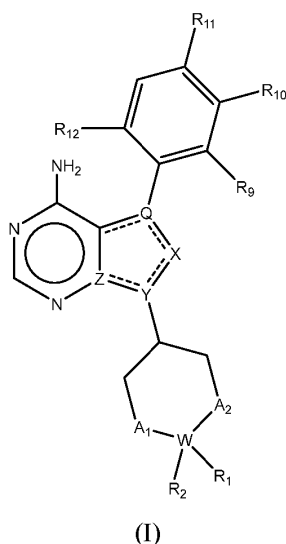


CLAIMS

We claim:

1. A compound of Formula (I):



wherein

each Q, Y and Z are independently selected from N and C, and X is N or C-R^a;

provided that at least one of Q, X, Y and Z is N, and

each dashed bond is independently a single or double bond such that the bicycle they form is a heteroaryl;

R₁ is selected from alkyl, alkenyl, alkynyl, amino, acylamino, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, aryl, arylalkyl, heteroaryl, and heteroaralkyl;

either

a) W is N, R₂ is absent, and A₁ and A₂ are each CH₂;

b) W is C, R₂ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, and amino, and A₁ and A₂ are each independently selected from CH₂ and O; or

c) W is C, and R₁ and R₂ are taken together to form a =CH₂-amido, cycloalkyl, and heterocyclyl, and A₁ and A₂ are each independently selected from CH₂ and O;

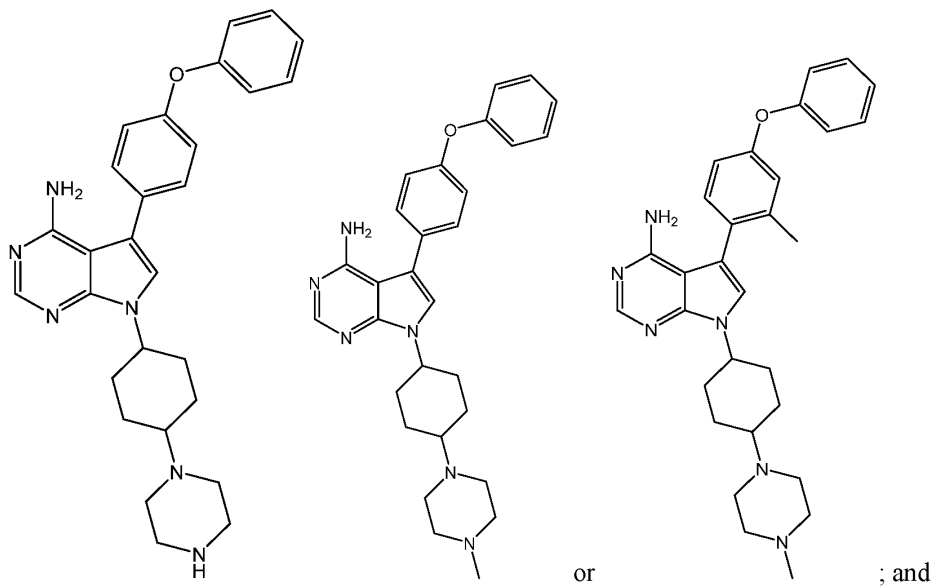
R^a is selected from H, halo, CN and alkyl;

R₉ is selected from H, halo, alkyl, alkoxy, hydroxy, acyloxy, and amino;

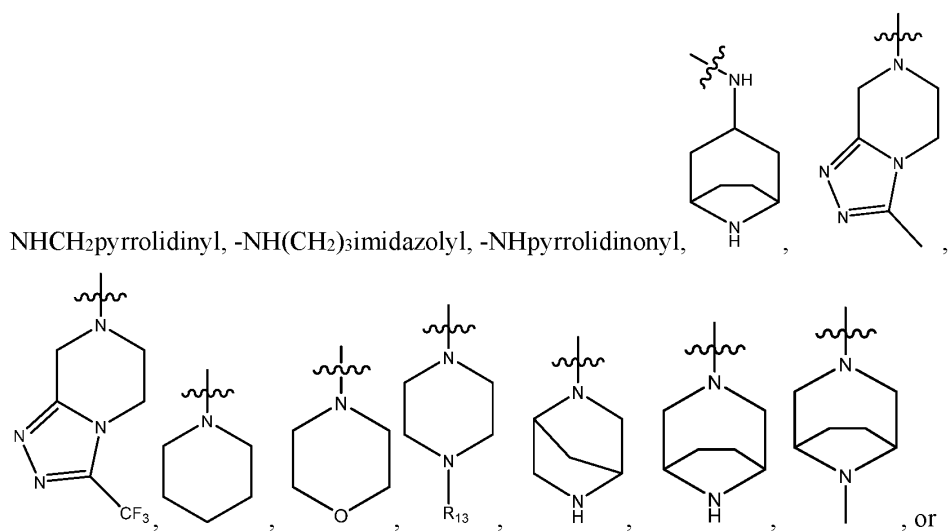
R₁₀ is H or alkoxy;

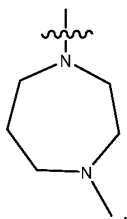
R₁₁ is aryloxy, heteroaryloxy, arylalkyl, alkoxycarbonyl, ureido or -C(O)-aryl; and

R₁₂ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, and acyloxy;
provided that the compound of Formula (I) is not



if W is C, R₂, R₉ and R₁₂ are each hydrogen, and R₁₁ is unsubstituted phenoxy, then
R₁ is not -NHCH₂OH, -NHCH₂COOH, -NHCH₂CONH₂, -NHCH₂CH₂NH₂, -
NH(CH₂)₂N(Me)₂, -NHCH₂-pyridinyl, -NHCO-pyridyl, -C(O)OEt, -NH-tetrahydropyran, -

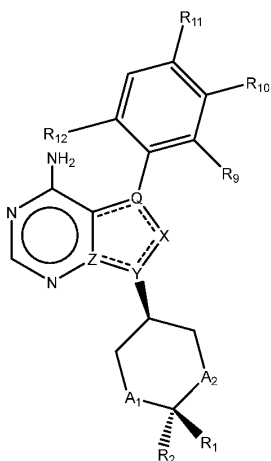




wherein R_{13} is selected from H, ethyl, isopropyl, t-butyl, $-\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{CH}_2\text{OCH}_3$; and

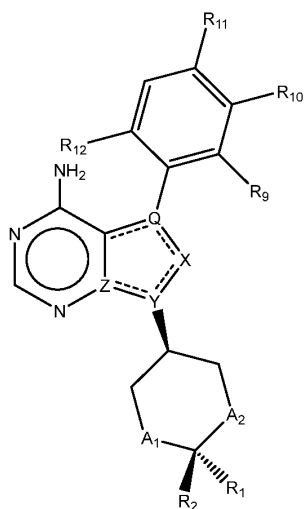
if W is N, R_9 and R_{12} are each hydrogen, and R_{11} is unsubstituted phenyloxy, then R_1 is not piperidinyl.

