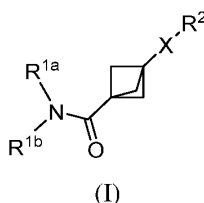


CLAIMS

What is claimed is:

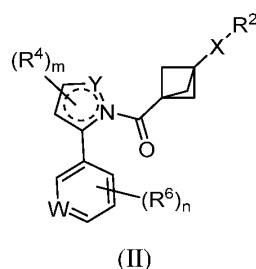
1. A compound of structural Formula I:



or a salt thereof, wherein:

- X is alkylene and is optionally substituted with one or more R⁷,
- or X is chosen from carbamoyl, carbonyl, and a bond;
- R^{1a} and R^{1b} are independently chosen from H and alkyl, which is optionally substituted with one R³, and which is optionally substituted with one or more R⁴,
- or R^{1a} and R^{1b}, together with the intervening nitrogen, combine to form heterocycloalkyl or heteroaryl, either of which is optionally substituted with one R³, and either of which is optionally substituted with one or more R⁴;
- R² is chosen from hydrogen, hydroxy, cyano, and halo,
- or R² is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R⁵;
- R³ is chosen from aryl, (aryl)oxy, heteroaryl, (heteroaryl)oxy, cycloalkyl, and heterocycloalkyl, any of which is optionally substituted with one or more R⁶;
- each R⁴ is independently chosen from alkyl, halo, cyano, and hydroxy;
- each R⁵ is independently chosen from halo, cyano, amido, alkyl, alkoxy, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, P(O)(CH₃)₂, SO₂CH₃, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with one or more alkyl;
- two R⁵, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;
- each R⁶ is independently chosen from halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy; and

- each R^7 is independently chosen from alkyl, cyano, halo, and hydroxy.
2. The compound as recited in claim 1, wherein R^{1a} and R^{1b} , together with the intervening nitrogen, combine to form heterocycloalkyl, which is substituted with one R^3 , and which is optionally substituted with one or more R^4 .
 3. The compound as recited in claim 2, wherein the heterocycloalkyl formed by R^{1a} and R^{1b} , together with the intervening nitrogen, is chosen from pyrazoline and pyrrolidine.
 4. The compound as recited in claim 2, wherein R^3 is aryl optionally substituted with one or more R^6 .
 5. The compound as recited in claim 3, wherein R^3 is any one of phenyl, phenoxy, and pyridinyl, any of which is optionally substituted with 1 or 2 R^6 .
 6. The compound as recited in claim 4, wherein R^6 is halo.
 7. The compound as recited in claim 4, wherein R^6 is fluoro.
 8. The compound as recited in any one of claims 1 – 7 wherein X is alkylene and is optionally substituted with one or more R^7 .
 9. The compound as recited in claim 8, wherein X is $-\text{CH}_2-$.
 10. The compound as recited in claim 9, wherein R^2 is chosen from aryl and heteroaryl.
 11. The compound as recited in claim 10, wherein R^2 is 5-10 membered heteroaryl.
 12. The compound as recited in claim 11, wherein R^2 is chosen from pyrazol-1-yl, 1*H*-indazol-1-yl, 2*H*-indazol-2-yl, 1*H*-pyrazolo[3,4-*c*]pyridin-1-yl, imidazol-1-yl, benzo[*d*]imidazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 2*H*-1,2,3-triazol-2-yl, 1*H*-benzo[*d*][1,2,3]triazol-1-yl, and 2*H*-benzo[*d*][1,2,3]triazol-2-yl.
 13. The compound as recited in any one of claims 1 – 12, wherein R^2 is optionally substituted with 1 or 2 R^5 .
 14. The compound as recited in claim 13, wherein each R^5 is independently chosen from fluoro, cyano, methyl, methoxy, hydroxymethyl, methoxymethyl, cyclopropyl, and trifluoromethyl.
 15. The compound as recited in claim 1, having structural Formula II:



or a salt thereof, wherein:

m is chosen from 0, 1, and 2;

n is chosen from 0, 1, 2, and 3;

W is chosen from C(R^{6a}) and N;

X is alkylene and is optionally substituted with one or more R⁷,

or X is chosen from carbamoyl, carbonyl, and a bond;

