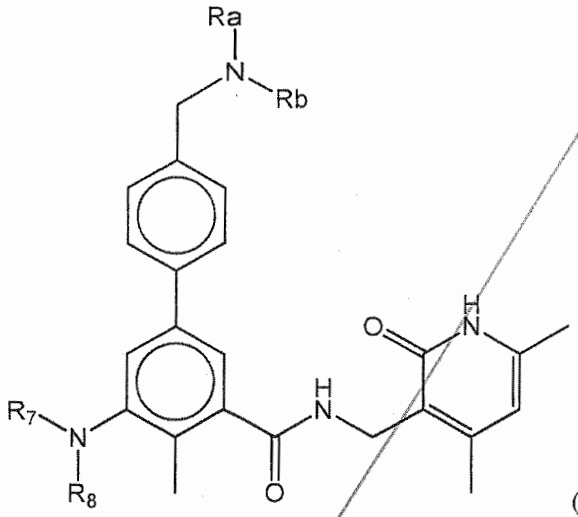
CLAIMS

What is claimed is:

1. A composition comprising a compound of Formula (IIa):



(IIa)

or pharmaceutically acceptable salts thereof, and one or more other therapeutic agents, wherein

each of R_a and R_b, independently, is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3$-T_3, in which Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker, and T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_d, $COOR_d$,-$S(O)_2R_d$, or $-NR_dR_e$, in which each of R_d and R_e is independently H or C_1-C_6 alkyl, or $-Q_3T_3$ is oxo;

R_7 is isopropyl or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, piperidinyl, tetrahydropyran, tetrahydro-2H-thiopyranyl,cyclopentyl, or cyclohexyl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5, in which Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered

heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; and

R_8 is H, methyl, or ethyl.

2. A composition comprising any one of the compounds listed in Table 1 or pharmaceutically acceptable salts thereof and one or more other therapeutic agents.

3. A composition comprising Compound 44, or pharmaceutically acceptable salts thereof, and one or more therapeutic agents.

4. The composition of any of claims 1-3, wherein said other therapeutic agents are anti-cancer agents or glucocorticoids.

5. The composition of any of claims 1-3, wherein said other therapeutic agents are selected from prednisone, prednisolone, cyclophosphamide, vincristine, doxorubicin, mafosfamide, cisplatin, AraC, everolimus, decitabine, dexamethasone, and analogs, derivatives, or combinations thereof.

6. The composition of any of claims 1-3, wherein said other therapeutic agents is prednisone, or an analog or derivative thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of any of claims 1-6 and a pharmaceutically acceptable carrier.

8. A method of treating or preventing a disease comprising administering to a subject in need thereof a therapeutically effective amount of a composition of claim 1.

9. The method of claim 8 wherein said disease can be influenced by modulating the methylation status of histones or other proteins.

10. The method of claim 8, wherein the disease is cancer or a precancerous condition.

11. A method of claim 9 wherein said methylation status is mediated at least in part by the activity of EZH2.

12. A method of treating or preventing cancer comprising administering to a subject in need thereof a therapeutically effective dose of a compound of Formula (IIa) and

one or more other therapeutic agents, wherein Formula (IIa) and said other therapeutic agents are administered simultaneously or sequentially.

13. A method of claim 12 wherein a compound of Formula (IIa) is administered prior to administration of said other therapeutic agents.

14. A method of treating or preventing cancer comprising administering to a subject in need thereof a therapeutically effective dose of a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, prior to administering a therapeutically effective dose of a composition of claim 1.

15. The method of claim 8 or 12, wherein the composition of claim 1 is administered to the subject in need thereof at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

16. The method of claim 12 or 14, wherein the compound of Formula (IIa) is administered at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

17. The method of claim 12 or 14, wherein each of the one or more other therapeutic agents are administered at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

18. The method of any of claims 8, 12, or 14, wherein said subject expresses mutant EZH2.

19. The method of claim 18, wherein said mutant EZH2 has one or more mutations, wherein the mutation is a substitution, a point mutation, a nonsense mutation, a missense mutation, a deletion, or an insertion.

20. The method claim 18, wherein said mutant EZH2 has one or more mutations in its substrate pocket domain as defined in SEQ ID NO: 6.

21. The method of claim 18, wherein said mutant EZH2 is a Y641 mutant.

22. The method of claim 21 wherein said Y641 mutant is selected from Y641F, Y641H, Y641N, and Y641S.

23. The method of claim 18, wherein the mutant EZH2 has a mutation at amino acid position 677, 687, 674, 685, or 641 of SEQ ID NO: 1.

24. The method of claim 18, wherein said mutant EZH2 has one or more mutations selected from the group consisting of a substitution of glycine (G) for the wild type residue alanine (A) at amino acid position 677 of SEQ ID NO: 1 (A677G); a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 687 of SEQ ID NO: 1 (A687V); a substitution of methionine (M) for the wild type residue valine (V) at amino acid position 674 of SEQ ID NO: 1 (V674M); a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685H); a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685C); a substitution of serine (S) for the wild type residue asparagine (N) at amino acid position 322 of SEQ ID NO: 3 (N322S), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 288 of SEQ ID NO: 3 (R288Q), a substitution of isoleucine (I) for the wild type residue threonine (T) at amino acid position 573 of SEQ ID NO: 3 (T573I), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664E), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 458 of SEQ ID NO: 5 (R458Q), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 249 of SEQ ID NO: 3 (E249K), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 684 of SEQ ID NO: 3 (R684C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 628 of SEQ ID NO: 21 (R628H), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID NO: 5 (Q501H), a substitution of asparagine (N) for the wild type residue aspartic acid (D) at amino acid position 192 of SEQ ID NO: 3 (D192N), a substitution of valine (V) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664V), a substitution of leucine (L) for the wild type residue valine (V) at amino acid position 704 of SEQ ID NO: 3 (V704L), a substitution of serine (S) for the wild type residue proline (P) at amino acid position 132 of SEQ ID NO: 3 (P132S), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 669 of SEQ ID NO: 21 (E669K), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 255 of SEQ ID NO: 3 (A255T), a substitution of valine (V) for the wild type residue glutamic acid (E) at amino acid position 726 of SEQ ID NO: 3 (E726V), a substitution of tyrosine (Y)

for the wild type residue cysteine (C) at amino acid position 571 of SEQ ID NO: 3 (C571Y), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145C), a substitution of threonine (T) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693T), a substitution of serine (S) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145S), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 109 of SEQ ID NO: 21 (Q109H), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 622 of SEQ ID NO: 21 (F622C), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 135 of SEQ ID NO: 3 (G135R), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 168 of SEQ ID NO: 5 (R168Q), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 159 of SEQ ID NO: 3 (G159R), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 310 of SEQ ID NO: 5 (R310C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 561 of SEQ ID NO: 3 (R561H), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 634 of SEQ ID NO: 21 (R634H), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 660 of SEQ ID NO: 3 (G660R), a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 181 of SEQ ID NO: 3 (Y181C), a substitution of arginine (R) for the wild type residue histidine (H) at amino acid position 297 of SEQ ID NO: 3 (H297R), a substitution of serine (S) for the wild type residue cysteine (C) at amino acid position 612 of SEQ ID NO: 21 (C612S), a substitution of tyrosine (Y) for the wild type residue histidine (H) at amino acid position 694 of SEQ ID NO: 3 (H694Y), a substitution of alanine (A) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664A), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 150 of SEQ ID NO: 3 (I150T), a substitution of arginine (R) for the wild type residue isoleucine (I) at amino acid position 264 of SEQ ID NO: 3 (I264R), a substitution of leucine (L) for the wild type residue proline (P) at amino acid position 636 of SEQ ID NO: 3 (P636L), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 713 of SEQ ID NO: 3 (I713T), a substitution of proline (P) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID

NO: 5 (Q501P), a substitution of glutamine (Q) for the wild type residue lysine (K) at amino acid position 243 of SEQ ID NO: 3 (K243Q), a substitution of aspartic acid (D) for the wild type residue glutamic acid (E) at amino acid position 130 of SEQ ID NO: 5 (E130D), a substitution of glycine (G) for the wild type residue arginine (R) at amino acid position 509 of SEQ ID NO: 3 (R509G), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 566 of SEQ ID NO: 3 (R566H), a substitution of histidine (H) for the wild type residue aspartic acid (D) at amino acid position 677 of SEQ ID NO: 3 (D677H), a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 466 of SEQ ID NO: 5 (K466N), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 78 of SEQ ID NO: 3 (R78H), a substitution of methionine (M) for the wild type residue lysine (K) at amino acid position 1 of SEQ ID NO: 6 (K6M), a substitution of leucine (L) for the wild type residue serine (S) at amino acid position 538 of SEQ ID NO: 3 (S538L), a substitution of glutamine (Q) for the wild type residue leucine (L) at amino acid position 149 of SEQ ID NO: 3 (L149Q), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 252 of SEQ ID NO: 3 (L252V), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 674 of SEQ ID NO: 3 (L674V), a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 656 of SEQ ID NO: 3 (A656V), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 731 of SEQ ID NO: 3 (Y731D), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 345 of SEQ ID NO: 3 (A345T), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 244 of SEQ ID NO: 3 (Y244D), a substitution of tryptophan (W) for the wild type residue cysteine (C) at amino acid position 576 of SEQ ID NO: 3 (C576W), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 640 of SEQ ID NO: 3 (N640K), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 675 of SEQ ID NO: 3 (N675K), a substitution of tyrosine (Y) for the wild type residue aspartic acid (D) at amino acid position 579 of SEQ ID NO: 21 (D579Y), a substitution of isoleucine (I) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693I), and a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693K).

