmol). More Raney-Nickel (200 mg) was added and the RM was shaken under 3.5 bar of H_2 at RT for 2 additional nights. The RM was filtered through a pad of Celite[®] filter aid, rinsed with ACN and MeOH, to afford a grey-green solid. The solid was diluted in ACN/MeOH, adsorbed on Isolute[®], concentrated until dryness, dried under HV pump and purified by reverse phase chromatography on a Redisep[®] C18 column eluting with ACN in an aq. solution of TFA (0.1%) (from 10 to 100%) to afford, after freeze drying, the title compound as a yellow solid TFA salt (147 mg). Method LCMS1: $R_t = 0.72$ min; $[M+H]^+ = 528.3$.

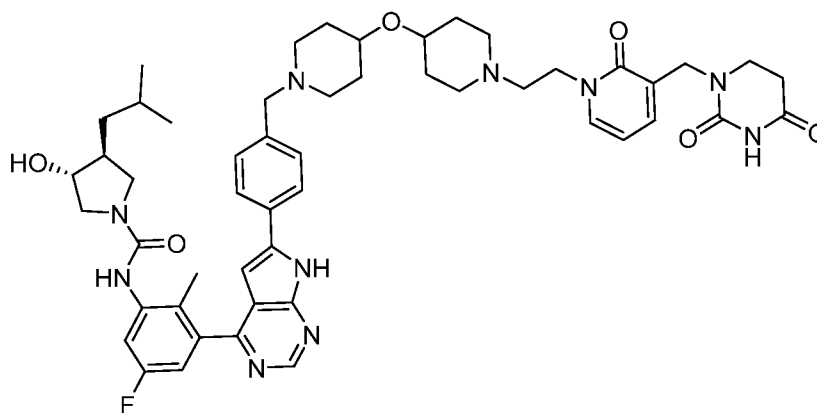
Step 2: N-(3-(6-(4-(((4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butyl)amino)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide



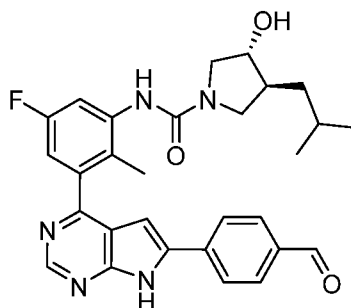
To a mixture of N-(3-(6-(4-(aminomethyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-2-fluoro-4-(2-hydroxypropan-2-yl)benzamide trifluoroacetate salt (110 mg, 0.219 mmol), K_2CO_3 (43 mg, 0.3135 mmol) and 4-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethoxy)butanal (ILB-5, 70 mg, 0.149 mmol) in DMSO (5 mL) was added ZnCl_2 (0.223 mL, 0.223 mmol). The mixture was stirred at RT for 30 min, then NaBH_3CN (56 mg, 0.892 mmol) was slowly added. The reaction mixture was stirred at room temperature for 4 h. The mixture filtered and directly purified by reverse-phase chromatography Method PB to obtain the title compound as a white solid. (15 mg). LC-MS Method H: $R_t = 1.93$ min, $(M+H)^+ = 848.3$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.74 (s, 1H), 10.16 (s, 1H), 9.96 (s, 1H), 8.85 (s, 1H), 7.93 (d, $J = 8.2$ Hz, 2H), 7.73 (t, $J = 7.9$ Hz, 1H), 7.66 (d, $J = 9.3$ Hz, 1H), 7.54 (d, $J = 5.0$ Hz, 1H), 7.42 (dd, $J = 13.8, 7.4$ Hz, 4H), 7.31-7.20 (m, 2H), 6.83 (s, 1H), 6.19 (t, $J = 6.8$ Hz, 1H), 5.31 (s, 1H), 4.26 (s, 2H), 4.05 (t, $J = 5.3$ Hz, 2H), 3.69 (s, 2H), 3.59 (t, $J = 5.4$ Hz, 2H), 3.40

(t, $J = 6.8$ Hz, 2H), 3.36-3.30 (m, 3H), 2.56 (t, $J = 6.8$ Hz, 2H), 2.44 (t, $J = 6.9$ Hz, 2H), 2.18 (s, 3H), 1.56 -1.34 (m, 10H).

Compound 35: (3R,4S)-N-(3-(6-(4-((4-((1-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



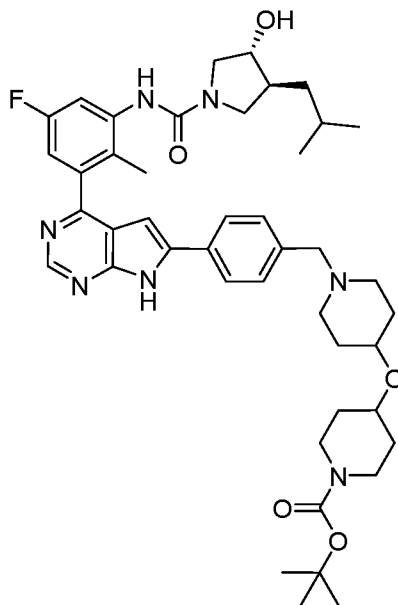
Step 1: (3R,4S)-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



In a round-bottomed flask was added 4-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzaldehyde (intermediate 3a in PCT/IB2019/052392, 150 mg, 0.582 mmol), (3R,4S)-N-(5-fluoro-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide (intermediate 7 in PCT/IB2019/052392, 269 mg, 0.640 mmol), and K_2CO_3 (201 mg, 1.455 mmol), $PdCl_2(dppf)$ (42.6 mg, 0.058 mmol) was added. The reaction mixture was diluted with dioxane (3 mL, Ratio: 1.0) and water (3 mL, Ratio: 1.0). The RM was heated at 100°C for 1.5h. The RM was absorbed on silica and purified by flash chromatography on a 12 g column

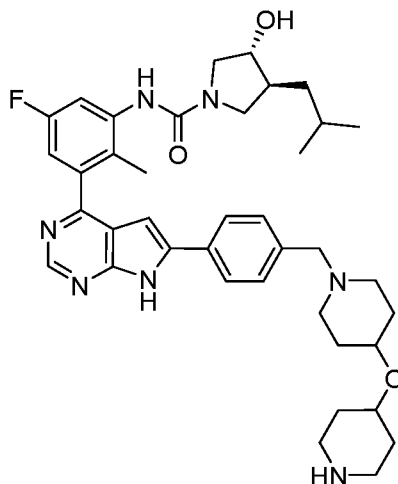
eluting DCM/MeOH to afford the title compound (90 mg). Method LCMS1: $R_t = 0.95$ min; $[M+H]^+ = 516.2$.

Step 2: *tert*-Butyl 4-((1-(4-(4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperidin-4-yl)oxy)piperidine-1-carboxylate



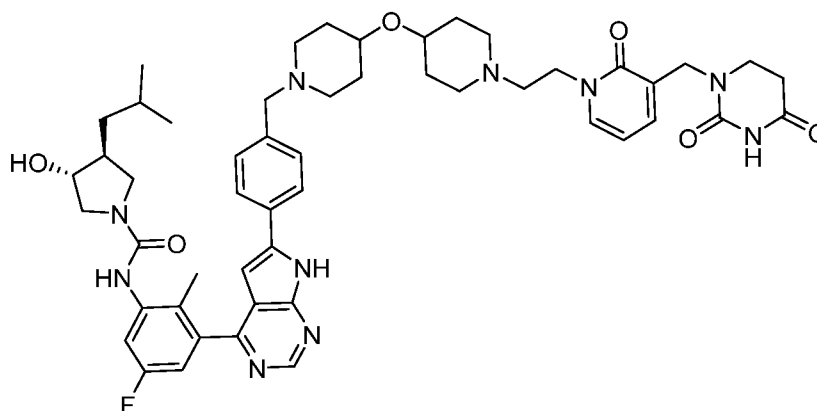
(3R,4S)-N-(5-fluoro-3-(6-(4-formylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide (624 mg, 1.2 mmol) in DMSO/MeOH (10 mL) was added *tert*-butyl 4-(piperidin-4-yloxy)piperidine-1-carboxylate (CAS No. [845305-83-1], 344 mg, 1.2 mmol) and $ZnCl_2$ 1M in THF (1.8 mL, 1.8 mmol) and the mixture was stirred at RT for 2 h. $NaBH_3CN$ (453 mg, 7.2 mmol) was added and the mixture was stirred at RT overnight. 10 mL of water was added to the mixture and stirred for 30 min and filtered to give crude product as the title compound. Method G: $R_t = 2.29$ min; $[M+H]^+ = 784$.

Step 3: (3R,4S)-N-(5-fluoro-2-methyl-3-(6-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



To a solution of *tert*-butyl 4-((1-(4-(4-(5-fluoro-3-((3R,4S)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamido)-2-methylphenyl)-7H-pyrrolo[2,3-d]pyrimidin-6-yl)benzyl)piperidin-4-yl)oxy)piperidine-1-carboxylate (1 g, 1.2 mmol) in THF (20 mL) and DCM (20 mL) was added HCl/dioxane (10 mL) at RT and the mixture was stirred at RT for 2 h. The RM was filtered and washed by DCM to afford the title compound (0.52 g). Method F: R_t = 1.32 min; $[M+H]^+ = 684$.

Step 4: (3R,4S)-N-(3-(6-(4-((4-((1-(2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-yl)methyl)-2-oxopyridin-1(2H)-yl)ethyl)piperidin-4-yl)oxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-5-fluoro-2-methylphenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide



To the mixture of (3R,4S)-N-(5-fluoro-2-methyl-3-(6-(4-((4-(piperidin-4-yloxy)piperidin-1-yl)methyl)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)phenyl)-3-hydroxy-4-isobutylpyrrolidine-1-carboxamide (327 mg, 0.36 mmol) in DMSO (4 mL) was added K_2CO_3 (57 mg, 0.41 mmol), the solution was stirred 10 min at RT, and then 2-(3-((2,4-dioxotetrahydropyrimidin-1(2H)-

yl)methyl)-2-oxopyridin-1(2H)-yl)acetaldehyde (91 mg, 0.35 mmol) and ZnCl₂ (0.9 mL, 1 M in THF) were added, after 0.5h, NaBH₃CN (177mg, 2.77 mmol) was added. The mixture was stirred at RT for 16 h. The mixture filtered to remove the solid and the filtrate was collected. The crude residue was purified by Prep-HPLC using method PB eluting with ACN and an aq. solution of NH₄HCO₃ aq. 10mM to afford, after freeze drying, the title compound (60 mg). Method G: Rt = 1.73min; [M+H]⁺ = 932. ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.72 (s, 1H), 10.14 (s, 1H), 8.83 (s, 1H), 7.92 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H), 7.59-9.54 (m, 1H), 7.50 (dd, J = 10.8, 2.8 Hz, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 6.6 Hz, 1H), 7.06 (dd, J = 8.9, 2.8 Hz, 1H), 6.76 (s, 1H), 6.19 (t, J = 6.8 Hz, 1H), 5.11 (d, J = 4.5 Hz, 1H), 4.26 (s, 2H), 3.98 (t, J = 6.3 Hz, 2H), 3.91 - 3.84 (m, 1H), 3.69-3.61 (m, 2H), 3.47 (s, 2H), 3.41 (t, J = 6.8 Hz, 4H), 3.22 - 3.15 (m, 1H), 3.12-3.04 (m, 1H), 2.72-2.62(m, 4H), 2.59-2.51(m, 4H), 2.16-2.00(m, 8H), 1.79-1.69 (m, 4H), 1.67 - 1.56 (m, 1H), 1.46 - 1.30 (m, 5H), 1.18 - 1.07 (m, 1H), 0.90 (dd, J = 10.7, 6.6 Hz, 6H).

Example 7

Biological Assays

Compounds were tested in the following biochemical and cellular assays. The data obtained is shown in Tables 4, 5, and 6 and FIGs. 3A-3E and 4A-4B. The compounds disclosed herein were tested in the following biochemical assay to demonstrate CRBN interaction. The data obtained is shown in **Table 4** and **5**, and AC₅₀ refers to the concentration at which 50% of the reference probe Compound HH is displaced.

CRBN Assay Format 1:

BodipyFL conjugated lenalidomide compound HH was used as a fluorescent probe.

Enzymatic reactions were conducted in 'assay buffer', comprising 50 mM Tris/HCl at pH 7.4, 100 mM NaCl, 0.1% (w/v) Pluronic F-127 and 1 mM TCEP. Protein and substrate were diluted in assay buffer.

All protein and probe containing solutions were handled in 'Maxymum Recovery' tubes (Axygen Scientific Inc., Union City, USA). Compound, protein and the substrate solutions were transferred to 384-well plates (Black Microtiter 384 Plate, round well; Cat. No. 95040020 Thermo Electron Oy, Finland) by means of a CyBi-Well 96-channel pipettor (CyBio AG, Jena, Germany).

For the plate measurements a PHERAstar reader (BMG Labtech, Offenburg, Germany) was used. The instrument was equipped with a specific optics module containing filters and dichroic mirrors for measuring the fluorescence polarization-type assay. With this module, the fluorescence of the Bodipy FL-based probe was excited at 485 nm and the emissions of the product were measured at 520 nm. The fluorescence in each well was excited by 10 flashes per measurement.

For the determination of AC₅₀ values, the assays were performed at room temperature in 384-well plates with a total assay volume of 10.1 µL per well. The test compound was dissolved in 90% (v/v) DMSO/water. For the assays, 100 nL of the 90% (v/v) DMSO/water solution or compound solution were added per well, followed by the addition of 5 µL protein solution (protein in 1× assay buffer).

The final assay concentration of the protein was nominally 100 nM. After 45 minutes of pre-incubation at room temperature, the competition for binding was started by the addition of 5 µL probe solution (probe dissolved in assay buffer). The final concentration of the probes in the assays was 5 nM. After the addition of the probe solution, the final DMSO concentration in the assay was 0.9% (v/v). The effect of the probe on the pre-established compound-protein complex equilibrium was determined after 45 minutes ($t = 45$ min). The AC₅₀ value was calculated from the plot of percentage of protein saturation versus the test compound concentration by a logistics fit according to: $y = A^2 + (A^1 - A^2) / (1 + (x/AC_{50})^p)$, where y is the %-saturation value at the test compound concentration, x . A^1 is the lowest saturation value, *i.e.*, 0%, and A^2 the maximum saturation value, *i.e.* 100%. The exponent, p , is the Hill coefficient.

CRBN Assay Format 2a:

BodipyFL conjugated lenalidomide compound HH was used as a fluorescent probe. Enzymatic reactions were conducted in 'assay buffer', comprising 50 mM Tris/HCl at pH 7.4, 100 mM NaCl, 0.1% (w/v) Pluronic F-127, 1 mM TCEP, and 2 mM EDTA in water. Protein and substrate were diluted in assay buffer.

Protein and substrate solutions were transferred to 1536-well plates (Black solid bottom 1536 microplate, HiBase; Cat. No. 789176-A Greiner Bio-One) by means of a GNF Systems WDII washer. Compounds were transferred using an Echo Liquid Handler (Echo 555, Labcyte).

For plate measurements, an Envision reader (Product number 2104-0010, Perkin Elmer) was used. The instrument was equipped with filters and a dichroic mirror for measuring fluorescence

polarization-type assays (Product numbers 2100-4070, 2100-5040, 2100-5140, and 2100-5150). The fluorescence of the Bodipy FL-based probe was excited at 480 nm and the emissions of the product were measured at 535 nm. The fluorescence in each well was excited by 30 flashes per measurement.

For the determination of AC₅₀ values, assays were performed at room temperature in 1536-well plates with a total assay volume of 6.03 µL per well. The test compounds were dissolved and diluted in 100% DMSO. For the assays, 30 nL of DMSO or compound solution were added per well, followed by the addition of 3 µL protein solution (80 nM protein in 1× assay buffer).

The final assay concentration of the protein was nominally 40 nM. After 45 minutes of pre-incubation at room temperature, the competition for binding was started by the addition of 3 µL probe solution (10 nM probe dissolved in assay buffer). The final concentration of the probe in the assays was 5 nM. After the addition of the probe solution, the final DMSO concentration in the assay was 0.5% (v/v). The effect of the probe on the pre-established compound-protein complex equilibrium was determined after 45 minutes (t = 45 min). The AC₅₀ value was calculated from the plot of percentage of protein saturation versus the test compound concentration by a logistics fit according to: $y = A^2 + (A^1 - A^2) / (1 + (x/AC_{50})^p)$, where y is the %-saturation value at the test compound concentration, x. A¹ is the lowest saturation value, i.e., 0%, and A² the maximum saturation value, i.e. 100%. The exponent, p, is the Hill coefficient.

CRBN Assay Format 2b:

Assay conditions are similar to Format 2a with the exception of

- a. The assay run in quadruplicate
- b. PHERAstar reader (BMG Labtech, Offenburg, Germany) was used instead of an Envision reader
- c. For the determination of AC₅₀ values, assays were performed at room temperature in 1536-well plates with a total assay volume of 8.03 µL per well. The test compounds were dissolved and diluted in 100% DMSO. For the assays, 30 nL of DMSO or compound solution were added per well, followed by the addition of 3 µL protein solution (80 nM protein in 1× assay buffer).

Table 4. CRBN Displacement Assay Results				
Compound	CRBN AC₅₀ [μM] Format 1	CRBN AC₅₀ [μM] Format 2a	CRBN Amax* (% at 50 μM) Format 2a	CRBN AC₅₀ [μM] Format 2b
ILB-1	11.03	4.79		
ILB-3	14.10	4.17		
ILB-6	19.75	8.36		
ILB-7	61.24	> 50	40	
ILB-8	> 100	> 50	21	
ILB-9		> 50	1	
ILB-10		> 50	0	
ILB-13		2.42		
ILB-14	13.02	5.79		
ILB-15	7.37	2.61		
ILB-16	11.71	7.34		
ILB-17		3.41		
ILB-18	11.23	3.79		
ILB-19	2.51	0.80		
ILB-20	5.37	2.01		
ILB-22		0.69		
ILB-24	2.85	0.68		
ILB-25	1.98	0.48		
ILB-26	2.92	1.26		
ILB-27	3.03	0.74		
ILB-28	3.41	1.30		
ILB-29	0.95			
ILB-31	9.64	5.10		
ILB-33	6.52	2.68		
ILB-34	3.65	1.91		
ILB-38	8.44	6.02		

ILB-39		3.15		
ILB-40	12.32	3.45		
ILB-43	2.99	2.93		
ILB-44		5.43		
ILB-45	13.47			
ILB-49		3.36		
ILB-53	14.94	2.16		
ILB-55	14.41	4.04		
ILB-56	1.26	0.23		
ILB-59	1.36	0.34		
ILB-60	2.80			
ILB-61		3.44		
ILB-65		26.15		
ILB-66		> 50	46	
ILB-68		4.70		
ILB-70		> 50	43	
ILB-71		6.01		8.00
ILB-72		29.37		18.02
ILB-73		15.05		11.89
ILB-74		6.28		4.61
ILB-75		> 50	40	28.69
ILB-76		8.09		15.32
ILB-77		0.50		0.30
ILB-78		5.72		5.07
ILB-79		7.15		6.78
ILB-80		9.41		8.34
ILB-81	12.33	2.38		
ILB-82		29.77		
ILB-83		45.61		
ILB-84		33.33		

ILB-85		> 50	47	
ILB-86		34.80		
ILB-87		5.34		
ILB-88		> 50	37	
ILB-89		16.71		
ILB-90		> 50	40	
ILB-91		5.22		
ILB-92		1.85		
ILB-93		10.91		
ILB-94		4.95		
* For compounds tested in format 2a, with AC ₅₀ values determined to be > 50 μ M, the values for the greatest effect (A _{max}) expressed as % displacement of the reference probe at the highest concentration tested (% at 50 μ M) are provided in column 4.				

BTK-GFP, CSK, ABL2, EPHA4 and YES1 protein abundance flow cytometry assay in HEK293A:

Degradation of BTK, CSK, ABL2, EPHA4 and YES1 was measured in HEK293A cells (Invitrogen R70507) expressing either BTK-GFP and RFP, CSK-GFP and mCherry, GFP-ABL2 and mCherry, EPHA4-GFP and mCherry, or YES1-GFP and mCherry from a stably integrated bicistronic BTK-GFP-iresRFP, CSK-GFP-CHYSEL-mCherry, GFP-ABL2-CHYSEL-mCherry, EPHA4-GFP-CHYSEL-mCherry, or YES1-GFP-CHYSEL-mCherry construct, respectively. Reduction of the GFP signal measured by flow cytometry served as readout for BTK, CSK, ABL2, EPHA4 and YES1 degradation after degrader treatment.

(A) Cloning of the pLenti6-BTK-GFP-Ires-RFP sensor vectors

The bicistronic BTK-GFP-iresRFP construct is based on a pLenti6-DEST vector backbone where GFP was introduced into the unique *Xho* I site downstream of the destination cassette (DEST) and RFP was cloned behind an internal ribosomal entry site (IRES).

In detail, the sensor construct was engineered by replacing NanoLuciferase (NLuc) by GFP and FireFly luciferase (FF) by RFP from pLenti6-DEST-NLuc-Ires-FF.

The pLenti6-DEST-NLuc-Ires-FF sensor construct was cloned by replacing eGFP from pLenti6-DEST-Ires-eGFP with a synthesized stuffer element (encoding Ires-FF with FF flanked by two *Nhe* I restriction sites) using blunt end cloning replacing Ires-eGFP between the two *Pml* I. To enable C-terminal tagging with NanoLuciferase (NLuc), NLuc was amplified from pNL1.1 (Promega #N1001) using linker primers with Xho1 sites for ligating into linearized pLenti6-DEST-Ires-FF using Xho1 digest resulting in the construct pLenti6-DEST-NLuc-Ires-FF.

The pLenti6-DEST-NLuc-Ires-FF served as base vector for cloning pLenti6-DEST-GFP-Ires-RFP using Gibson assembly to replace FF with RFP and NLuc with GFP. In a first round FF was replaced by RFP by amplifying RFP from a template using the following Gibson assembly linker primers to clone into pLenti6-DEST-NLuc-Ires-FF digested with *Nhe*I and gel-purified to remove the FF fragment.

Gibson- <i>Nhe</i> I RFPfw:	CGATGAATTCGCCACCgctagcATGGTGAGCAAG	SEQ ID NO:
	GGCGAGGAGC	1
Gibson- <i>Nhe</i> I RFP-Stoprev:	CTCATTACTAACCGGctagcTTACTTGTACAGCT	SEQ ID NO:
	CGTCCATGC	2

The resulting pLenti6-DEST-NLuc-Ires-RFP vector served as the template to replace NLuc with GFP by amplifying GFP from a template using following Gibson assembly linker primers to clone into pLenti6-DEST-NLuc-Ires-RFP digested with Xho1 and gel-purified to remove the NLuc fragment.

Gibson-Xho1 GFPfw	CCAGCACAGTGGCGGCCGCTCGAGcATGGTGAGC	SEQ ID NO:
	AAGGGCGAGGAGCTGTTTCACC	3
Gibson-Xho1 GFP-Stoprev	CCGCGGGCCCTCTAGACTCGAGTTACTTGTACAG	SEQ ID NO:
	CTCGTCCATGCCGAGAGT	4

All Gibson assembly reactions were performed with Gibson assembly Master Mix (New England Biolabs NEB E2611L) according to manufacturer's manual, resulting in the destination vector pLenti6-DEST-GFP-Ires-RFP to allow Gateway cloning.

To enable gateway cloning and C-terminal GFP tagging of BTK, the BTK open reading frame (ORF) was first shuttled from a pcDNA-DEST40-BTK vector (Invitrogen library ID INV_20090504v1) into pDONR221 (Invitrogen 12536-017) vector using a gateway BP reaction according to the manufacturer's manual (Invitrogen 11789-013) resulting in the novel construct pENTR221-BTK. For C-terminal tagging the STOP codon was mutated to a leucine performing a mutagenesis reaction with the following primers using the QuikChange Lightning mutagenesis

kit (Agilent Technologies #210518) according to the manufacturer's manual, resulting in pENTR221-BTK (STOP-Leu).

pENTR221-BTK	gtcatggatgaagaatccTTGaaccagcttttcttgt	SEQ ID
Quikchange STOP-Leu	ac	NO: 5
fw		
pENTR221-BTK	gtacaagaaagctgggttCAAggattcttcatccatg	SEQ ID
Quikchange STOP-Leu	ac	NO: 6
REVC		

To get the final pLenti6-BTK-GFP-Ires-RFP sensor construct, a Gateway LR reaction was performed between pLenti6-DEST-GFP-Ires-RFP and pENTR221-BTK (STOP-Leu) using the LR Clonase kit (Invitrogen 11791-019) according to the manufacturer's manual. All vectors described above have been sequenced for verification.

(B) Cloning of the pLenti6-CSK-GFP-CHYSEL-mCherry, mCherry-CHYSEL-GFP-ABL2, BTK(C481S)-GFP-CHYSEL-mCherry, -EPHA4-GFP-CHYSEL-mCherry and -YES1-GFP-CHYSEL-mCherry sensor vectors

The bicistronic GFP-CHYSEL-mCherry constructs are based on a pLenti6-DEST vector backbone where two cassettes were introduced: Xho1-EGFPCHYSEL-mCherry-Xho1 or Spe1-mCherryCHYSEL-EGFP-Spe1 to generate either pL6-CMV-DEST-GFP-CHYSEL-mCherry or pL6-CMV-mCherry-CHYSEL-GFP-DEST destination vectors for LR cloning, respectively. Both cassettes were synthesized by an external vendor (GeneART) and cloned into linearized pLenti6-DEST vector using Gibson assembly (GA) according to manufacturer's manual (New England Biolabs E5510).