Y is chosen from CH₂, CH, NH, and N;

Y and the intervening carbons and nitrogen combine to form heterocycloalkyl or heteroaryl;

R² is chosen from hydrogen, hydroxy, cyano, and halo,

or R² is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R⁵;

each R⁴ is independently chosen from halo, cyano, and hydroxy;

each R⁵ is independently chosen from halo, cyano, amido, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, P(O)(CH₃)₂, SO₂CH₃, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with one or more alkyl;

two R⁵, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;

each R⁶ is independently chosen from halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy;

R^{6a} is chosen from H, halo, alkyl, cyano, alkoxy, hydroxy, haloalkyl, and haloalkoxy; and

each R⁷ is independently chosen from alkyl, cyano, halo, and hydroxy.

16. The compound as recited in claim 15, wherein m is chosen from 0 and 1.

17. The compound as recited in claim 16, wherein n is chosen from 0, 1, and 2.

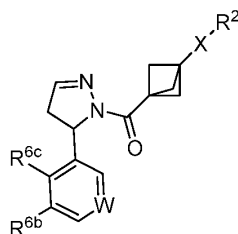
18. The compound as recited in claim 17, wherein Y is N and m is 0.

19. The compound as recited in claim 17, wherein Y is NH and m is 1.

20. The compound as recited in claim 16, wherein W is C(R^{6a}).

21. The compound as recited in claim 20, wherein R^{6a} is chosen from H, fluoro, methyl, cyano, and methoxy.

22. The compound as recited in any one of claims 16 – 21, wherein each R^6 is independently chosen from fluoro, methyl, cyano, and methoxy.
23. The compound as recited in claim 22, wherein n is chosen from 1 and 2.
24. The compound as recited in claim 15, having structural Formula III:



(III)

or a salt thereof, wherein:

W is chosen from $C(R^{6a})$ and N;

X is alkylene and is optionally substituted with one or more R^7 ,

or X is chosen from carbamoyl, carbonyl, and a bond;

R^2 is chosen from hydrogen, hydroxy, cyano, and halo,

or R^2 is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy,

(alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl,

(alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and

(heteroaryl)amino, any of which is optionally substituted with one or more R^5 ;

each R^5 is independently chosen from halo, cyano, amido, alkyl, alkoxy,

hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, $P(O)(CH_3)_2$, SO_2CH_3 , aryl

optionally substituted with one or more alkyl, and heteroaryl optionally

substituted with one or more alkyl;

two R^5 , together with the intervening atoms, optionally combine to form a cycloalkyl

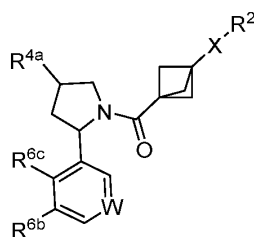
or heterocycloalkyl;

R^{6a} , R^{6b} , and R^{6c} are independently chosen from H, halo, alkyl, cyano, alkoxy,

hydroxy, haloalkyl, and haloalkoxy; and

each R^7 is independently chosen from alkyl, cyano, halo, and hydroxy.

25. The compound as recited in claim 15, having structural Formula IV:



(IV)

or a salt thereof, wherein:

W is chosen from C(R^{6a}) and N;

X is alkylene and is optionally substituted with one or more R⁷,

or X is chosen from carbamoyl, carbonyl, and a bond;

R² is chosen from hydrogen, hydroxy, cyano, and halo,

or R² is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy, (alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl, (alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and (heteroaryl)amino, any of which is optionally substituted with one or more R⁵;

R^{4a} is chosen from H, halo, cyano, and hydroxy;

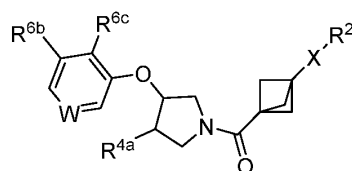
each R⁵ is independently chosen from halo, cyano, amido, alkyl, alkoxy, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, P(O)(CH₃)₂, SO₂CH₃, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with alkyl;

two R⁵, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl;

R^{6a}, R^{6b}, and R^{6c} are independently chosen from H, halo, alkyl, cyano, alkoxy, hydroxy, haloalkyl, and haloalkoxy; and

each R⁷ is independently chosen from alkyl, cyano, halo, and hydroxy.