25. The method of claim 18, wherein said mutant EZH2 has a frameshift at amino acid position 730, 391, 461, 441, 235, 254, 564, 662, 715, 405, 685, 64, 73, 656, 718, 374, 592, 505, 730, or 363 of SEQ ID NO: 3, 5 or 21 or the corresponding nucleotide position of the nucleic acid sequence encoding SEQ ID NO: 3, 5, or 21.

26. The method of claim 18, wherein said mutant EZH2 has a deletion of glutamic acid (E) and leucine (L) at amino acid positions 148 and 149 of SEQ ID NO: 3, 5 or 21.

27. The method of claim 18, wherein said mutant EZH2 has a nonsense mutation at amino acid position 733, 25, 317, 62, 553, 328, 58, 207, 123, 63, 137, or 60 of SEQ ID NO: 3, 5 or 21.

28. The method of any of claims 8, 12, or 14, wherein said subject has demonstrated resistance to any one of the components of the composition of claim 1 when administered as a single agent.

29. A method of inhibiting cancer cell proliferation comprising contacting said cancer cell with the composition of claim 1.

30. A method of inhibiting cancer cell proliferation comprising contacting said cancer cell with a compound of Formula (IIa) and one or more other therapeutic agents, wherein Formula (IIa) and said other therapeutic agents are delivered simultaneously or sequentially.

31. The method of claim 30 wherein a compound of Formula (IIa) is administered prior to administration of said other therapeutic agents.

32. A method of inhibiting cancer cell proliferation comprising administering a therapeutically effective dose of a compound of Formula (IIa), or a pharmaceutically acceptable salt thereof, prior to administering a therapeutically effective dose of a composition of claim 1.

33. The method of claims 12 or 30, wherein said other therapeutic agents is prednisone or prednisolone, or an analog or derivative thereof.

34. The method of any of claims 12, 14, 29, 30, or 32, wherein the cancer is lymphoma, leukemia, or melanoma.

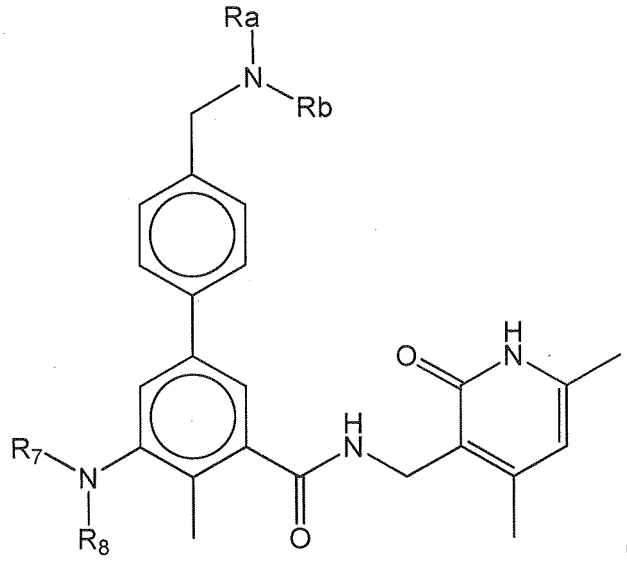
35. The method of claim 34, wherein the lymphoma is selected from the group consisting of non-Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma.

36. The method of claim 34, wherein the leukemia is chronic myelogenous leukemia (CML).

37. The method of claim 34, wherein the precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).

CLAIMS

1. A composition comprising a compound of Formula (IIa):



(IIa)

or pharmaceutically acceptable salts thereof, and one or more other therapeutic agents, wherein

each of R_a and R_b, independently, is H or C_1-C_6 alkyl optionally substituted with one or more $-Q_3$-T_3, or

R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, where the 4 to 7-membered heterocycloalkyl ring is optionally substituted with one or more $-Q_3$-T_3,

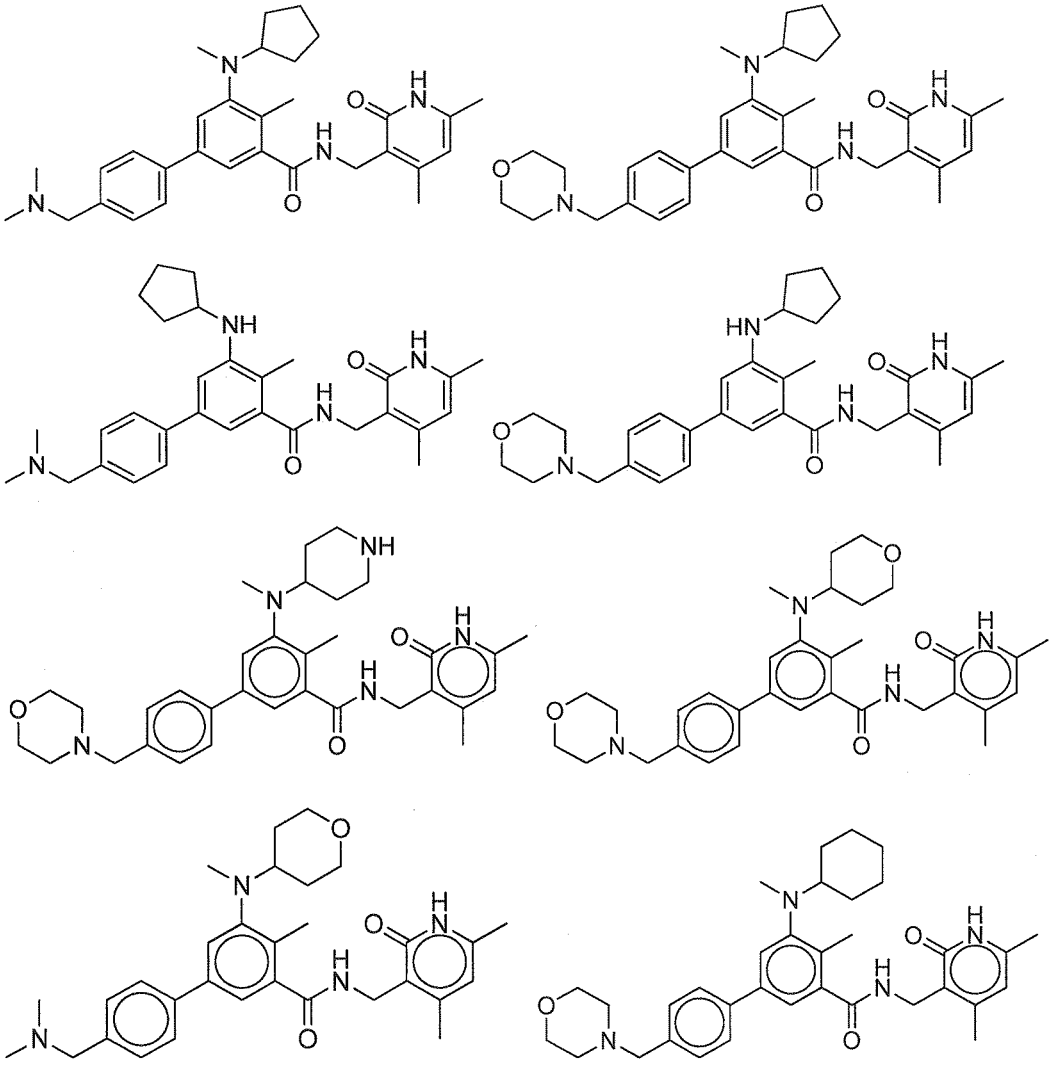
in which Q_3 is a bond or unsubstituted or substituted C_1-C_3 alkyl linker, and T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1-C_3 alkyl, OR_d, $COOR_d$,-$S(O)_2R_d$, or $-NR_dR_e$, in which each of R_d and R_e is independently H or C_1-C_6 alkyl, or $-Q_3T_3$ is oxo;