Xho1-EGFPCHY-mCherry

```

1  GATATCCAGC ACAGTGGCGG CCGCTCGAGC ATGGTGAGCA AGGGCGAGGA
   GCTGTTACCC
61  GGGGTGGTGC CCATCCTGGT CGAGCTGGAC GGCGACGTAA ACGGCCACAA
   GTTCAGCGTG
121 TCCGGCGAGG GCGAGGGCGA TGCCACCTAC GGCAAGCTGA CCCTGAAGTT
   CATCTGCACC

```

181 ACCGGCAAGC TGCCCGTGCC CTGGCCCACC CTCGTGACCA CCCTGACCTA
CGGCGTGACG

241 TGCTTCAGCC GCTACCCCGA CCACATGAAG CAGCACGACT TCTTCAAGTC
CGCCATGCCC

5 301 GAAGGCTACG TCCAGGAGCG CACCATCTTC TTCAAGGACG ACGGCAACTA
CAAGACCCGC

361 GCCGAGGTGA AGTTCGAGGG CGACACCCTG GTGAACCGCA TCGAGCTGAA
GGGCATCGAC

421 TTCAAGGAGG ACGGCAACAT CCTGGGGCAC AAGCTGGAGT ACAACTACAA
10 CAGCCACAAC

481 GTCTATATCA TGGCCGACAA GCAGAAGAAC GGCATCAAGG TGAAC TTCAA
GATCCGCCAC

541 AACATCGAGG ACGGCAGCGT GCAGCTCGCC GACCACTACC AGCAGAACAC
CCCCATCGGC

15 601 GACGGCCCCG TGCTGCTGCC CGACAACCAC TACCTGAGCA CCCAGTCCGC
CCTGAGCAAA

661 GACCCCAACG AGAAGCGCGA TCACATGGTC CTGCTGGAGT TCGTGACCGC
CGCCGGGATC

721 ACTCTCGGCA TGGACGAGCT GTACAAGGGA AGCGGAGCGA CGAATTTTAG
20 TCTACTGAAA

781 CAAGCGGGAG ACGTGGAGGA AAACCCTGGA CCTATGGTGA GCAAGGGCGA
GGAGGATAAC

841 ATGGCCATCA TCAAGGAGTT CATGCGCTTC AAGGTGCACA TGGAGGGCTC
CGTGAACGGC

25 901 CACGAGTTCG AGATCGAGGG CGAGGGCGAG GGCCGCCCCT ACGAGGGCAC
CCAGACCGCC

961 AAGCTGAAGG TGACCAAGGG TGGCCCCCTG CCCTTCGCCT GGGACATCCT
GTCCCCTCAG

1021 TTCATGTACG GCTCCAAGGC CTACGTGAAG CACCCCGCCG ACATCCCCGA
30 CTACTTGAAG

1081 CTGTCCTTCC CCGAGGGCTT CAAGTGGGAG CGCGTGATGA ACTTCGAGGA
CGGCGGCGTG

1141 GTGACCGTGA CCCAGGACTC CTCCCTGCAG GACGGCGAGT TCATCTACAA
GGTGAAGCTG

1201 CGCGGCACCA ACTTCCCCTC CGACGGCCCC GTAATGCAGA AGAAGACCAT
GGGCTGGGAG

5 1261 GCCTCCTCCG AGCGGATGTA CCCCAGAGGAC GGCGCCCTGA AGGGCGAGAT
CAAGCAGAGG

1321 CTGAAGCTGA AGGACGGCGG CCACTACGAC GCTGAGGTCA AGACCACCTA
CAAGGCCAAG

1381 AAGCCCGTGC AGCTGCCCCG CGCCTACAAC GTCAACATCA AGTTGGACAT
10 CACCTCCCAC

1441 AACGAGGACT ACACCATCGT GGAACAGTAC GAACGCGCCG AGGGCCGCCA
CTCCACCGGC

1501 GGCATGGACG AGCTGTACAA GTAGCTCGAG TCTAGAGGGC CCGCGGTAA C
(SEQ ID NO: 7)

15

SpeI-mCherryCHY-EGFP ORIGIN

1 AGTACTCTAG AGGATCCACT AGTCGCCACC ATGGTGAGCA AGGGCGAGGA
GGATAACATG

61 GCCATCATCA AGGAGTTCAT GCGCTTCAAG GTGCACATGG AGGGCTCCGT
20 GAACGGCCAC

121 GAGTTCGAGA TCGAGGGCGA GGGCGAGGGC CGCCCCTACG AGGGCACCCA
GACCGCCAAG

181 CTGAAGGTGA CCAAGGGTGG CCCCCTGCCC TTCGCCTGGG ACATCCTGTC
CCCTCAGTTC

241 ATGTACGGCT CCAAGGCCTA CGTGAAGCAC CCCGCCGACA TCCCCGACTA
25 CTTGAAGCTG

301 TCCTTCCCCG AGGGCTTCAA GTGGGAGCGC GTGATGAACT TCGAGGACGG
CGGCGTGGTG

361 ACCGTGACCC AGGACTCCTC CCTGCAGGAC GGCGAGTTCA TCTACAAGGT
30 GAAGCTGCGC

421 GGCACCAACT TCCCCTCCGA CGGCCCCGTA ATGCAGAAGA AGACCATGGG
CTGGGAGGCC

481 TCCTCCGAGC GGATGTACCC CGAGGACGGC GCCCTGAAGG GCGAGATCAA
GCAGAGGCTG

541 AAGCTGAAGG ACGGCGGCCA CTACGACGCT GAGGTCAAGA CCACCTACAA
GGCCAAGAAG

5 601 CCCGTGCAGC TGCCCGGCGC CTACAACGTC AACATCAAGT TGGACATCAC
CTCCCACAAC

661 GAGGACTACA CCATCGTGGA ACAGTACGAA CGCGCCGAGG GCCGCCACTC
CACCGGCGGC

721 ATGGACGAGC TGTACAAGGG AAGCGGAGCG ACGAATTTTA GTCTACTGAA
10 ACAAGCGGGA

781 GACGTGGAGG AAAACCCTGG ACCTATGGTG AGCAAGGGCG AGGAGCTGTT
CACCGGGGTG

841 GTGCCCATCC TGGTCGAGCT GGACGGCGAC GTAAACGGCC ACAAGTTCAG
CGTGTCCGGC

15 901 GAGGGCGAGG GCGATGCCAC CTACGGCAAG CTGACCCTGA AGTTCATCTG
CACCACCGGC

961 AAGCTGCCCCG TGCCCTGGCC CACCCTCGTG ACCACCCTGA CCTACGGCGT
GCAGTGCTTC

1021 AGCCGCTACC CCGACCACAT GAAGCAGCAC GACTTCTTCA AGTCCGCCAT
20 GCCCCAAGGC

1081 TACGTCCAGG AGCGCACCAT CTTCTTCAAG GACGACGGCA ACTACAAGAC
CCGCGCCGAG

1141 GTGAAGTTCG AGGGCGACAC CCTGGTGAAC CGCATCGAGC TGAAGGGCAT
CGACTTCAAG

25 1201 GAGGACGGCA ACATCCTGGG GCACAAGCTG GAGTACAACT ACAACAGCCA
CAACGTCTAT

1261 ATCATGGCCG ACAAGCAGAA GAACGGCATC AAGGTGAACT TCAAGATCCG
CCACAACATC

1321 GAGGACGGCA GCGTGCAGCT CGCCGACCAC TACCAGCAGA ACACCCCCAT
30 CGGCGACGGC

1381 CCCGTGCTGC TGCCCGACAA CCACTACCTG AGCACCCAGT CCGCCCTGAG
CAAAGACCCC

1441 AACGAGAAGC GCGATCACAT GGTCTGCTG GAGTTCGTGA CCGCCGCCGG
GATCACTCTC

1501 GGCATGGACG AGCTGTACAA GGCAC TAGTC CAGTGTGGTG GAATTCTGCA
GATATC

5 (SEQ ID NO: 8)

Linearisation of pLenti6-DEST with XhoI and GA with XhoI-EGFPCHYSEL-mCherry-
XhoI fragment resulted in gateway compatible pLenti6-DEST- EGFPCHYSEL-mCherry vector,
linearisation of pLenti6-DEST with SpeI and GA with SpeI-mCherryCHYSEL-EGFP-SpeI
10 fragment resulted in gateway compatible pLenti6-mCherryCHYSEL-EGFP-DEST vector.

pLenti6-mCherryCHYSEL-EGFP-ABL2 was generated by gateway LR cloning between
pENTR221-ABL2 and pLenti6-mCherryCHYSEL-EGFP-DEST vectors. To clone the pLenti6-
BTK(C481S)-GFP-CHYSEL-mCherry , pLenti6-CSK-GFP-CHYSEL-mCherry, -EPA4-GFP-
CHYSEL-mCherry and -YES1-GFP-CHYSEL-mCherry sensor vectors, the STOP codon had first
15 to be mutated to a Leucine using a Quikchange reaction on existing pENTR221-CSK, -EPA4
and -YES vectors using following primers resulting in novel vectors pENTR221-CSK(STOP-
Leu), pENTR221-EPA4(STOP-Leu) and pENTR221-YES(STOP-Leu).

pENTR221_CSQ_Quik change_STOP-LEU_fw	caagaaagctgggttcaacaggtgcagctcgtg	SEQ ID NO: 9
pENTR221_CSQ_Quik change_STOP-LEU_rev	cacgagctgcacctgttgaaccagctttcttg	SEQ ID NO: 10
pENTR221_EPHA4_Qu ikchange_STOP- LEU_fw	gtacaagaaagctgggttcaagacgggaaccattct g	SEQ ID NO: 11
pENTR221_EPHA4_Qu ikchange_STOP- LEU_rev	cagaatgggttcccgctcttgaaccagctttcttgta c	SEQ ID NO: 12
pENTR221_YES_Quik hange_STOP-LEU_fw	gaaagctgggttcaataaattttctcctggctggta c	SEQ ID NO: 13
pENTR221_YES_Quik hange_STOP-LEU_rev	gtaccagccaggagaaaatttattgaaccagcttt c	SEQ ID NO: 14

20 LR gateway cloning between pLenti6-DEST-GFP-CHYSEL-mCherry with pENTR221-
CSK(STOP-Leu) or pENTR221-EPHA4(STOP-Leu), pENTR221-BTK(C481S)(STOP-Leu) or
pENTR221-YES(STOP-Leu) vectors resulted in pLenti6-CSK-GFP-CHYSEL-mCherry, -

EPHA4-GFP-CHYSEL-mCherry and -YES1-GFP-CHYSEL-mCherry sensor vectors, respectively. All vectors described were sequenced for verification.

(C) Engineering of stably expressing 293A BTK-GFP-Ires-RFP, CSK-GFP-CHYSEL-mCherry, GFP-ABL2-CHYSEL-mCherry, EPHA4-GFP-CHYSEL-mCherry, or YES1-GFP-CHYSEL-mCherry construct sensor cells

293A BTK-GFP-Ires-RFP, CSK-GFP-CHYSEL-mCherry, GFP-ABL2-CHYSEL-mCherry, EPHA4-GFP-CHYSEL-mCherry, or YES1-GFP-CHYSEL-mCherry sensor cells were generated by lentiviral vector transduction using the pLenti6-BTK-GFP-Ires-RFP, pLenti6-mCherryCHYSEL-EGFP-ABL2, pLenti6-CSK-GFP-CHYSEL-mCherry, pLenti6-EPHA4-GFP-CHYSEL-mCherry or pLenti6-YES1-GFP-CHYSEL-mCherry sensor construct described before. Lentiviral particles were produced in HEK293FT cells (Invitrogen R70007) by co-transfection of 500 ng pLenti6-BTK-GFP-Ires-RFP or pLenti6-IKZF3-GFP-Ires-RFP, 500 ng delta8.71 and 200 ng pVSVG diluted in 100 μ L OptiMEM serum free medium (Invitrogen # 11058-021) that was mixed after 5 min preincubation with 3 μ L of Lipofectamine2000 (Invitrogen # 11668-019) in 97 μ L OptiMEM serum free medium. The mix was incubated for another 20 min at RT and then added on 1 mL of a freshly prepared suspension of HEK293FT cells in a well of a 6-well plate (concentration 1.2×10^6 cells/mL). 1 day after transfection, the medium was replaced with 1.5 mL of complete growth medium (DMEM high Glucose + 10% FCS + 1% L-Glutamine + 1% NEAA + 1% NaPyr.). 48 h post transfection supernatant containing viral transducing particles was collected and frozen at -80°C .

2 days before transduction with viral particles 1×10^5 HEK293A cells (Invitrogen R70507) were seeded in 2 mL growth medium in a well of a 6-well plate. Infection was performed with 90 μ L of collected supernatant containing viral transducing particles in 1 mL medium including 8 μ g/mL polybrene. 24 h post infection, stably transfected cells were selected with blasticidin at a concentration of 8 μ g/mL referred to as stable HEK293A sensor cells.

(D) Quantitative BTK-GFP, CSK-GFP, GFP-ABL2, EPHA4-GFP and YES1-GFP abundance measurements in stable HEK293A sensor cells

Stable HEK293A sensor cells were maintained in complete growth medium (DMEM high Glucose + 10% FCS + 1% L-Glutamine + 1% NEAA + 1% NaPyr.) with passaging performed

twice per week. On Day 0, stable HEK293A sensor cells were seeded at 10,000 cells/well in a 96-well microtiter plate in 260 μ L complete medium. On Day 1, cells were treated in duplicate with 10-point 1:3 dilution series of compound using the HP D300 Digital Dispenser (Tecan). DMSO concentrations were normalized across the plate to 0.1%. On Day 2, after 24 h of incubation at 37 °C, treatment media was discarded, cells rinsed with 100 μ L/well PBS and then detached using 40 μ L trypsin/well for 5 min. Trypsin was neutralized with 100 μ L/well PBS + 20% FCS). Flow cytometry was performed on the samples using the BD FACS CANTO II (Becton Dickinson). Cell identification was then performed using forward (FSC) vs. side scatter (SSC) plots. Single cell discrimination is performed using SSC-Width (SSC-W) vs. SSC-Height (SSC-H) plots. Median GFP values for 5,000 single cells are used to determine BTK levels. Median GFP values from HEK293A-iresRFP are used as a background signal and thus defining 0% BTK signal. Median GFP values from DMSO treated HEK293A-BTK-GFP-iresRFP are used to define 100% BTK signal for subsequent DC₅₀ curves (concentration at 50% BTK degradation). GFP and RFP are read in the channels called FITC and PE, respectively.

Concentration response curves plotting relative reduction of the GFP signal (measured by flow cytometry) versus 10 compound concentrations (starting concentration 10 μ M, 3 fold dilution steps) of the compounds allowed generation of DC₅₀ values. Protein abundance measured for the second generation vectors having a chysel was done in close analogy to the above described method for measuring BTK abundance.

HEK293 cells overexpressing hTNNI3K WT (stable clonal line)

HEK293-hTNNI3K stable cells were seeded at 400,000 cells/well in 6-well plate and incubated at 37 °C and 5% CO₂ overnight in DMEM containing 10% FBS. The following day growth media was replaced with low-serum media containing DMEM with 0.5% FBS and incubated at 37 °C and 5% CO₂ overnight. Following overnight serum starvation, cells were treated with compounds at 20 μ M starting dose with 1:5 serial dilution prepared in low-serum media. Media was removed and compounds were added to 6-well plate at 2 mL per well and cells were incubated at 37 °C and 5% CO₂ for 18 hours. Following compound treatment cells were washed with cold DPBS containing protease/phosphatase inhibitor cocktail (Thermo #1861284) and lysed in RIPA buffer on ice (Pierce #89900, also containing protease/phosphatase inhibitors). Following sonication and frequent vortexing at 4 °C for approximately 1 hour, samples were centrifuged at

14,000 rpm for 20 minutes. Supernatants were collected for protein samples. Protein concentration was determined using BioRad DC Protein Assay (FIGs. 3A and 3C).

Samples for western blotting were prepared in loading buffer (Thermo #NP0007) and 8 μ g protein was loaded per lane in 4–12% Novex Bis-Tris gel and run at 60V for approximately 1 hour. Gels were transferred to PVDF membrane using semi-dry transfer device iBlot 2 from Thermo Scientific. Blots were blocked using Superblock T20 blocking solution for 2 hours at room temperature (Thermo #37536). Blots were then incubated with primary antibodies overnight with gentle shaking at 4°C (TNNT3K #ab136954 and Beta-Actin CST #3700) at 1:1000 and 1:2000 dilution respectively. Following overnight primary antibody incubation, blots were washed 3 times on rocker for 5 minutes each with 1 $\times$ TBS-T at room temperature. Blots were then incubated with secondary HRP-anti-rabbit at 1:2000 dilution (CST #7074) for 2 hours at room temperature. Blots were then washed with 1X TBS-T 3 times on rocker for 5 minutes each. Protein bands were detected using BioRad Chemi-Doc station and Supersignal West Dura substrate (Thermo #34075). Protein bands were quantified using ImageJ software. TNNT3K bands were normalized to beta-actin loading control. Data are graphed by fold change of cpd over DMSO control.

Table 5 columns are defined as follows: DC₅₀ refers to the concentration at which 50% maximal degradation was observed; deg A_{max} is the extent of degradation and the value refers to the % protein remaining at the concentration at which maximum degradation is seen. Compounds depicted in the table show BTK degradation with a broad range of degradation, ranking from partial degradation, *e.g.* > 50% degradation (A_{max} < 50) to more than 95% degradation (A_{max} < 5). Compound 01 is a negative control in this table. Despite Compound 01 interacting with CRBN and BTK, no significant BTK degradation was observed, which is in line with the outcome of the *in silico* method described above, where ternary complex would not be enabled by this linker.

Table 5. BTK Degradation Assay Results			
Compound	CRBN AC₅₀ [μM] Format1	BTK DC₅₀ [μM]	BTK degradation A_{max}
01	1.593	> 3.3333	98
02	0.587	0.0021	4.5
03	0.257	0.0248	41.9
06	0.162	0.0047	2.1
07	0.496	0.0093	0.9
08	2.102	> 3.3333	55.1
09	1.403	0.0032	3.9

10	0.466	0.0033	3.1
11	0.599	0.0022	2.3
12	7.161	0.0107	2.3
13	0.575	0.0037	4.6
14	0.504	0.0259	25.9
15	4.107	0.0217	28.8
16	0.916	0.0226	15.9
17	3.552	0.1007	16.6
18	3.093	0.3073	7.6
19	0.104	0.2285	48.2
20	> 100	0.0277	37.1
23	> 50.5	0.0028	9.6
24	5.189	0.024	55.7
25	4.473	> 3.3333	51.1
26	3.92	0.0112	10.6
27	1.94	0.022	21.7
28	nd	0.0092	40
29	2.391	0.0402	40.5
30	nd	0.0098	12.2
31	nd	0.0557	32.8
32	nd	0.0014	16.7
33	0.915	0.0021	6.1
34	0.736	0.642	40.3
35	0.742	0.0021	6.6

Discussion of Compounds 06 and 07 Degradation

Table 6 columns are defined as follows: DC₅₀ refers to the concentration at which 50% maximal degradation was observed; deg A_{max} is the extent of degradation and the value refers to the % protein remaining at the concentration at which maximum degradation is seen. Compound 06 and Compound 07 show degradation of 4 target proteins CSK, ABL2, EPHA4 and YES1 with a range of DC₅₀ values as depicted in the table.

Table 6:								
Compound	CSK		ABL2		EPHA4		YES1	
	DC₅₀ [nM]	A_{max}	DC₅₀ [nM]	A_{max}	DC₅₀ [nM]	A_{max}	DC₅₀ [nM]	A_{max}
06	4	4	2	22	4	9	9	4
07	23	1	63	27	83	9	124	11

Proteomics Experiment

FIG. 3E shows the volcano plots depicting the identification of degrader-dependent CRBN substrate candidates. HEK293 and TMD8 cells were treated for 6 hours with DMSO (3 replicates), 1 μ M dasatinib (2 replicates), 1 μ M compound 06 (3 replicates) and 1 μ M compound 07 (3 replicates), respectively. TMT11plex-labeled peptides were generated with the PreOmics iST-NHS kit according to the manufacturer's protocol (PreOmics, Germany). The complexity of the samples was reduced by high pH fraction as described in Yang F *et al.* High-pH reversed-phase chromatography with fraction concatenation for 2D proteomic analysis. *Expert Rev Proteomics*. 2012, 9(2):129-134, and the resulting 72 fractions were pooled into 24 fractions. The 24 fractions were analyzed with a 25 cm x 75 μ m ID, 1.6 μ m C18 Aurora Series emitter column (IonOpticks, Australia) on an EASY-nLC 1200 system coupled to an Orbitrap™ Fusion Lumos mass spectrometer (Thermo Fisher Scientific, USA). Data was acquired with a synchronous precursor selection method as described in McAlister GC *et al.* MultiNotch MS3 enables accurate, sensitive, and multiplexed detection of differential expression across cancer cell line proteomes. *Anal Chem*. 2014, 86(14):7150-7158. The Proteome Discoverer™ 2.1 software and the SEQUEST algorithm was used for protein identification and relative quantification. Log₂ fold changes of protein abundances and p-values were calculated in Python and R with the limma package (Ritchie ME *et al.* Limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Res*. 2015, 43(7):e47). The data show that bifunctional compounds of formula (I) can recruit and degrade multiple different targets. For instance, compounds 06 and 07 containing a promiscuous kinase binding motif, are able to degrade several of the targets to which they bind. By contrast, the dasatinib control molecule is an inhibitor that does not bear an E3-ligase binding motif and so does not appreciably degrade the targets to which it binds.

Discussion of TNNI3K Degradation

FIGs. 4A-4B shows the amount of target protein (TNNI3K) that can be degraded by comparing initial levels of target protein TNNI3K before Compound 21 and Compound 22 treatment, respectively, in a concentration dependent matter. Both compounds showed full degradation. Starting at 6 nM and 32 nM no residual TNNI3K was detected. An alternative way to determine degradation is depicted in FIGs. 3A-3D.

Here the amount of total normalized TNNT3K expression levels were monitored upon compound treatment in a dose dependent manner. IC₅₀ refers to the concentration at which 50% reduction in protein expression was observed. A wide range of IC₅₀s was observed. For example the experimentally observed IC₅₀s ranked from 8.3 nM to 350 nM for Compound 22 and
5 Compound 21, respectively.

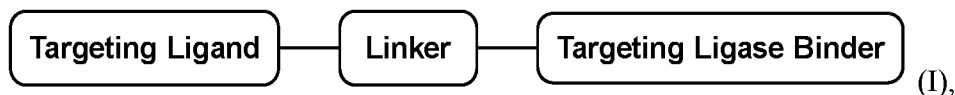
Having thus described several aspects of several embodiments, it is to be appreciated various alterations, modifications, and improvements will readily occur to those skilled in the art. Such alterations, modifications, and improvements are intended to be part of this disclosure, and
10 are intended to be within the spirit and scope of the disclosure. Accordingly, the foregoing description and drawings are by way of example only.

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

CLAIMS

What is claimed is:

1. A bifunctional compound of Formula (I):



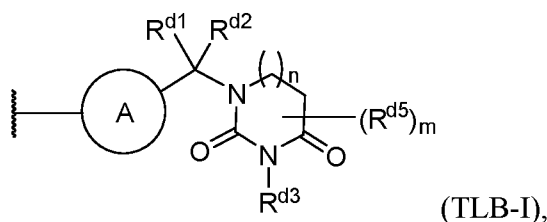
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

the Targeting Ligand is a group that is capable of binding to a Target Protein;

the Linker is a group that covalently links the Targeting Ligand to the Targeting Ligase Binder; and

the Targeting Ligase Binder is a group that is capable of binding to a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase).

2. The bifunctional compound of claim 1, wherein the Targeting Ligase Binder has a Formula (TLB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

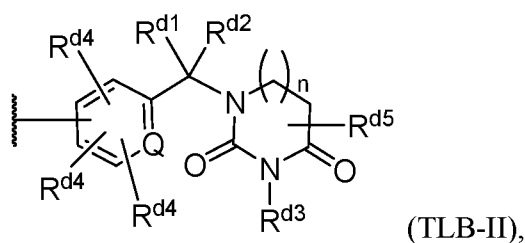
R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2.

3. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.
4. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.
5. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-CH_2OP(O)(OR^p)_2$.
6. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl.
7. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered heteroaryl.

8. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered nitrogen-containing heteroaryl.
9. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered heteroaryl.
10. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered nitrogen-containing heteroaryl.
11. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is pyridyl or pyridonyl.
12. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is hydroxyl or C_{1-6} alkoxyl.
13. The bifunctional of any one of the preceding claims, wherein the Targeting Ligase Binder has a Formula (TLB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,
wherein:

— denotes the point of attachment to the Linker in Formula (I);

Q is N or CR^{d4} ,

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

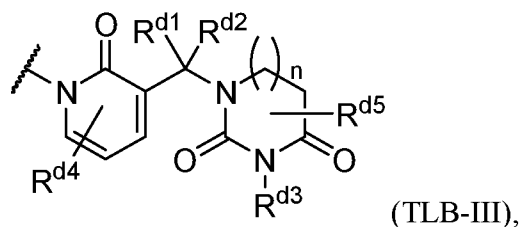
14. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

15. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

16. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

17. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is hydroxyl or C₁₋₆ alkoxy.

18. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Targeting Ligase Binder has a Formula (TLB-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

— denotes the point of attachment to the Linker in Formula (I);

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

19. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

20. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

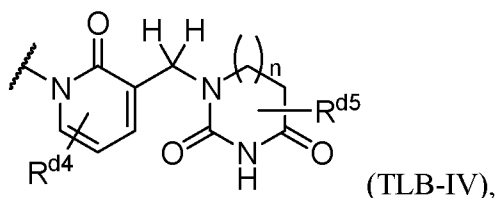
21. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

22. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} is H.

23. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d2} is H.

24. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} and R^{d2} are both H.

25. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder has a Formula (TLB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl; and

n is 1 or 2.

26. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

27. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

28. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

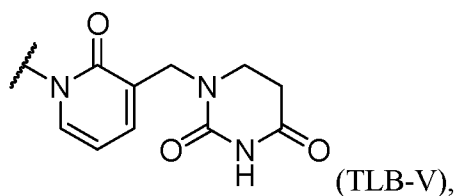
29. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is H or C_{1-3} alkyl.

30. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is H.

31. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d5} is H or C_{1-3} alkyl.

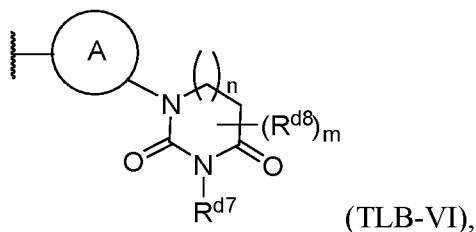
32. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d5} is H.

33. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Targeting Ligase Binder has a Formula (TLB-V):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

34. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Targeting Ligase Binder has a Formula (TLB-VI):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2.

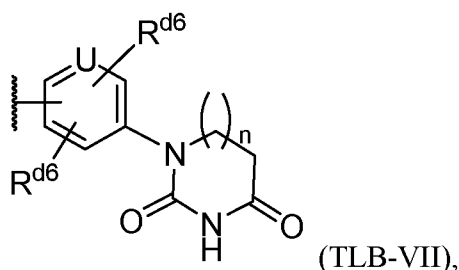
35. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl.

36. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a nitrogen-containing 6-membered heteroaryl.

37. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is pyridyl.
38. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.
39. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.
40. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.
41. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is H.
42. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d8} is H.
43. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} and R^{d8} are both H.
44. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is H.
45. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is selected from the group consisting of H, halogen, C₁₋₆ alkyl, and C₁₋₆ alkoxy.

46. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^{d7} , and R^{d8} are each H.

47. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder has a Formula (TLB-VII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

denotes the point of attachment to the Linker in Formula (I);

U is $-CR^{d6}$ or N;

each R^{d6} is independently selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

48. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

49. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

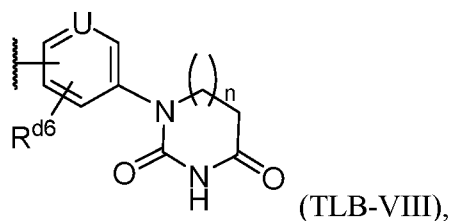
50. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein each R^{d6} is independently selected from the group consisting of H, halogen, C_{1-3} alkyl, and C_{1-3} alkoxy.

51. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein each R^{d6} is H.

52. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of R^{d6} is H.

53. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of R^{d6} is not H.

54. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder has a Formula (TLB-VIII):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

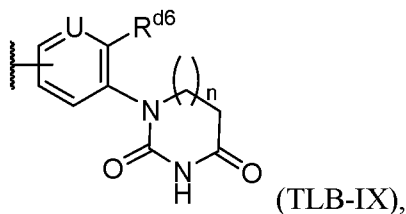
 denotes the point of attachment to the Linker in Formula (I);

U is $-CR^{d6}$ or N;

R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

55. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Targeting Ligase Binder has a Formula (TLB-IX):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Linker in Formula (I);

U is independently $-\text{CR}^{\text{d6}}$ or N;

R^{d6} is selected from the group consisting of H, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl; and

n is 1 or 2.

56. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

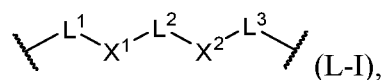
57. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

58. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein U is N.

59. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein U is $-\text{CR}^{\text{d6}}$.

60. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein each R^{d6} is independently selected from the group consisting of H, methyl, halogen, methoxy, and methoxymethyl.

61. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is H.
62. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is methyl.
63. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is halogen.
64. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is methoxy.
65. The bifunctional compound of any one of the preceding claims, wherein the Linker has Formula (L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, O, NR' , $C(O)$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand in Formula (I);

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, O, NR' , $C(O)$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $C(O)$, $S(O)_2$, O , NR' , $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in (L-I), wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond; and R' is hydrogen or C_{1-6} alkyl.

66. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

67. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is not a bond.

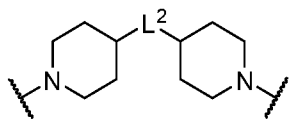
68. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl.

69. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

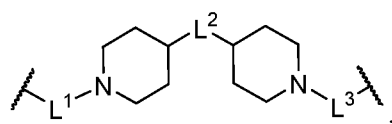
70. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X^1 and X^2 are each independently selected from piperidinyl and piperazinyl.

71. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X^1 and X^2 are both piperidinyl.

72. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $-X^1-L^2-X^2-$ is:

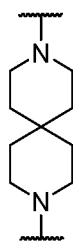


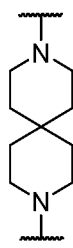
73. The bifunctional compound of any one of the preceding claims, wherein the Linker is a compound having the following formula:



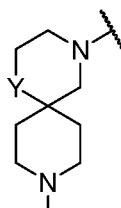
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

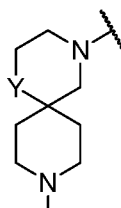
74. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $-X^1-L^2-X^2-$



forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^a , wherein each R^a is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl.

75. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $-X^1-L^2-X^2-$



forms a spiroheterocyclyl having the structure, , substituted with 0–4 occurrences of R^b , wherein Y is selected from CH_2 , oxygen, and nitrogen; and each R^b is independently selected from C_{1-6} alkyl, C_{1-6} alkoxy, and C_{1-6} hydroxyalkyl.

76. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein X^1 and X^2 are each a bond.

77. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is independently selected from the group consisting of $-C(O)-$, C_{2-6} alkynylene, or C_{1-6} heteroalkylene; and L^1 is $-C(O)-$, C_{1-8} alkylene, C_{1-8} heteroalkylene, and $*C_{1-6}$ alkylene- $C(O)$.

78. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of $-C(O)-$, $-O-C_{1-6}$ alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene.

79. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is $-C(O)-$ or C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene.

80. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is a bond or $-O-$; and L^1 is $-C(O)-$ or C_{1-8} heteroalkylene.

81. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, and C_{1-6} heteroalkylene; and L^1 is C_{1-8} alkylene or C_{1-8} heteroalkylene.

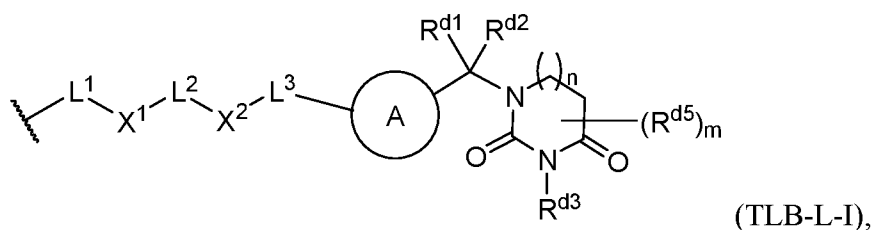
82. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^2 is $-C(O)-$, $-NR'-$, or C_{1-6} alkylene.

83. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene.

84. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^2 is C_{1-6} alkylene.

85. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^2 is selected from the group consisting of $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene.

86. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)-$, and $*C_{1-6}$ heteroalkylene- $C(O)-$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-I);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0–4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^p is H or C_{1-6} alkyl;

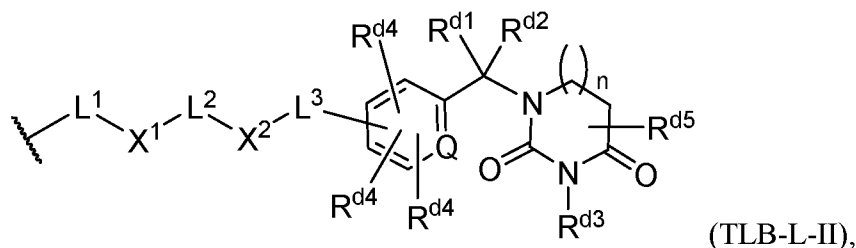
m is 1 or 2; and

n is 1 or 2.

87. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl.

88. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered heteroaryl.
89. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered nitrogen-containing heteroaryl.
90. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered heteroaryl.
91. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered nitrogen-containing heteroaryl.
92. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is pyridyl.
93. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.
94. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.
95. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

96. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)-$, and $*C_{1-6}$ heteroalkylene- $C(O)-$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-II);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Q is N or CR^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

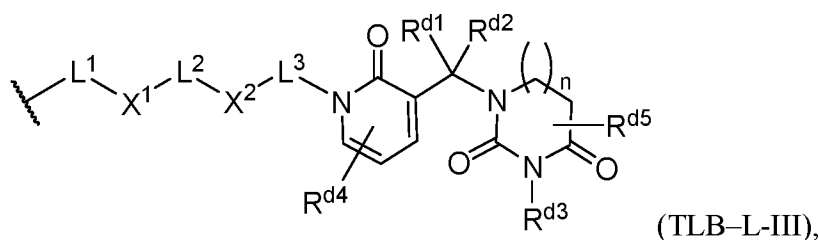
n is 1 or 2.

97. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

98. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

99. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-CH_2OP(O)(OR^p)_2$.

100. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

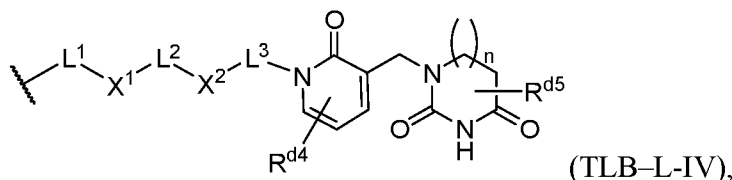
n is 1 or 2.

101. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

102. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

103. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

104. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$^*\text{C}(\text{O})\text{NR}'-\text{C}_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$, $^*\text{C}(\text{O})-\text{C}_{1-9}$ alkylene, and $^*\text{C}(\text{O})-\text{C}_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-IV);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-V);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl; and

n is 1 or 2.

108. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

109. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

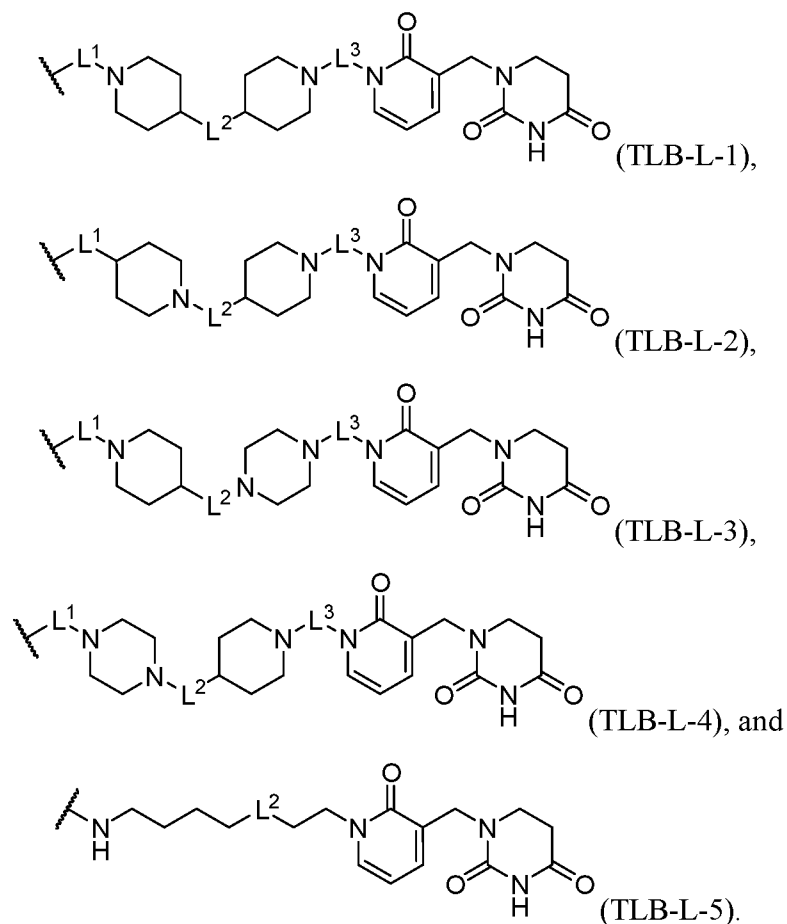
110. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

111. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is not a bond.

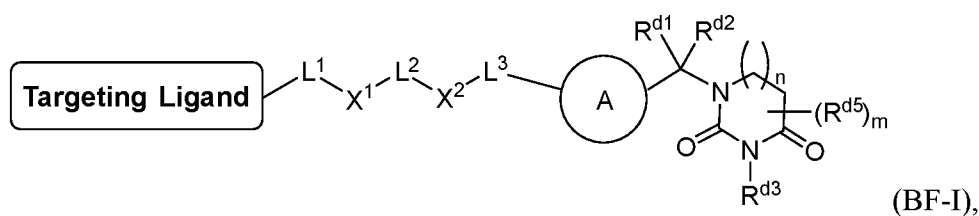
112. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl.

113. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

114. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:



115. The bifunctional compound of any one of the preceding claims, wherein the compound has the Formula (BF-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene;

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-I);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Ring A is a 6-membered aryl, or 5- or 6-membered heteroaryl, each of which is substituted with 0-4 occurrences of R^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, hydroxyl, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

116. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is selected from the group consisting of phenyl, pyridyl, pyridonyl, pyrazinyl, thiophenyl, pyrazolyl, imidazolyl, and pyrrolyl.

117. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered heteroaryl.

118. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 5-membered nitrogen-containing heteroaryl.

119. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered heteroaryl.

120. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is a 6-membered nitrogen-containing heteroaryl.

121. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is pyridyl.

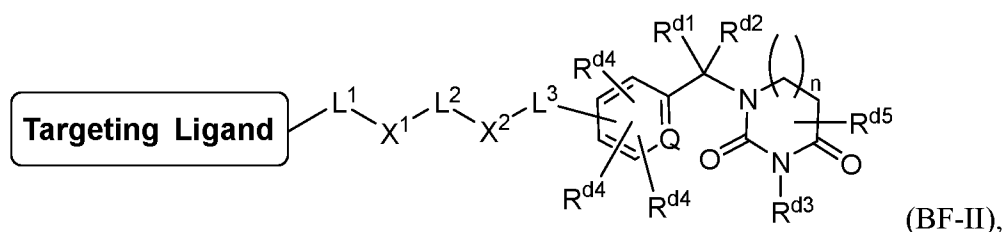
122. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

123. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

124. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

125. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

126. The bifunctional compound of any one of the preceding claims, wherein the compound has the Formula (BF-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and $^*\text{C}_{1-6}$ heteroalkylene- $\text{C}(\text{O})$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $^*\text{C}(\text{O})\text{NR}'-\text{C}_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$, $^*\text{C}(\text{O})-\text{C}_{1-9}$ alkylene, and $^*\text{C}(\text{O})-\text{C}_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-II);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

Q is N or CR^{d4} ;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

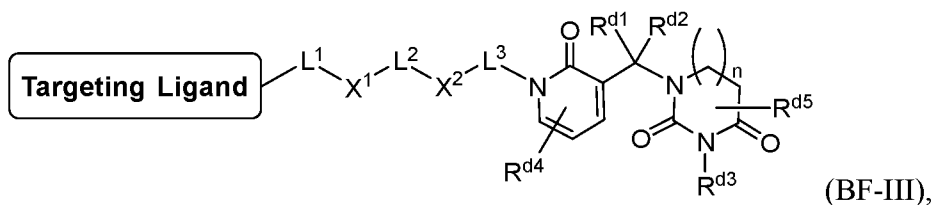
127. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

128. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

129. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-CH_2OP(O)(OR^p)_2$.

130. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

131. The bifunctional compound of any one of the preceding claims, wherein the compound has the Formula (BF-III):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^{d4} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

R^{d5} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

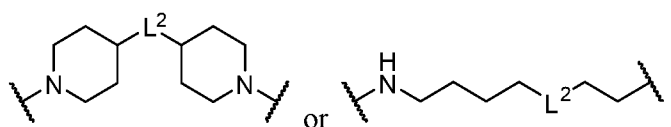
132. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

133. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

134. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

135. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

136. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $-\text{X}^1-\text{L}^2-\text{X}^2-$ is:



137. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^1 is $-\text{O}-$ or C_{1-6} alkylene.

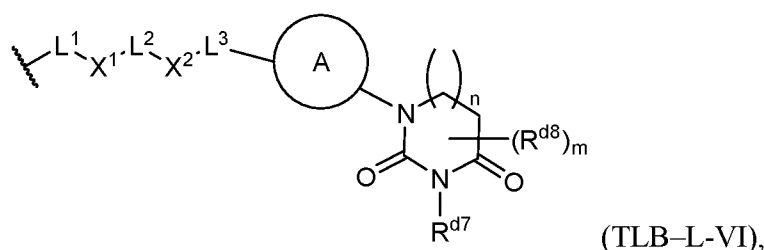
138. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} and R^{d2} are both methyl.

139. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} and R^{d2} are both H.

140. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is H or C_{1-3} alkyl.

141. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d5} is H or C_{1-3} alkyl.

142. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-VI):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

 denotes the point of attachment to the Targeting Ligand in Formula (I);

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$

heteroalkylene, wherein * denotes the point of attachment of L^3 to X^2 in Formula (TLB-L-VI);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{HOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2.

143. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

144. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

145. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

146. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

R^{d7} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})R^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(R^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2.

148. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

149. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

150. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

151. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

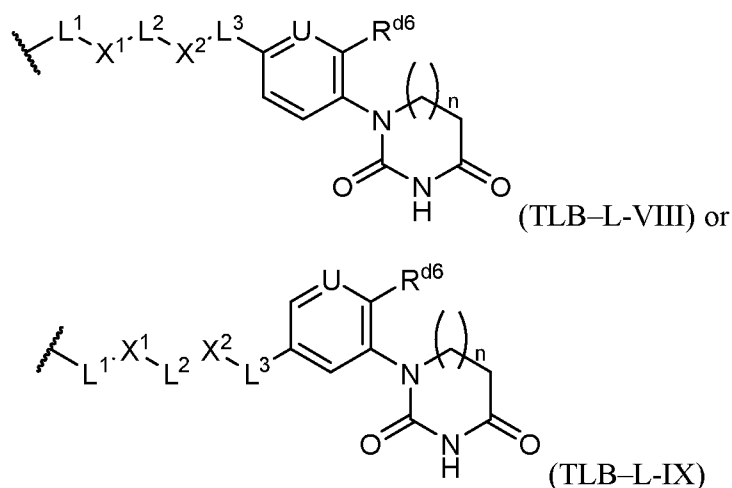
152. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{C}(\text{O})-$, $-\text{S}(\text{O})_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

153. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is not a bond.

154. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a carbocyclyl or heterocyclyl.

155. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein one of X^1 and X^2 is a bond, and the other is a heterocyclyl.

156. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker has Formula (TLB-L-VIII or TLB-L-IX):

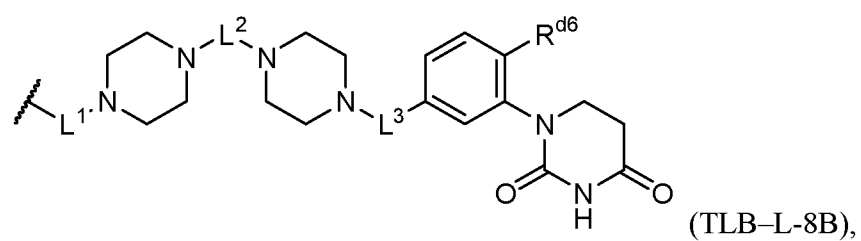
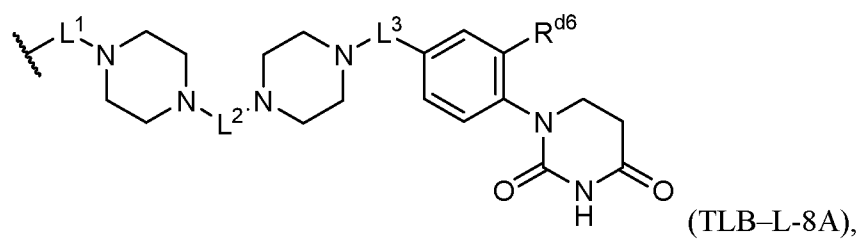
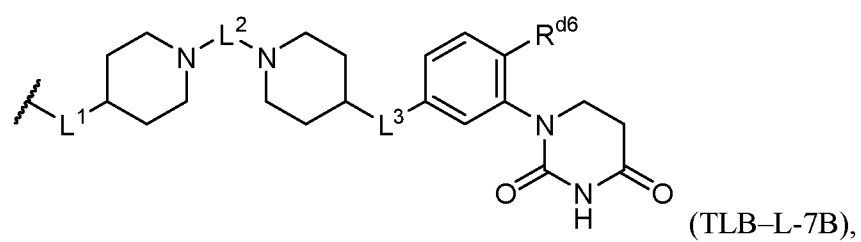
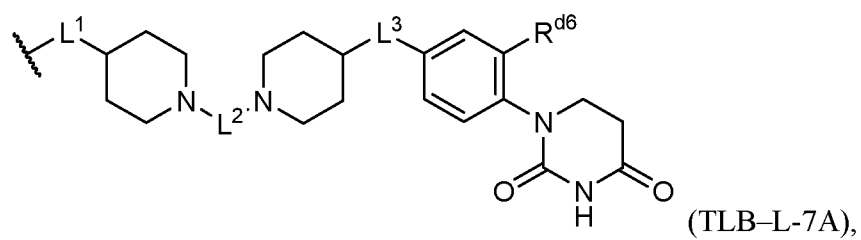
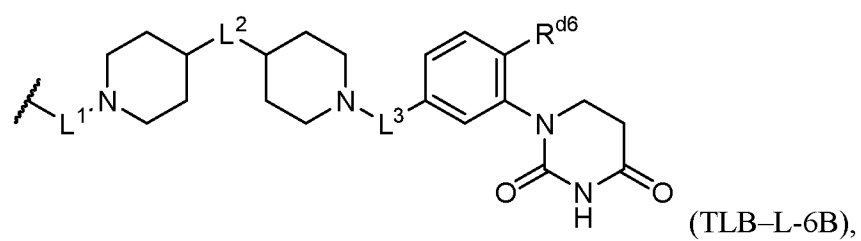
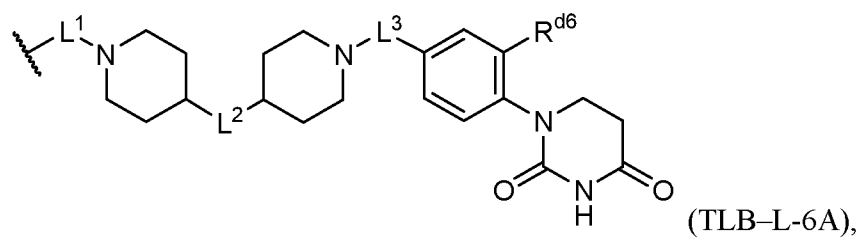


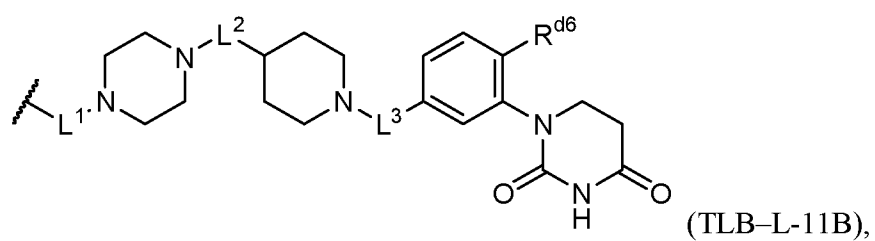
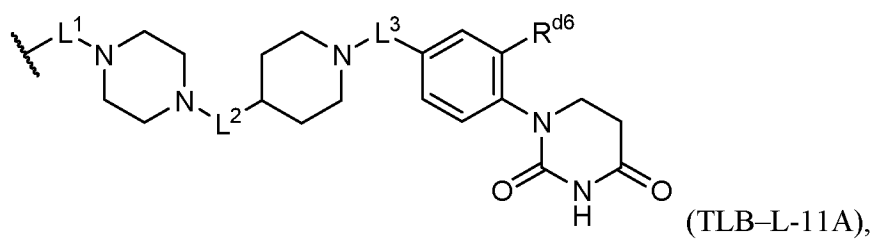
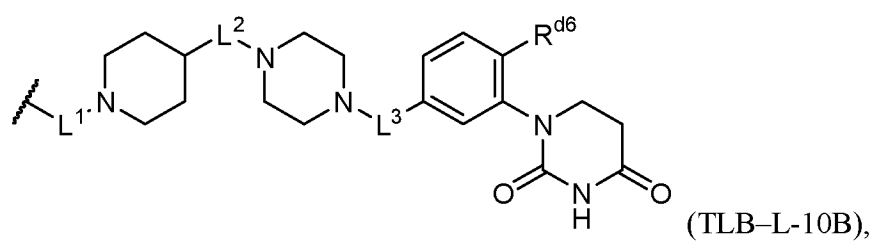
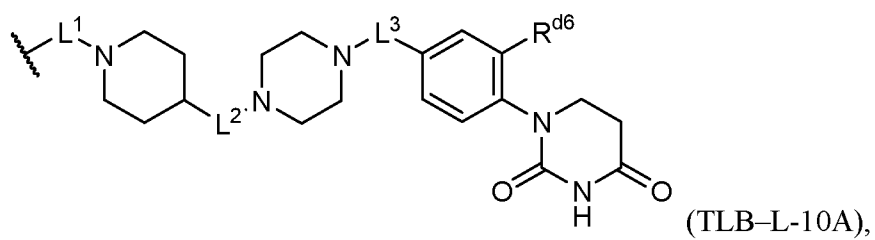
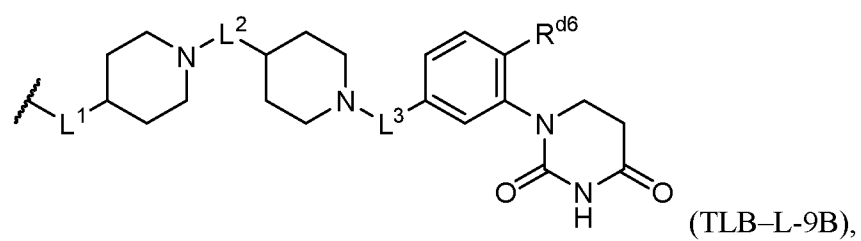
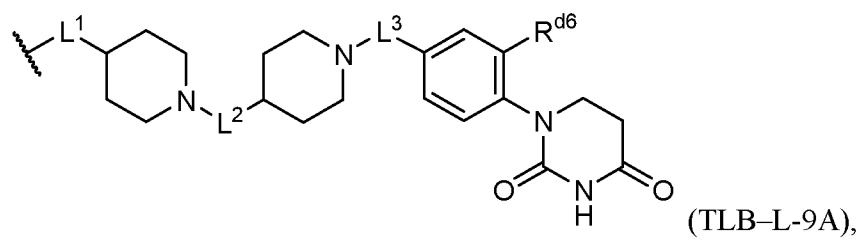
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the point of attachment to the Targeting Ligand is through L¹.