2. The compound of claim 1, having the structure:



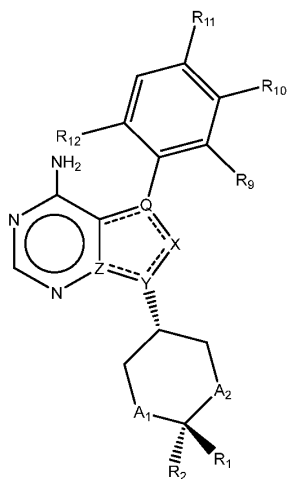
wherein R_2 is H.

3. The compound of claim 1, having the structure:



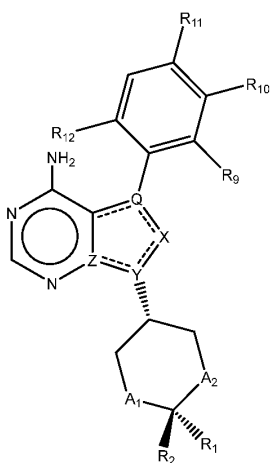
wherein R₂ is H.

4. The compound of claim 1, having the structure:

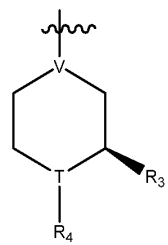


wherein R₂ is H.

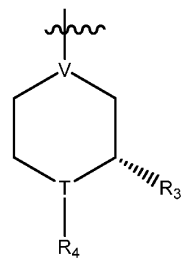
5. The compound of claim 1, having the structure:



wherein R₂ is H.

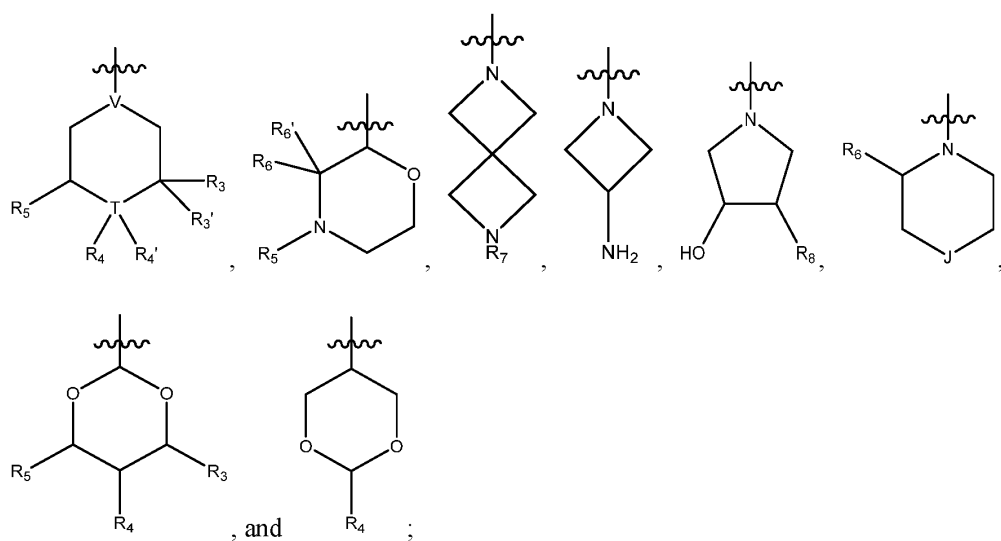


6. The compound of any one of claims 1-5, wherein R₁ is
 V is N or CH;
 T is N or CH;
 R₃ is alkyl; and
 R₄ is H or alkyl.



7. The compound of any one of claims 1-5, wherein R₁ is
 V is N or CH;
 T is N or CH;
 R₃ is alkyl; and
 R₄ is H or alkyl.

8. The compound of any one of claims 1-7, wherein
Q is C, X is C-R^a, R^a is H, Y is N and Z is C;
Q is C, X is C-R^a, R^a is halo, Y is N and Z is C;
Q is C, X is N, Y is C and Z is N;
Q is C, X is N, Y is N and Z is C;
Q is N, X is C-R^a, R^a is H, Y is C and Z is C;
Q is C, X is C-R^a, R^a is H, Y is C and Z is N; or
Q is C, X is C-R^a, R^a is H, Y is N and Z is C.
9. The compound of any one of claims 1-8, wherein
Q is C, X is N, Y is C and Z is N;
Q is C, X is C-R^a, R^a is H, Y is N and Z is C; or
Q is C, X is N, Y is N and Z is C.
10. The compound of any one of claims 1-9, wherein A₁ and A₂ are both CH₂.
11. The compound of any one of claims 1-9, wherein A₁ and A₂ are both O.
12. The compound of any one of claims 1-11, wherein W is N and R₂ is absent.
13. The compound of any one of claims 1-11, wherein W is C.
14. The compound of claim 13, wherein R₂ is selected from H, hydroxy and amino.
15. The compound of any one of claims 1-14, wherein R₁ is selected from alkyl, amino, cycloalkyl, heterocyclyl, heterocyclalkyl, and heteroaryl.
16. The compound of any one of claims 1-15, wherein R₁ is a 6-membered heterocyclyl.
17. The compound of claim 16, wherein the 6-membered heterocyclyl comprises 2 nitrogen ring atoms.
18. The compound of claim 17, wherein R₁ is a 1,4-piperazinyl ring.
19. The compound of any one of claims 1-15, wherein R₁ is selected from