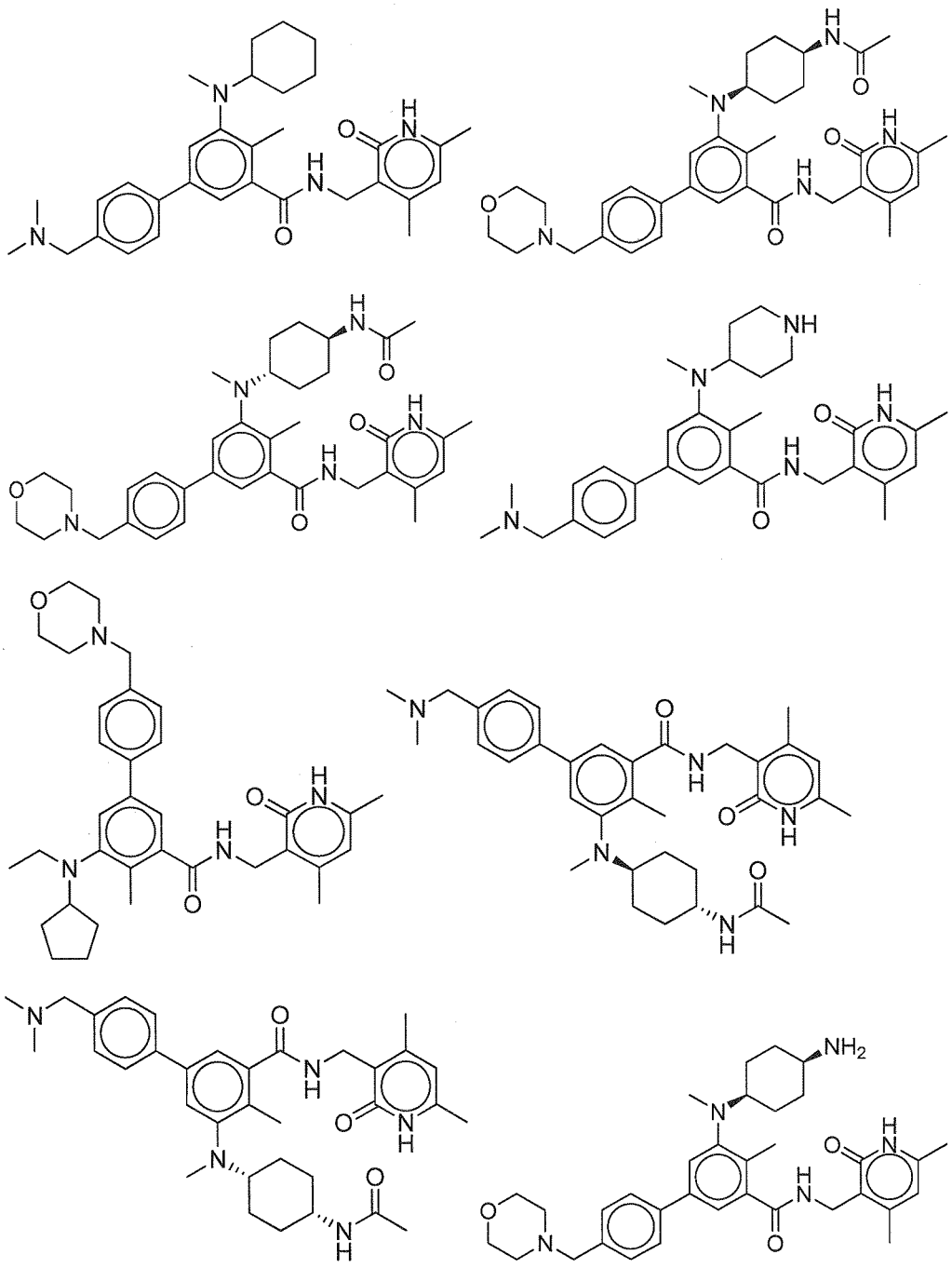
R_7 is isopropyl or C_1-C_6 alkyl, C_3-C_8 cycloalkyl, piperidinyl, tetrahydropyran, tetrahydro-2H-thiopyranyl,cyclopentyl, or cyclohexyl, or 4 to 12-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5$-T_5, in which Q_5 is a bond, C(O), $C(O)NR_k$, $NR_kC(O)$, $S(O)_2$, or C_1-C_3 alkyl linker, R_k being H or C_1-C_6 alkyl, and T_5 is H, halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or $S(O)_qR_q$ in which q is 0, 1, or 2 and R_q is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-

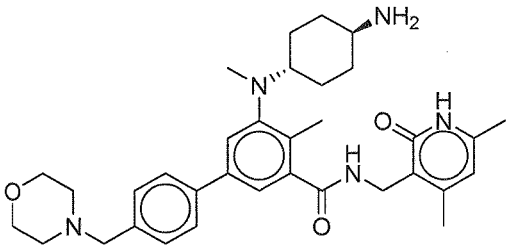
membered heteroaryl, and T_5 is optionally substituted with one or more substituents selected from the group consisting of halo, C_1-C_6 alkyl, hydroxyl, cyano, C_1-C_6 alkoxyl, amino, mono-C_1-C_6 alkylamino, di-C_1-C_6 alkylamino, C_3-C_8 cycloalkyl, C_6-C_{10} aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T_5 is H, halo, hydroxyl, or cyano; or $-Q_5$-T_5 is oxo; and

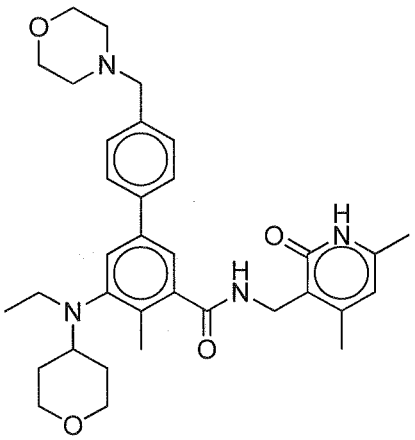
R_8 is H, methyl, or ethyl.

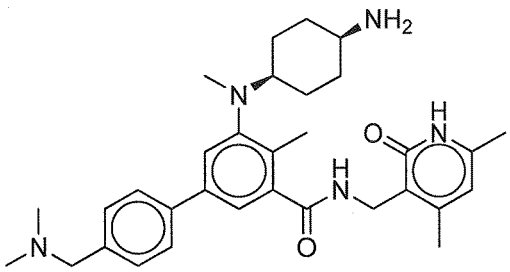
2. A composition comprising any one of the compounds depicted below:

