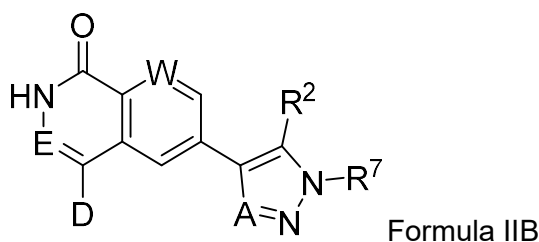
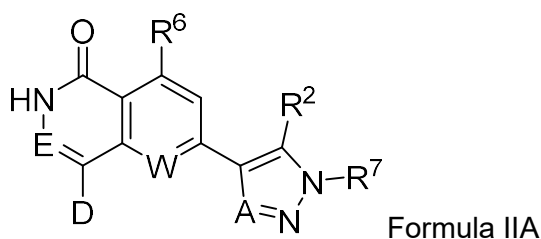
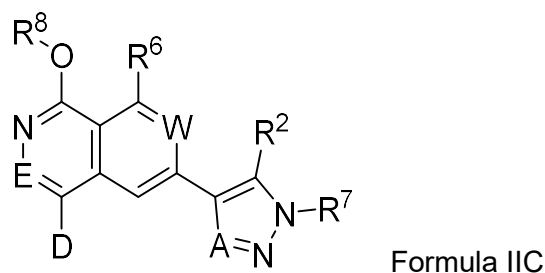


What is claimed is:

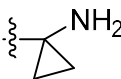
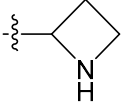
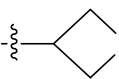
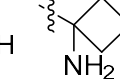
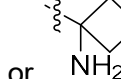
1. Use of a BCL-2 family inhibitor and a protein arginine N-methyl transferase 5 (PRMT5) inhibitor in the manufacture of a medicament for treating cancer in a subject, wherein: a therapeutically effective amount of the BCL-2 family inhibitor and a therapeutically effective amount of the protein arginine N-methyl transferase 5 (PRMT5) inhibitor are to be administered to the subject.
2. The use of claim 1, wherein the cancer is associated with a methylthioadenosine phosphorylase (MTAP) gene homozygous deletion.
3. The use of claim 1 or 2, wherein the PRMT5 inhibitor is a methylthioadenosine (MTA)-cooperative PRMT5 inhibitor.
4. The use of claim 1 or 2, wherein the cancer is lung cancer, non-small cell lung cancer, pancreatic cancer, colon cancer, bladder cancer, head and neck cancer, bladder cancer, esophageal cancer, diffuse large B cell lymphoma, lymphoma, stomach cancer, melanoma, breast cancer, brain cancer, cholangiocarcinoma, mesothelioma or malignant peripheral nerve sheath tumors.
5. The use of claim 3, wherein the cancer is mesothelioma.
6. The use of claim 3 or 4, wherein the cancer is non-small cell lung cancer.
7. The use of any of claims 1 to 6, wherein the PRMT5 inhibitor is compound of Formula IIA, IIB or IIC:

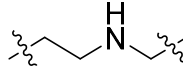




or a pharmaceutically acceptable salt thereof, wherein:

A is CR⁹ or N;

D is (C(R⁹)₂)₁₋₂-NH₂, , , , , or ; or D is

 where the methylene is bonded to E where E is C;

E is C, CR⁹ or N;

each L is independently a bond or C₁-C₃ alkylene;

W is CR⁹ or N;

each X is independently a bond, O, S, -NR⁴- or -NR⁴C(O)-;

each Z is independently a bond, -SO-, -SO₂-, -CH(OH)- or -C(O)-;

each R² is independently hydroxy, halogen, cyano, cyanomethyl, -(NR⁴)₂, hydroxyalkyl, alkoxy, -SO₂C₁-C₃alkyl, -X-(C₁-C₃ alkyl)-aryl, heteroalkyl, C₂-C₄ alkynyl, -X-haloalkyl, -X-C₁-C₅ alkyl, -Z-C₁-C₅ alkyl, heterocyclyl, -X-L-cycloalkyl, -Z-cycloalkyl, -X-aryl, -Z-aryl, or -X-heteroaryl, wherein the heterocyclyl, the cycloalkyl, the aryl and the heteroaryl are optionally substituted with one or more R⁵;

each R⁴ is independently hydrogen or C₁-C₃ alkyl;