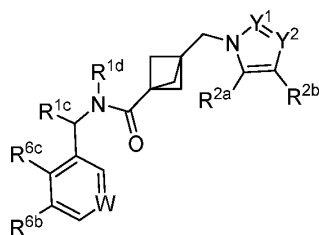
26. The compound as recited in claim 15, having structural Formula V:



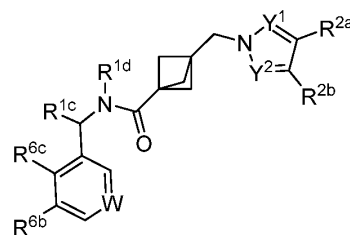
(V)

or a salt thereof, wherein:

- W is chosen from C(R^{6a}) and N;
- X is alkylene and is optionally substituted with one or more R⁷,
or X is chosen from carbamoyl, carbonyl, and a bond;
- R² is chosen from hydrogen, hydroxy, cyano, and halo,
or R² is chosen from alkyl, amino, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,
alkoxy, (cycloalkyl)oxy, (heterocycloalkyl)oxy, (aryl)oxy, (heteroaryl)oxy,
(alkyl)carbonyl, (cycloalkyl)carbonyl, (heterocycloalkyl)carbonyl, (aryl)carbonyl,
(alkyl)amino, (cycloalkyl)amino, (heterocycloalkyl)amino, (aryl)amino, and
(heteroaryl)amino, any of which is optionally substituted with one or more R⁵;
- R^{4a} is chosen from H, halo, cyano, and hydroxy;
- each R⁵ is independently chosen from halo, cyano, amido, alkyl, alkoxy,
hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, P(O)(CH₃)₂, SO₂CH₃, aryl
optionally substituted with one or more alkyl, and heteroaryl optionally
substituted with alkyl;
- two R⁵, together with the intervening atoms, optionally combine to form a cycloalkyl
or heterocycloalkyl;
- R^{6a}, R^{6b}, and R^{6c} are independently chosen from H, halo, alkyl, cyano, alkoxy,
hydroxy, haloalkyl, and haloalkoxy; and
- each R⁷ is independently chosen from alkyl, cyano, halo, and hydroxy.
27. The compound as recited in any one of claims 24 – 26, wherein X is -CH₂-.
28. The compound as recited in claim 27, wherein W is C(R^{6a}).
29. The compound as recited in claim 28, wherein R^{6a}, R^{6b}, and R^{6c} are independently
chosen from H, fluoro, methyl, cyano, and methoxy.
30. The compound as recited in claim 29, wherein R^{6a}, R^{6b}, and R^{6c} are independently
chosen from H and fluoro.
31. The compound as recited in any one of claims 20 – 30, wherein R² is chosen from aryl,
heteroaryl, (aryl)oxy, and (heteroaryl)oxy.
32. The compound as recited in claim 1, having either structural Formula (VIa) or
structural Formula (VIb):



(VIa)



(VIb)

or a salt thereof, wherein:

W is chosen from C(R^{6a}) and N;

Y¹ and Y² are independently chosen from CH, C(R⁵), and N;

R^{1c} and R^{1d}, together with the intervening carbon and nitrogen, combine to form a 5-membered heterocycloalkyl which is optionally substituted with one R⁴;

R^{2a} and R^{2b} are independently chosen from H, hydroxy, cyano, halo, and alkyl,

or R^{2a} and R^{2b} combine to form alkylene or heteroalkylene, either of which is optionally substituted with 1 or 2 R⁵;

R⁴ is chosen from halo, cyano, and hydroxy;

each R⁵ is independently chosen from halo, cyano, amido, alkyl, alkoxy,

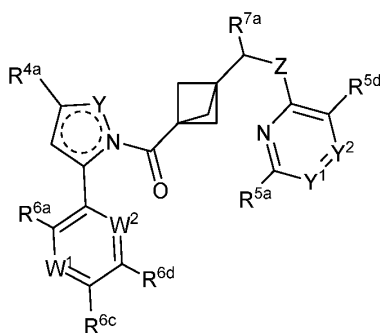
hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, oxo, P(O)(CH₃)₂, SO₂CH₃, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with alkyl;

two R⁵, together with the intervening atoms, optionally combine to form a cycloalkyl or heterocycloalkyl; and

R^{6a}, R^{6b}, and R^{6c} are independently chosen from H, halo, alkyl, cyano, alkoxy, hydroxy, haloalkyl, and haloalkoxy.