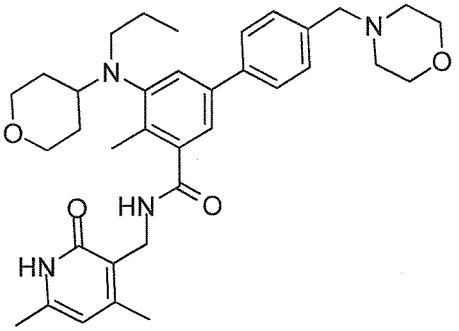


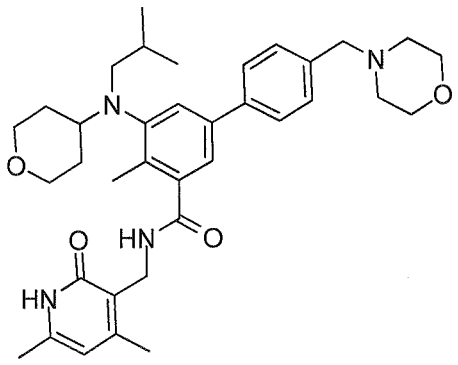


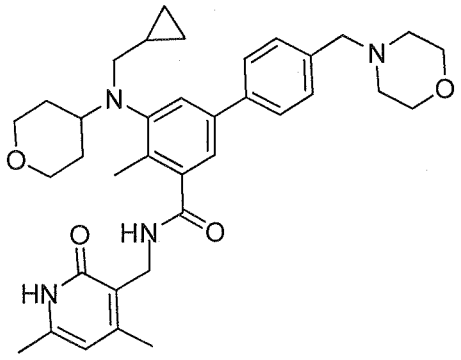


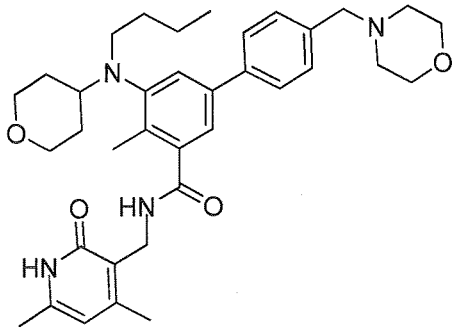


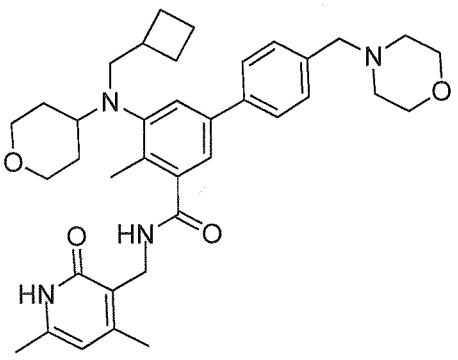


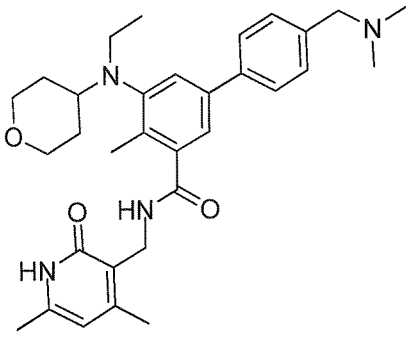


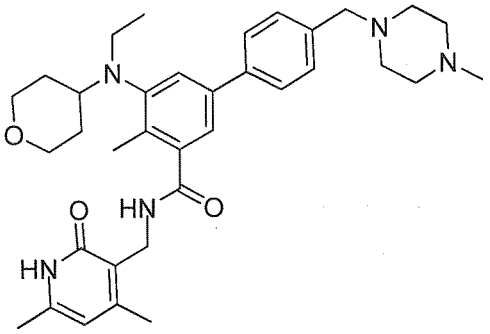


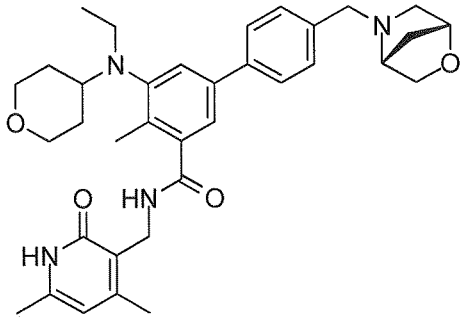


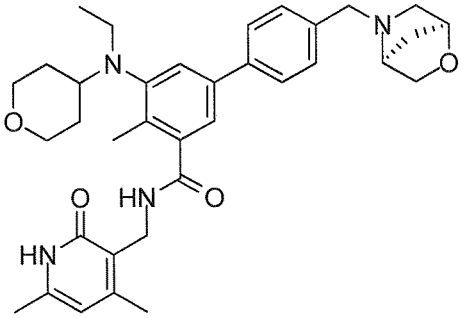


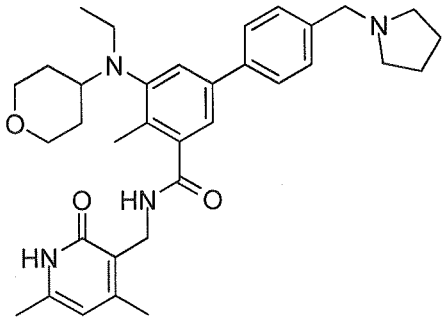


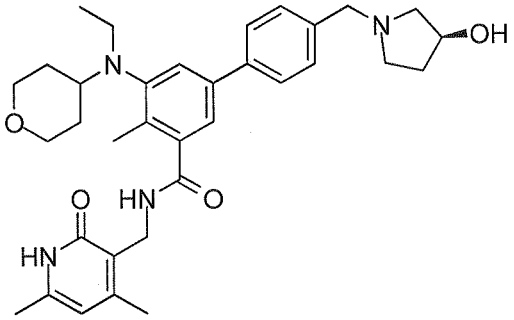


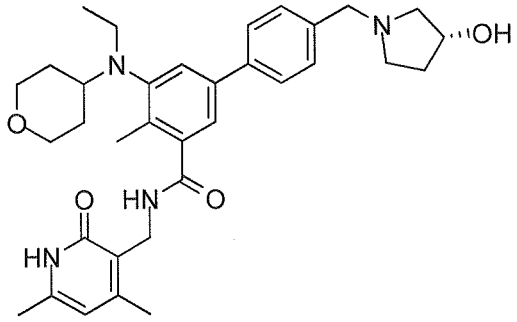


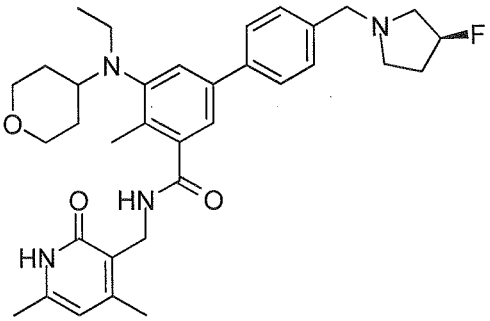


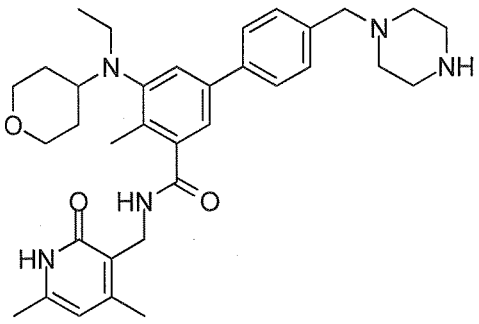


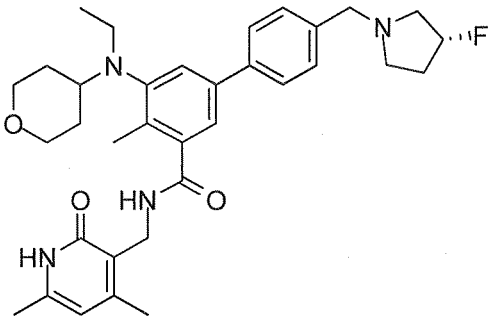


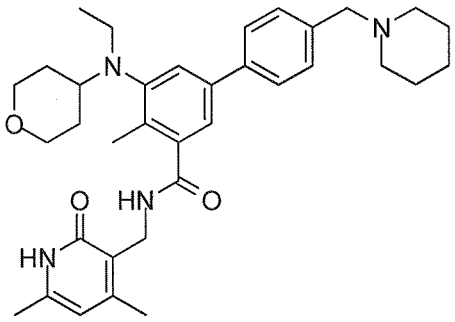


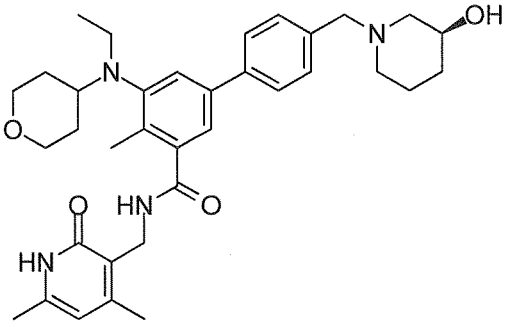


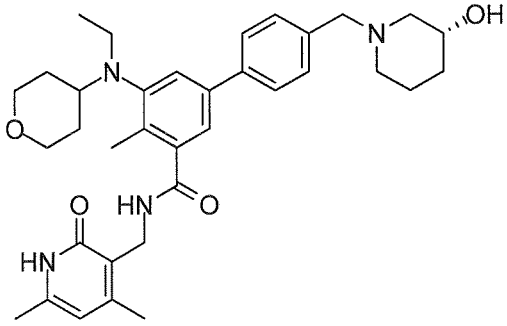


