DEUBIQUITINASE-TARGETING CHIMERAS AND RELATED METHODS

RELATED APPLICATIONS

This application claims the benefit of and priority to U.S. Provisional Application No. 63/311,781, filed February 18, 2022; U.S. Provisional Application No. 63/273,118, filed October 28, 2021; U.S. Provisional Application No. 63/186, 739, filed May 10, 2021; and U.S. Provisional Application No. 63/181,796, filed on April 29, 2021. The entire contents of each of the foregoing applications is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

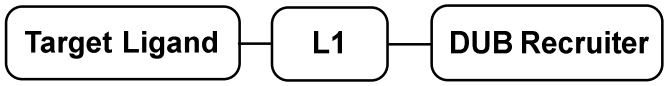
Described herein are bifunctional compounds that bind to both a target protein and a deubiquitinase, as well as related compositions and methods of use, e.g., for stabilization of the target protein and/or the treatment of a disease, disorder, or condition.

BACKGROUND

The Ubiquitin-Proteasome Pathway (UPP) is a critical process that plays a role in a variety of cellular functions, including protein degradation, quality control, trafficking, and signaling. Ubiquitin and other ubiquitin-like proteins (collectively, "Ubls") are covalently attached to specific protein substrates, which depending on the specific modification, either ultimately targets these proteins for degradation by the proteasome or affects protein function in other ways. These Ubls, however, may be removed through the action of deubiquitinases (DUBs), which hydrolyze the Ubl from a target protein. Removal of a Ubl from a ubiquitinated target protein can modulate the function of the target protein in a number of ways, including improving stability and preventing proteasomal degradation. As degradation of certain cellular proteins has been linked to disease progression, there is a need for new tools to stabilize certain proteins and slow or inhibit their degradation.

SUMMARY

In one aspect, there is provided a bifunctional compound of Formula (I):



(I),

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

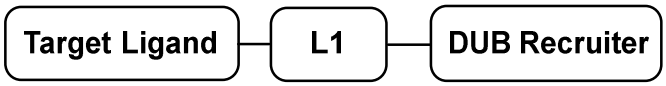
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a pharmaceutical composition comprising a bifunctional compound, or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, and one or more pharmaceutically acceptable carriers.

In another aspect, there is provided a composition for use in providing a compound to a subject, wherein the composition comprises a bifunctional compound of Formula (I):



(I),

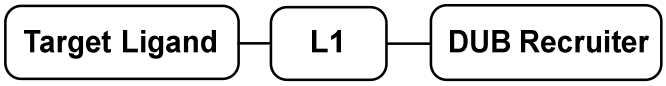
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a use of a composition in the manufacture of a medicament for treating a disease, disorder, or condition in a subject, the composition comprising a bifunctional compound of Formula (I):



(I),

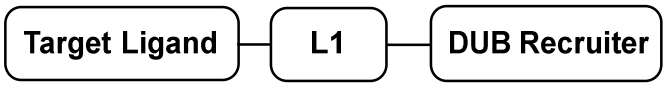
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a use of a composition in the manufacture of a medicament for treating cystic fibrosis in a subject, the composition comprising a bifunctional compound of Formula (I):



(I),

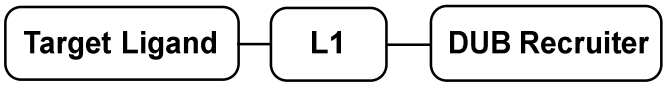
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a composition for use in modulating a protein in a cell or subject comprising a bifunctional compound of Formula (I):



(I),

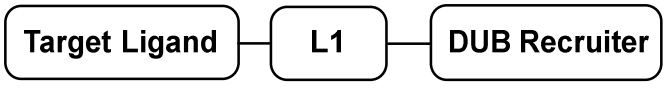
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a composition for use in recruiting a deubiquitinase to a target protein in a cell or subject, wherein the composition comprises a bifunctional compound of Formula (I):



(I),

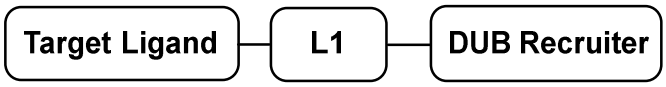
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a composition for use in deubiquitinating a protein comprising a bifunctional compound of Formula (I):



(I),

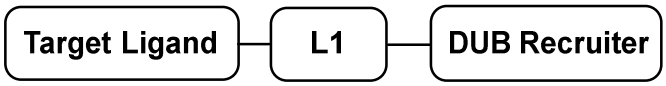
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a use of a compound comprising a bifunctional compound of Formula (I):