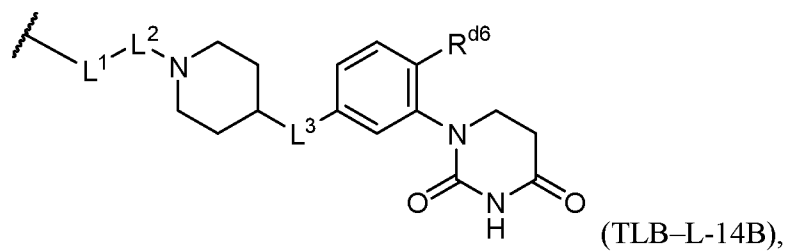
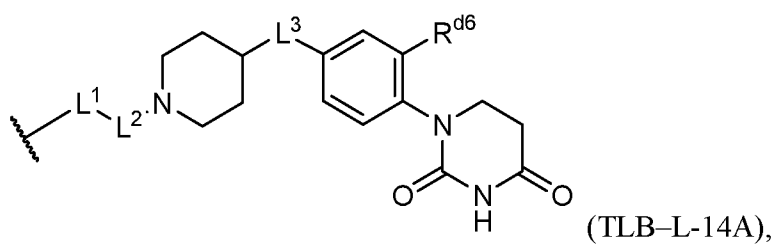
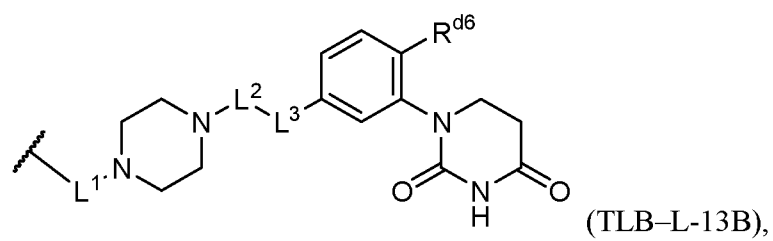
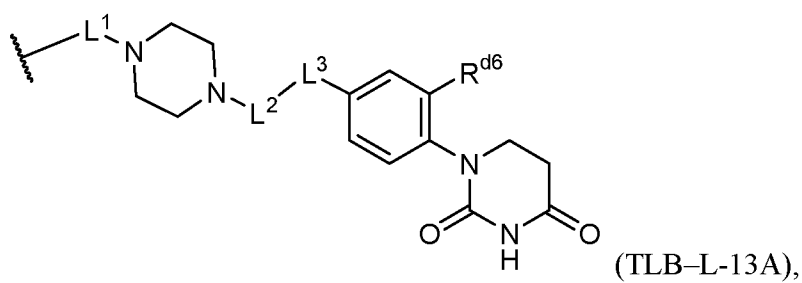
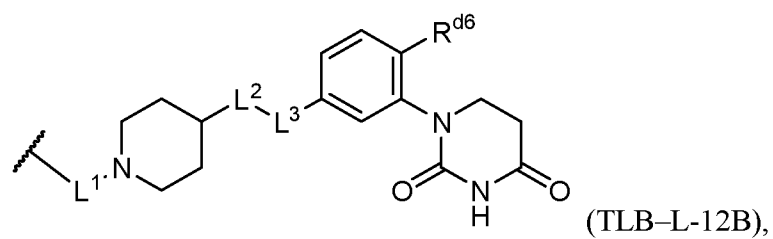
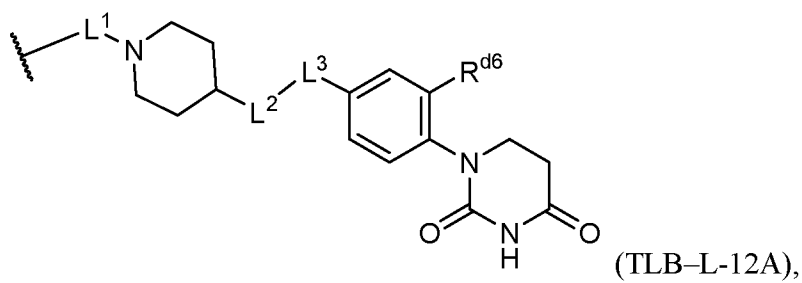
157. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

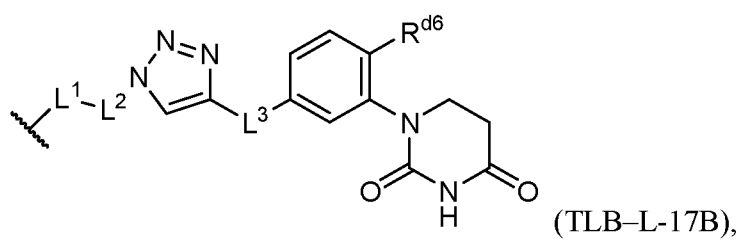
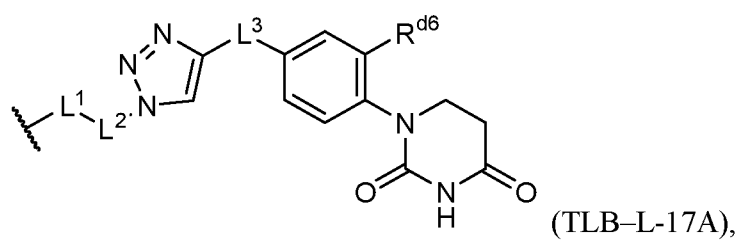
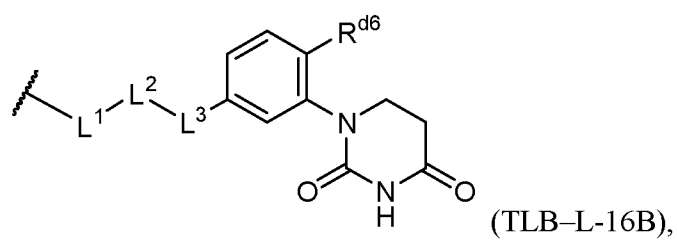
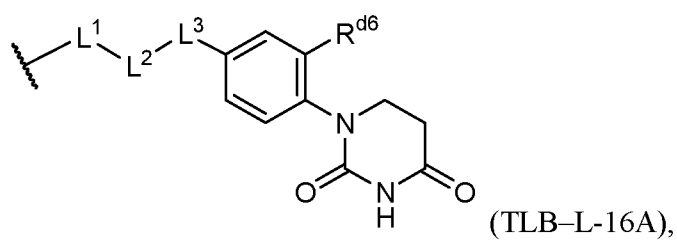
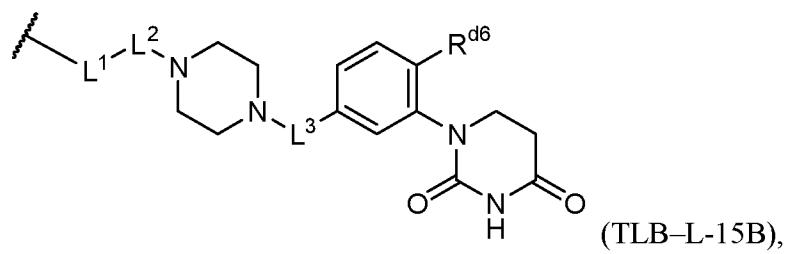
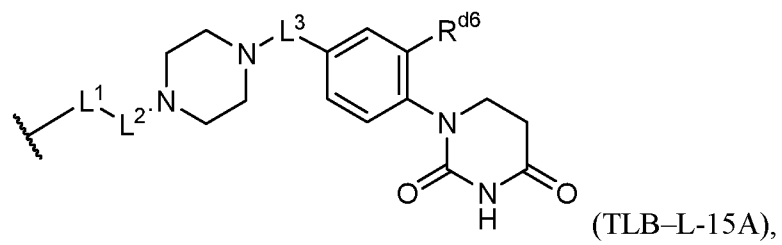
158. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

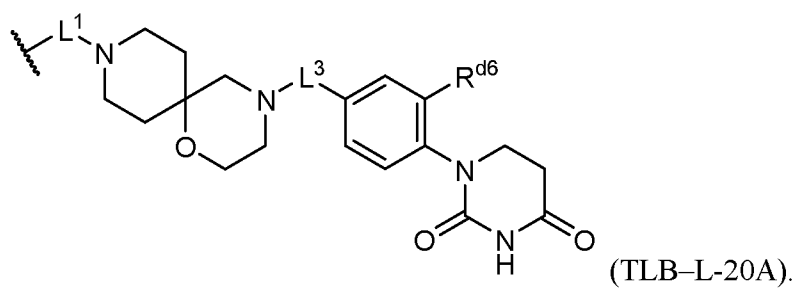
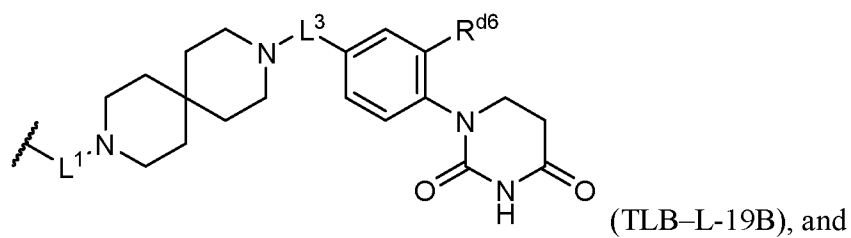
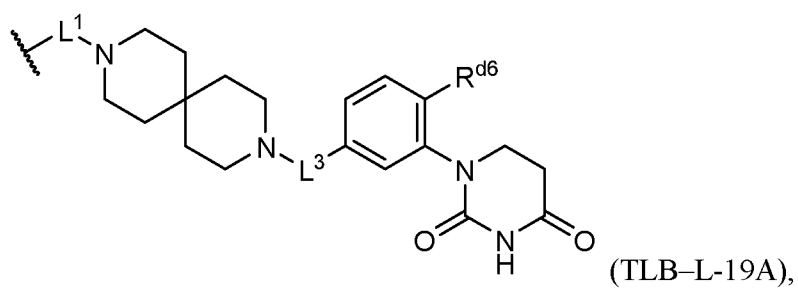
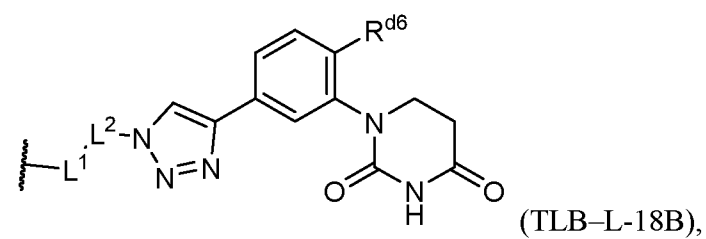
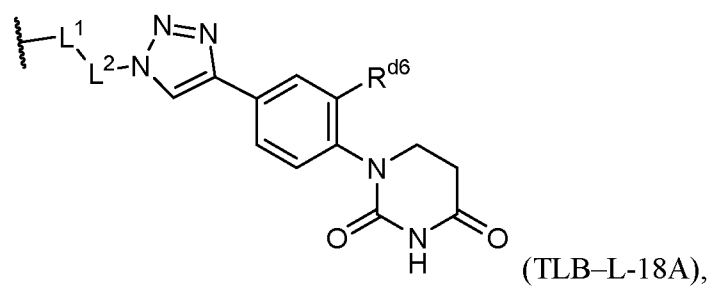
159. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligase Binder-Linker, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, has a Formula selected from:



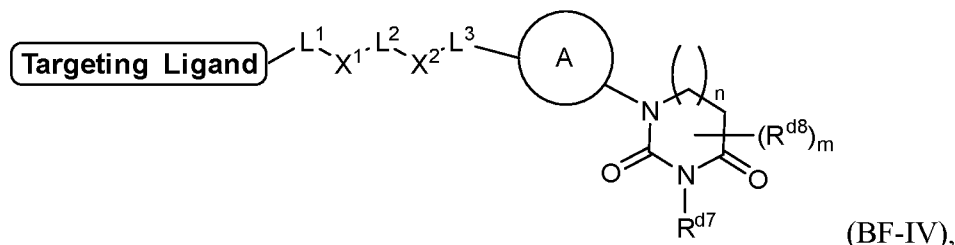








160. The bifunctional compound of any one of the preceding claims, wherein the compound has the Formula (BF-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-IV);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

Ring A is a 6-membered aryl or 6-membered heteroaryl, each of which is independently substituted with 0–4 occurrences of R^{d6} ;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^p is H or C_{1-6} alkyl;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

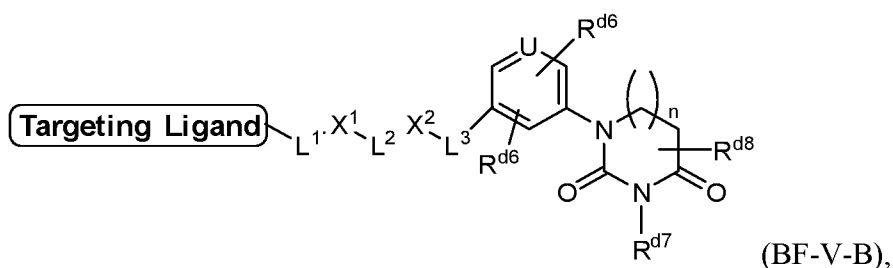
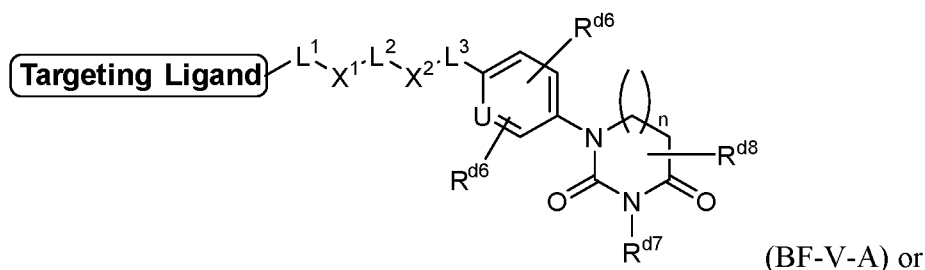
or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

m is 1 or 2; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

161. The bifunctional compound of any one of the preceding claims, wherein the compound has the Formula (BF-V-A) or (BF-V-B):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein * denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and

$*C(O)NR'-C_{1-6}$ alkylene, wherein * denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-V-A or BF-V-B);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

U is $-CR^{d6}$ or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^{d7} is selected from the group consisting of H, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

R^{d8} is selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl; and

n is 1 or 2, wherein the Targeting Ligand is a group capable of binding to a Target Protein.

162. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

163. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

164. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is $-CH_2OP(O)(OR^p)_2$.

165. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is H.

166. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein U is $-CR^{d6}$.

167. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d8} is H.

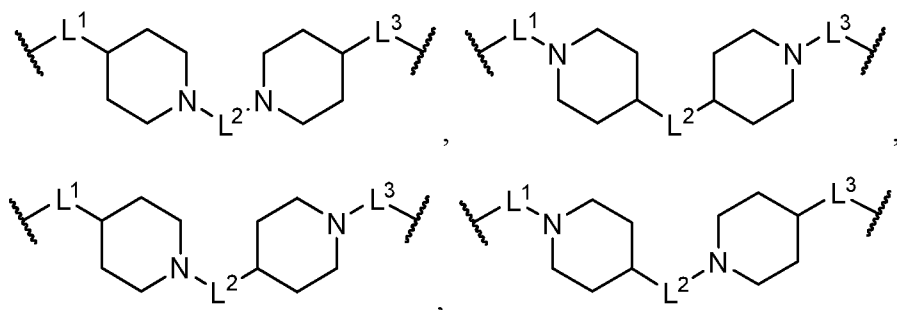
168. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} and R^{d8} are each independently H.

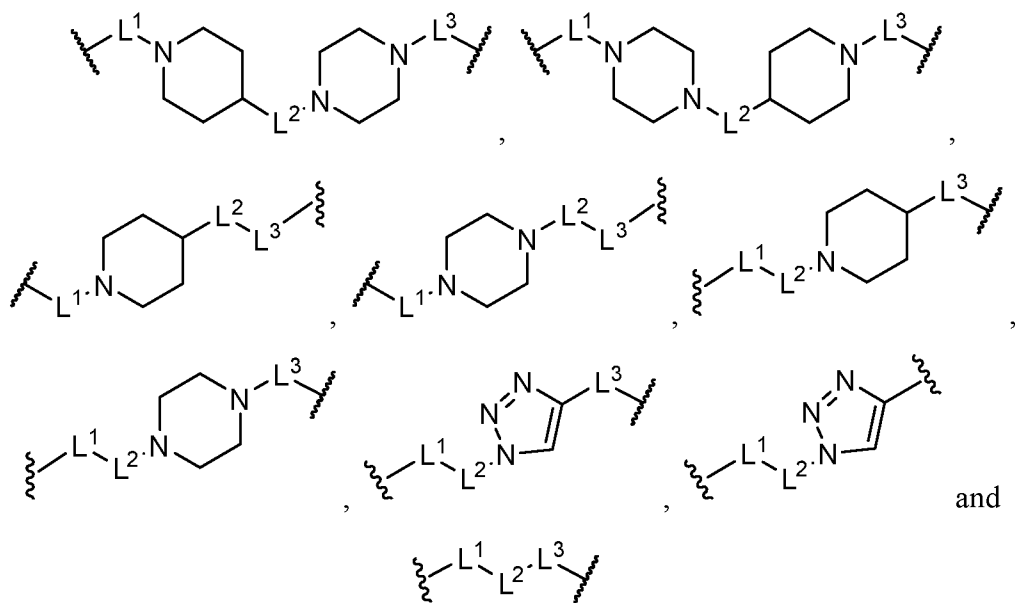
169. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is H.

170. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy.

171. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d6} is selected from the group consisting of H, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; and R^{d7} , and R^{d8} are each H.

172. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $L^1-X^1-L^2-X^2-L^3$ is selected from the group consisting of:



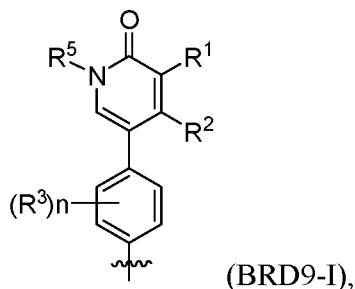


173. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L³ is selected from the group consisting of a bond, -O-, -C(O)-, -S(O)₂-, C₁₋₆ alkylene, C₂₋₆ alkynylene, and C₁₋₆ heteroalkylene.

174. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Target Protein is selected from the group listed in **Table 1**.

175. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Target Protein is selected from the group listed in **Table 2**.

176. The bifunctional compound of any one of the preceding claims, wherein the Targeting is a BRD9 targeting ligand of Formula (BRD9-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

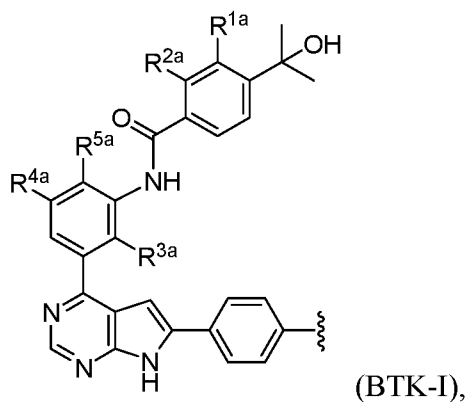
R^1 and R^2 are independently selected from the group consisting of hydrogen and C_{1-6} alkyl; or R^1 and R^2 together with the atoms to which they are attached form an aryl or heteroaryl;

R^3 are each independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} alkoxy, and halogen;

R^5 is selected from the group consisting of hydrogen and C_{1-3} alkyl;

n is 0, 1, or 2.

177. The bifunctional compound of any one of the preceding claims, wherein the Targeting Ligand is a BTK targeting ligand of Formula (BTK-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo; and

R^{5a} is H or halo.

178. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

179. A pharmaceutical combination comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and one or more additional therapeutic agent(s).

180. A method for inducing degradation of a Target Protein in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

181. A method of inhibiting, reducing, or eliminating the activity of a Target Protein, the method comprising administering to the subject a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

182. The method of any one of the preceding claims, wherein inhibiting, reducing, or eliminating the activity of a Target Protein comprises recruiting a ligase (*e.g.*, Cereblon E3 Ubiquitin ligase) with the Targeting Ligase Binder, *e.g.*, a Targeting Ligase Binder described herein, of the bifunctional compound, *e.g.*, a bifunctional compound described herein, forming a ternary complex of the Target Protein, bifunctional compound, and the ligase, to thereby inhibit, reduce or eliminate the activity of the Target Protein.

183. The method of any one of the preceding claims, wherein the Target Protein is selected from the group listed in **Table 1** or **Table 2**.

184. A method of treating a Target Protein-mediated disorder, disease, or condition in a patient comprising administering to the patient the compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

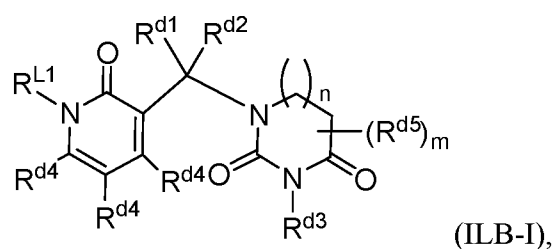
185. The method of any one of the preceding claims, wherein the disorder is selected from a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder.

186. The method of any one of the preceding claims, wherein the disorder is a proliferative disorder.

187. The method of any one of the preceding claims, wherein the proliferative disorder is cancer.

188. A method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

189. A compound of Formula (ILB-I):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d4} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy; C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ heteroalkyl, and C₃₋₆ cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C₃₋₄ spirocycloalkyl;

R^{L1} is selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, C₃₋₆ heteroalkyl, C₂₋₆ haloalkyl, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{1-3}O(CH_2)_{1-3}C(O)H$, $-(CH_2)_{0-3}C_{3-7}$ carbocyclyl, $-(CH_2)_{0-3}$ heterocyclyl, C₆ aryl, and heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and heteroaryl is substituted with 0-2 occurrences of -O-heterocyclyl, -O-carbocyclyl, -C(O)-heterocyclyl, -C(O)-carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C₁₋₄ alkyl, or C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl;

m is 1 or 2; and

n is 1 or 2.

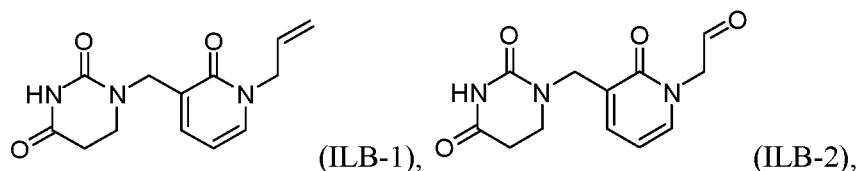
190. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

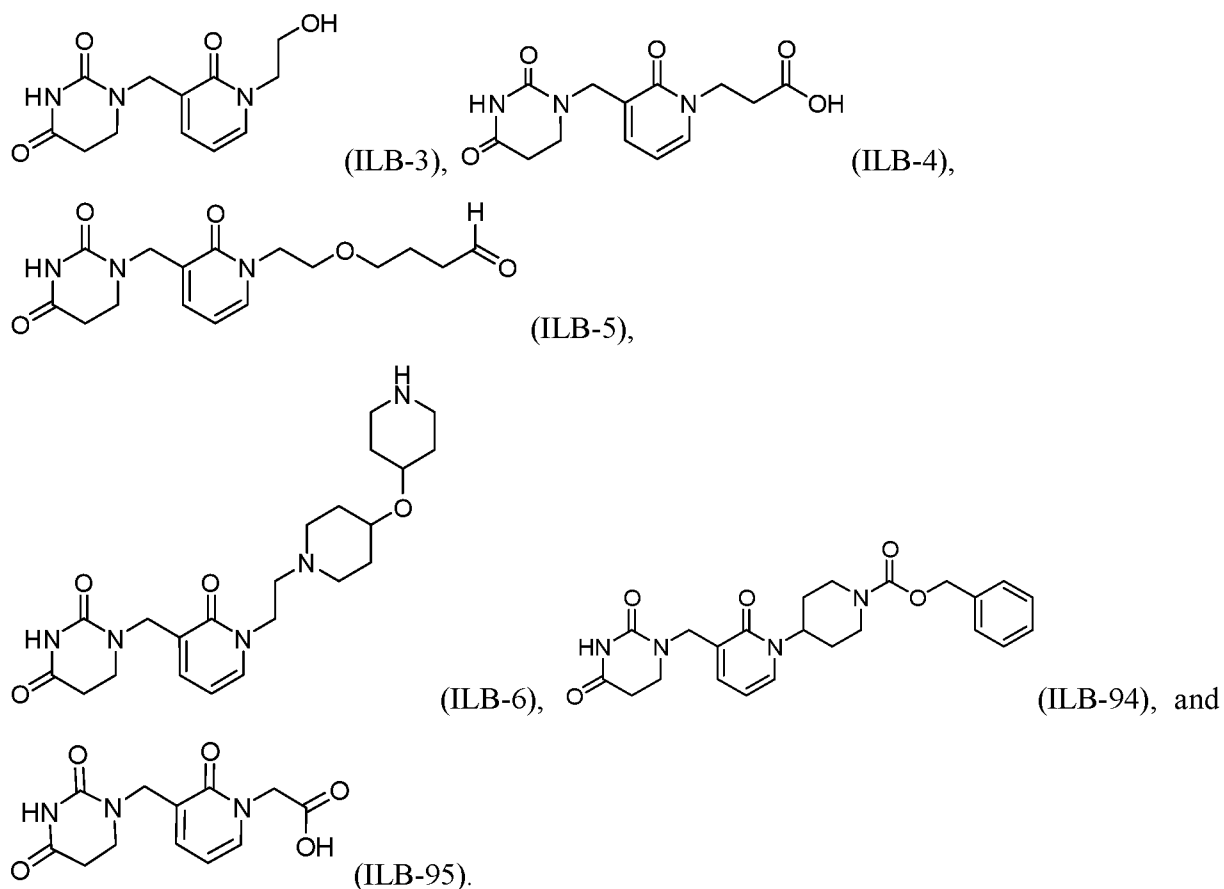
191. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

192. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-CH_2OP(O)(OR^p)_2$.