33. The compound as recited in claim 32, wherein Y¹ and Y² are independently chosen from CH and N.
34. The compound as recited in claim 33, wherein R^{2a} and R^{2b} combine to form alkylene or heteroalkylene chosen from -CH₂CH₂CH₂-, -CH=CH-CH=CH-, -N=CH-CH=CH-, -CH=N-CH=CH-, -CH=CH-N=CH-, and -CH=CH-CH=N-, any of which is optionally substituted with 1 or 2 R⁵.
35. The compound as recited in claim 34, wherein each R⁵ is independently chosen from fluoro, cyano, methyl, methoxy, hydroxymethyl, methoxymethyl, cyclopropyl, and trifluoromethyl.
36. The compound as recited in claim 35, wherein R⁵ is fluoro.

37. The compound as recited in claim 1, having structural Formula (VII):



(VII)

or a salt thereof, wherein:

W¹ is chosen from C(R^{6b}) and N;

W² is chosen from C(R^{6c}) and N;

Y is chosen from CH₂, CH, NH, and N;

Y and the intervening carbons and nitrogen combine to form heterocycloalkyl;

Y¹ is chosen from C(R^{5b}) and N;

Y² is chosen from C(R^{5c}) and N;

Z is chosen from O, NH, and N(CH₃);

R^{1c} and R^{1d}, together with the intervening carbon and nitrogen, combine to form a 5-membered heterocycloalkyl which is optionally substituted with one R⁴;

R^{2a} and R^{2b} are independently chosen from H, hydroxy, cyano, halo, and alkyl,

or R^{2a} and R^{2b} combine to form alkylene or heteroalkylene, either of which is optionally substituted with 1 or 2 R⁵;

R^{4a} is chosen from H, halo, cyano, and hydroxy;

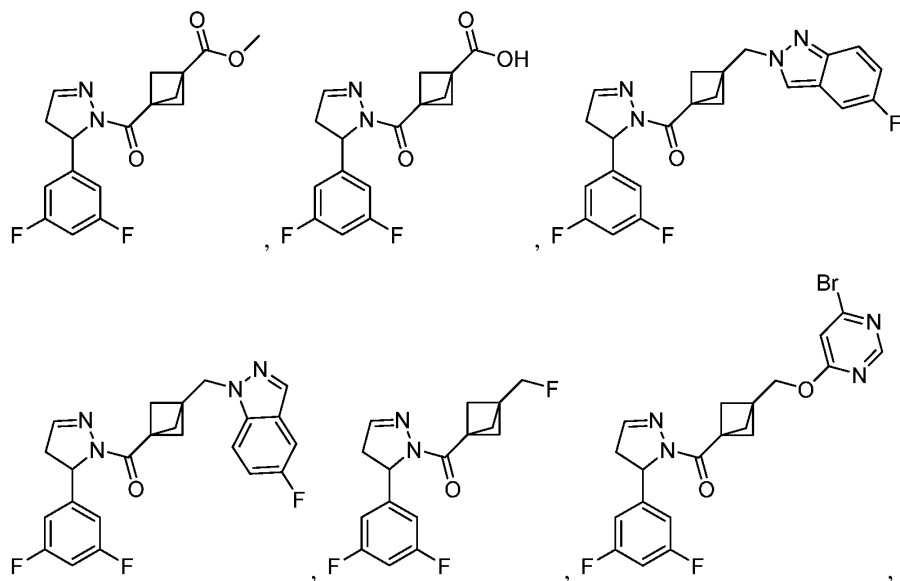
R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently chosen from H, halo, cyano, amido, alkyl, alkoxy, cyanoalkyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, haloalkyl, P(O)(CH₃)₂, SO₂CH₃, aryl optionally substituted with one or more alkyl, and heteroaryl optionally substituted with alkyl;