(I),

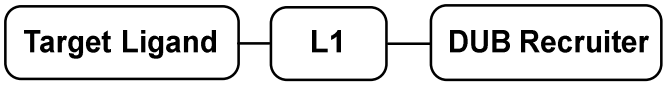
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for providing the compound to a subject, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a use of a bifunctional compound of Formula (I):



(I),

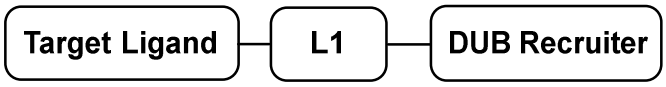
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease, disorder, or condition in a subject wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

In another aspect, there is provided a use of a bifunctional compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject wherein:

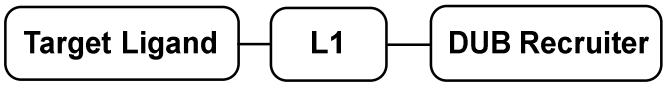
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby treating cystic fibrosis.

In another aspect, there is provided a method of modulating a protein in a cell or subject comprising contacting the cell or administering to the subject a bifunctional compound of Formula (I):



(I),

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

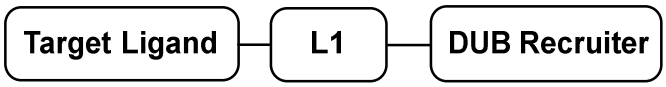
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby modulating a protein in a cell or subject.

In another aspect, there is provided a method of recruiting a deubiquitinase to a target protein comprising contacting a mixture (e.g., in a cell or sample) with a bifunctional compound of Formula (I):



(I),

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

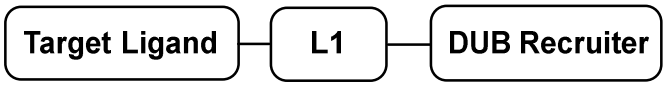
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby recruiting a deubiquitinase to a target protein in a mixture, e.g., a cell or subject.

In another aspect, there is provided a method of deubiquitinating a protein comprising contacting a cell or sample with a bifunctional compound of Formula (I):



(I),

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

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

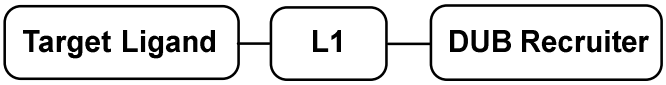
(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby deubiquitinating a protein in a cell or subject.

BRIEF DESCRIPTION OF DRAWINGS

CLAIMS

1. A bifunctional compound of Formula (I):



(I),

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

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

2. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 1, wherein the target protein is selected from the group consisting of enzyme, receptor, membrane channel, and a hormone, or a fragment thereof.

3. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is a soluble protein or a membrane protein.

4. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is mutated or misfolded.

5. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is glycosylated.

6. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is ubiquitinated (e.g., polyubiquitinated).

7. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is a tumor suppressor.

8. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is selected from the group consisting of a tumor suppressor, a membrane channel, a kinase, a transcription factor, an ion channel, an apoptotic factor, an oncogenic protein, and an epigenetic regulator.

9. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein is selected from the group consisting of TP53, CDKN1A, CDN1C, BAX, glucokinase, the cystic fibrosis transmembrane conductance regulator (CFTR), WEE1, or a mutant or fragment thereof.

10. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein comprises the cystic fibrosis transmembrane conductance regulator (CFTR) or a mutant or fragment thereof.

11. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the target protein comprises ΔF508-CFTR.

12. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 1-10 wherein the target protein comprises the tumor suppressor kinase WEE1 or a mutant or fragment thereof.

13. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the deubiquitinase is capable of cleaving a lysine-linked polyubiquitin chain.

14. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 12, wherein the lysine-linked polyubiquitin chain comprises a K43-linked polyubiquitin chain.

15. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the deubiquitinase is a cysteine protease or a metalloprotease.

16. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the deubiquitinase is a cysteine protease.

17. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound binds to a site other than a catalytic site within the deubiquitinase.

18. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound binds to an allosteric site within the deubiquitinase.

19. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound binds to a cysteine amino acid residue within the deubiquitinase.

20. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 19, wherein the cysteine amino acid residue is an allosteric cysteine amino acid residue.

21. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound preferentially binds to an allosteric amino acid residue (e.g., an allosteric amino acid residue) over a catalytic amino acid residue (e.g., a catalytic cysteine amino acid residue).

22. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound does not substantially bind to a cysteine amino acid residue in the catalytic site of the deubiquitinase (e.g., a catalytic cysteine).

23. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to according to any one of the preceding claims, wherein the deubiquitinase is selected from Table 1.

24. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to according to any one of the preceding claims, wherein the deubiquitinase is selected from WDR48, YOD1, OYUD3, OTUB1, OTUD5, USP8, USP5, USP15, USP16, UCHL3, UCHL1, and USP14.

25. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to according to any one of the preceding claims, wherein the deubiquitinase comprises OTUB1.

26. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 24, wherein the bifunctional compound binds to cysteine 23 (C23) within the OTUB1 sequence.

27. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 25-26, wherein the bifunctional

compound binds preferentially to cysteine 23 (C23) over cysteine 91 (C91) within the OTUB1 sequence.

28. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 25-27, wherein the bifunctional compound does not substantially bind to cysteine 91 (C91) within the OTUB1 sequence.

29. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 1-24, wherein the deubiquitinase comprises OTUD5.

30. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 29, wherein the bifunctional compound binds to cysteine 434 (C434) within the OTUD5 sequence.

31. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 28-30, wherein the bifunctional compound binds preferentially to cysteine 434 (C434) over cysteine 244 (C244) within the OTUD5 sequence.

32. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 28-31, wherein the bifunctional compound does not substantially bind to cysteine 244 (C244) within the OTUD5 sequence.

33. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 1-24, wherein the deubiquitinase comprises USP15.

34. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 33, wherein the bifunctional compound binds to cysteine 264 (C264) within the USP15 sequence.

35. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 33-34, wherein the bifunctional compound binds preferentially to cysteine 264 (C264) over cysteine 298 (C298) within the USP15 sequence.

36. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 33-35, wherein the bifunctional compound does not substantially bind to cysteine 298 (C298) within the USP15 sequence.

37. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the Target Ligand binds to (e.g., covalently binds to) the target protein.

38. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the Target Ligand is capable of modulating the target protein.

39. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 38, wherein the modulating comprises one or more of:

(i) modulating the folding of the target protein;
(ii) modulating the half-life of the target protein;
(iii) modulating trafficking of the target protein to the proteasome;
(iv) modulating the level of ubiquitination of the target protein;
(v) modulating degradation (e.g., proteasomal degradation) of the target protein;
(vi) modulating target protein signaling;
(vii) modulating target protein localization;
(viii) modulating trafficking of the target protein to the lysozome; and
(ix) modulating target protein interactions with other proteins.

40. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising (i).

41. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising (ii).

42. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising (iii).

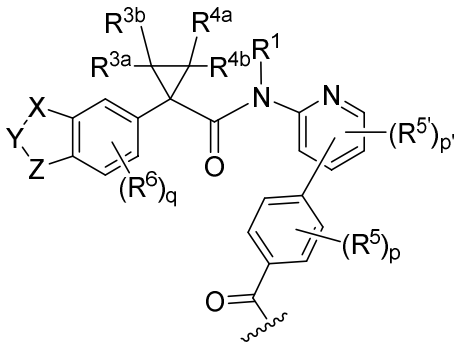
43. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising (iv).

44. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising (v).

45. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 39, comprising each of (i)-(v).

46. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the Target Ligand is a chemical chaperone.

47. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the Target Ligand has the structure of Formula (I-a):



(I-a)

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

X and Z are each independently O, S, or $C(R^{7a})(R^{7b})$;

Y is $C(R^{7a})(R^{7b})$ or NR^{7c};

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

R^{3a}, R^{3b}, R^{4a}, R^{4b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$;

each R^5, $R^{5'}$, and R^6 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^{7c} is H or C_{1-6} alkyl;

R^A, R^B, R^C, and R^D are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

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

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

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

 denotes the point of attachment to L1 in Formula (I).

48. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 47, wherein each of X and Z is independently O.

49. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 47-48, wherein Y is $C(R^{7a})(R^{7b})$.

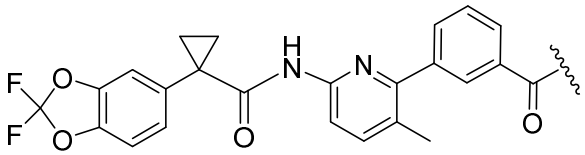
50. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 47-49, wherein each of R^{7a} and R^{7b} is independently halo (e.g., fluoro).

51. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 47-50, wherein each of R^{3a}, R^{3b}, R^{4a}, R^{4b} is independently H.

52. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 47-51, wherein R^1 is H.

53. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 47-52, wherein each of p and q is 0.