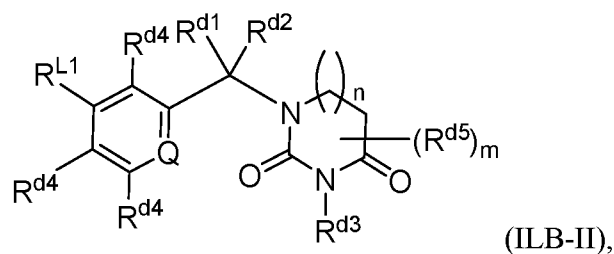
193. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

194. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:





195. A compound of Formula (ILB-II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

Q is N or $\mathbb{C}R^{d4}$;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d3} is selected from the group consisting of H, $-CH_2(O)(CH_2)_2Si(CH_3)_3$, $-CH_2OC(O)R^p$, $-CH_2OP(O)OHOR^p$, $-CH_2OP(O)(R^p)_2$, and $-CH_2OP(O)(OR^p)_2$;

each R^{d4} is independently selected from the group consisting of H, oxo, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} alkoxyalkyl, and C_{1-6} heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, halogen, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

or two R^{d5} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d5} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L1} is selected from the group consisting of C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, C_{3-6} heteroalkyl, C_{2-6} haloalkyl, $-(CH_2)_{0-3}C(O)OH$, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{0-3}C_{3-7}$ carbocyclyl, $-(CH_2)_{0-3}$ heterocyclyl, C_6 aryl, and heteroaryl, wherein the carbocyclyl, heterocyclyl, aryl, and heteroaryl is substituted with 0–2 occurrences of $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, or C_{1-6} heteroalkyl;

R^p is H or C_{1-6} alkyl;

m is 1 or 2; and

n is 1 or 2.

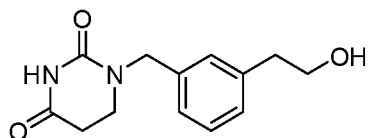
196. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

197. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

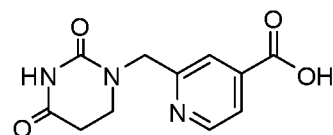
198. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is $-CH_2OP(O)(OR^p)_2$.

199. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.

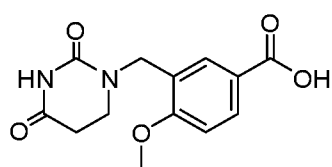
200. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:



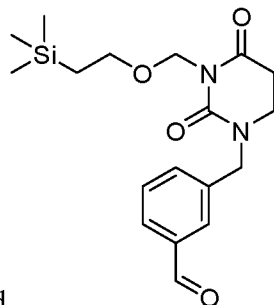
(ILB-7),



(ILB-8),

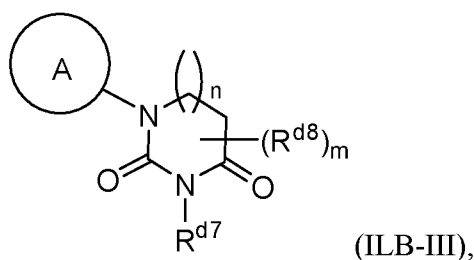


(ILB-9), and



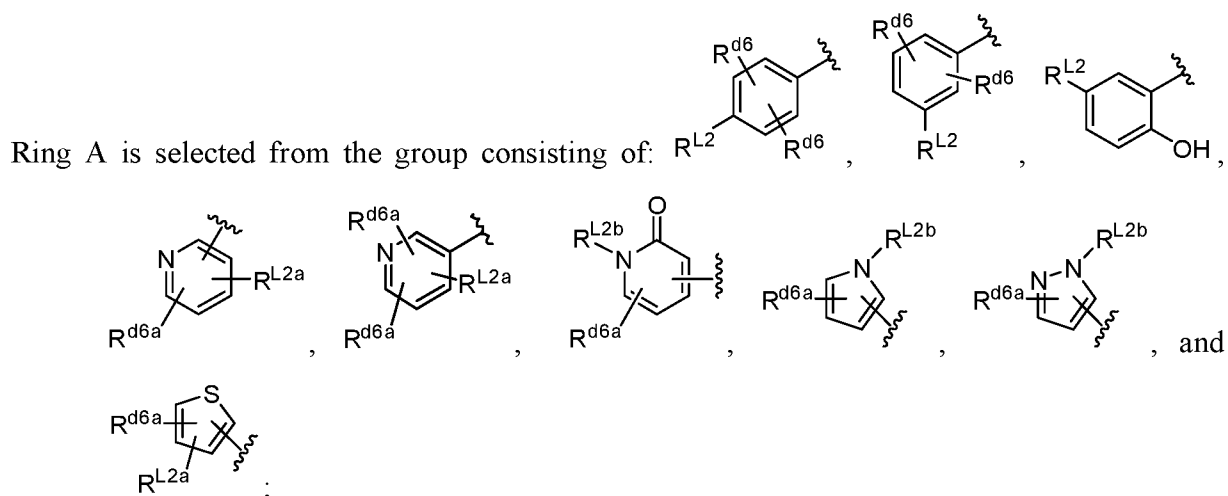
(ILB-10).

201. A compound of Formula (ILB-III):



(ILB-III),

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:



— denotes the point of attachment to the base molecule of (ILB-III);

each R^{d6} is independently selected from the group consisting of H, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

each R^{d6a} is independently selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-OC_{1-7}$ heteroalkyl;

R^{d7} is H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

each R^{d8} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L2} is selected from the group consisting of hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{4-8} heteroalkyl, C_{2-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^c$, $-\text{O}-C_{2-6}$ alkenyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})$ -heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{N}(\text{R}^c)_2$, heterocyclyl, heteroaryl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl, wherein the heterocyclyl and heteroaryl is substituted with 0-2 occurrences of halogen;

R^{L2a} is selected from the group consisting of H, hydroxyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{1-8} heteroalkyl, C_{1-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OR}^c$, $-\text{O}-C_{2-6}$ alkenyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}\text{C}(\text{O})$ -heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{2-6}\text{N}(\text{R}^c)_2$, heterocyclyl, $-\text{O}$ -heterocyclyl, $-\text{O}$ -carbocyclyl, $-\text{C}(\text{O})$ -heterocyclyl, $-\text{C}(\text{O})$ -carbocyclyl, C_{1-6} alkyl, C_{1-6}

alkoxyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl, wherein the heterocyclyl is substituted with 0-2 occurrences of halogen;

RL^{2b} is selected from the group consisting of H, polyethylene glycol (PEG), C₁₋₃ alkyl, C₃₋₆ cycloalkyl, C₃₋₆ alkenyl, C₃₋₆ alkynyl, C₂₋₆ hydroxyalkyl, $-(CH_2)_{2-6}NHR^c$, $-(CH_2)_{2-6}NR^cR^d$, C₂₋₈ heteroalkyl, C₂₋₆ haloalkyl, $-(CH_2)_{1-3}C(O)OH$, $-(CH_2)_{1-3}C(O)H$, $-(CH_2)_{0-3}$ heterocyclyl, $-C(O)-(CH_2)_{0-3}$ heterocyclyl, $-C_{3-6}$ alkynyl-heterocyclyl, and heteroaryl, wherein the alkynyl, heterocyclyl, heteroalkyl, carbocyclyl, and heteroaryl is substituted with 0-2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-(CH_2)_{2-6}NHR^c$, heterocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, and C₁₋₆ haloalkyl;

R^c is H, C₁₋₄ alkyl, C₁₋₆ heteroalkyl, and $-C(O)OC_{1-6}$ alkyl;

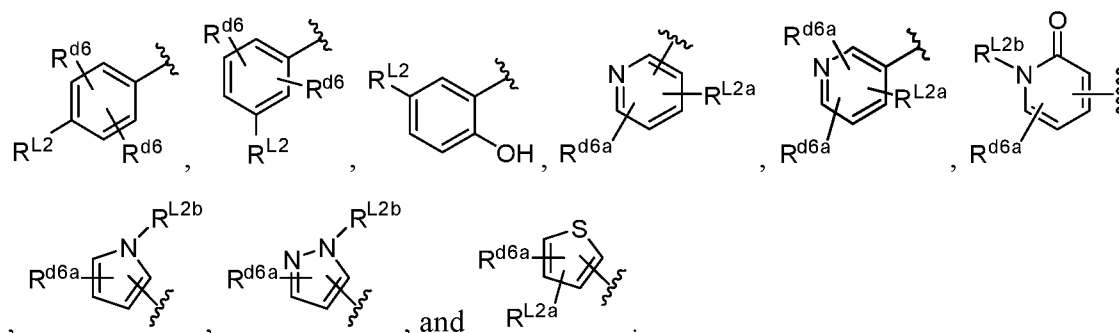
R^d is H or C₁₋₄ alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0-2 occurrences of $-O$ -heterocyclyl,

R^p is H or C₁₋₆ alkyl;

m is 1 or 2; and

n is 1 or 2.

202. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein ring A is selected from the group consisting of:



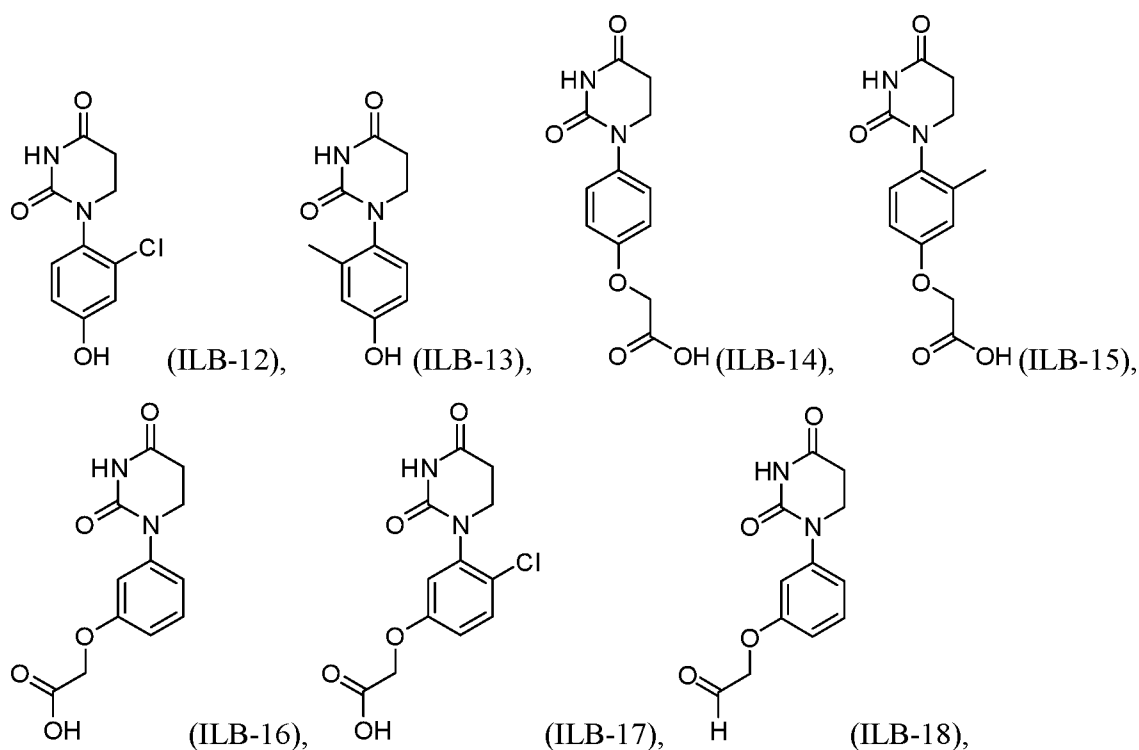
203. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.

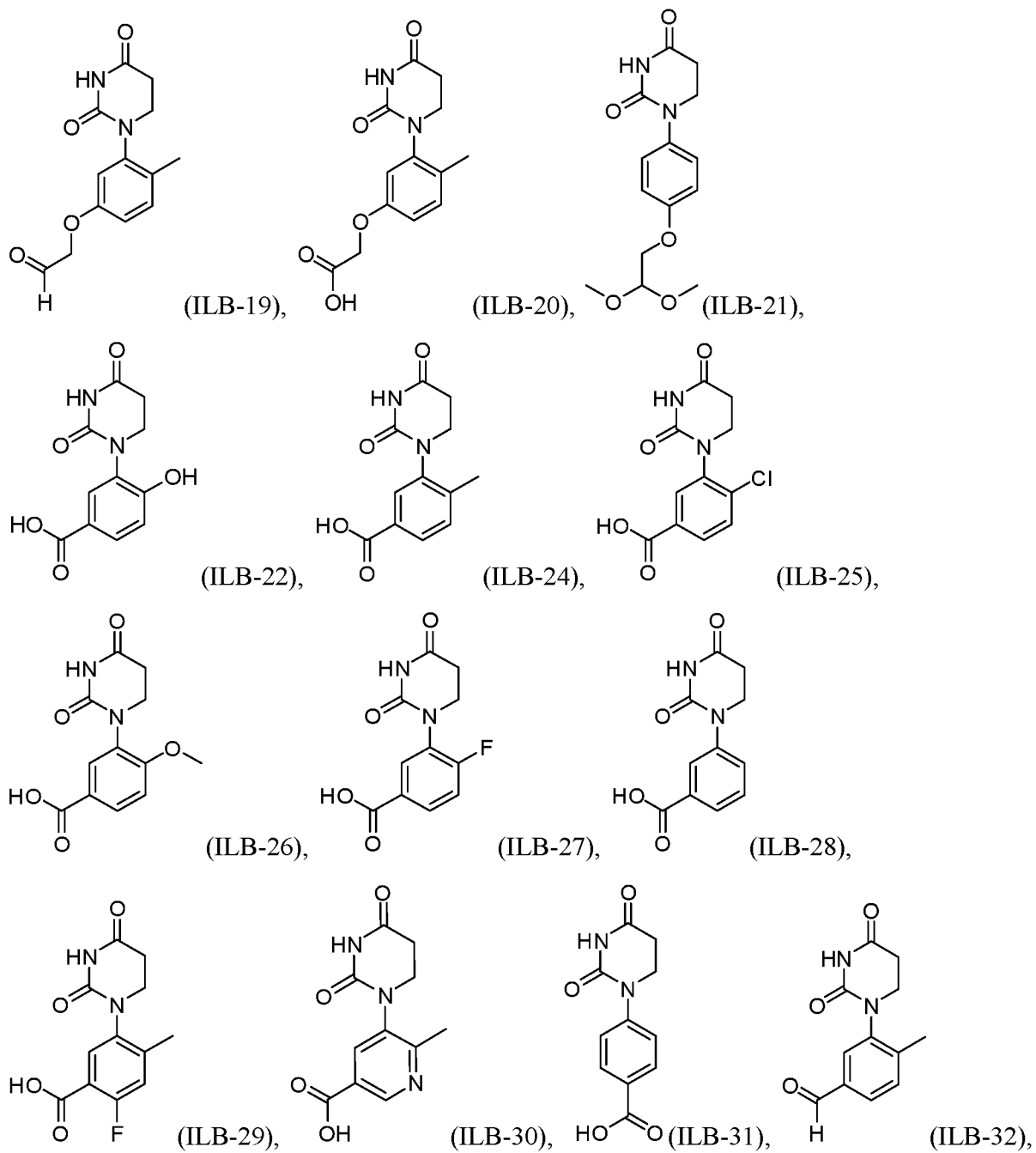
204. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 2.

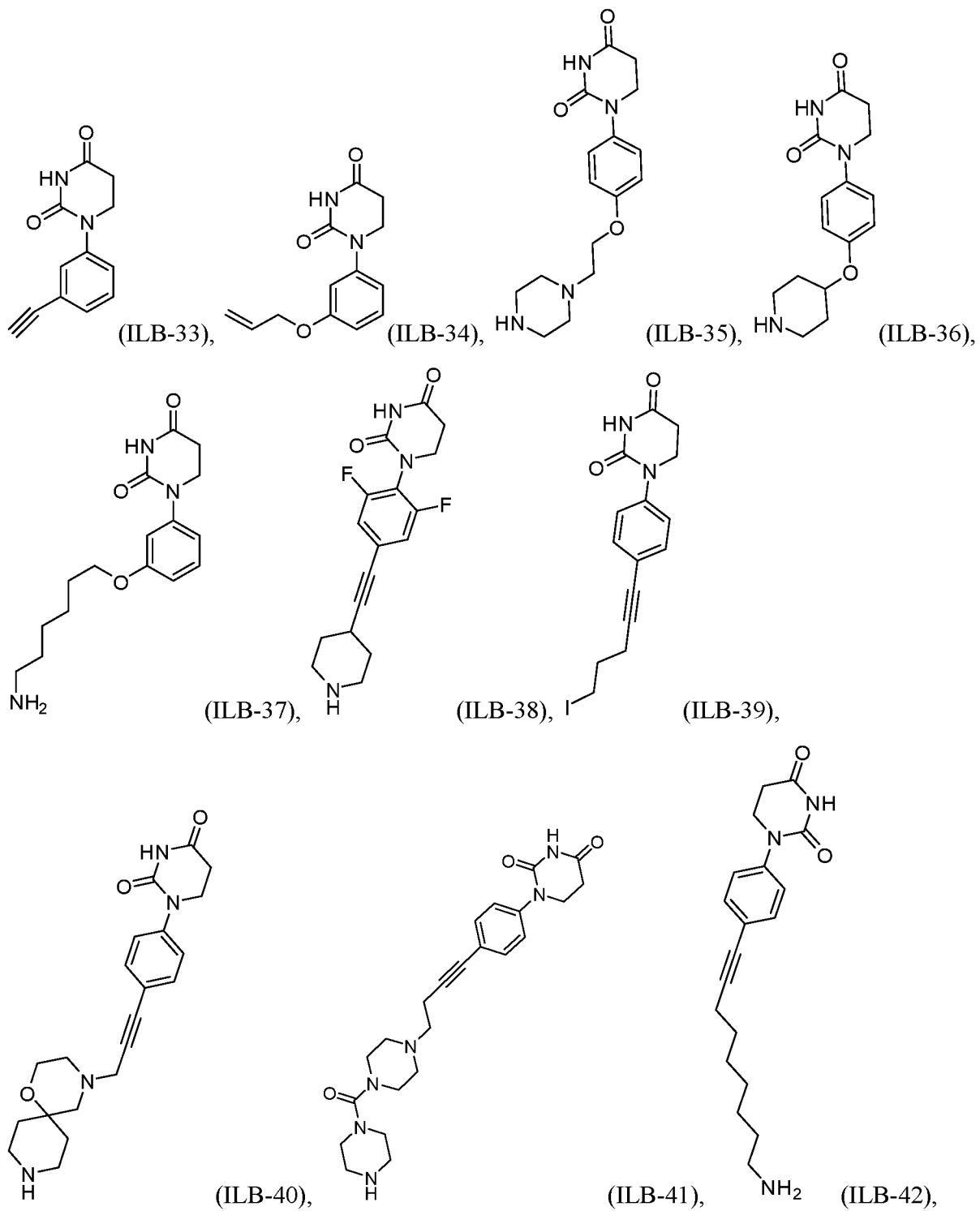
205. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$.

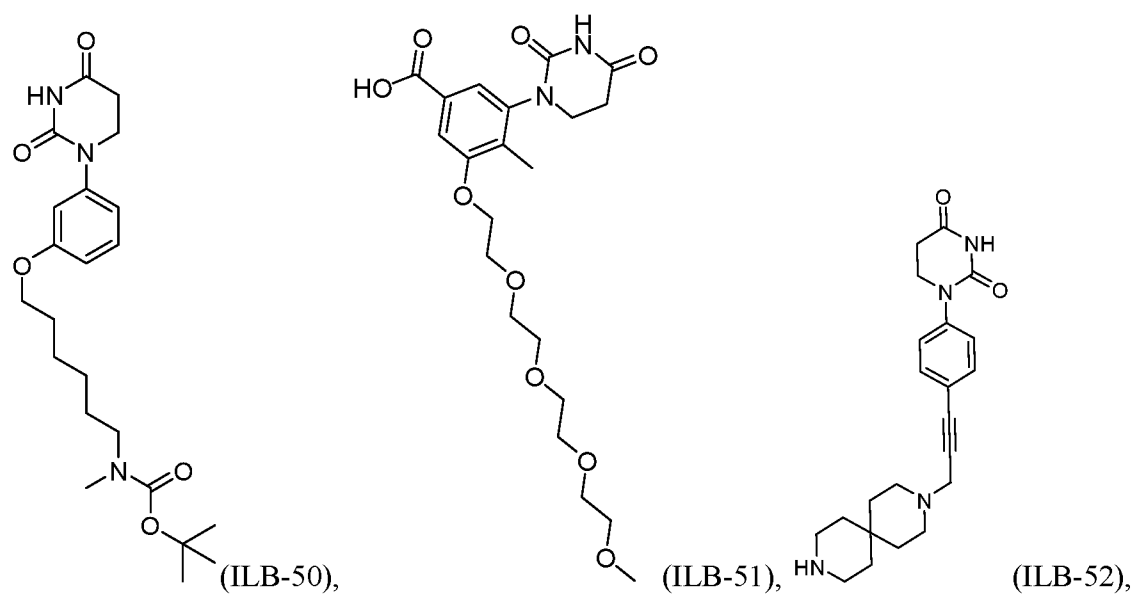
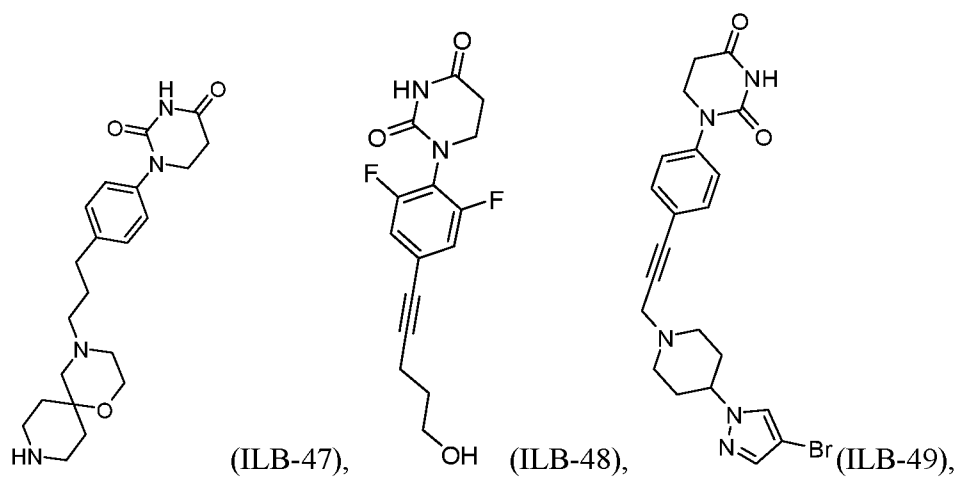
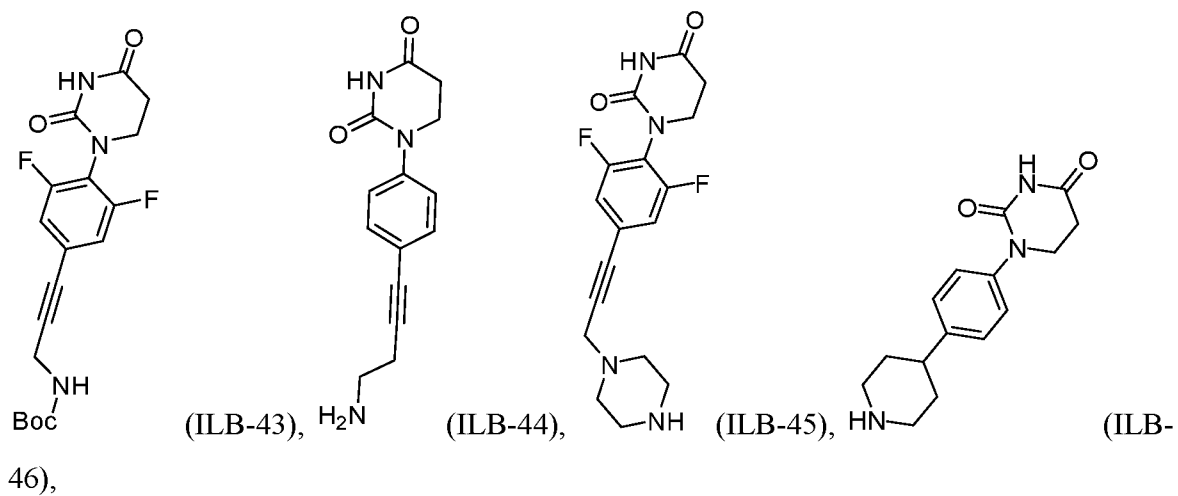
206. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d7} is H.