V is N or CH;

either T is N and R_4' is absent, or T is C;

J is selected from sulfonyl, C(H)sulfonamido, and >P(=O)-alkyl;

R₃ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, amino, amido, cycloalkyl, heterocyclyl, carboxy, and alkoxy carbonyl;

R₃' is H or alkyl, or

R₃ and R₃' taken together with the carbon atom to which they are attached form a cycloalkyl;

R₄ is selected from H, halo, CN, alkyl, alkoxy, acyloxy, amino, and amido;

R₄' is H or alkyl;

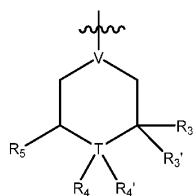
R₅ is H or alkyl;

R_6 and R_6' are each H;

R₆ and R₆' together with the carbon atom to which they are attached form an oxo;

R₇ is H or alkyl; and

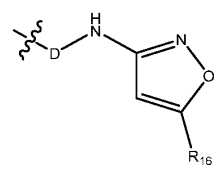
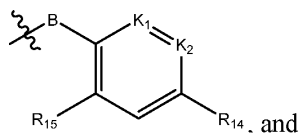
R₈ is H, hydroxy, acyloxy, or amino.



20. The compound of claim 19, wherein R₁ is

21. The compound of claim 20, wherein V is N.
22. The compound of claim 20, wherein V is CH.
23. The compound of any one of claims 20-22, wherein T is N.
24. The compound of any one of claims 20-22, wherein T is C.
25. The compound of claim 19 or 20, wherein
W is C,
R₂ is H,
V is CH, and
T is N.
26. The compound of claim 19 or 20, wherein
W is C,
R₂ is H,
V is N and
T is C.
27. The compound of claim 19 or 20, wherein
W is C,
R₂ is H,
V is N and
T is N.
28. The compound of claim 19 or 20, wherein
W is N,
R₂ is absent,
V is CH and
T is N.
29. The compound of any one of claim 19-28, wherein R₃ is selected from H, alkyl, amino, cycloalkyl, heterocyclyl, carboxy, and alkoxycarbonyl.

30. The compound of any one of claims 19-29, wherein R₃ is H.
31. The compound of any one of claims 19-29, wherein R₃ is alkyl.
32. The compound of claim 31, wherein R₃ is methyl.
33. The compound of any one of claim 19-32, wherein each R₄ is independently selected from H, alkyl, amino, and amido.
34. The compound of any one of claim 19-33, wherein R₄ is H.
35. The compound of any one of claim 19-33, wherein R₄ is alkyl.
36. The compound of claim 35, wherein R₄ is methyl.
37. The compound of any one of claim 19-36, wherein R₅ is H.
38. The compound of any one of claims 19-37, wherein R₉ is H or halo.
39. The compound of any one of claims 19-38, wherein R₉ is H.
40. The compound of any one of claims 19-37, wherein R₉ is selected from halo, alkyl, alkoxy, hydroxy, acyloxy, and amino.
41. The compound of any one of claims 19-38, wherein R₉ is halo.
42. The compound of any one of claims 19-38, wherein R₉ is F.
43. The compound of any one of claims 19-42, wherein R₁₂ is H or halo.
44. The compound of any one of claims 19-43, wherein



R₁₁ is selected from amido,

B is selected from -O-, CH₂, CHOH, NH, N(C₁₋₆alkyl) and carbonyl;

K₁ and K₂ are independently selected from N and CR₁₃;

D is selected from -CH₂-C(O)-, -NH-C(O)-, N(C₁₋₆alkyl)-C(O), and -CH₂S(O)₂-;

R₁₃ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxy carbonyl, amino, amido, and alkoxy carbonyl;

R₁₄ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxy carbonyl, amino, amido, and alkoxy carbonyl;

R₁₅ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, alkoxy carbonyl, amino, amido, and alkoxy carbonyl; and

R₁₆ is selected from H, halo, CN, alkyl, alkoxy, hydroxy, acyloxy, amino, amido, and alkoxy carbonyl.

45. The compound of claim 44, wherein B is -O-.

46. The compound of claim 44 or 45, wherein K₁ is CR₁₃.

47. The compound of any one of claims 44-46, wherein R₁₃ is selected from H, halo, CN, and alkyl.

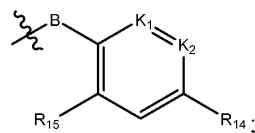
48. The compound of any one of claims 44-46, wherein R₁₃ is H or F.

49. The compound of any one of claims 44-48, wherein R₁₄ is H or alkyl.

50. The compound of any one of claims 44-49, wherein R₁₅ is H or halo.

51. The compound of any one of claims 44-50, wherein D is -NHC(O)-.

52. The compound of any one of claims 44-51, wherein R₁₆ is H or alkyl.



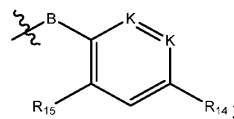
53. The compound of claim 44, wherein R₁₁ is

B is O;

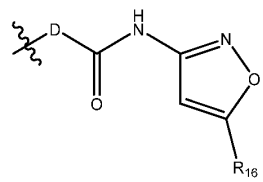
K₁ and K₂ are each CH;

R₁₄ is H; and

R₁₅ is H.



54. The compound of claim 44, wherein R₁₁ is K₁ and K₂ are each N; and R₁₄ and R₁₅ are each H.



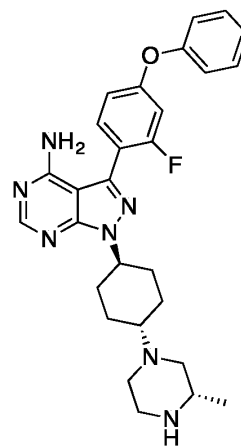
55. The compound of claim 44, wherein R₁₁ is D is NH; and R₁₆ is alkyl.