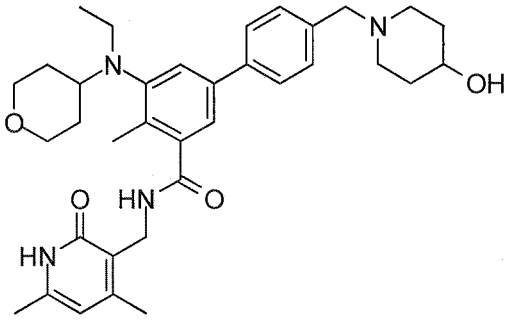


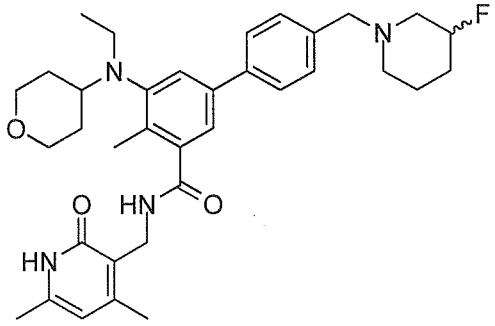


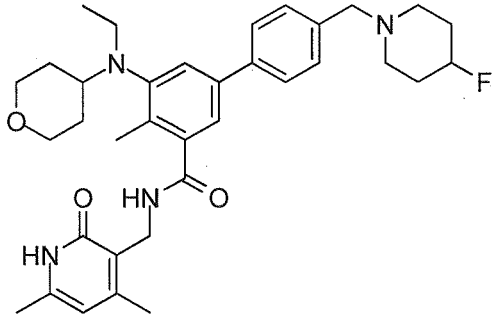


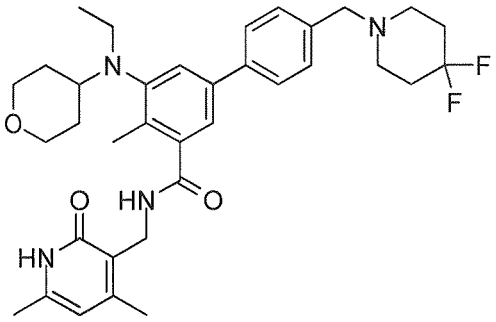


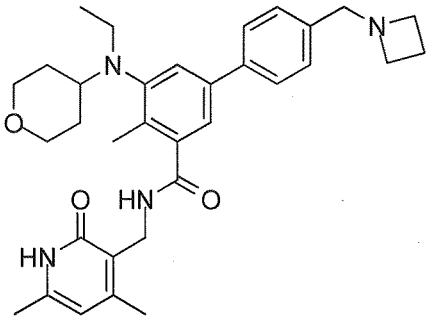


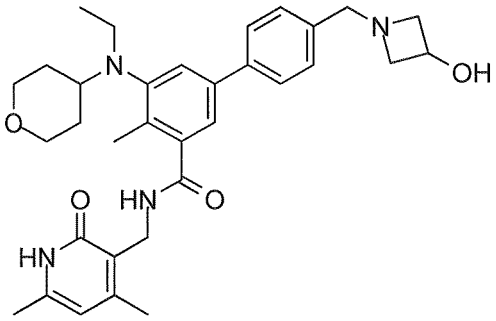


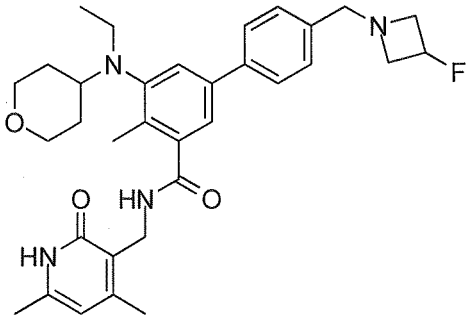


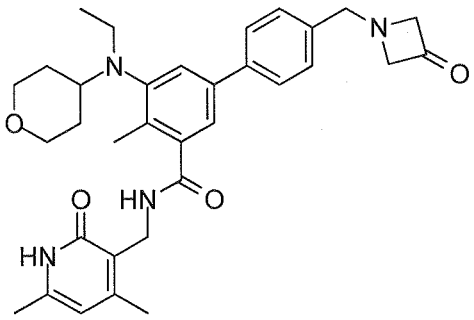


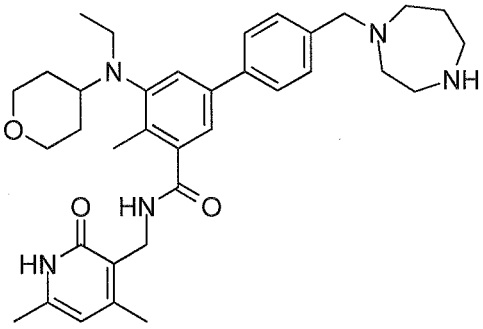


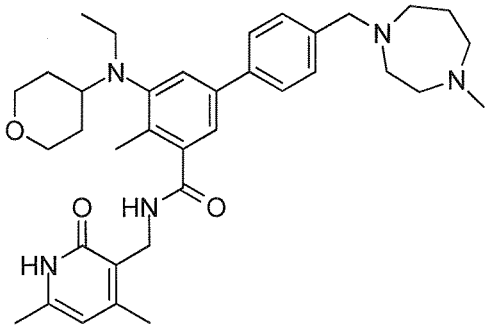


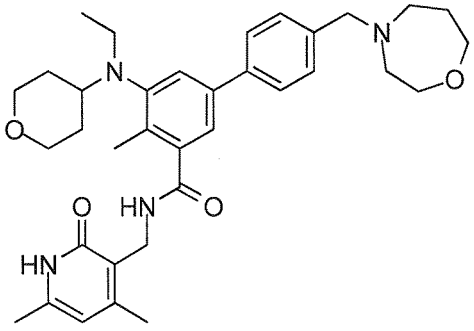


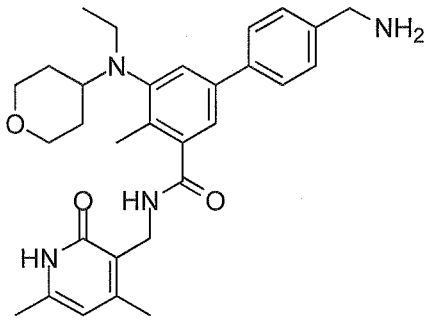
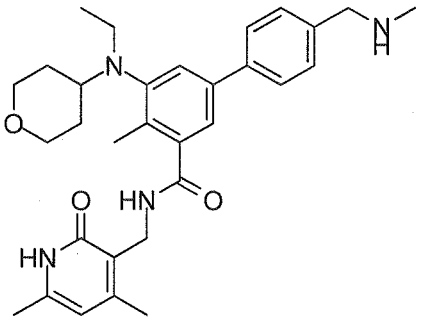
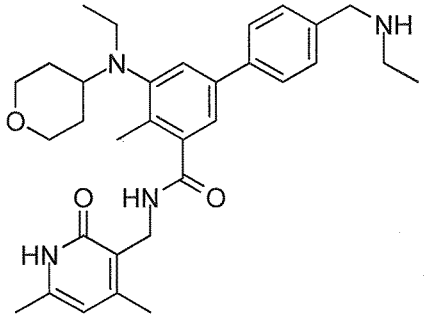
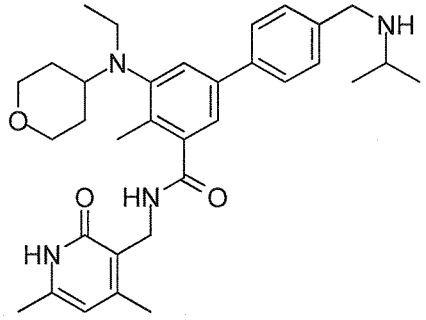
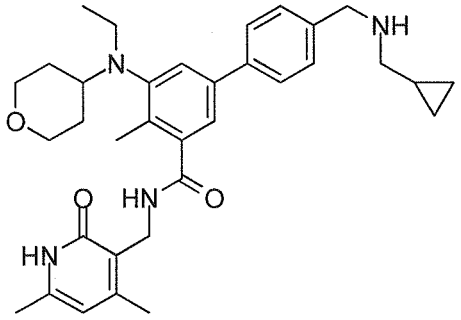
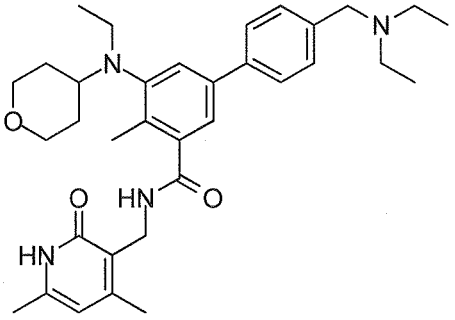
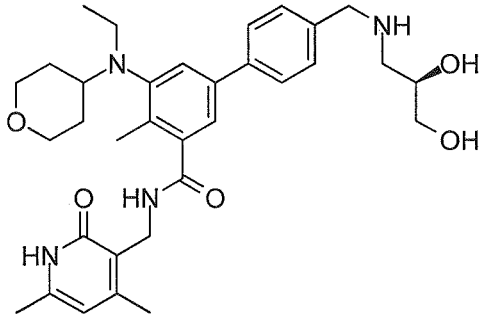
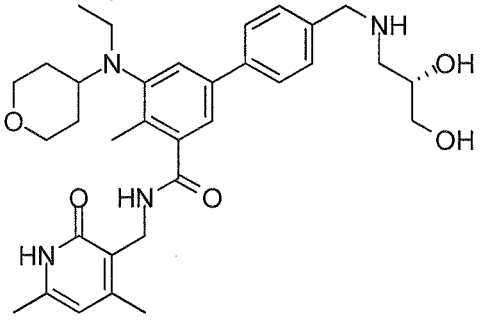