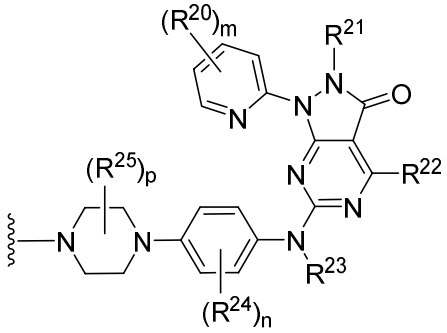
54. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the Target Ligand has the structure of Formula (I-f):



(I-f)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein  denotes the point of attachment to L1 in Formula (I).

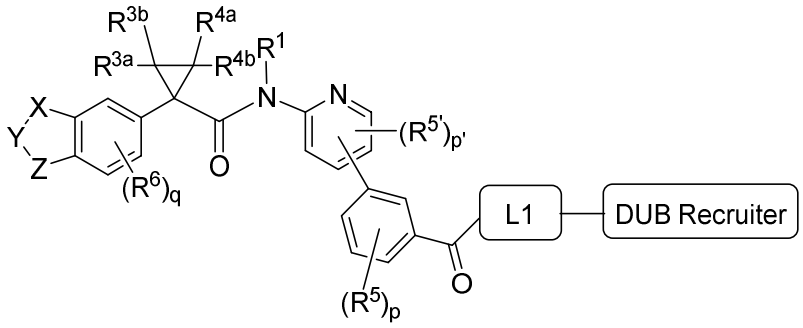
55. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure of Formula (I-h):



(I-h)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein each R^{20}, R^{24}, and R^{25} is independently $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$; R^{21} and R^{23} are each independently H or $C_{1–6}$ alkyl; R^{22} is $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$; R^A, R^B, R^C, and R^D are each independently H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; m and n are each independently 0, 1, 2, 3, or 4; p is 0, 1, 2, 3, 4, 5, 6, 7, or 8; and ⊢ denotes the point of attachment to L1 in Formula (I).

56. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-a):



(II-a)

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

X and Z are each independently O, S, or $C(R^{7a})(R^{7b})$;

Y is $C(R^{7a})(R^{7b})$ or NR^{7c};

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

R^{3a}, R^{3b}, R^{4a}, R^{4b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$;

each R^5, $R^{5'}$, and R^6 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^{7c} is H or C_{1-6} alkyl;

R^A, R^B, R^C, and R^D are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

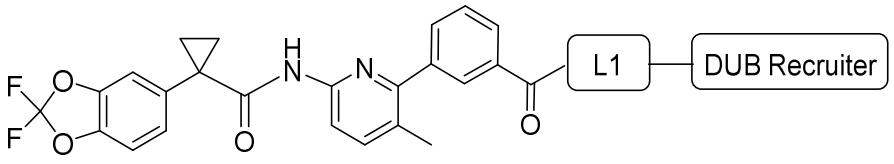
p is 0, 1, 2, 3, or 4;

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

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

L1 and DUB Recruiter are as defined in claim 1.

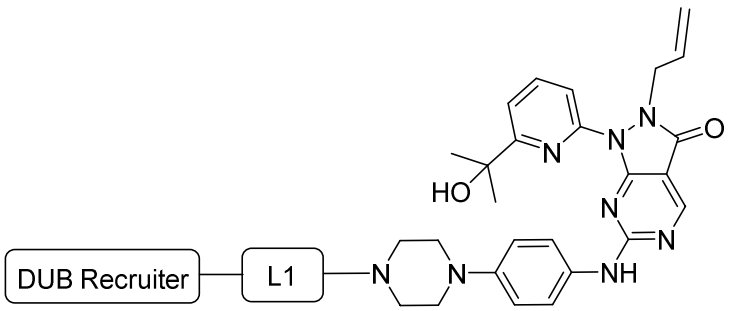
57. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-d):



(II-d)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L1 and DUB Recruiter are as defined in claim 1.

58. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-k):



(II-k)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein L1 and DUB Recruiter are as defined for Formula (I).

59. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter binds to (e.g., covalently binds to) the deubiquitinase.

60. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the binding of the DUB Recruiter to the deubiquitinase does not substantially inhibit the activity of the deubiquitinase.

61. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter binds to a site other than a catalytic site within the deubiquitinase.

62. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter binds to an allosteric site within the deubiquitinase.

63. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter binds to a cysteine amino acid residue within the deubiquitinase.

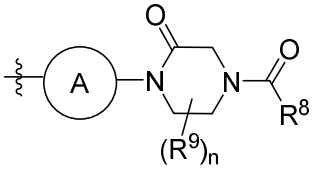
64. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter preferentially binds to an allosteric amino acid residue (e.g., an allosteric amino acid residue) over a catalytic amino acid residue (e.g., a catalytic cysteine amino acid residue).

65. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter does not substantially bind to a cysteine amino acid residue in the catalytic site of the deubiquitinase (e.g., a catalytic cysteine).

66. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter comprises an acrylamide moiety.

67. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter comprises a furan moiety.

68. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter has the structure of Formula (V-b):



(V-b)

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

Ring A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0-12 R^{10};

R^8 is H, $C_{1–6}$ alkyl, or an electrophilic moiety;

each R^9 is independently $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, or $-OR^A$;

each R^{10} is independently $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, or halo;

R^A is H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

n is 0, 1, 2, 3, 4, 5, or 6.

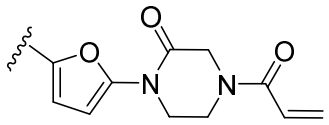
69. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 68, wherein Ring A is heteroaryl (e.g., a monocyclic heteroaryl).

70. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 68-69, wherein Ring A is a 5-membered heteroaryl (e.g., furanyl).

71. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according any one of claims 68-70, wherein R^8 is an electrophilic moiety.

72. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according any one of claims 68-71, wherein R^8 is $C_{2–6}$ alkenyl (e.g., $CH=CH_2$).

73. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the DUB Recruiter has the structure of Compound 100:



(100)

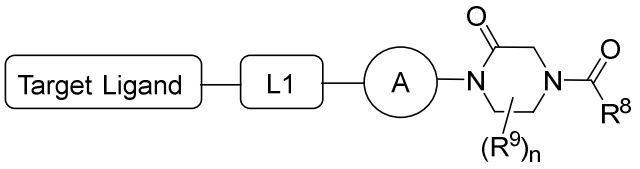
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein  denotes the point of attachment to L1 in Formula (I).

74. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 1-28 and 29-65, wherein the DUB Recruiter binds to cysteine 23 (C23) within the OTUB1 sequence.

75. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims1-28 and 29-66, wherein the DUB Recruiter binds preferentially to cysteine 23 (C23) over cysteine 91 (C91) within the OTUB1 sequence.

76. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims1-28 and 29-67, wherein the DUB Recruiter does not substantially bind to cysteine 91 (C91) within the OTUB1 sequence.

77. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-k):



(II-k)

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

Ring A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0-12 R^{10};

R^8 is H, $C_{1–6}$ alkyl, or an electrophilic moiety;

each R^9 is independently $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, or -OR^A;

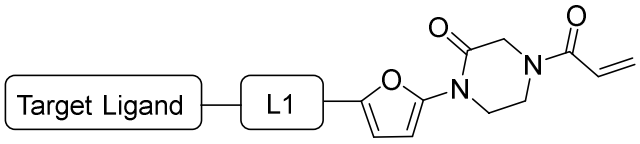
each R^{10} is independently $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, or halo;

R^A is H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

n is 0, 1, 2, 3, 4, 5, or 6;

wherein the Target Ligand and L1 are as defined in claim 1.

78. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-l):



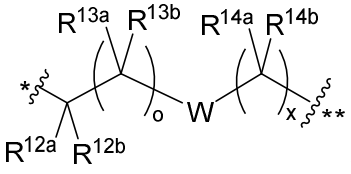
(II-l)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein the Target Ligand and L1 are as defined in claim 1.

79. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 is a non-cleavable linker.

80. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 comprises an alkylene or heteroalkylene.

81. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 has the structure of Formula (III-a):



(III-a)

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

R^{12a}, R^{12b}, R^{13a}, R^{13b}, R^{14a}, and R^{14b} are each independently H, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cyano, or -OR^A; or

each of R^{12a} and R^{12b}, R^{13a} and R^{13b}, and R^{14a} and R^{14b} independently may be taken together with the carbon atom to which they are attached to form an oxo group.

W is $C(R^{15a})(R^{15b})$, O, $N(R^{16})$, or S;

R^{15a} and R^{15b} are each independently H, $C_{1–6}$ alkyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, halo, cyano, or -OR^A; or

R^{15a} and R^{15b} may be taken together with the carbon atom to which they are attached to form an oxo group;

R^{16} is H or $C_{1–6}$ alkyl;

R^A is H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

o and x are each independently an integer between 0 and 10;

*├ denotes the point of attachment to the Target Ligand in Formula (I); and

**├ denotes the point of attachment to the DUB Recruiter in Formula (I).

82. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to claim 81, wherein each of R^{12a}, R^{12b}, R^{13a}, and R^{13b} is independently H.

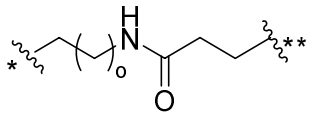
83. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 81-82, wherein each of R^{14a} and R^{14b} are taken together with the carbon atom to which they are attached form an oxo group.

84. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 81-83, wherein W is N(R^{16}) (e.g., NH).

85. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 81-84, wherein o is selected from 2, 3, 4, 5, and 6.

86. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of claims 81-85, wherein p is selected from 1, 2, and 3.

87. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 has the structure of Formula (III-b):



(III-b)

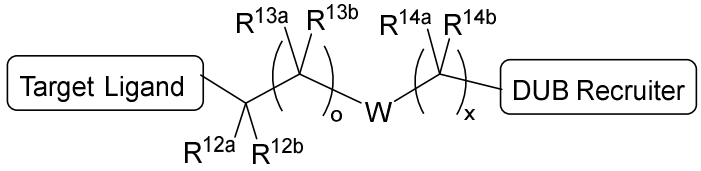
or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein:

o is an integer between 0 and 10;

* denotes the point of attachment to the Target Ligand in Formula (I); and

** denotes the point of attachment to the DUB Recruiter in Formula (I).

88. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 has the structure of Formula (III-c):



(III-c)

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

R^{12a}, R^{12b}, R^{13a}, R^{13b}, R^{14a}, and R^{14b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^{A}$; or

each of R^{12a} and R^{12b}, R^{13a} and R^{13b}, and R^{14a} and R^{14b} independently may be taken together with the carbon atom to which they are attached to form an oxo group.

W is $C(R^{15a})(R^{15b})$, O, $N(R^{16})$, or S;

R^{15a} and R^{15b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^{A}$; or

R^{15a} and R^{15b} may be taken together with the carbon atom to which they are attached to form an oxo group;

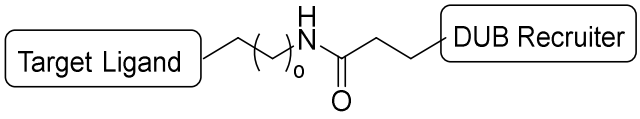
R^{16} is H or $C_{1–6}$ alkyl;

R^A is H, $C_{1–6}$ alkyl, $C_{2–6}$ alkenyl, $C_{2–6}$ alkynyl, $C_{1–6}$ haloalkyl, $C_{1–6}$ heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

o and x are each independently an integer between 0 and 10; and

the Target Ligand and DUB Recruiter are as defined in claim 1.

89. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein L1 has the structure of Formula (III-d):



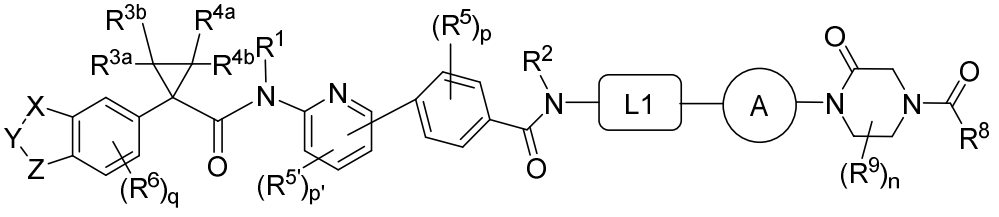
(III-d)

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

o is an integer between 0 and 10; and

the Target Ligand and DUB Recruiter are as defined in claim 1.

90. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-n):



(II-n)

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

X and Z are each independently O, S, or $C(R^{7a})(R^{7b})$;

Y is $C(R^{7a})(R^{7b})$ or NR^{7c};

Ring A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0-12 R^{10};

R^1 is H or $C_{1–6}$ alkyl;

R^2 is H or C_{1-6} alkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$;

each R^5, $R^{5'}$, and R^6 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^{7c} is H or C_{1-6} alkyl;

R^8 is H, C_{1-6} alkyl, or an electrophilic moiety;

each R^9 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, or $-OR^A$;

each R^{10} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^A, R^B, R^C, and R^D are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

n is 0, 1, 2, 3, 4, 5, or 6;

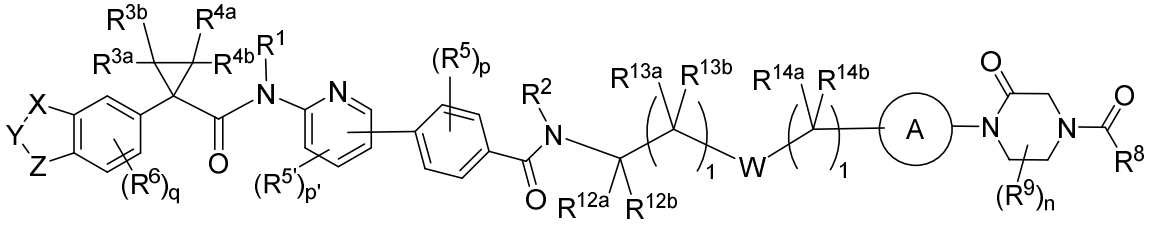
p is 0, 1, 2, 3, or 4;

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

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

L1 is as defined in claim 1.

91. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-o):



(II-o)

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

X and Z are each independently O, S, or $C(R^{7a})(R^{7b})$;

Y is $C(R^{7a})(R^{7b})$ or NR^{7c};

Ring A is cycloalkyl, heterocyclyl, aryl, or heteroaryl, each of which is substituted with 0-12 R^{10};

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

R^2 is H or C_{1-6} alkyl;

R^{3a}, R^{3b}, R^{4a}, R^{4b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$;

each R^5, $R^{5'}$, and R^6 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, $-OR^A$, $-C(O)N(R^B)(R^C)$, or $-N(R^B)CO(R^D)$;

R^{7a} and R^{7b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^{7c} is H or C_{1-6} alkyl;

R^8 is H, C_{1-6} alkyl, or an electrophilic moiety;

each R^9 is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, or $-OR^A$;

each R^{10} is independently C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, or halo;

R^{12a}, R^{12b}, R^{13a}, R^{13b}, R^{14a}, and R^{14b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$; or

each of R^{12a} and R^{12b}, R^{13a} and R^{13b}, and R^{14a} and R^{14b} independently may be taken together with the carbon atom to which they are attached to form an oxo group.

W is $C(R^{15a})(R^{15b})$, O, $N(R^{16})$, or S;

R^{15a} and R^{15b} are each independently H, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, halo, cyano, or $-OR^A$; or

R^{15a} and R^{15b} may be taken together with the carbon atom to which they are attached to form an oxo group;

R^{16} is H or C_{1-6} alkyl;

R^A, R^B, R^C, and R^D are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} haloalkyl, C_{1-6} heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

n is 0, 1, 2, 3, 4, 5, or 6;

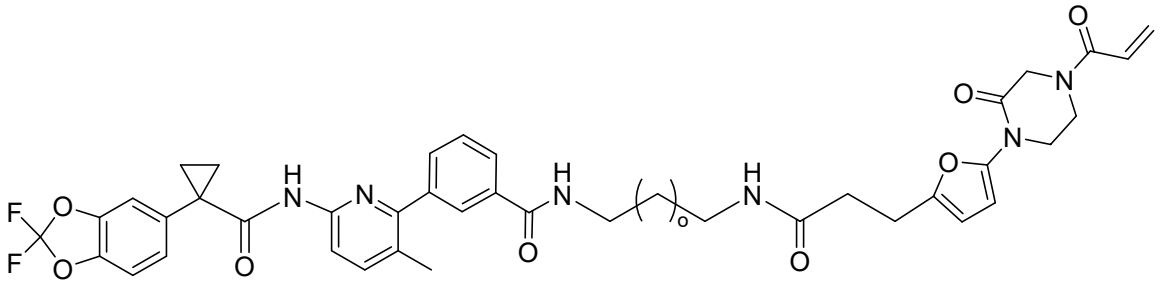
o and x are each independently an integer between 0 and 10;

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

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

q is 0, 1, 2, or 3.

92. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) has the structure (II-q):



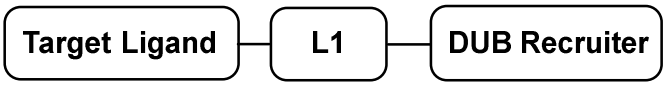
(II-q)

or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof, wherein o is selected from 0, 1, 2, 3, 4, 5, and 6.

93. The bifunctional compound or pharmaceutically acceptable salt hydrate, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, wherein the bifunctional compound of Formula (I) is selected from a bifunctional compound provided in Table 2, or a pharmaceutically acceptable salt, hydrate, solvate, prodrug, stereoisomer, or tautomer thereof.

94. A pharmaceutical composition comprising a bifunctional compound, or pharmaceutically acceptable salt, solvate, stereoisomer, or tautomer thereof according to any one of the preceding claims, and one or more pharmaceutically acceptable carriers.

95. A composition for use in providing a compound to a subject, wherein the composition comprises a bifunctional compound of Formula (I):



(I),

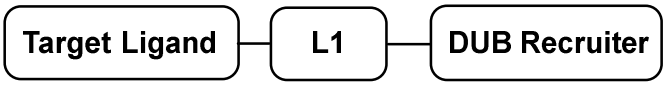
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

96. Use of a composition in the manufacture of a medicament for treating a disease, disorder, or condition in a subject, the composition comprising a bifunctional compound of Formula (I):



(I),

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

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

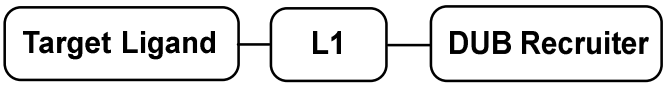
(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

97. The use of claim 96, wherein administering the composition ameliorates a symptom or element of the disease, disorder, or condition.