56. A method of co-inhibiting HCK and BCL-2 in a cell, comprising contacting the cell with a compound of formula (I) according to any one of claims 1-55 and a BCL-2 inhibitor.
57. A method of killing a cell having an FLT3-ITD mutation, comprising contacting the cell with a compound of formula (I) according to any one of claims 1-55 and a BCL-2 inhibitor.
58. The method of claim 56 or 57, wherein the compound of formula (I) is a HCK inhibitor.
59. The method of any one of claims 56-58, further comprising contacting the cell with an FLT3-ITD inhibitor.
60. The method of claim 58, wherein the HCK inhibitor is a dual HCK/FLT3-ITD inhibitor.
61. A method of treating acute myeloid leukemia, comprising conjointly administering to a subject a compound of formula (I) according to any one of claims 1-55 and a BCL-2 inhibitor.
62. The method of claim 61, wherein the subject has FLT3-ITD+ acute myeloid leukemia.

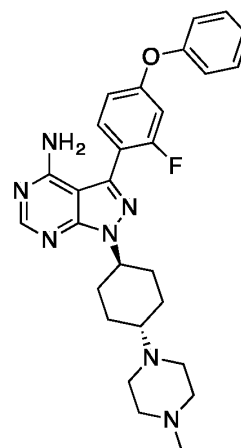
63. The method of claim 61 or 62, wherein the subject has malignant hematopoiesis and/or non-malignant multilineage hematopoiesis characterized by cells having one or more mutations in a gene selected from DNMT3A, IDH2, IDH1, NPM1, TET2, CEBPA, ASXL1, EZH2, SETBP1, SMC3, KIT, NRAS, and WT1.
64. The method of any one of claims 61-63, wherein the compound of formula (I) is a HCK inhibitor.
65. The method of any one of claims 61-64, further comprising conjointly administering a FLT3-ITD inhibitor.
66. The method of claim 64, wherein the HCK inhibitor is a dual HCK/FLT3-ITD inhibitor.
67. The method of claim 65 or 66, wherein the HCK inhibitor, the FLT3-ITD inhibitor, and the BCL-2 inhibitor are administered simultaneously or sequentially in separate unit dosage forms.
68. The method of claim 64, comprising administering a single unit dosage form comprising an HCK inhibitor, a BCL-2 inhibitor, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
69. The method of claim 68, wherein the single unit dosage form further comprises an FLT3-ITD inhibitor, or wherein the HCK inhibitor is a dual HCK/FLT3-ITD inhibitor.
70. The method of any one of claims 59, 65, 67, and 69, wherein the FLT3-ITD inhibitor is selected from AC220, sorafenib, PKC412, CEP-701, UNC2025, MLN518, KW-2449 and AMG-925, sunitinib, SU5614, AC2206, crenolanib, and PLX3397.
71. The method of any preceding claim, wherein the BCL-2 inhibitor is selected from AT-101, TW-37, TM-1206, gossypolic acid, gossypolonic acid, apogossypol, apogossypolone, A385358, ABT-737, ABT-263, ABT-199, WEHI-539, BXI-61, BXI-72, obatoclax, JY-1-106, and SAHB peptides.
72. The method of claim 71, wherein the BCL-2 inhibitor is selected from gossypol,

obatoclax, ABT-737, ABT-199, and ABT-263.

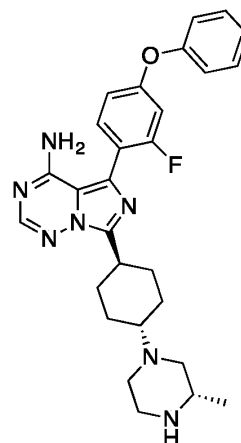
73. The method of claim 72, wherein the BCL-2 inhibitor is ABT-199.



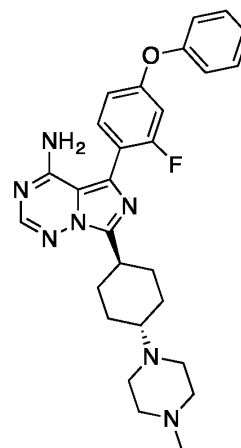
74. The method of claim 73, wherein the HCK inhibitor is
the BCL-2 inhibitor is ABT-199.



75. The method of claim 73, wherein the HCK inhibitor is
the BCL-2 inhibitor is ABT-199.



76. The method of claim 73, wherein the HCK inhibitor is
the BCL-2 inhibitor is ABT-199. and



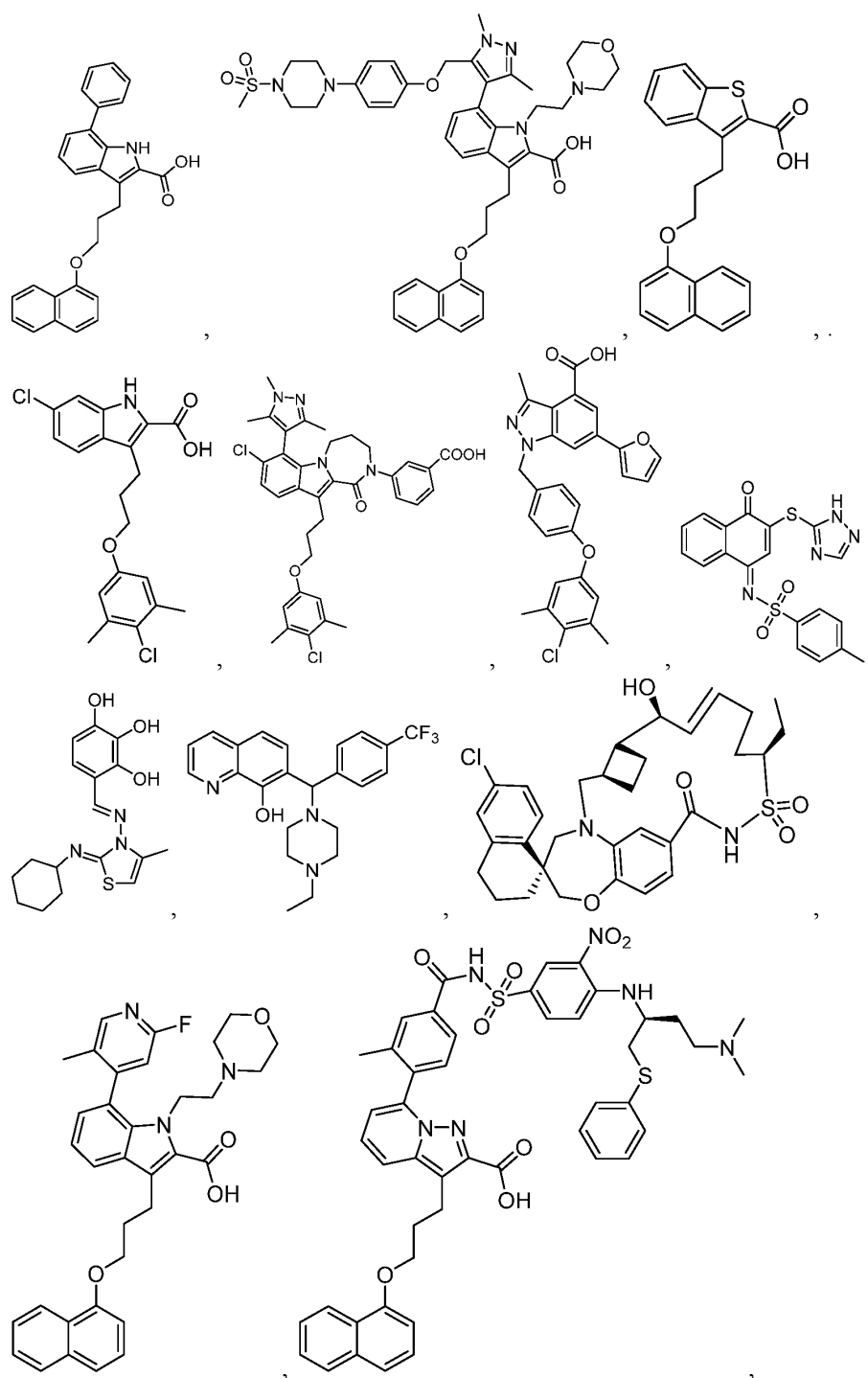
77. The method of claim 73, wherein the HCK inhibitor is
the BCL-2 inhibitor is ABT-199. and