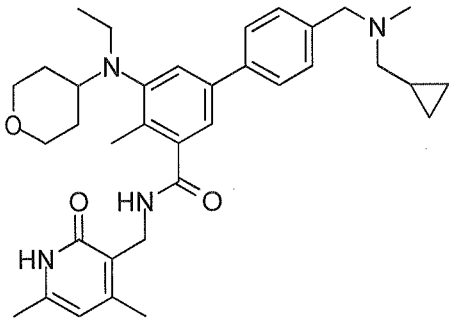


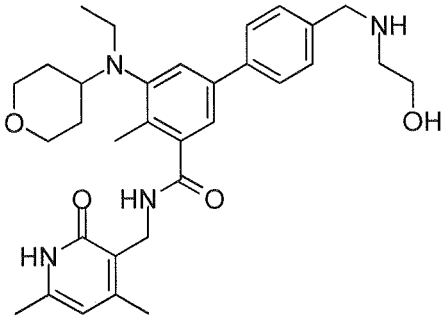


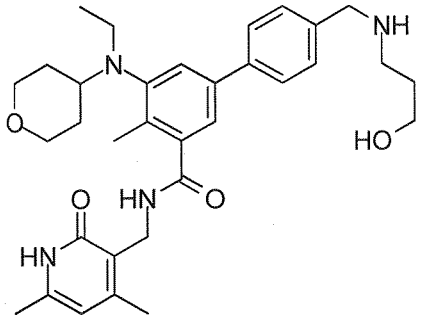


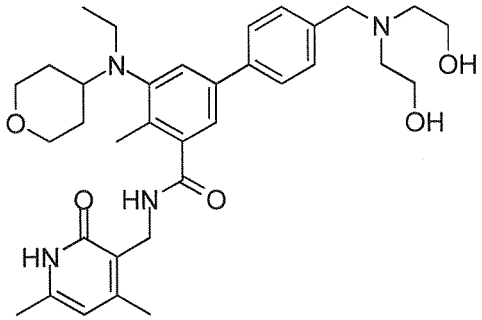


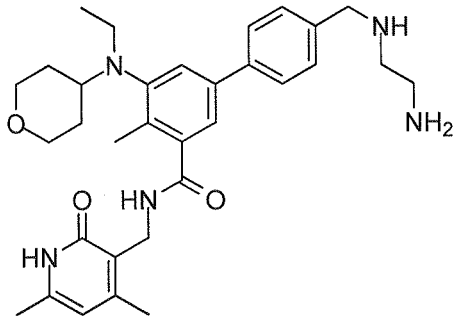









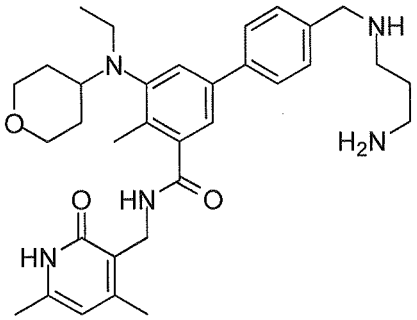


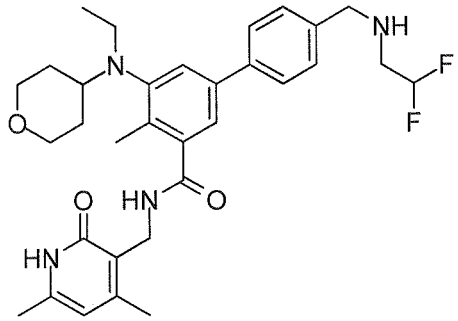


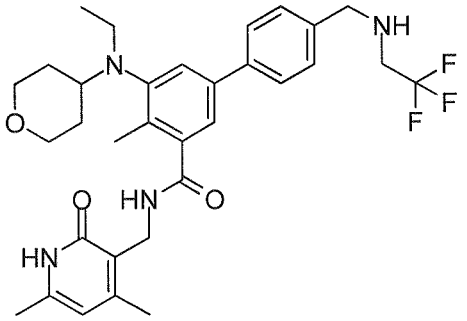


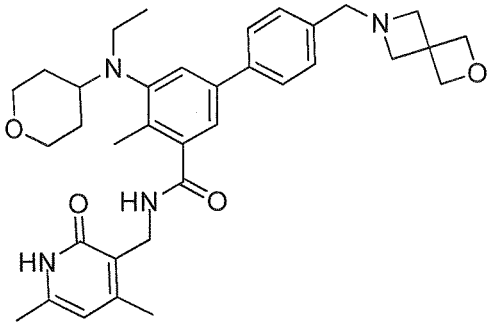


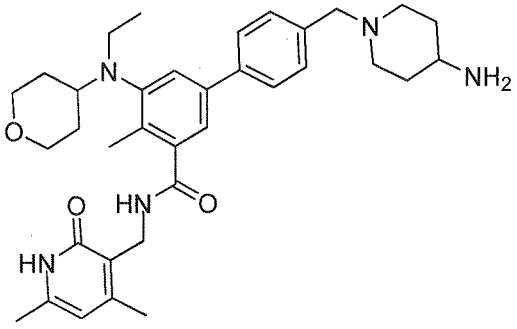


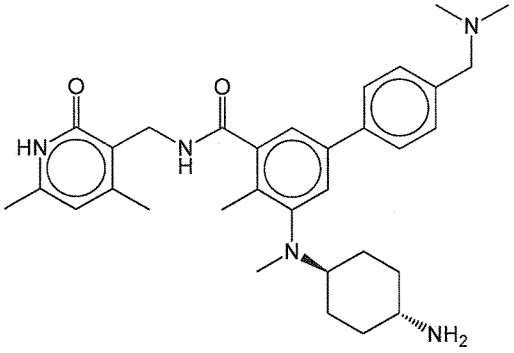


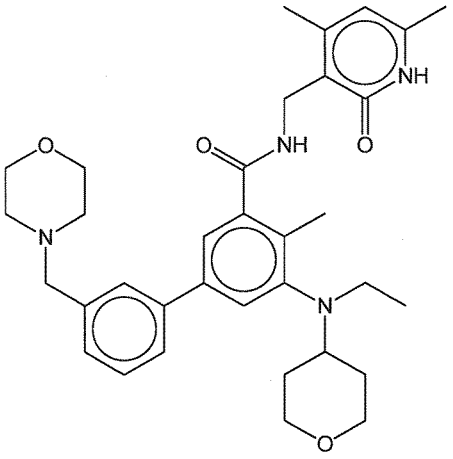


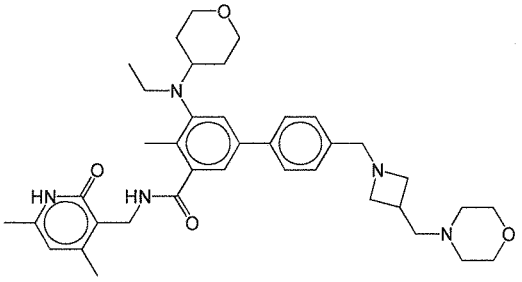


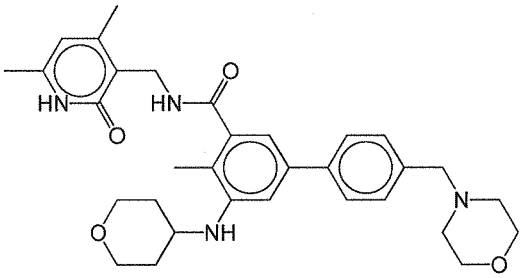


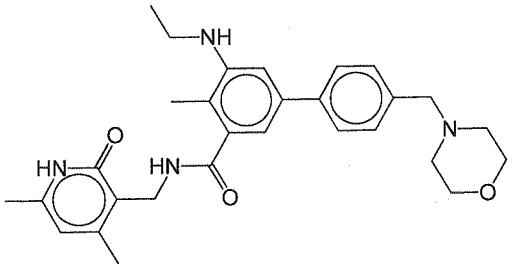


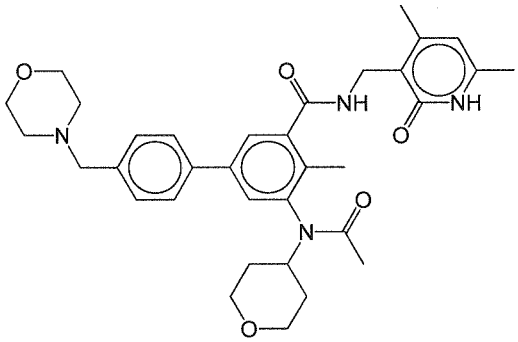


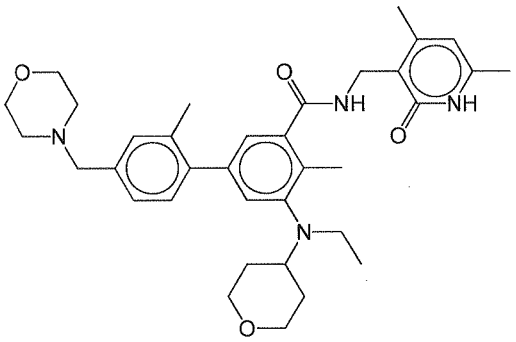


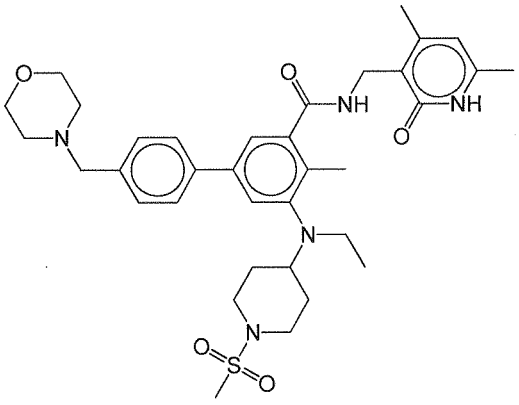


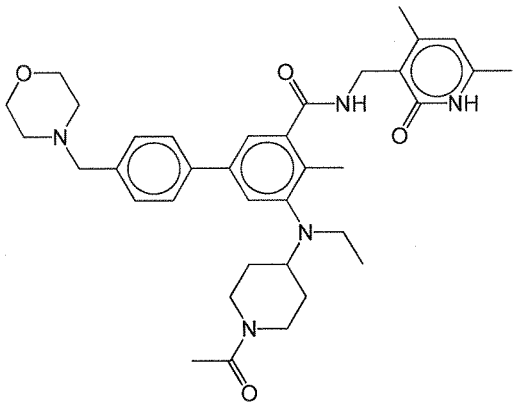


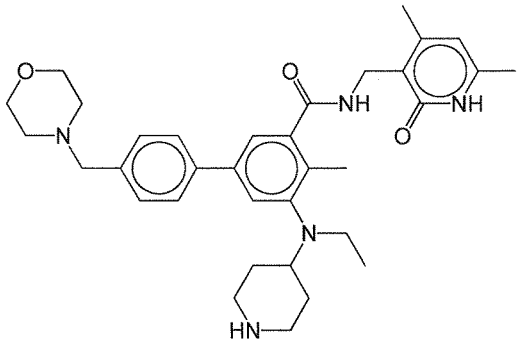


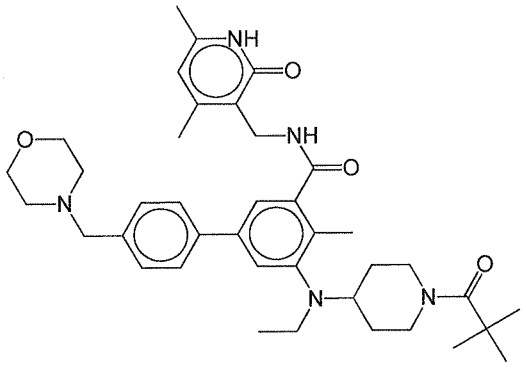


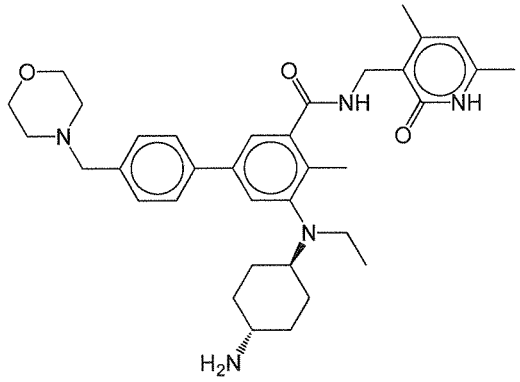


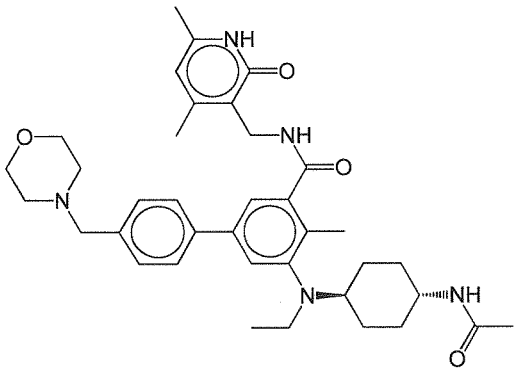


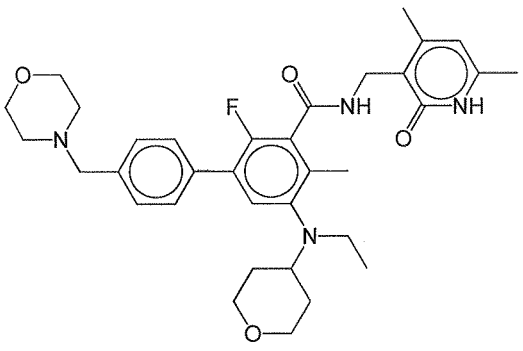


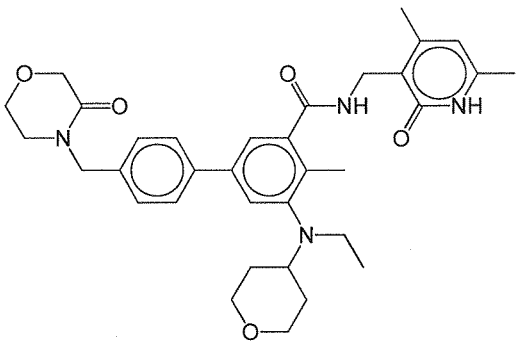


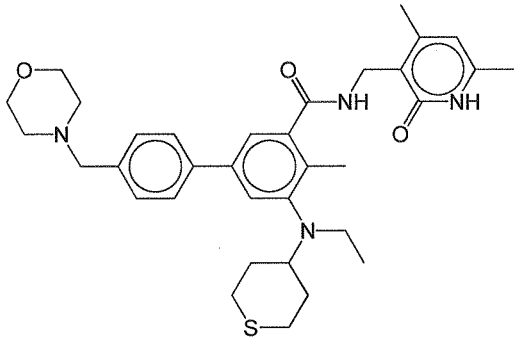


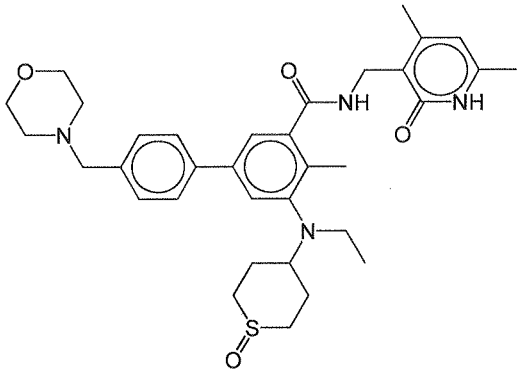


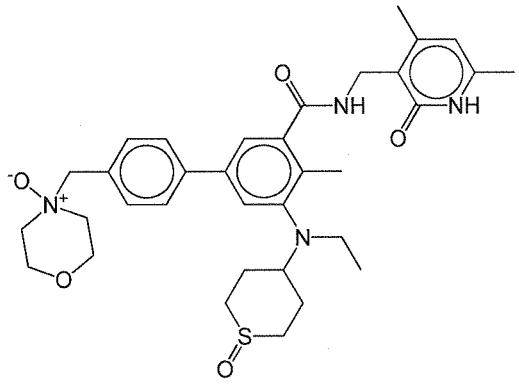


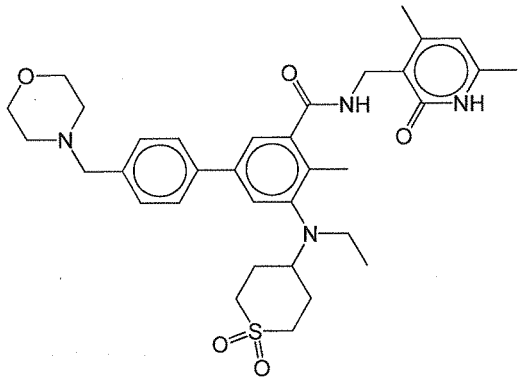


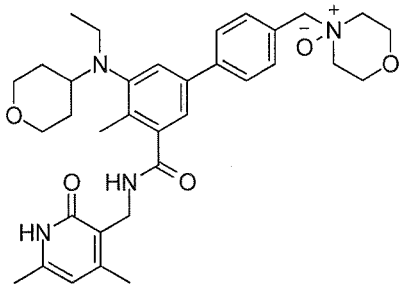


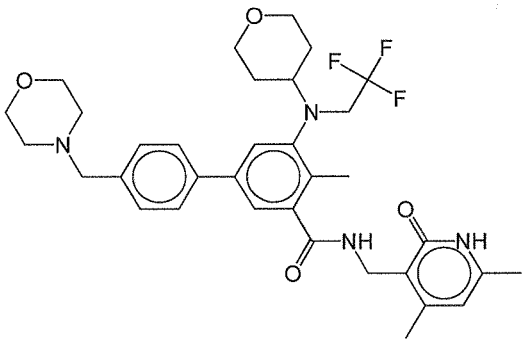


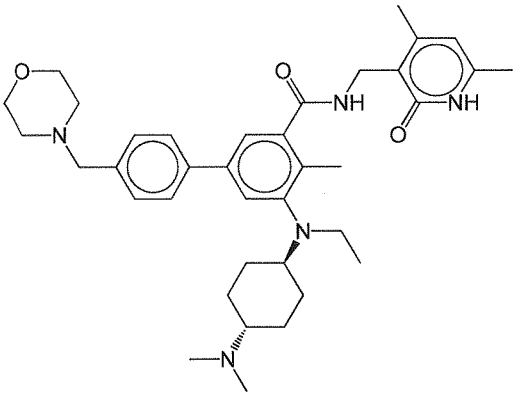
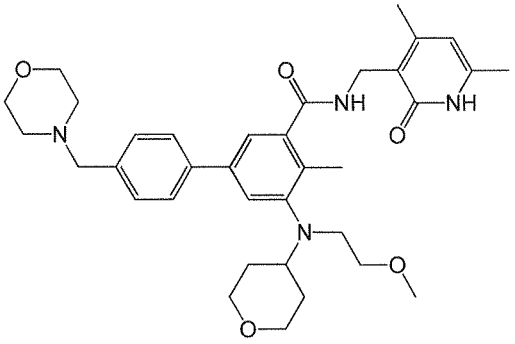
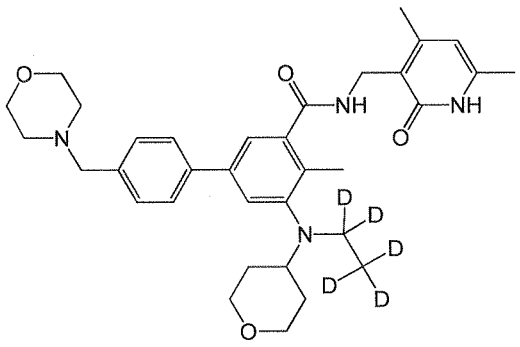
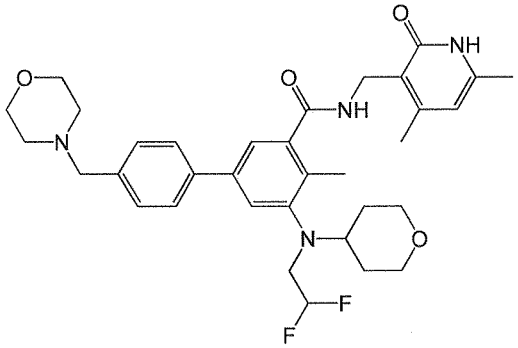
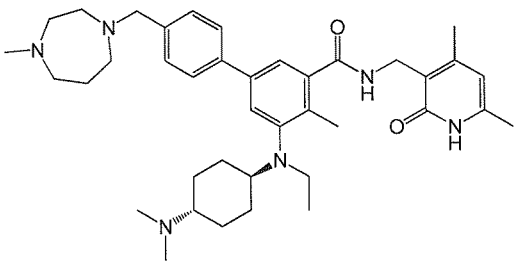
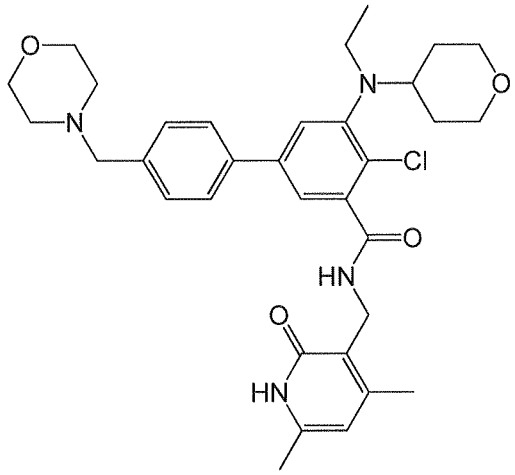






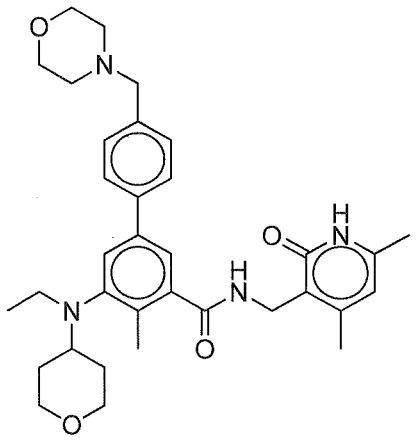




or pharmaceutically acceptable salts thereof and one or more other therapeutic agents.

3. A composition comprising the compound depicted below:



or pharmaceutically acceptable salt thereof, and one or more therapeutic agents.