each R⁵ is independently cyano, oxo, halogen, C₁-C₃ alkyl, hydroxyalkyl, hydroxy, alkoxy, alkoxy-C₁-C₃ alkyl, -X-haloalkyl, -Z-cycloalkyl, X-(C₁-C₃ alkyl)-aryl, X-(C₁-C₃ alkyl)-aryl substituted with cyano, -X-L-cycloalkyl optionally substituted with C₁-C₃ alkyl or oxo, -X-L-heteroaryl optionally substituted with one or more C₁-C₃ alkyl or oxo, -X-L-heterocyclyl optionally substituted with one or more C₁-C₃ alkyl or oxo, or -X-aryl;

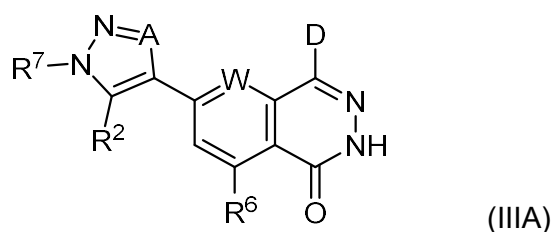
R⁶ is hydrogen, halogen, C₁-C₃ alkyl, haloalkyl, hydroxy, alkoxy, C₁-C₃ alkyl-alkoxy, N(R⁹)₂, NR⁹C(O)R⁹, C(O)R⁹, oxetane and THF;

R⁷ is H or C₁-C₃ alkyl optionally substituted with one or more halogen;

R⁸ is H or C₁-C₃ alkyl; and

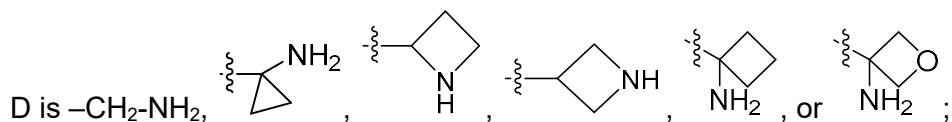
each R⁹ is independently H or C₁-C₃ alkyl, halogen or haloalkyl.

8. The use of any of claims 1 to 7, wherein the PRMT5 inhibitor is compound of Formula IIIA:



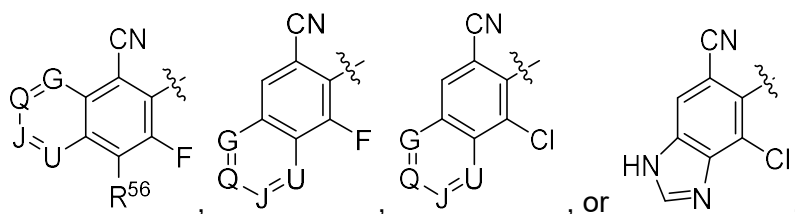
or a pharmaceutically acceptable salt thereof, wherein

A is CR⁹ or N;



W is CR⁹ or N, where R⁹ is H or C₁-C₃ alkyl;

R² is



where R⁵⁶ is hydrogen, fluoro, chloro, or methyl,

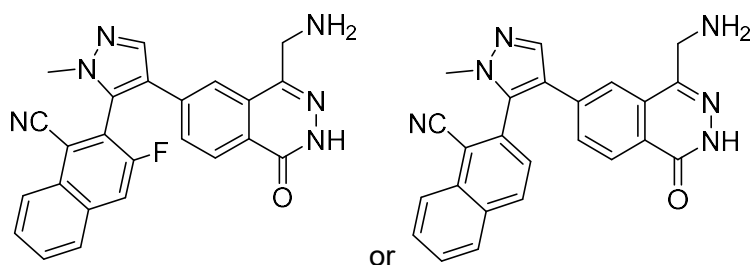
G, Q, J and U are independently selected from C(H), C(R⁵), and N, provided only one or two of G, Q, J, and U can be N;

each R⁵ is independently hydroxy, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkoxy, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, or C₁-C₃ alkoxyC₁-C₃ alkyl;