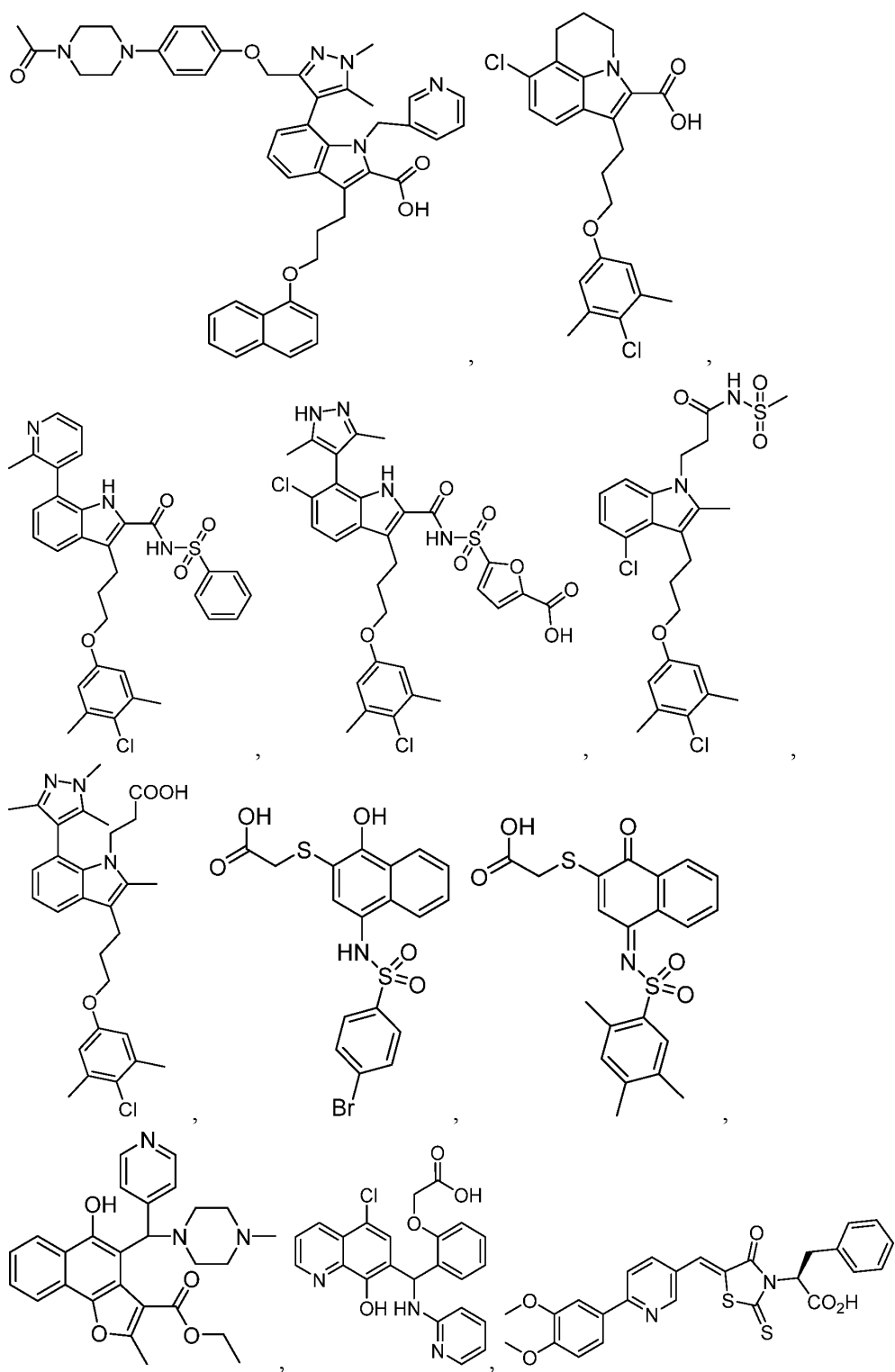
78. The method of claim 73, wherein the FLT3-ITD inhibitor is AC220 and the BCL-2 inhibitor is ABT-199.

79. The method of claim 72, wherein the FLT3-ITD inhibitor is SU5614 and the BCL-2 inhibitor is ABT-737.

80. The method of any preceding claim, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is each present as a pharmaceutically acceptable salt.