4. The composition of any of claims 1-3, wherein said other therapeutic agents are anti-cancer agents or glucocorticoids.

5. The composition of any of claims 1-3, wherein said other therapeutic agents are selected from prednisone, prednisolone, cyclophosphamide, vincristine, doxorubicin, mafosfamide, cisplatin, AraC, everolimus, decitabine, dexamethasone, and analogs, derivatives, or combinations thereof.

6. The composition of any of claims 1-3, wherein said other therapeutic agents is prednisone, or an analog or derivative thereof.

7. A pharmaceutical composition comprising a therapeutically effective amount of any of claims 1-6 and a pharmaceutically acceptable carrier.

8. A composition according to any one of claims 1-7 for use in the treatment or prevention of a disease.

9. The use of the composition according to any of claims 1-7 in the manufacture of a medicament for treating or preventing a disease, wherein a subject in need thereof is administered a therapeutically effective dose of said composition..

10. The use of claim 9 wherein said disease can be influenced by modulating the methylation status of histones or other proteins.

11. The use of claim 10, wherein the disease is cancer or a precancerous condition.

12. The use of claim 10 wherein said methylation status is mediated at least in part by the activity of EZH2.

13. The use of the composition according to any one of claims 1-7 in the manufacture of a medicament for treating or preventing cancer, wherein a subject in need thereof is administered a therapeutically effective dose of a compound of Formula (IIa), as defined in any one of claims 1-7, and one or more other therapeutic agents, wherein Formula (IIa) and said other therapeutic agents are administered simultaneously or sequentially.