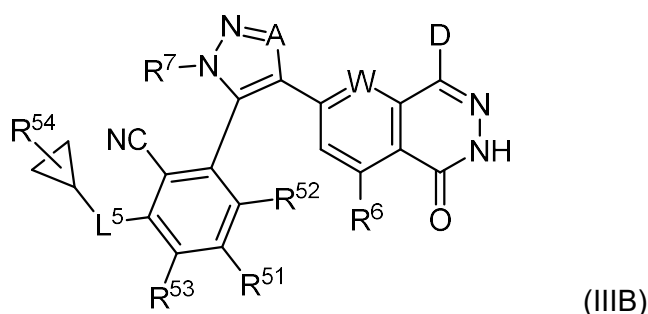
R⁶ is hydrogen, halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, C₁-C₃ alkoxyC₁-C₃ alkyl, C₃-C₆ heterocycloalkyl, -C(O)-C₁-C₃ haloalkyl, or -NR¹⁵(CO)R¹⁶, where R¹⁵ is hydrogen or methyl, and R¹⁶ is C₁-C₃ alkyl; and

R⁷ is C₁-C₃ alkyl or C₁-C₃ haloalkyl.

9. The use of claim 8, wherein the PRMT5 inhibitor is:

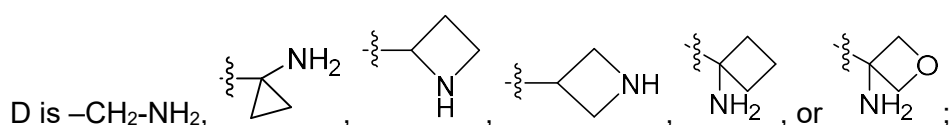


10. The use of any of claims 1 to 9, wherein the PRMT5 inhibitor is compound of Formula IIIB:



or a pharmaceutically acceptable salt thereof, wherein

A is CR⁹ or N;



W is CR⁹ or N, where R⁹ is H or C₁-C₃ alkyl;

R⁵¹ is hydrogen, fluoro, chloro, or methyl, or R⁵¹ and R⁵² together with atoms to which they are attached form a C₄-C₆ heterocycloalkyl (e.g., hydrofuranyl);

R⁵² is fluoro, chloro, or methyl, or R⁵² and R⁵³ together with atoms to which they are attached form a phenyl;

R⁵³ is hydrogen, fluoro, chloro, or methyl;

R⁵⁴ is hydrogen, halogen, C₁-C₃ alkyl, or C₁-C₃ alkoxy;

L⁵ is -O- or -CH₂-;

R⁶ is hydrogen, halogen, C₁-C₆ alkyl, hydroxy, C₁-C₆ alkoxy, C₁-C₃ alkoxyC₁-C₃ alkyl, C₃-C₆ heterocycloalkyl, -C(O)-C₁-C₃ haloalkyl, or -NR¹⁵(CO)R¹⁶, where R¹⁵ is hydrogen or methyl, and R¹⁶ is C₁-C₃ alkyl;

R⁷ is C₁-C₃ alkyl or C₁-C₃ haloalkyl.

11. The use of claim 10, wherein:

A is -CH or -CCH₃;

D is -CH₂-NH₂;

W is -CH, -CCH₃, or N;

R⁵¹, R⁵², R⁵³, and R⁵⁴ are each independently selected from hydrogen, fluoro, chloro, or methyl;

L⁵ is -O-;

R⁶ is hydrogen, fluoro, chloro, or methyl; and

R⁷ is C₁-C₂ alkyl or C₁-C₂ haloalkyl.

12. The use of claim 10 or claim 11, wherein:

A and W are -CH;

D is -CH₂-NH₂;

R⁵¹, R⁵², and R⁵³ are each independently selected from hydrogen, fluoro, chloro, and methyl;

R⁵⁴ is hydrogen;

L⁵ is -O-;

R⁶ is hydrogen; and

R⁷ is methyl.

13. The use of any of claims 10-12, wherein:

A and W are -CH;

D is -CH₂-NH₂;

R⁵¹ and R⁵² are each independently selected from fluoro, chloro, and methyl;

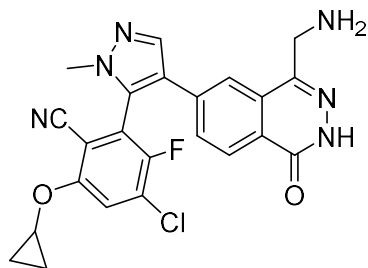
R⁵³ and R⁵⁴ are hydrogen;

L⁵ is -O-;

R⁶ is hydrogen; and

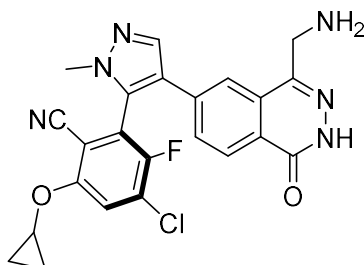
R⁷ is methyl.