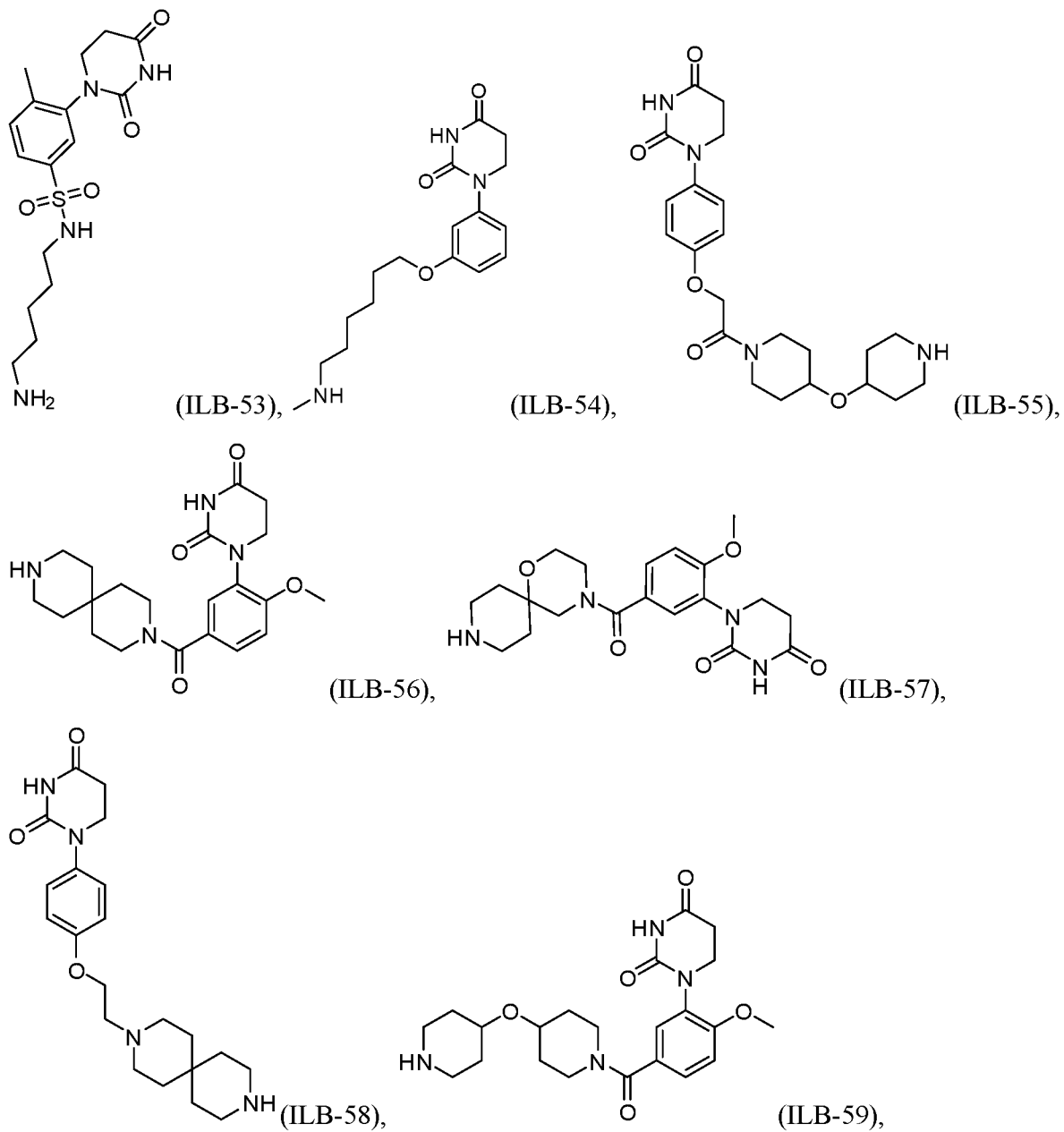
207. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from:

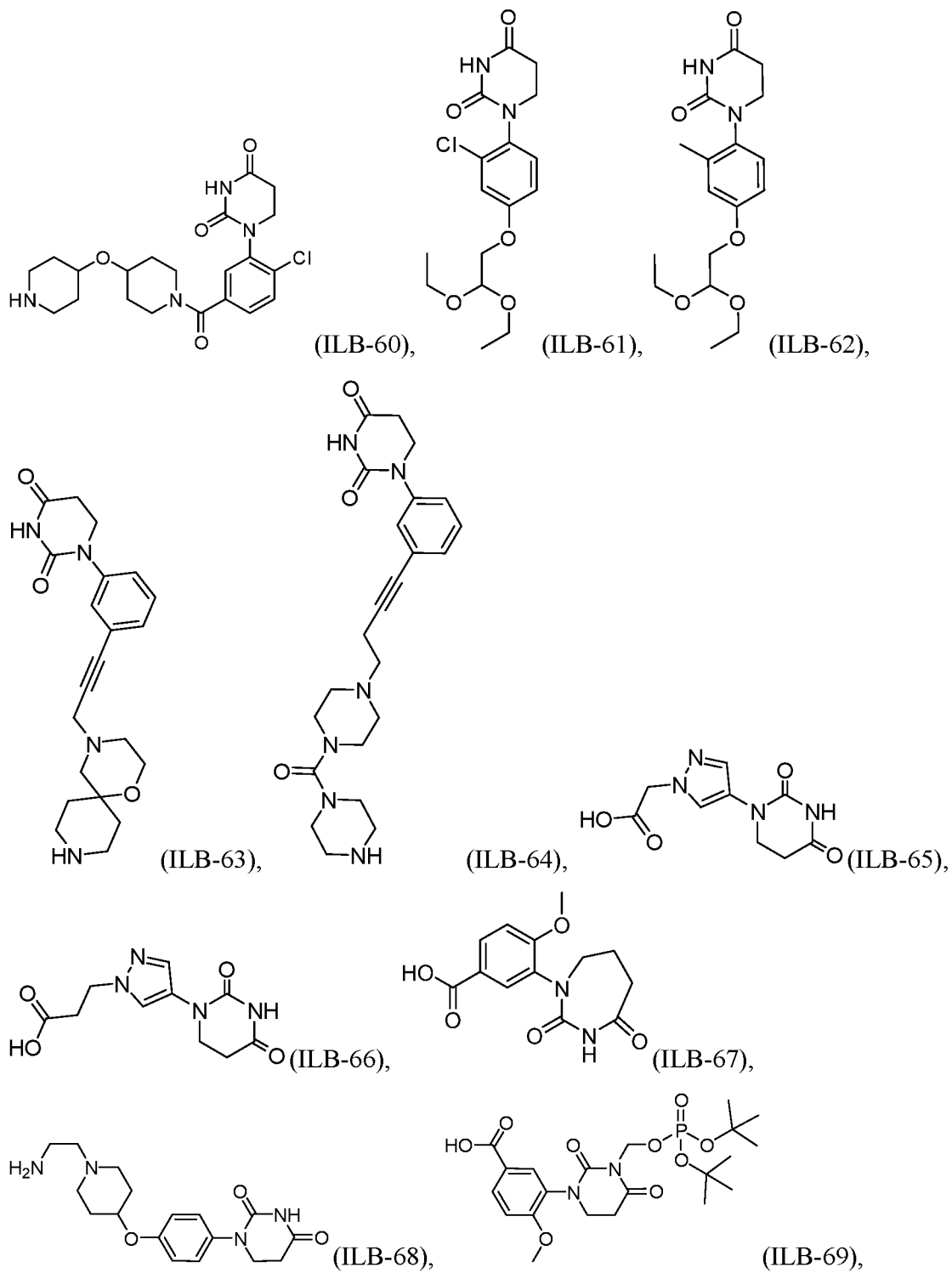


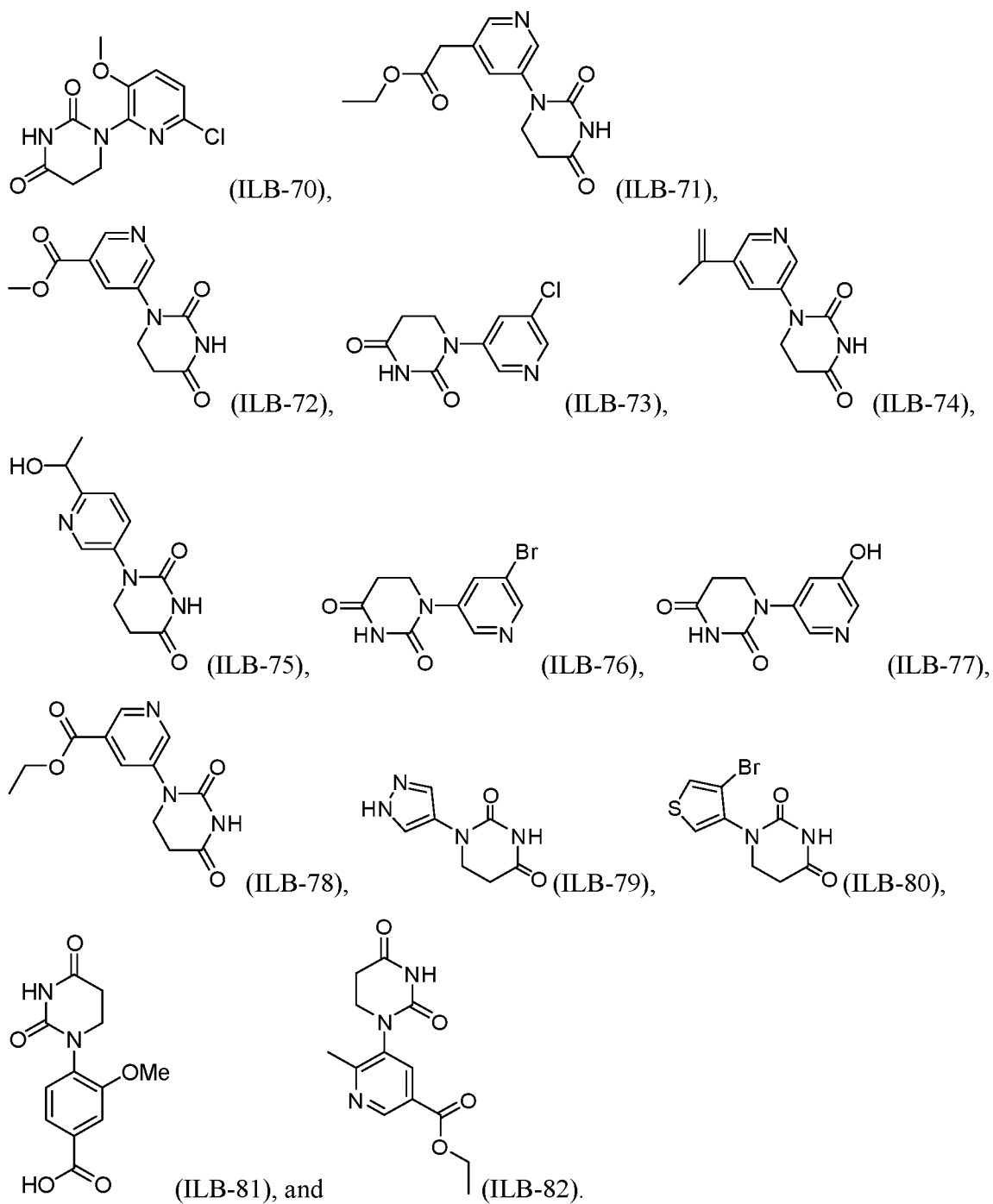




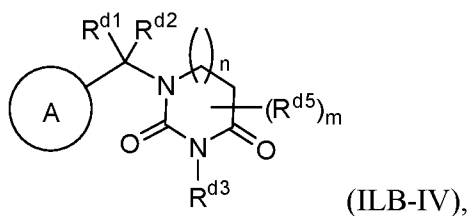




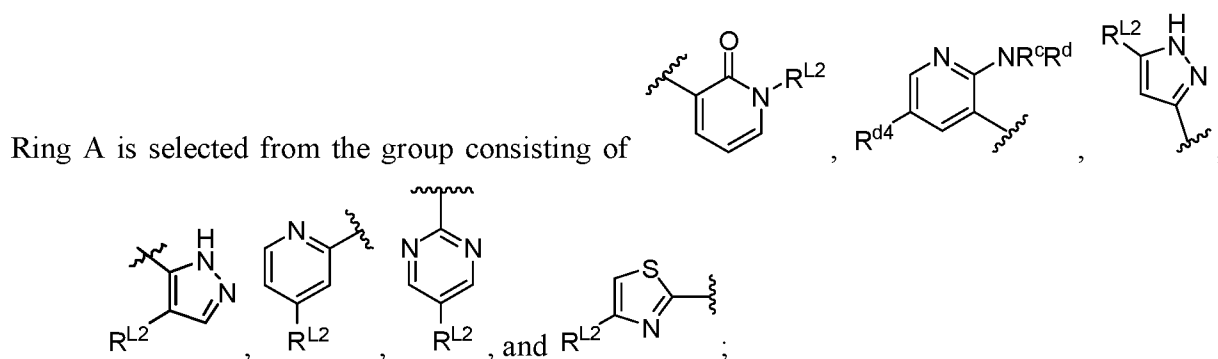




208. A compound of Formula (ILB-IV):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:



— denotes the point of attachment to the base molecule of (ILB-IV);

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and C_{3-6} cycloalkyl;

R^{d3} is H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, hydroxyl, oxo, polyethylene glycol (PEG), halogen, C_{1-3} alkyl, C_{3-6} cycloalkyl, C_{1-3} alkoxy, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, and $-\text{OC}_{1-7}$ heteroalkyl;

each R^{d5} is independently selected from the group consisting of H, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl;

or two R^{d8} together with the carbon atoms to which they are attached form a cycloalkyl;

or two R^{d8} attached to the same carbon atom form a C_{3-4} spirocycloalkyl;

R^{L2} is selected from the group consisting of hydroxyl, halogen, C_{2-6} alkyl, C_{1-3} alkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{2-6} hydroxyalkyl, $-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-6}\text{NR}^c\text{R}^d$, $-\text{O}-(\text{CH}_2)_{2-6}\text{NHR}^c$, C_{3-8} heteroalkyl, C_{1-6} haloalkyl, $-\text{SO}_2\text{-NH}-(\text{CH}_2)_{2-6}\text{NHR}^c$, $-(\text{CH}_2)_{0-3}\text{C}(\text{O})\text{OH}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{H}$, $-\text{O}-(\text{CH}_2)_{1-3}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-3}\text{C}_{3-7}$ carbocyclyl, $-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}(\text{O})-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{O}-(\text{CH}_2)_{0-3}$ heterocyclyl, $-\text{C}_{2-6}$

alkynyl-heterocyclyl, $-C_{2-6}$ alkynyl-heterocyclyl-heteraryl, C_6 aryl, and heteroaryl, wherein the alkynyl, alkoxy, heterocyclyl, heteroalkyl, carbocyclyl, aryl, and heteroaryl is substituted with 0–2 occurrences of halogen, hydroxyl, $-(CH_2)_{0-3}C(O)H$, $-C(O)O$ -benzyl, $-(CH_2)_{2-6}NHR^c$, heterocyclyl, $-O$ -heterocyclyl, $-O$ -carbocyclyl, $-C(O)$ -heterocyclyl, $-C(O)$ -carbocyclyl, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, and C_{1-6} haloalkyl;

R^c is H, C_{1-4} alkyl, C_{1-6} heteroalkyl, and $-C(O)OC_{1-6}$ alkyl;

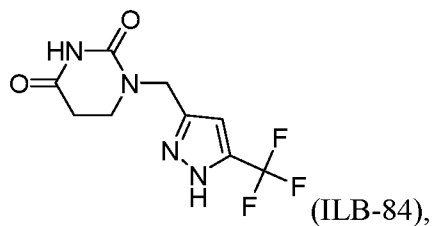
R^d is H or C_{1-4} alkyl; or R^c and R^d together with the nitrogen atom to which they are attached form a heterocyclyl substituted with 0–2 occurrences of $-O$ -heterocyclyl,

R^p is H or C_{1-6} alkyl;

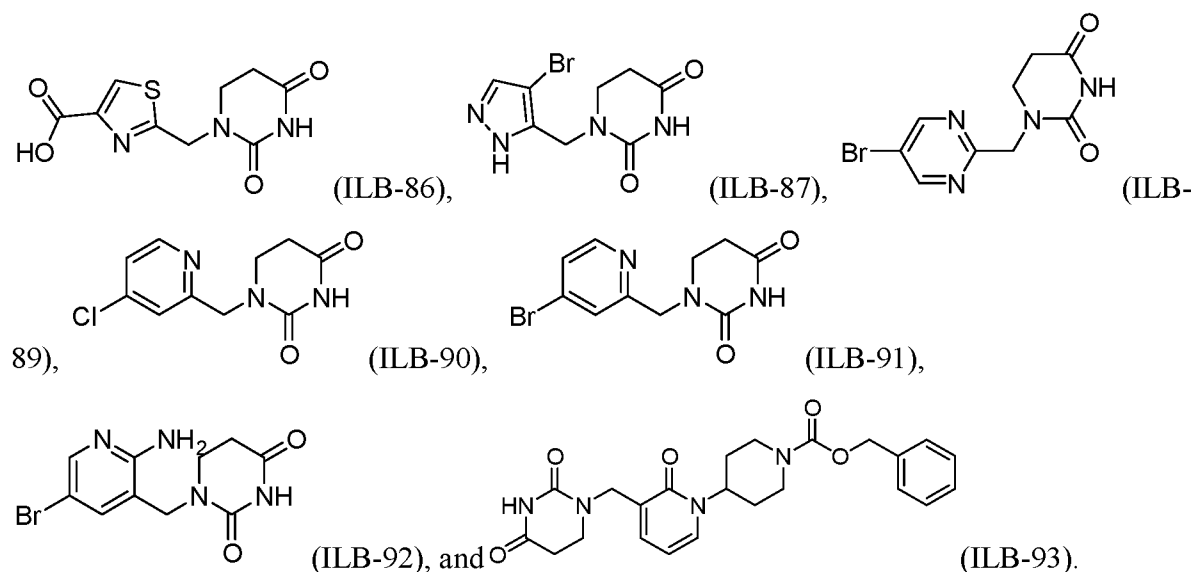
m is 1 or 2; and

n is 1 or 2.

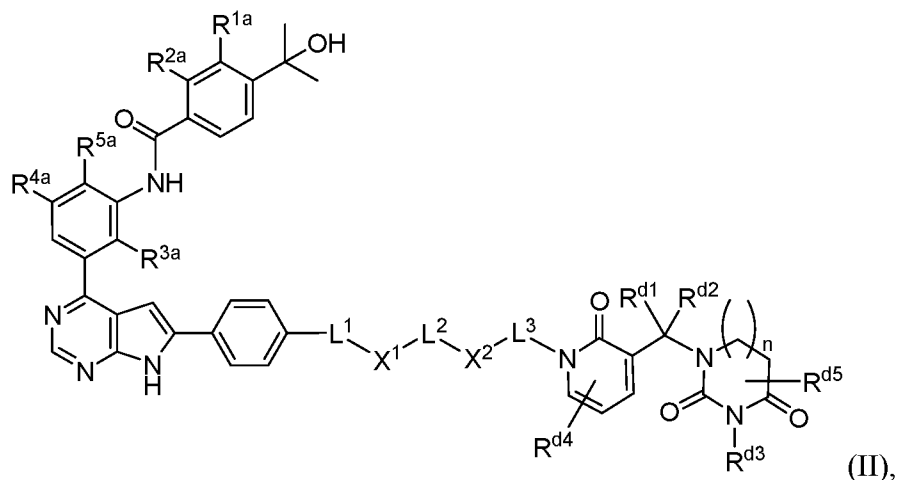
209. The compound of any one of the preceding claims, or a pharmaceutically acceptable salt,



hydrate, solvate, prodrug, stereoisomer, or tautomer thereof,



210. A bifunctional compound of Formula (II):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C_{1-6} alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

L^1 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-9} alkylene, C_{1-9} heteroalkylene, $*C(O)-C_{1-6}$ alkylene, $*C(O)-C_{1-6}$ heteroalkylene, $*C_{1-6}$ alkylene- $C(O)$, and $*C_{1-6}$ heteroalkylene- $C(O)$, wherein $*$ denotes the point of attachment of L^1 to the Targeting Ligand;

X^1 and X^2 are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L^2 is selected from the group consisting of a bond, $-O-$, $-NR'-$, $-C(O)-$, C_{1-6} alkylene, C_{1-6} heteroalkylene, and $*C(O)NR'-C_{1-6}$ alkylene, wherein $*$ denotes the point of attachment of L^2 to X^2 ; or

$X^1-L^2-X^2$ form a spiroheterocyclyl;

L^3 is selected from the group consisting of a bond, C_{1-6} alkylene, C_{2-6} alkenylene, C_{2-6} alkynylene, C_{1-6} heteroalkylene, $-C(O)-$, $-S(O)_2-$, $-O-$, $*C(O)-C_{1-9}$ alkylene, and $*C(O)-C_{1-9}$ heteroalkylene, wherein $*$ denotes the point of attachment of L^3 to X^2 in Formula (BF-III);

wherein no more than 2 of L^1 , X^1 , X^2 , L^2 , and L^3 can simultaneously be a bond;

R' is hydrogen or C_{1-6} alkyl;

R^{d1} and R^{d2} are each independently selected from the group consisting of H, C₁₋₆ alkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

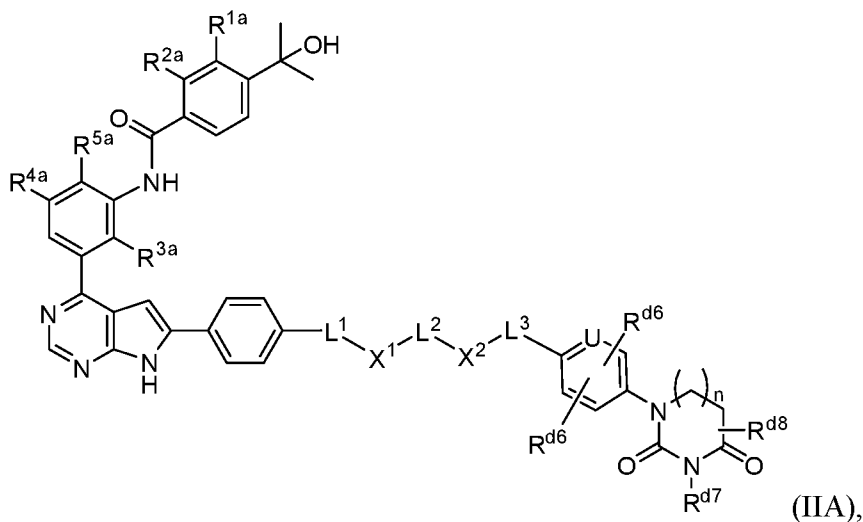
R^{d3} is selected from the group consisting of H, $-\text{CH}_2\text{OC}(\text{O})\text{R}^p$, $-\text{CH}_2\text{OP}(\text{O})\text{OHOR}^p$, $-\text{CH}_2\text{OP}(\text{O})(\text{R}^p)_2$, and $-\text{CH}_2\text{OP}(\text{O})(\text{OR}^p)_2$;

R^{d4} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ alkoxy, C₁₋₆ alkoxyalkyl, and C₁₋₆ heteroalkyl;

R^{d5} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl; and

R^p is H or C₁₋₆ alkyl.

211. A bifunctional compound of Formula (IIA):



or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

R^{1a} is H or halo;

R^{2a} is halo;

R^{3a} is C₁₋₆ alkyl;

R^{4a} is halo;

R^{5a} is H or halo;

L^1 is selected from the group consisting of a bond, $-\text{O}-$, $-\text{NR}'-$, $-\text{C}(\text{O})-$, C₁₋₉ alkylene, C₁₋₉ heteroalkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ alkylene, $^*\text{C}(\text{O})-\text{C}_{1-6}$ heteroalkylene, $^*\text{C}_{1-6}$ alkylene- $\text{C}(\text{O})$, and

*C₁₋₆ heteroalkylene-C(O), wherein * denotes the point of attachment of L¹ to the Targeting Ligand;

X¹ and X² are each independently selected from the group consisting of a bond, carbocyclyl, heterocyclyl, and heteroaryl;

L² is selected from the group consisting of a bond, -O-, -NR'-, -C(O)-, C₁₋₆ alkylene, C₁₋₆ heteroalkylene, and *C(O)NR'-C₁₋₆ alkylene, wherein * denotes the point of attachment of L² to X²; or

X¹-L²-X² form a spiroheterocyclyl;

L³ is selected from the group consisting of a bond, C₁₋₆ alkylene, C₂₋₆ alkenylene, C₂₋₆ alkynylene, C₁₋₆ heteroalkylene, -C(O)-, -S(O)₂-, -O-, *C(O)-C₁₋₉ alkylene, and *C(O)-C₁₋₉ heteroalkylene, wherein * denotes the point of attachment of L³ to X² in Formula (BF-III);

wherein no more than 2 of L¹, X¹, X², L², and L³ can simultaneously be a bond;

R' is hydrogen or C₁₋₆ alkyl;

U is -CR^{d6} or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

U is -CR^{d6} or N;

each R^{d6} is independently selected from the group consisting of H, oxo, C₁₋₆ alkyl, halogen, C₁₋₆ alkoxy, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^{d7} is selected from the group consisting of H, -CH₂OC(O)R^p, -CH₂OP(O)OHOR^p, -CH₂OP(O)(R^p)₂, and -CH₂OP(O)(OR^p)₂;

R^{d8} is selected from the group consisting of H, C₁₋₆ alkyl, halogen, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl;

R^p is H or C₁₋₆ alkyl; and

n is 1 or 2.

212. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{2a} is fluoro.

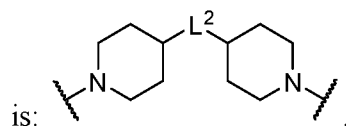
213. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{3a} is C_{1-3} alkyl.

214. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{3a} is methyl.

215. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{4a} is fluoro.

216. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^1 is C_{1-9} alkylene.

217. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein $-X^1-L^2-X^2-$

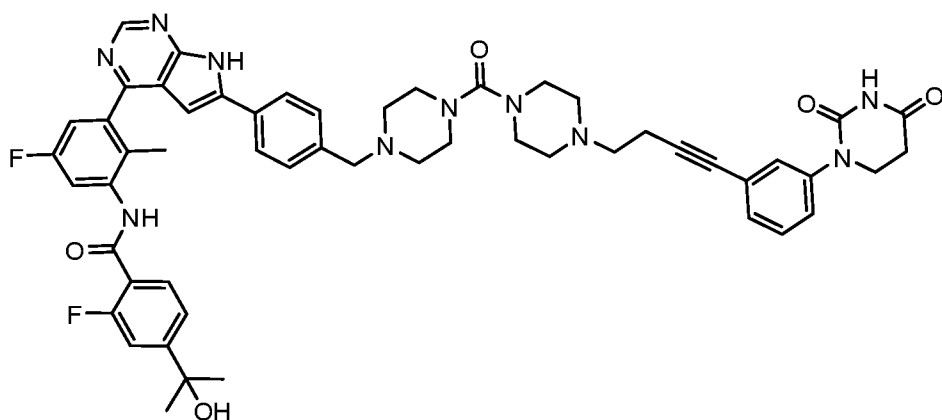


218. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^2 is $-C(O)-$, $-O-$, or C_{1-6} alkylene.