14. The use of claim 13 wherein a compound of Formula (IIa), as defined in any one of claims 1-7, is administered prior to administration of said other therapeutic agents.

15. The use of the composition according to any of claims 1-7 in the manufacture of a medicament for treating or preventing cancer, whereina subject in need thereof is administered a therapeutically effective dose of a compound of Formula (IIa), as defined in any one of claims 1-7, or a pharmaceutically acceptable salt thereof, prior to administering a therapeutically effective dose of said composition.

16. The use of any one of claims 9 or 13, wherein the said composition is administered to the subject in need thereof at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

17. The use of claim 13 or 15, wherein the compound of Formula (IIa) is administered at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

18. The use of claim 13 or 15, wherein each of the one or more other therapeutic agents are administered at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

19. The use of any of claims 9, 13, or 15, wherein said subject expresses mutant EZH2.

20. The use of claim 19, wherein said mutant EZH2 has one or more mutations, wherein the mutation is a substitution, a point mutation, a nonsense mutation, a missense mutation, a deletion, or an insertion.

21. The use of claim 19, wherein said mutant EZH2 has one or more mutations in its substrate pocket domain as defined in SEQ ID NO: 6.

22. The use of claim 19, wherein said mutant EZH2 is a Y641 mutant.

23. The use of claim 22 wherein said Y641 mutant is selected from Y641F, Y641H, Y641N, and Y641S.

24. The use of claim 19, wherein the mutant EZH2 has a mutation at amino acid position 677, 687, 674, 685, or 641 of SEQ ID NO: 1.

25. The use of claim 19, wherein said mutant EZH2 has one or more mutations selected from the group consisting of a substitution of glycine (G) for the wild type residue alanine (A) at amino acid position 677 of SEQ ID NO: 1 (A677G); a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 687 of SEQ ID NO: 1 (A687V); a substitution of methionine (M) for the wild type residue valine (V) at amino acid position 674 of SEQ ID NO: 1 (V674M); a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685H); a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 685 of SEQ ID NO: 1 (R685C); a substitution of serine (S) for the wild type residue asparagine (N) at amino acid position 322 of SEQ ID NO: 3 (N322S), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 288 of SEQ ID NO: 3 (R288Q), a substitution of isoleucine (I) for the wild type residue threonine (T) at amino acid position 573 of SEQ ID NO: 3 (T573I), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664E), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 458 of SEQ ID NO: 5 (R458Q), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 249 of SEQ ID NO: 3 (E249K), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 684 of SEQ ID NO: 3 (R684C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 628 of SEQ ID NO: 21 (R628H), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID NO: 5 (Q501H), a substitution of asparagine (N) for the wild type residue aspartic acid (D) at amino acid position 192 of SEQ ID NO: 3 (D192N), a substitution of valine (V) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664V), a substitution of leucine (L) for the wild type residue valine (V) at amino acid position 704 of SEQ ID NO: 3 (V704L), a

substitution of serine (S) for the wild type residue proline (P) at amino acid position 132 of SEQ ID NO: 3 (P132S), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 669 of SEQ ID NO: 21 (E669K), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 255 of SEQ ID NO: 3 (A255T), a substitution of valine (V) for the wild type residue glutamic acid (E) at amino acid position 726 of SEQ ID NO: 3 (E726V), a substitution of tyrosine (Y) for the wild type residue cysteine (C) at amino acid position 571 of SEQ ID NO: 3 (C571Y), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145C), a substitution of threonine (T) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693T), a substitution of serine (S) for the wild type residue phenylalanine (F) at amino acid position 145 of SEQ ID NO: 3 (F145S), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 109 of SEQ ID NO: 21 (Q109H), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 622 of SEQ ID NO: 21 (F622C), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 135 of SEQ ID NO: 3 (G135R), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 168 of SEQ ID NO: 5 (R168Q), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 159 of SEQ ID NO: 3 (G159R), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 310 of SEQ ID NO: 5 (R310C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 561 of SEQ ID NO: 3 (R561H), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 634 of SEQ ID NO: 21 (R634H), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 660 of SEQ ID NO: 3 (G660R), a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 181 of SEQ ID NO: 3 (Y181C), a substitution of arginine (R) for the wild type residue histidine (H) at amino acid position 297 of SEQ ID NO: 3 (H297R), a substitution of serine (S) for the wild type residue cysteine (C) at amino acid position 612 of SEQ ID NO: 21 (C612S), a substitution of tyrosine (Y) for the wild type residue histidine (H) at amino acid position 694 of SEQ ID NO: 3 (H694Y), a substitution of alanine (A) for the wild type residue aspartic acid (D) at amino acid position 664 of SEQ ID NO: 3 (D664A), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino

acid position 150 of SEQ ID NO: 3 (I150T), a substitution of arginine (R) for the wild type residue isoleucine (I) at amino acid position 264 of SEQ ID NO: 3 (I264R), a substitution of leucine (L) for the wild type residue proline (P) at amino acid position 636 of SEQ ID NO: 3 (P636L), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 713 of SEQ ID NO: 3 (I713T), a substitution of proline (P) for the wild type residue glutamine (Q) at amino acid position 501 of SEQ ID NO: 5 (Q501P), a substitution of glutamine (Q) for the wild type residue lysine (K) at amino acid position 243 of SEQ ID NO: 3 (K243Q), a substitution of aspartic acid (D) for the wild type residue glutamic acid (E) at amino acid position 130 of SEQ ID NO: 5 (E130D), a substitution of glycine (G) for the wild type residue arginine (R) at amino acid position 509 of SEQ ID NO: 3 (R509G), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 566 of SEQ ID NO: 3 (R566H), a substitution of histidine (H) for the wild type residue aspartic acid (D) at amino acid position 677 of SEQ ID NO: 3 (D677H), a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 466 of SEQ ID NO: 5 (K466N), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 78 of SEQ ID NO: 3 (R78H), a substitution of methionine (M) for the wild type residue lysine (K) at amino acid position 1 of SEQ ID NO: 6 (K6M), a substitution of leucine (L) for the wild type residue serine (S) at amino acid position 538 of SEQ ID NO: 3 (S538L), a substitution of glutamine (Q) for the wild type residue leucine (L) at amino acid position 149 of SEQ ID NO: 3 (L149Q), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 252 of SEQ ID NO: 3 (L252V), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 674 of SEQ ID NO: 3 (L674V), a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 656 of SEQ ID NO: 3 (A656V), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 731 of SEQ ID NO: 3 (Y731D), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 345 of SEQ ID NO: 3 (A345T), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 244 of SEQ ID NO: 3 (Y244D), a substitution of tryptophan (W) for the wild type residue cysteine (C) at amino acid position 576 of SEQ ID NO: 3 (C576W), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 640 of SEQ ID NO: 3 (N640K), a substitution of lysine (K) for the wild type residue asparagine

(N) at amino acid position 675 of SEQ ID NO: 3 (N675K), a substitution of tyrosine (Y) for the wild type residue aspartic acid (D) at amino acid position 579 of SEQ ID NO: 21 (D579Y), a substitution of isoleucine (I) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693I), and a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 693 of SEQ ID NO: 3 (N693K).

26. The use of claim 19, wherein said mutant EZH2 has a frameshift at amino acid position 730, 391, 461, 441, 235, 254, 564, 662, 715, 405, 685, 64, 73, 656, 718, 374, 592, 505, 730, or 363 of SEQ ID NO: 3, 5 or 21 or the corresponding nucleotide position of the nucleic acid sequence encoding SEQ ID NO: 3, 5, or 21.

27. The use of claim 19, wherein said mutant EZH2 has a deletion of glutamic acid (E) and leucine (L) at amino acid positions 148 and 149 of SEQ ID NO: 3, 5 or 21.

28. The use of claim 19, wherein said mutant EZH2 has a nonsense mutation at amino acid position 733, 25, 317, 62, 553, 328, 58, 207, 123, 63, 137, or 60 of SEQ ID NO: 3, 5 or 21.

29. The use of any of claims 9, 13, or 15, wherein said subject has demonstrated resistance to any one of the components of the composition according to any one of claims 1-7 when administered as a single agent.

30. The use of the composition according to any of claims 1-7 in the manufacture of a medicament for inhibiting cancer cell proliferation comprising contacting said cancer cell with the composition of any one of claims 1-7.

31. The use of the composition according to any of claims 1-7 in the manufacture of a medicament for inhibiting cancer cell proliferation comprising contacting said cancer cell with a compound of Formula (IIa), as defined in any of claims 1-7.and one or more other therapeutic agents, wherein Formula (IIa) and said other therapeutic agents are delivered simultaneously or sequentially.

32. The use of claim 31 wherein said compound of Formula (IIa) is administered prior to administration of said other therapeutic agents.

33. The use of the composition according to any of claims 1-7 in the manufacture of a medicament for inhibiting cancer cell proliferation comprising administering a

therapeutically effective dose of a compound of Formula (IIa), as defined in any of claims 1-7, or a pharmaceutically acceptable salt thereof, prior to administering a therapeutically effective dose of a composition of any one of claims 1-7.

34. The use of claims 13 or 31, wherein said other therapeutic agents is prednisone or prednisolone, or an analog or derivative thereof.

35. The use of any of claims 13, 15, 30, 31, or 33, wherein the cancer is lymphoma, leukemia, or melanoma.

36. The use of claim 35, wherein the lymphoma is selected from the group consisting of non-Hodgkin lymphoma, follicular lymphoma, and diffuse large B-cell lymphoma.

37. The use of claim 35, wherein the leukemia is chronic myelogenous leukemia (CML).

38. The use of claim 35, wherein the precancerous condition is myelodysplastic syndromes (MDS, formerly known as preleukemia).