14. The use of claim 10, wherein the PRMT5 inhibitor is:



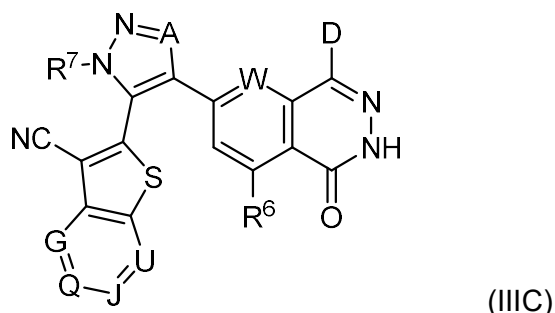
or a pharmaceutically acceptable salt thereof.

15. The use of claim 11, wherein the PRMT5 inhibitor is:



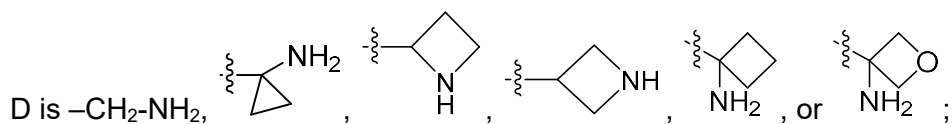
or a pharmaceutically acceptable salt thereof.

16. The use of any of claims 1 to 10, wherein the PRMT5 inhibitor is compound of Formula IIIC:



or a pharmaceutically acceptable salt thereof, wherein

A is CR⁹ or N;



W is CR⁹ or N, where R⁹ is H or C₁-C₃ alkyl;

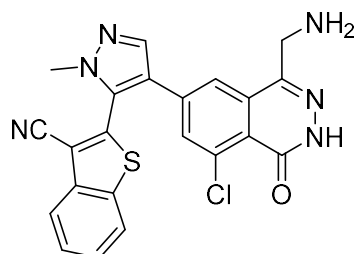
G, Q, J and U are independently selected from C(H), C(R⁵), and N, provided only one or two of G, Q, J, and U can be N;

each R⁵ is independently hydroxy, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₃-C₆ cycloalkoxy, C₃-C₆ cycloalkyl, C₃-C₆ heterocycloalkyl, or C₁-C₃ alkoxyC₁-C₃ alkyl;

R⁶ is hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ haloalkyl, hydroxy, C₁-C₆ alkoxy, C₁-C₃ alkoxyC₁-C₃ alkyl, C₃-C₆ heterocycloalkyl, -C(O)-C₁-C₃ haloalkyl, -N(R⁹)₂, or -NR¹⁵(CO)R¹⁶, where each R⁹ is independently H or C₁-C₃ alkyl, R¹⁵ is hydrogen or methyl, and R¹⁶ is C₁-C₃ alkyl; and

R⁷ is C₁-C₃ alkyl or C₁-C₃ haloalkyl.

17. The use of claim 16, wherein the PRMT5 inhibitor is:

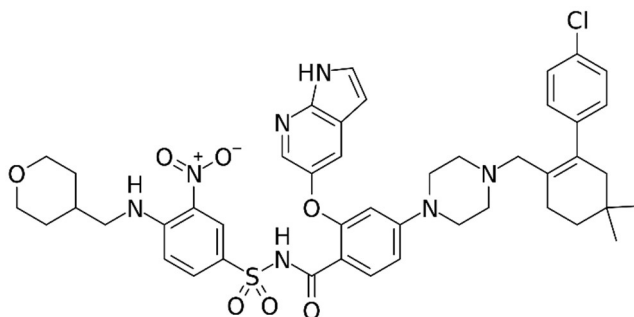


or a pharmaceutically acceptable salt thereof.

18. The use of any one of claims 1 to 17, wherein the therapeutically effective amount of the PRMT5 inhibitor is in the range of about 0.01 to 300 mg/kg per day.