98. The use of any one of claims 96-97, wherein the disease, disorder, or condition is cystic fibrosis.

99. Use of a composition in the manufacture of a medicament for treating cystic fibrosis in a subject, the composition comprising a bifunctional compound of Formula (I):



(I),

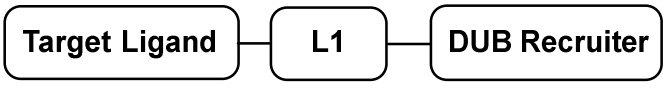
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

100. A composition for use in modulating a protein in a cell or subject comprising a bifunctional compound of Formula (I):



(I),

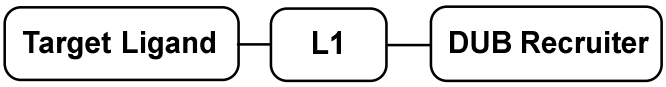
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

101. A composition for use in recruiting a deubiquitinase to a target protein in a cell or subject, wherein the composition comprises a bifunctional compound of Formula (I):



(I),

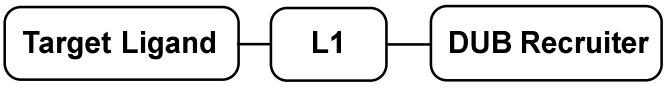
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

102. A composition for use in deubiquitinating a protein comprising a bifunctional compound of Formula (I):



(I),

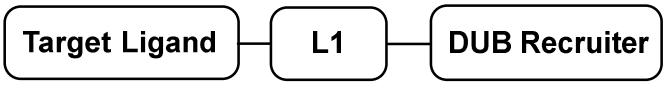
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

103. Use of a compound comprising a bifunctional compound of Formula (I):



(I),

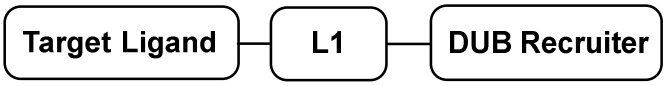
or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for providing the compound to a subject, wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

104. Use of a bifunctional compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating a disease, disorder, or condition in a subject wherein:

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

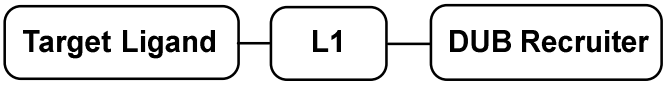
(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase.

105. The use of claim 104, wherein the use comprises ameliorating a symptom or element of the disease, disorder, or condition.

106. The use of any one of claims 104-105, wherein the disease, disorder, or condition is cystic fibrosis.

107. Use of a bifunctional compound of Formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, or tautomer thereof, in the manufacture of a medicament for treating cystic fibrosis in a subject wherein:

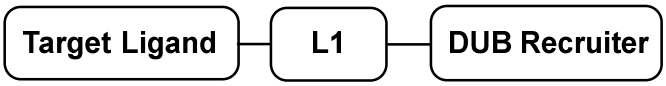
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker; and

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby treating cystic fibrosis.

108. A method of modulating a protein in a cell or subject comprising contacting the cell or administering to the subject a bifunctional compound of Formula (I):



(I),

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

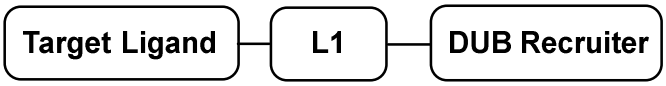
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby modulating a protein in a cell or subject.

109. A method of recruiting a deubiquitinase to a target protein comprising contacting a mixture (e.g., in a cell or sample) with a bifunctional compound of Formula (I):



(I),

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

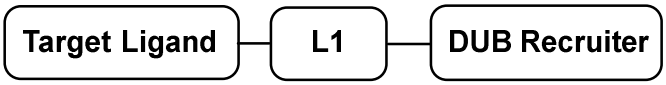
(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby recruiting a deubiquitinase to a target protein in a mixture, e.g., a cell or subject.

110. A method of deubiquitinating a protein comprising contacting a cell or sample with a bifunctional compound of Formula (I):



(I),

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

(i) the Target Ligand comprises a moiety capable of binding to a target protein;

(ii) L1 comprises a linker;

(iii) the DUB Recruiter comprises a moiety capable of binding to a deubiquitinase,

thereby deubiquitinating a protein in a cell or subject.