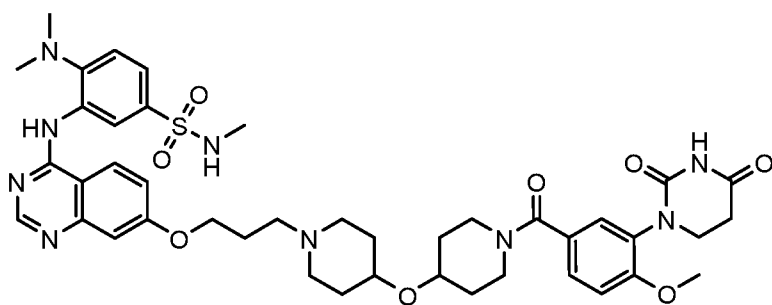
219. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L^3 is selected from the group consisting of a bond, $-O-$, $-C(O)-$, $-S(O)_2-$, C_{1-6} alkylene, C_{2-6} alkynylene, and C_{1-6} heteroalkylene.

220. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d4} is H.

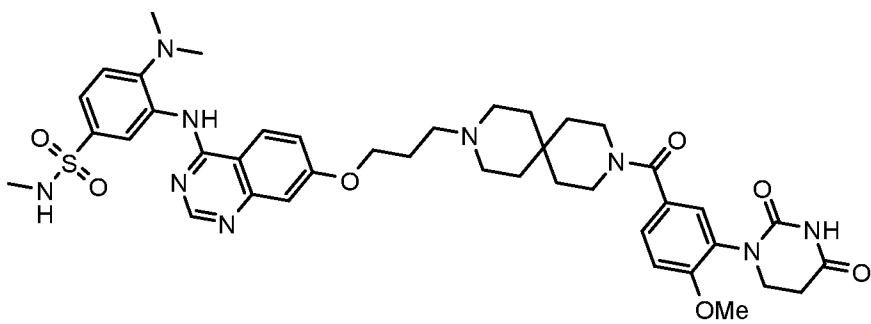
221. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} is H.
222. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d2} is H.
223. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d1} and R^{d2} are both H.
224. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein n is 1.
225. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d3} is H.
226. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d5} is H or C_{1-3} alkyl.
227. The bifunctional compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein R^{d5} is H.
228. A bifunctional compound, pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, selected from the group consisting of:



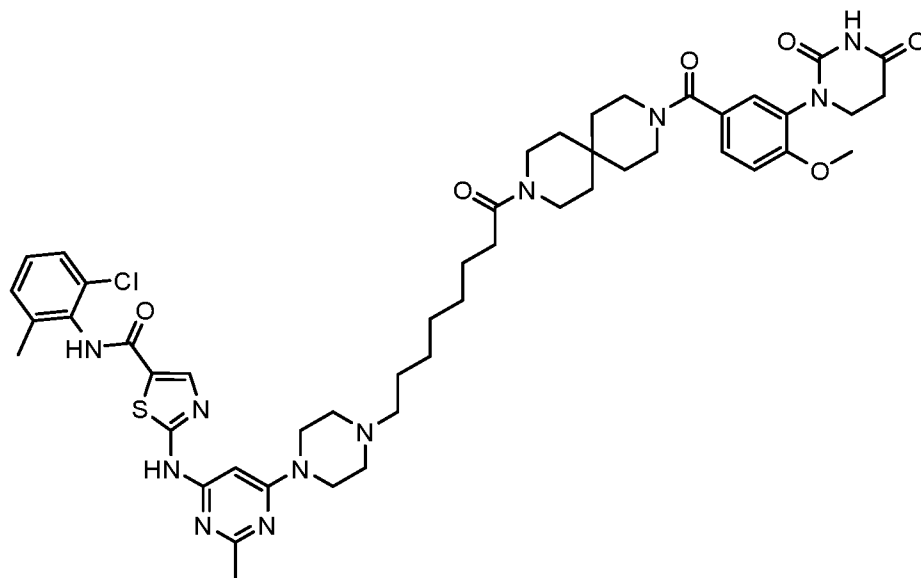
(Compound 03),



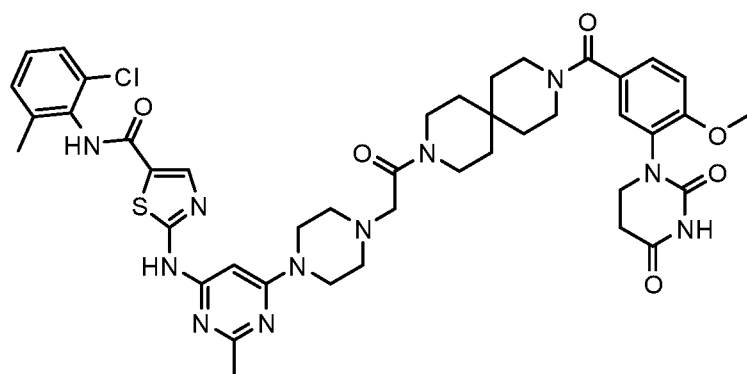
(Compound 04),



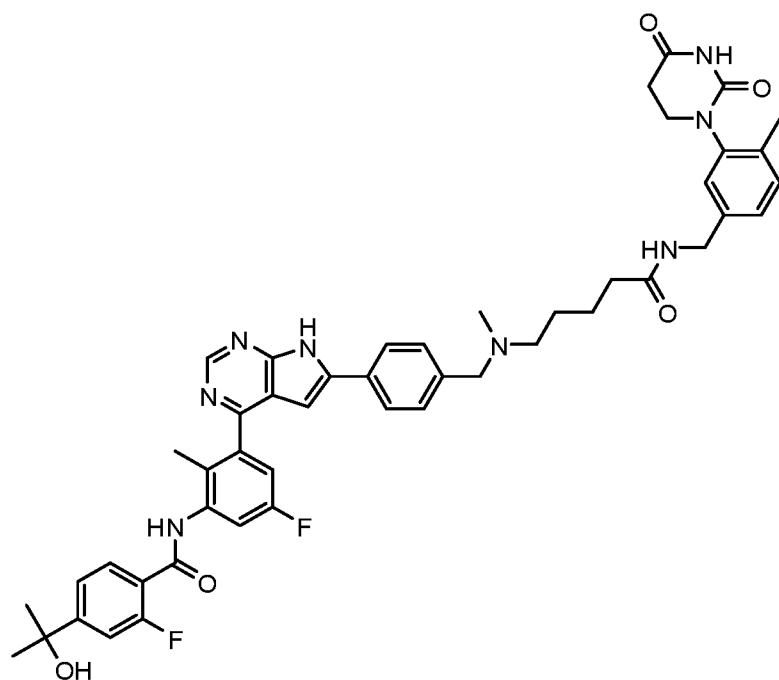
(Compound 05),



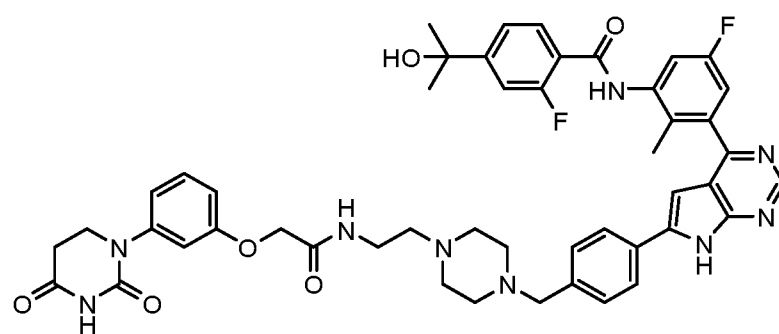
(Compound 06),



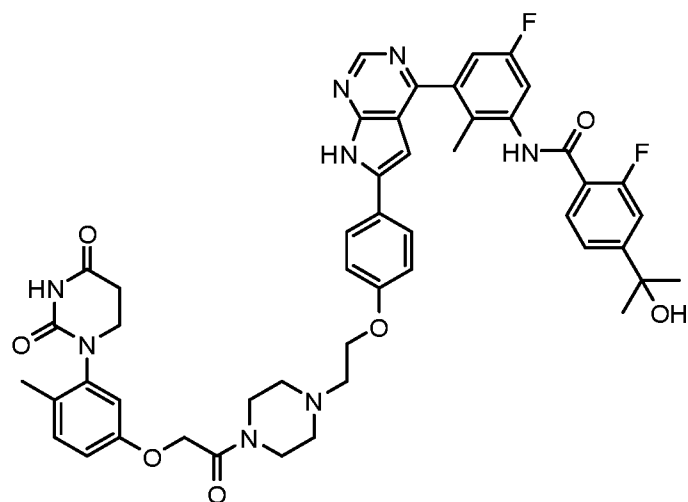
(Compound 07),



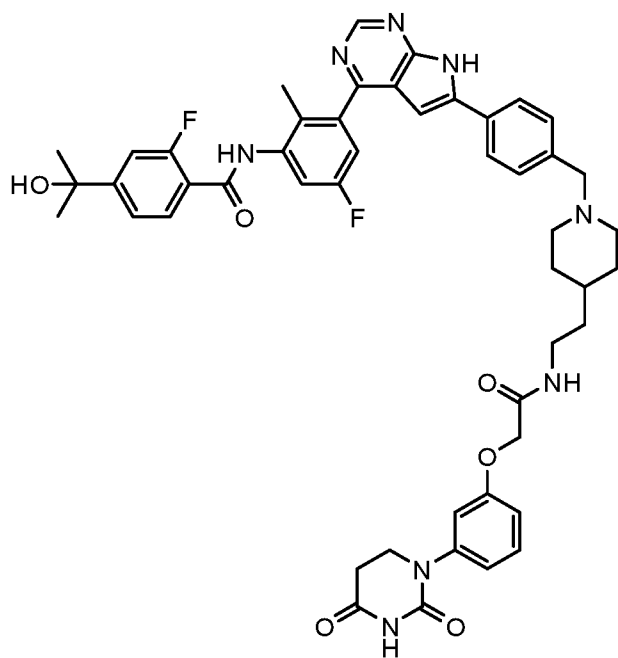
(Compound 08),



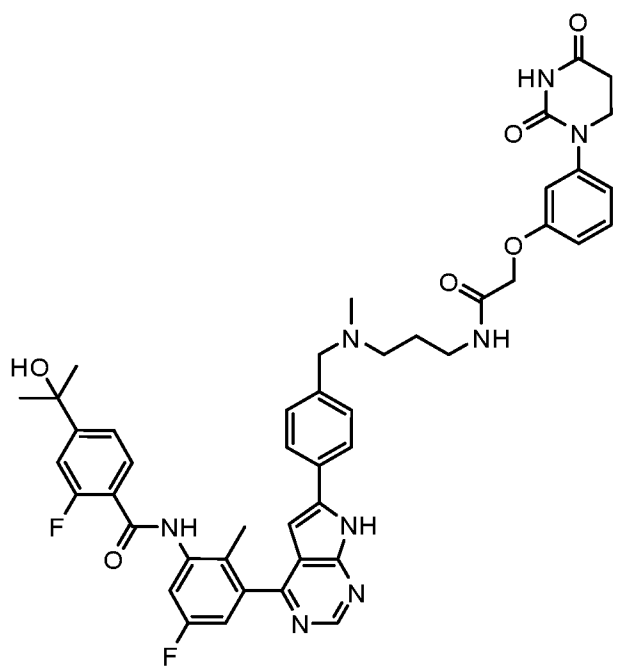
(Compound 09),



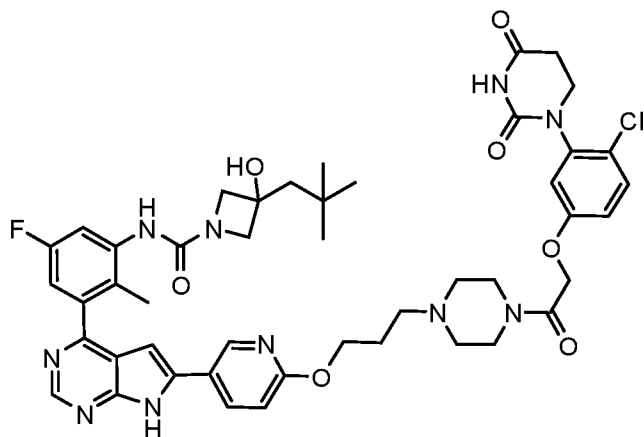
(Compound 10),



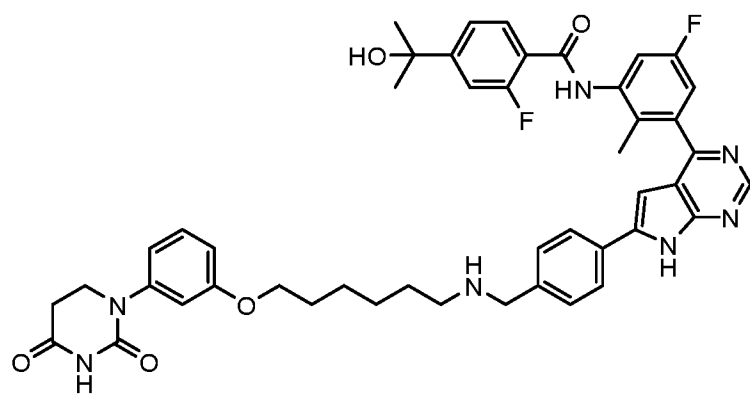
(Compound 11),



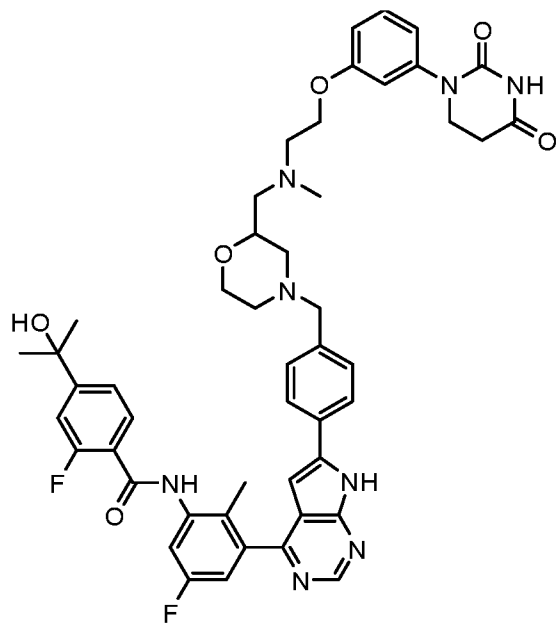
(Compound 12),



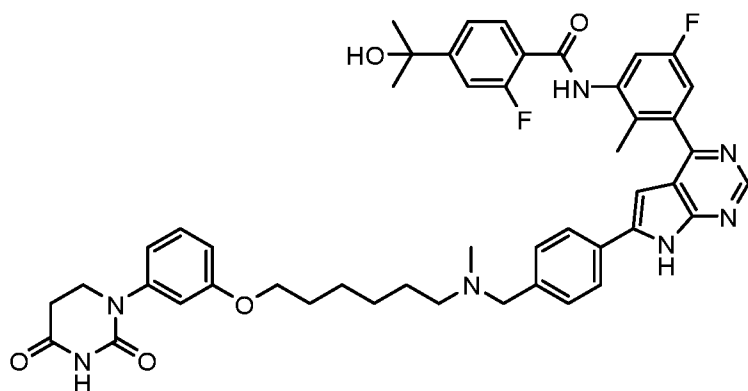
(Compound 13),



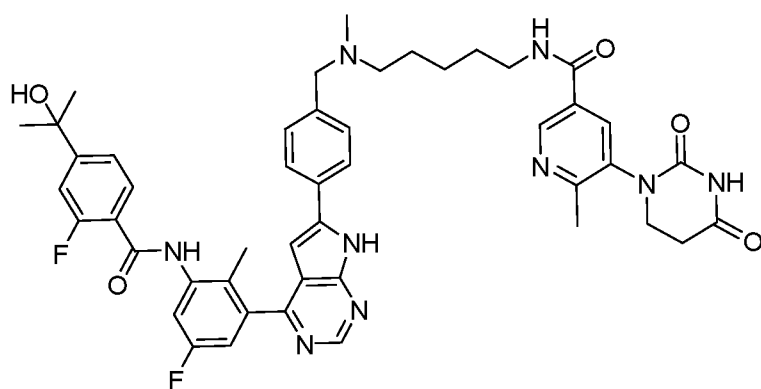
(Compound 14),



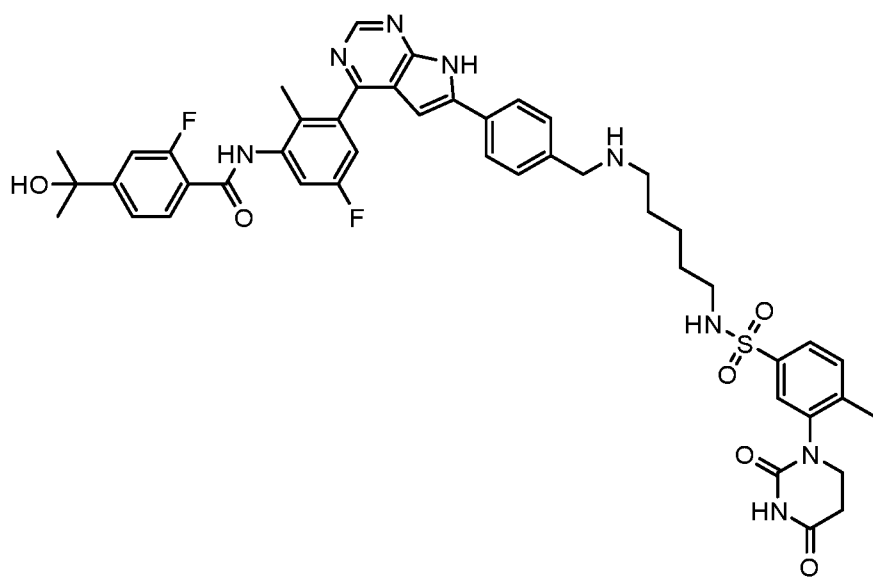
(Compound 15),



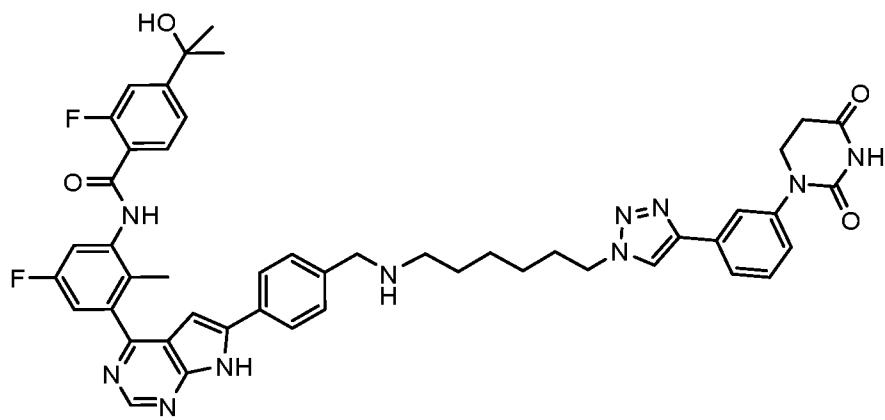
(Compound 16),



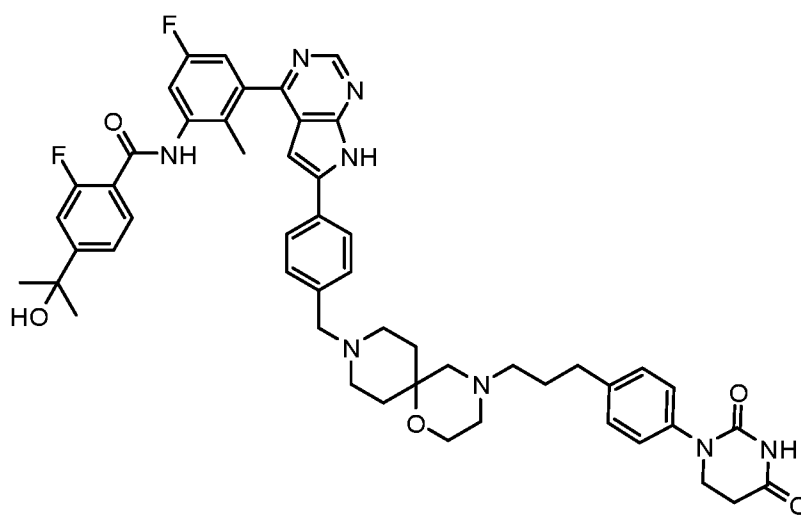
(Compound 17),



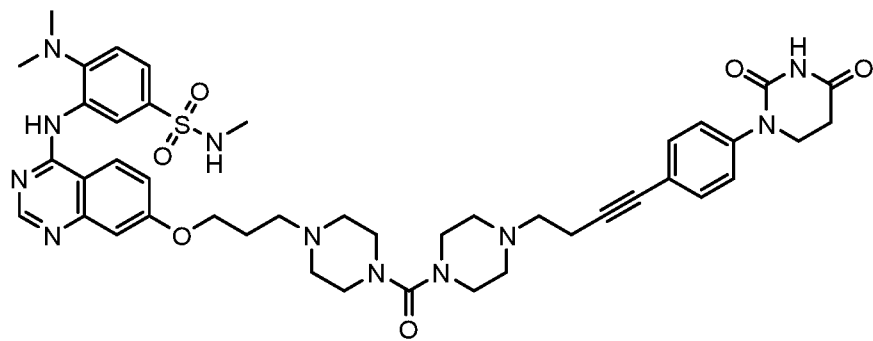
(Compound 18),



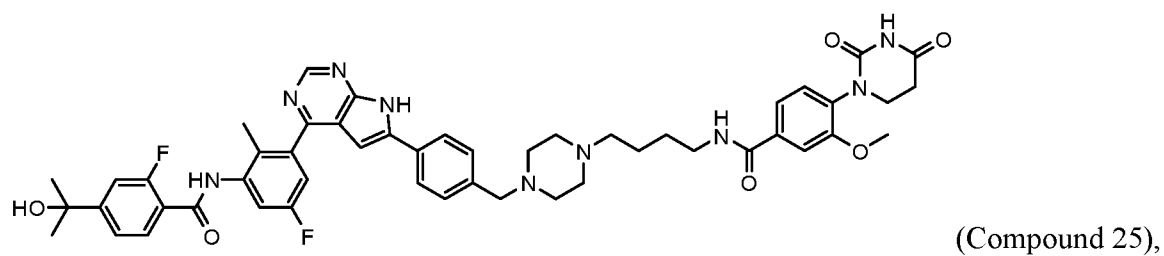
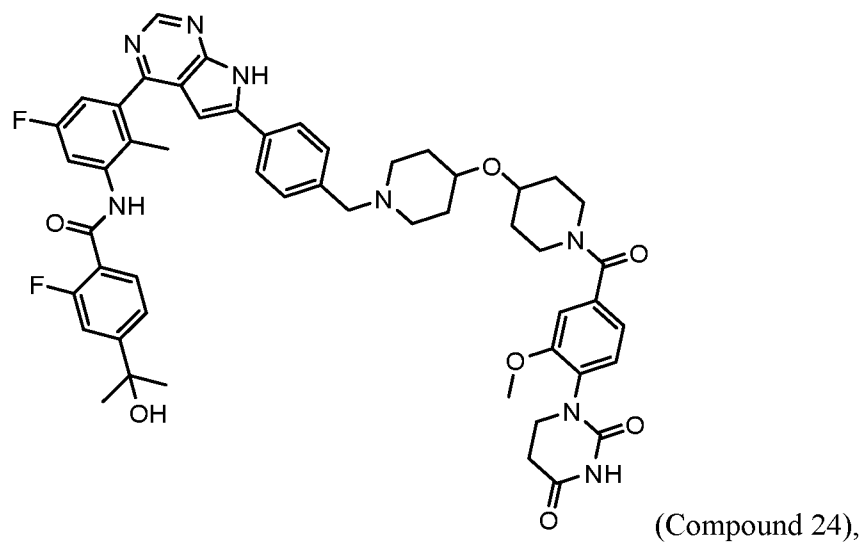
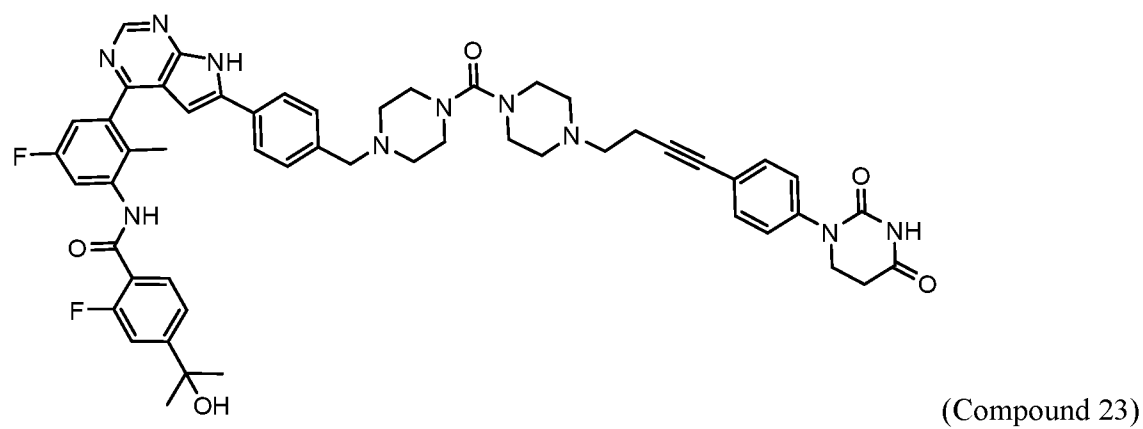
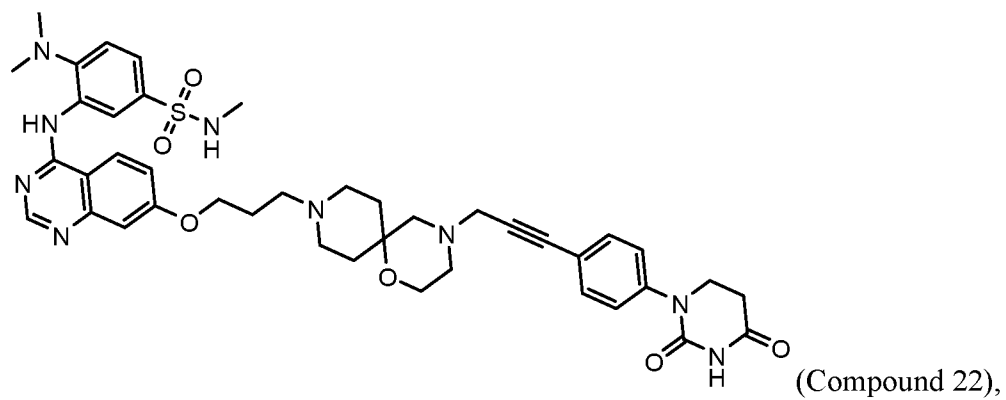
(Compound 19),