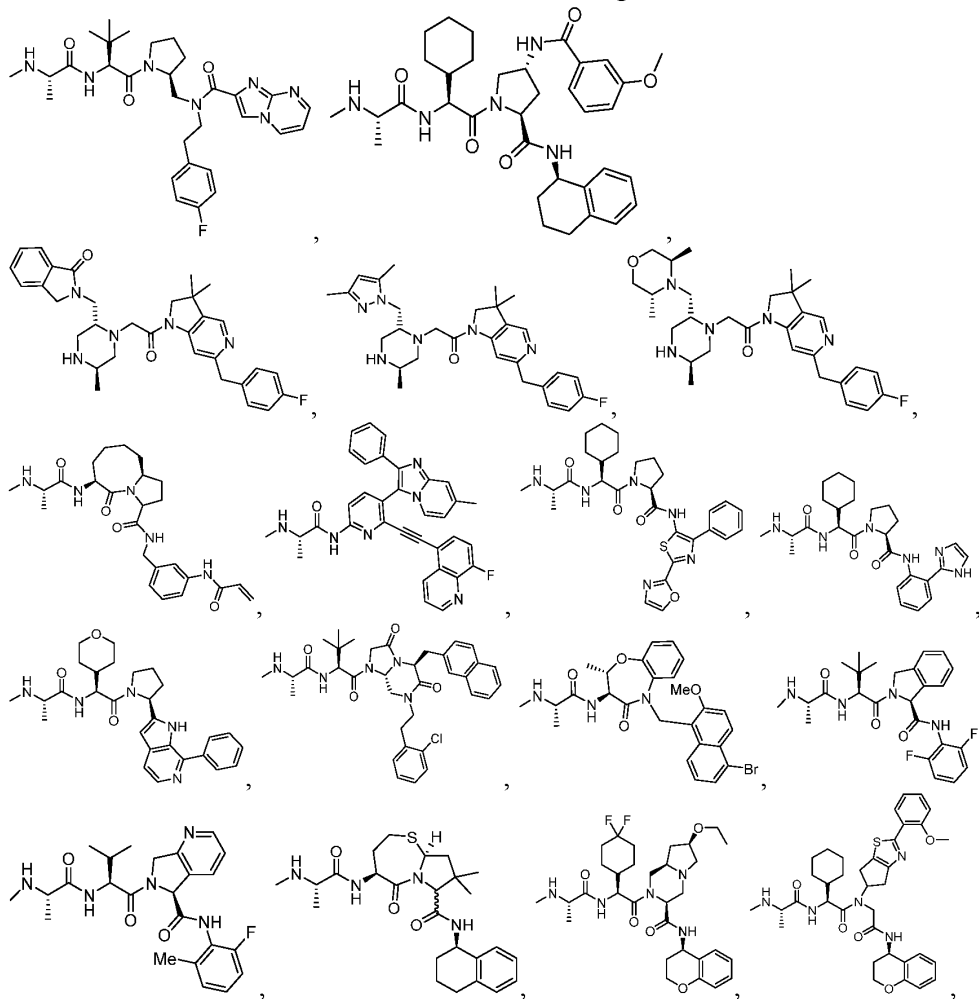
81. The method of any preceding claim, wherein the HCK inhibitor, and/or FLT3-ITD