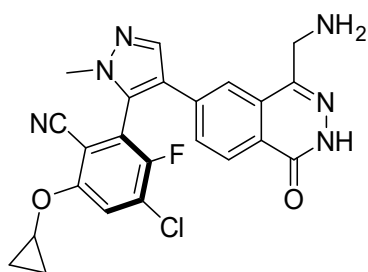
19. The use of any one of claims 1 to 17, wherein the therapeutically effective amount of the PRMT5 inhibitor is in the range of about 0.1 to 100 mg/kg per day.
20. The use of any one of claims 1 to 17, wherein the therapeutically effective amount of the PRMT5 inhibitor is less than 1% of, e.g., less than 10%, or less than 25%, or less than 50% of the clinically-established therapeutic amount.
21. The use of any one of claims 1-20, wherein the BCL-2 family inhibitor is selected from one or more of: ABT-199 (venetoclax), ABT-263 (navitoclax), A-1155463, A-1331852, obatoclax (GX15-070), ABT-737, TW-37, gossypol, (R)-(-)-gossypol, HA14-1, sabutoclax and DT2216).
22. The use of any one of claims 1-21, wherein the BCL-2 family inhibitor comprises ABT-199.
23. The use of claim 22, wherein the BCL-2 family inhibitor is ABT-199.
24. The use of any one of claims 1-21, wherein the BCL-2 family inhibitor comprises ABT-263.
25. The use of claim 24, wherein the BCL-2 family inhibitor is ABT-263.
26. The use of any one of claims 1 to 25, wherein the therapeutically effective amount of the BCL-2 family inhibitor is in the range of about 1 to 500 mg/m² per day.
27. The use of any one of claims 1 to 25, wherein the therapeutically effective amount of the BCL-2 family inhibitor is in the range of about 10 to 300 mg/m² per day.
28. The use of any one of claims 1 to 27, wherein the therapeutically effective amount of the BCL-2 family inhibitor is less than 1% of, e.g., less than 10%, or less than 25%, or less than 50% of the clinically-established therapeutic amount.
29. The use of any of claims 1 to 28, wherein the BCL-2 family inhibitor and the PRMT5 inhibitor are to be administered sequentially.
30. The use of any of claims 1 to 28, wherein the BCL-2 family inhibitor and the PRMT5 inhibitor are to be administered simultaneously.
31. The use of any one of claims 1 to 30, wherein the subject previously received or completed a first-line chemotherapy.

32. The use of claim 31, wherein the first-line chemotherapy is gemcitabine, nab-paclitaxel, 5-FU, irinotecan, oxaliplatin, capecitabine, cisplatin, carboplatin, fludarabine, cyclophosphamide, fluoropyrimidine, pemetrexed, doxorubicin, ifosfamide, epirubicin or paxlitaxel.



33. Use of ABT-199 (venetoclax):

; and

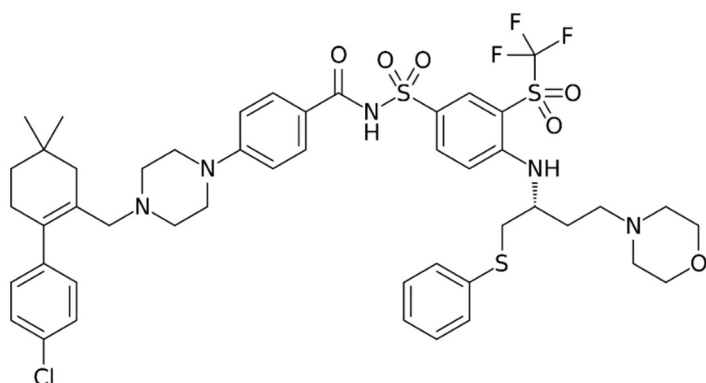


a PRMT5 inhibitor of formula:

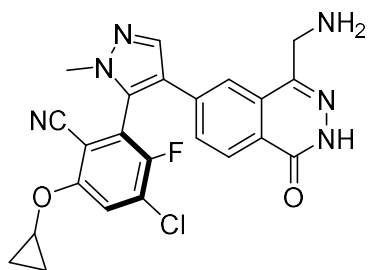
in the manufacture of a

medicament for treating cancer in a subject, wherein a therapeutically effective amount of ABT-199 (venetoclax) and a therapeutically effective amount of the PRMT5 inhibitor are to be administered to the subject.

34. Use of ABT-263 (navitoclax):



; and



a PRMT5 inhibitor of formula:  in the manufacture of a medicament for treating cancer in a subject, wherein a therapeutically effective amount of ABT-199 (venetoclax) and a therapeutically effective amount of the PRMT5 inhibitor are to be administered to the subject.