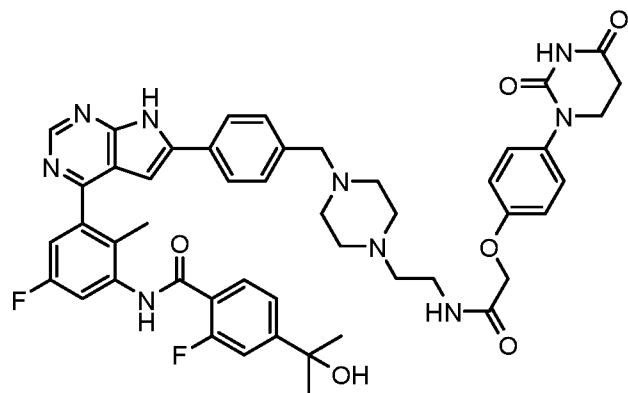


(Compound 20),

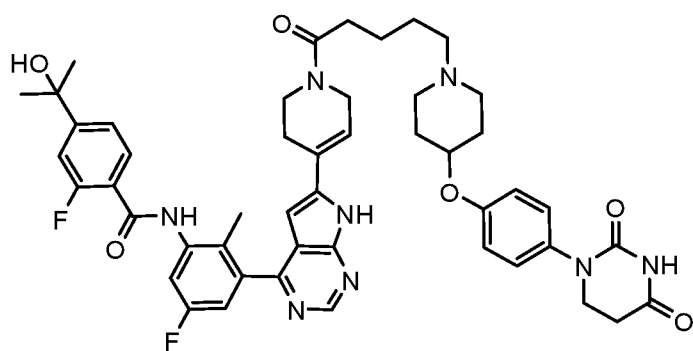


(Compound 21),

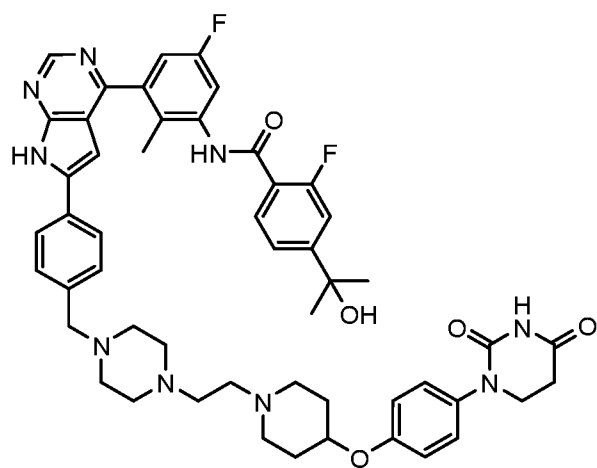




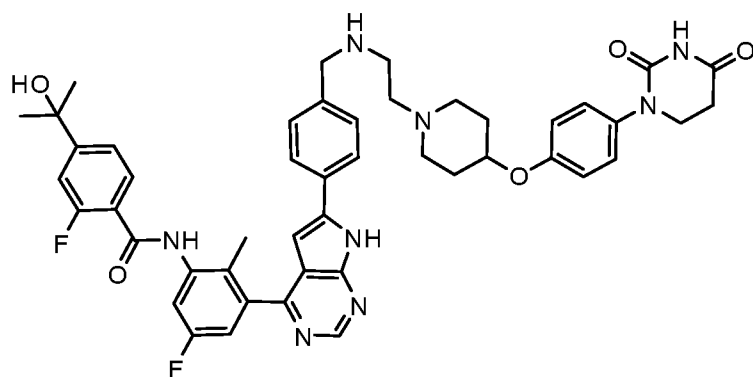
(Compound 26),



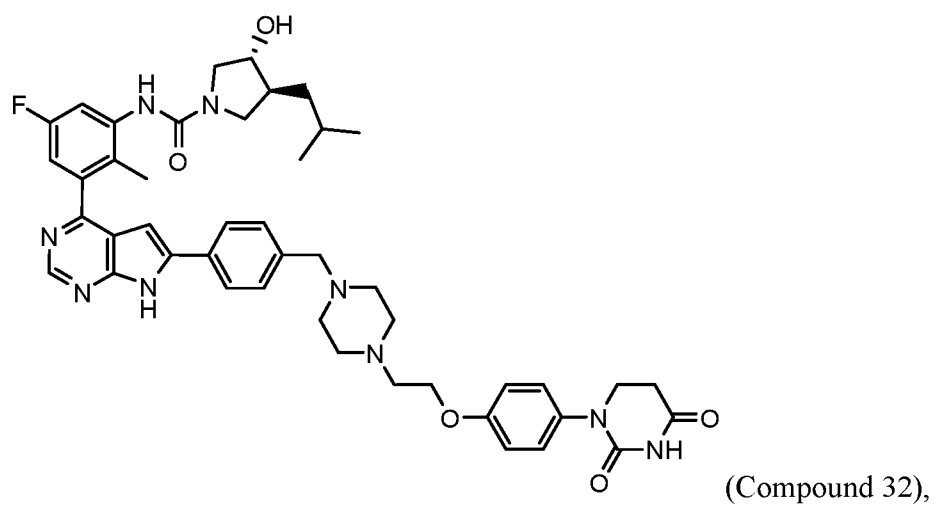
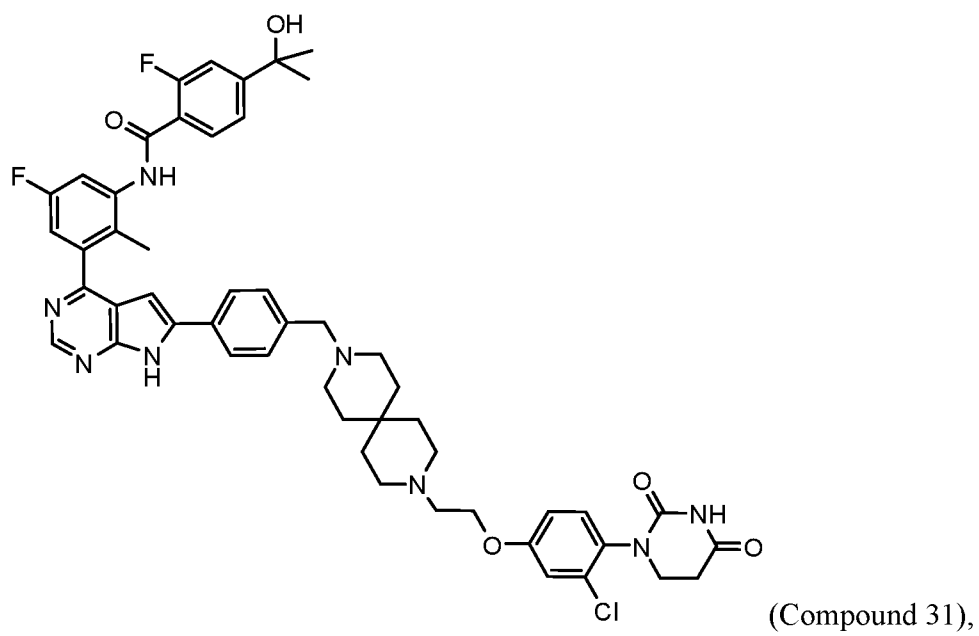
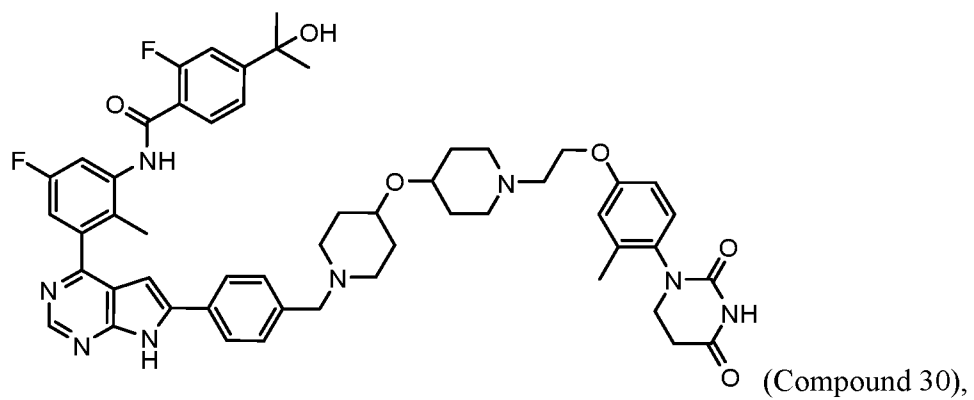
(Compound 27),

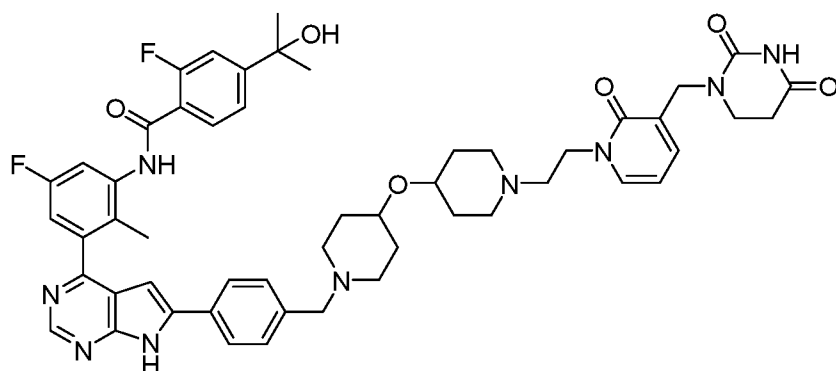


(Compound 28),

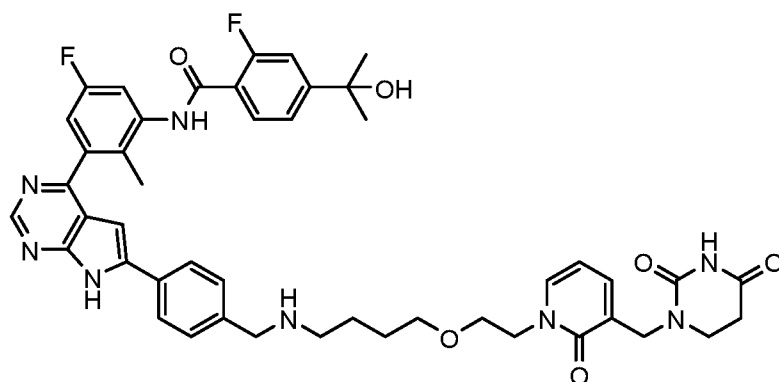


(Compound 29),

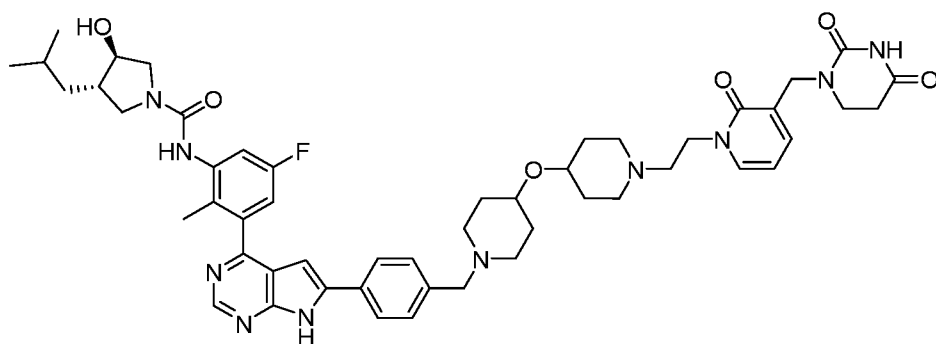




(Compound 33),



(Compound 34), and



(Compound 35).

229. A pharmaceutical composition comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a pharmaceutically acceptable carrier.

230. A pharmaceutical combination comprising a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, and a therapeutic agent.

231. A method of treating or preventing a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt thereof.
232. The method of any one of the preceding claims, wherein the disorder is a proliferative disorder.
233. The method of any one of the preceding claims, wherein the proliferative disorder is cancer.
234. Use of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof in the preparation of a medicament for treating a respiratory disorder, a proliferative disorder, an autoimmune disorder, an autoinflammatory disorder, an inflammatory disorder, a neurological disorder, and an infectious disease or disorder in a subject in need thereof.
235. Use of a compound of any one of the preceding claims, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof for treating cancer.

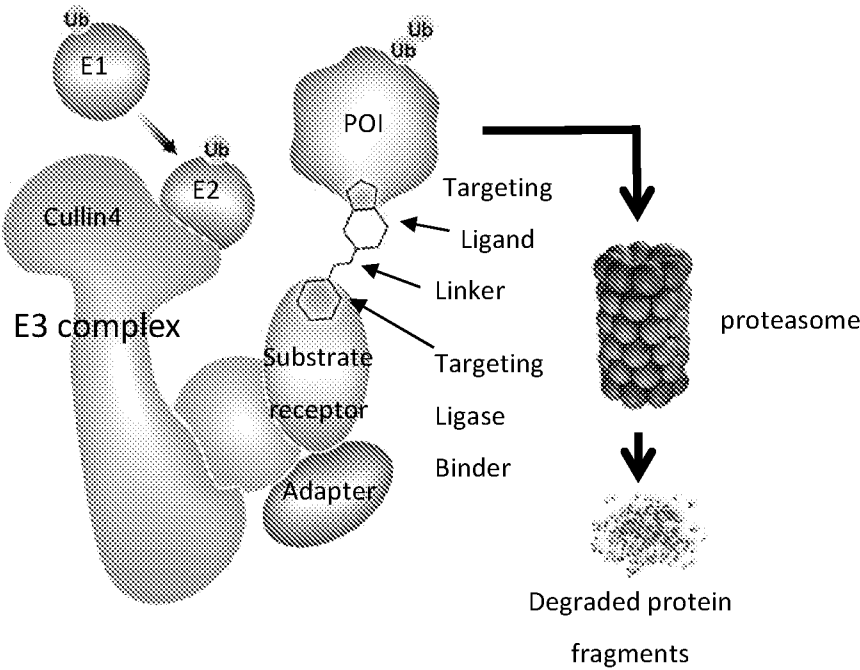


FIG. 1

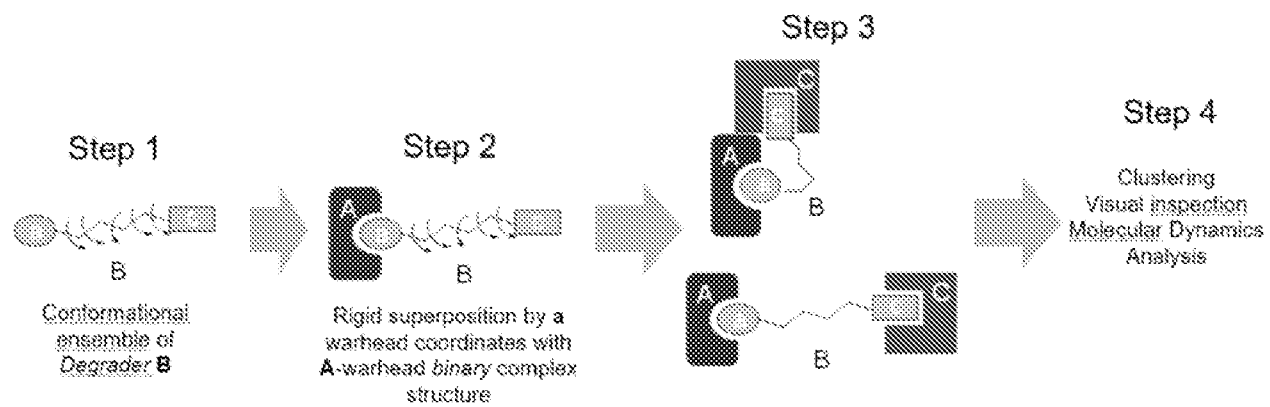
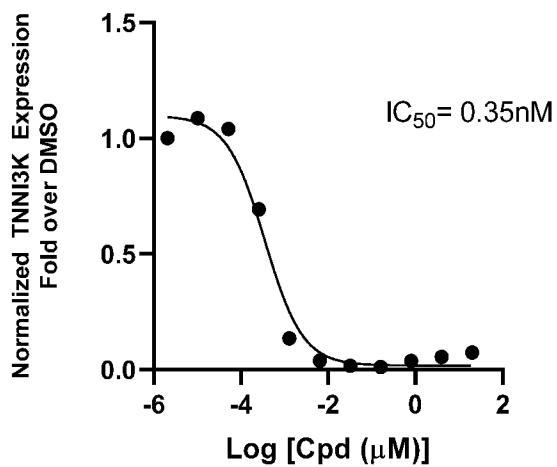
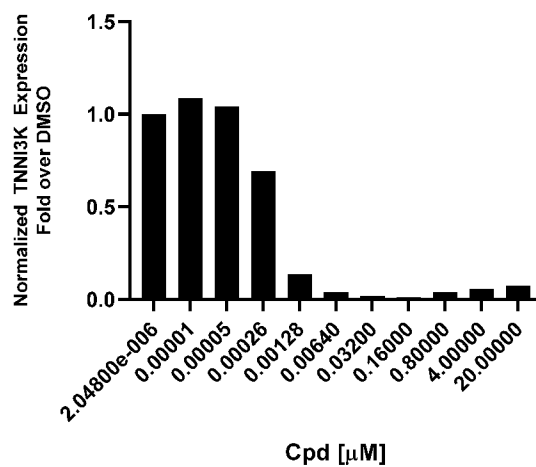


FIG. 2

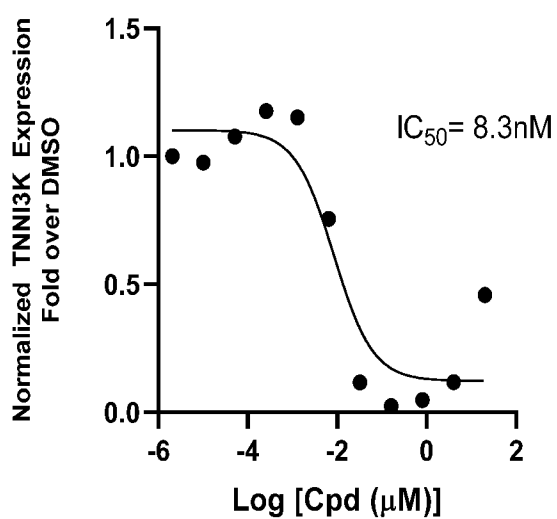
3A



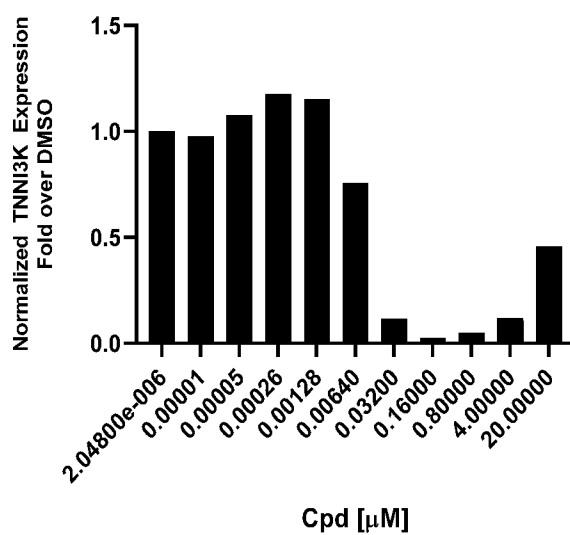
3B



3C



3D



FIGS. 3A-3D

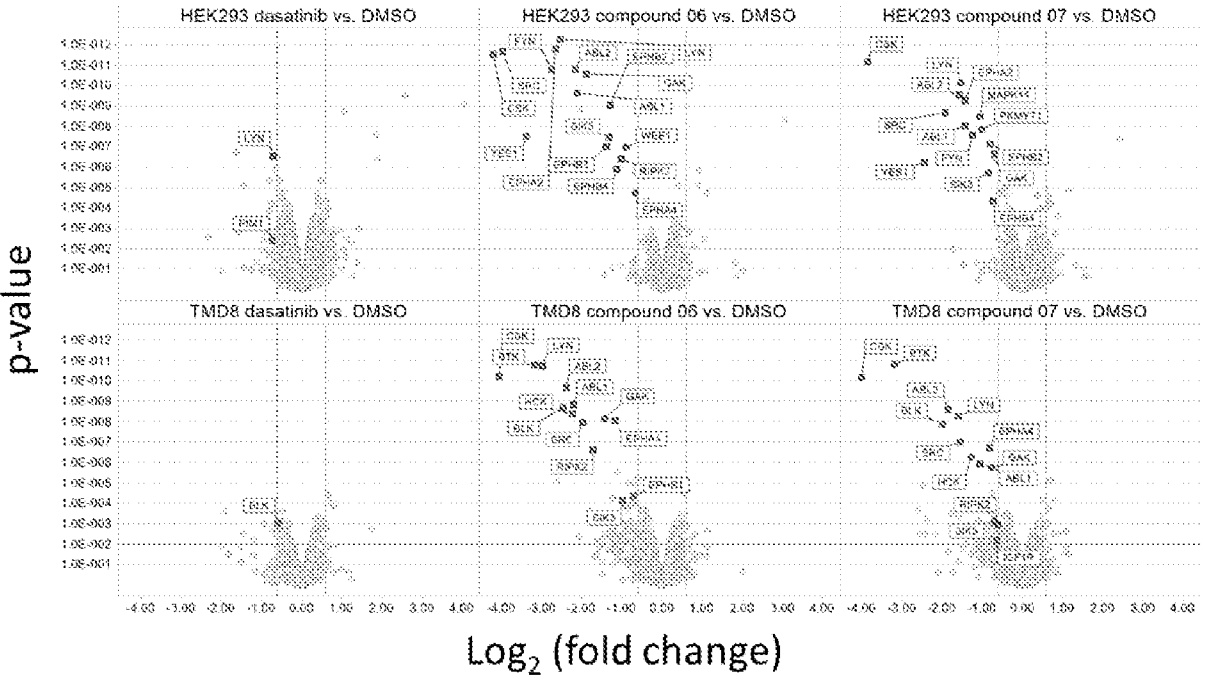
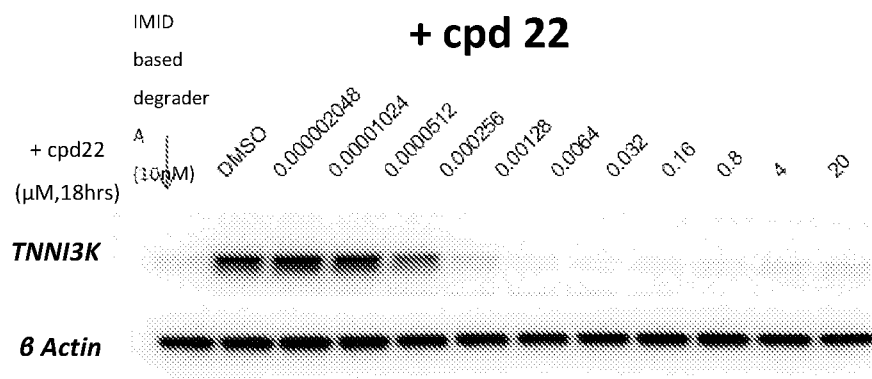
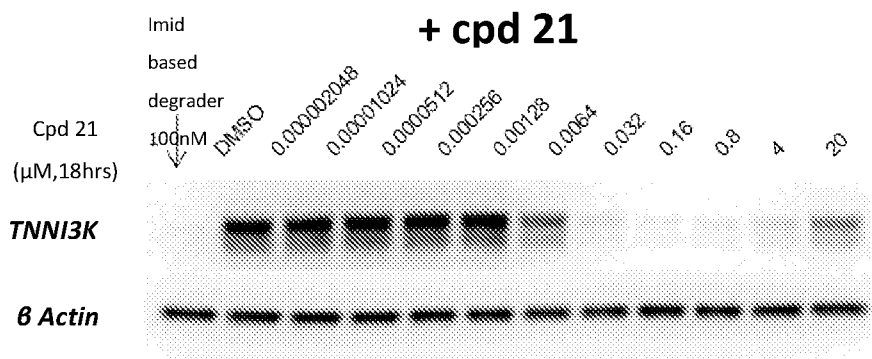


FIG. 3E

4A



4B



FIGs. 4A-4B

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A. CLASSIFICATION OF SUBJECT MATTER INV. A61P35/00 C07D239/22 C07D401/06 C07D401/12 C07D401/14 C07D471/10 C07D471/14 C07D487/14 A61K31/513 ADD. According to International Patent Classification (IPC) or to both national classification and IPC																	
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61P C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, WPI Data																	
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category*</th> <th style="width: 70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">X</td> <td>WO 2017/185023 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,14,15 -----</td> <td style="text-align: center;">1,65,66, 76</td> </tr> <tr> <td style="text-align: center;">X</td> <td>WO 2017/185034 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,23, 24 -----</td> <td style="text-align: center;">1,65,66, 76</td> </tr> <tr> <td style="text-align: center;">X</td> <td>WO 2017/185031 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,18,19 -----</td> <td style="text-align: center;">1,65,66, 76</td> </tr> <tr> <td style="text-align: center;">X</td> <td>US 2018/099940 A1 (CREW ANDREW P [US] ET AL) 12 April 2018 (2018-04-12) claims 1,18 ----- -/-</td> <td style="text-align: center;">1,65-70</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 2017/185023 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,14,15 -----	1,65,66, 76	X	WO 2017/185034 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,23, 24 -----	1,65,66, 76	X	WO 2017/185031 A1 (DANA-FARBER CANCER INST INC [US]) 26 October 2017 (2017-10-26) claims 1,18,19 -----	1,65,66, 76	X	US 2018/099940 A1 (CREW ANDREW P [US] ET AL) 12 April 2018 (2018-04-12) claims 1,18 ----- -/-	1,65-70
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.																	
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family																	
Date of the actual completion of the international search 5 November 2020		Date of mailing of the international search report 23/11/2020															
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schuemacher, Anne															

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