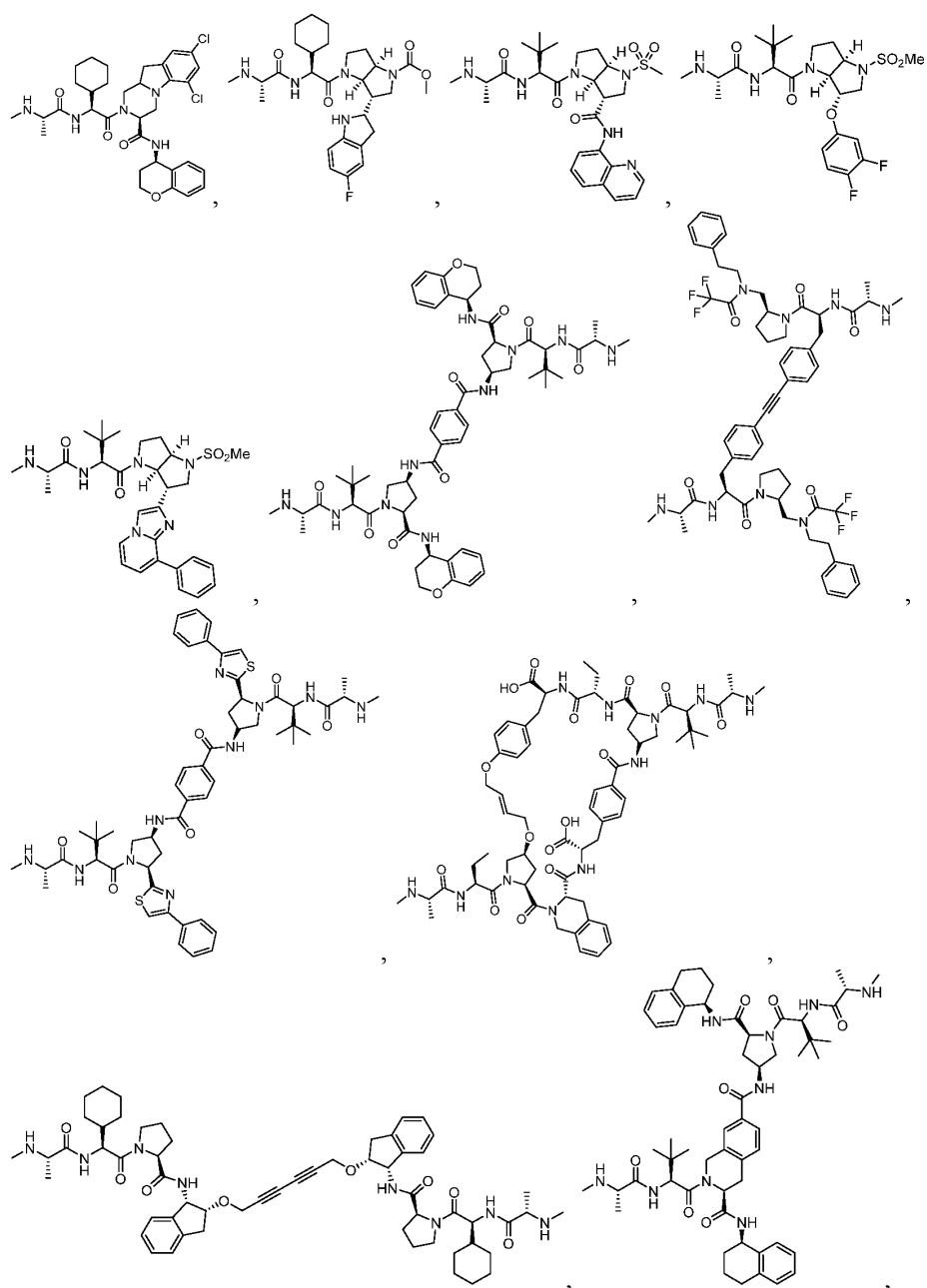


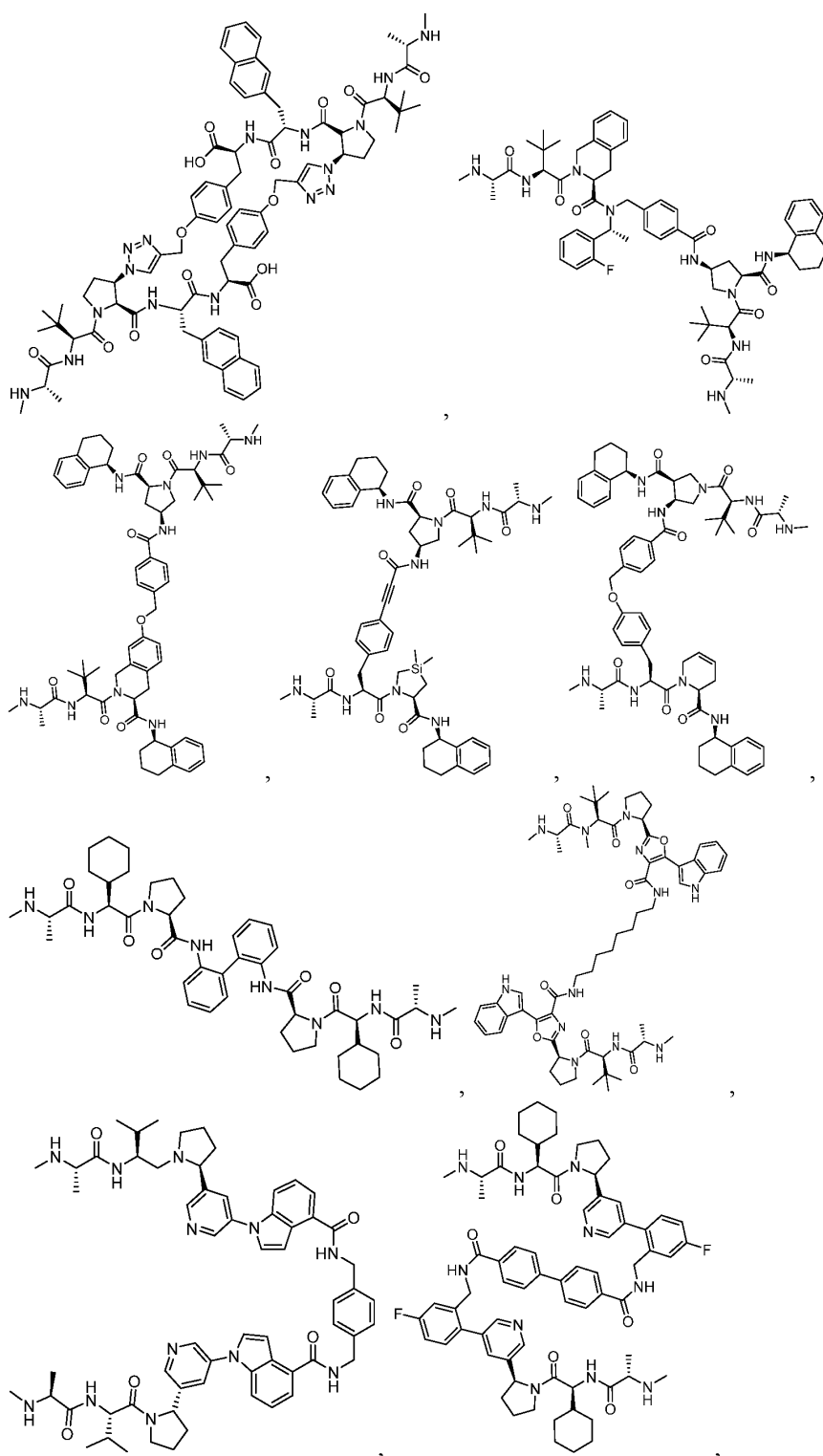


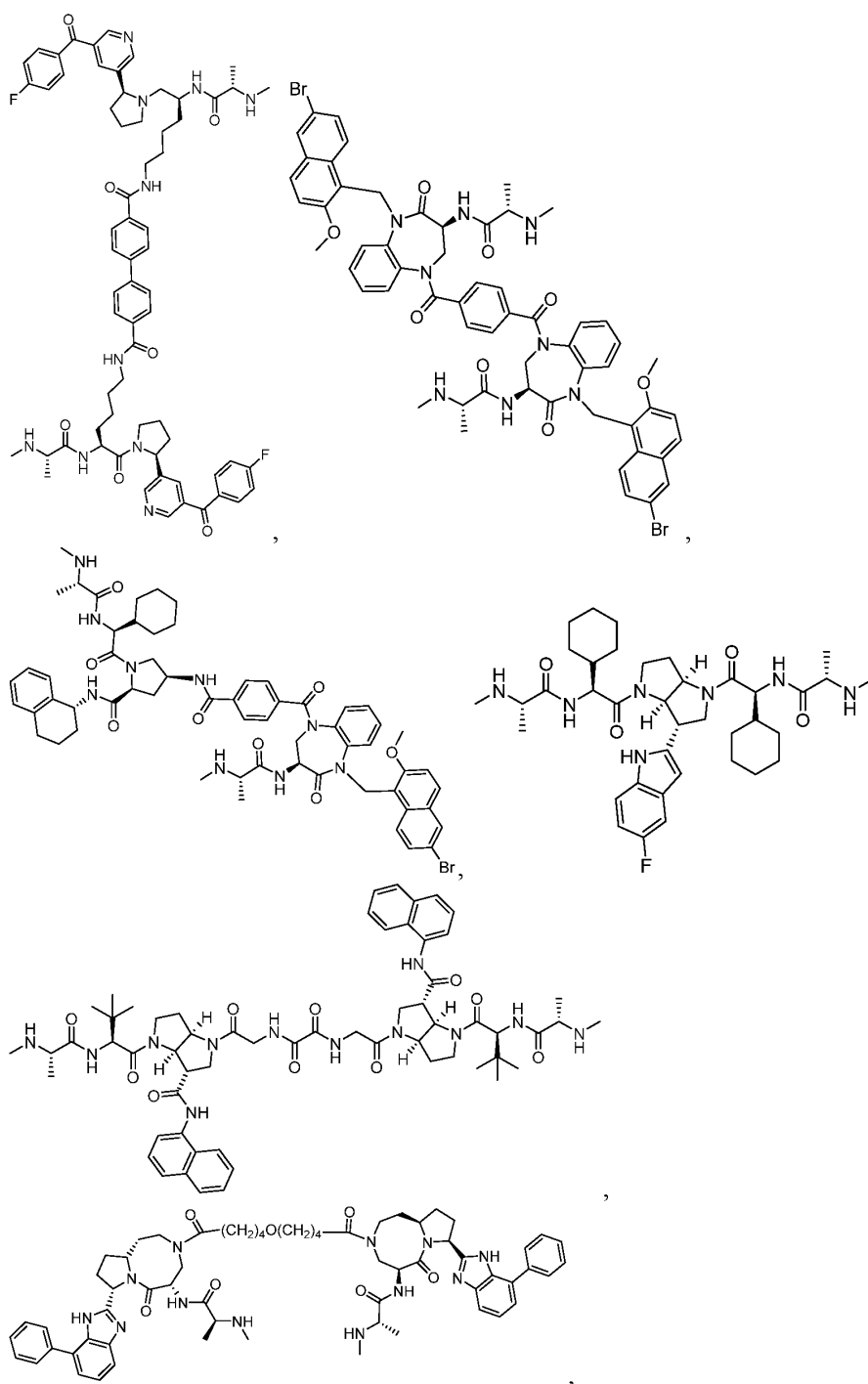


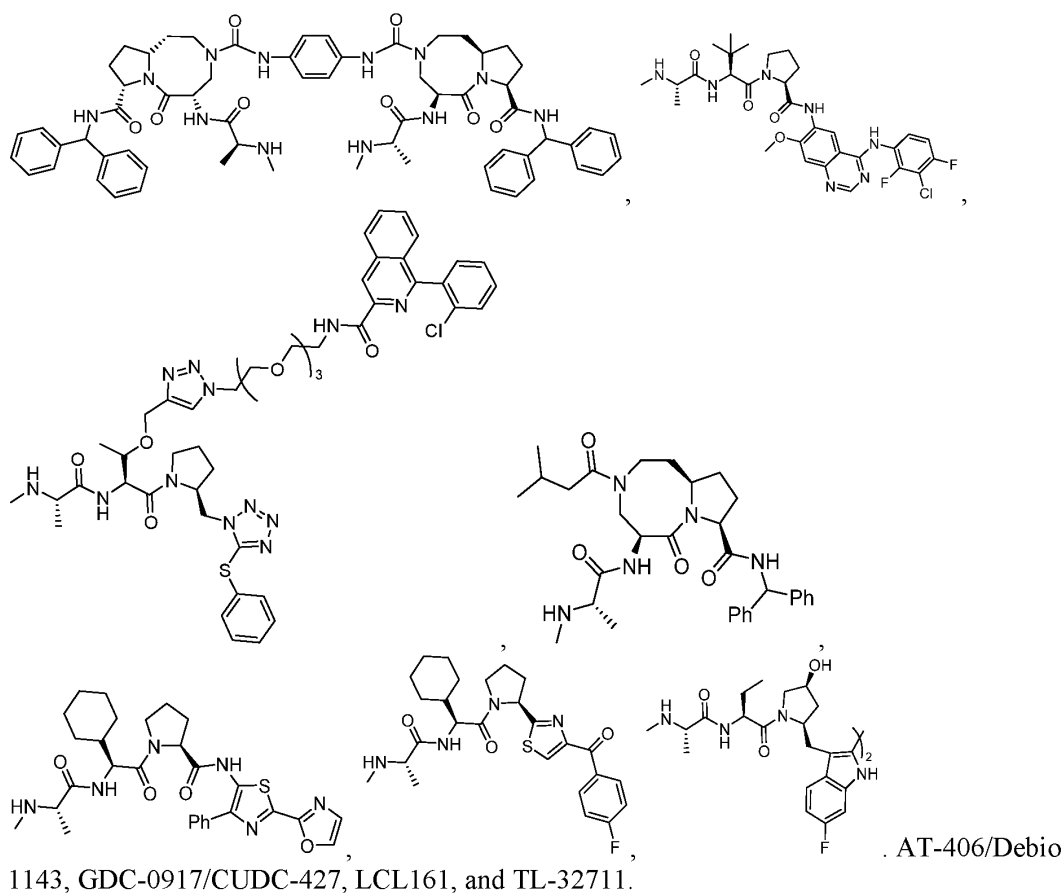
88. The method of claim 87, wherein the IAP antagonist is











89. The method of any preceding claim, wherein the HCK inhibitor, and/or FLT3-ITD inhibitor, and/or the BCL-2 inhibitor is administered conjointly with a cell-cycle inhibitor.

90. The method of claim 89, wherein the cell cycle inhibitor is selected from palbociclib, ribociclib, abemaciclib, flavopiridol, AT9283, alisertib, and MK-1775.