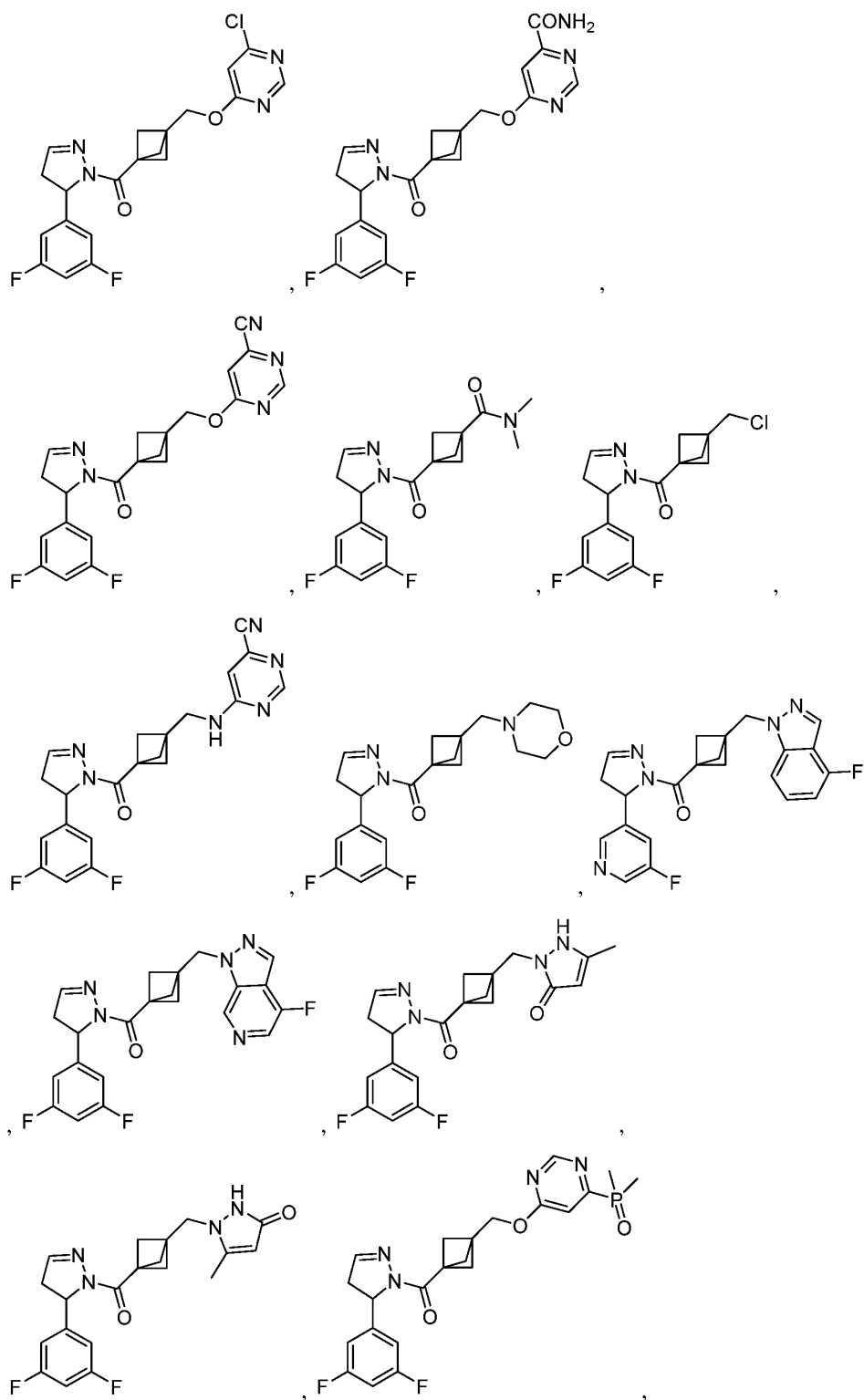
R^{6a}, R^{6b}, R^{6c}, R^{6d}, and R^{6e} are independently chosen from H, halo, alkyl, cycloalkyl, cyano, alkoxy, hydroxy, haloalkyl, hydroxyalkyl, and haloalkoxy; and

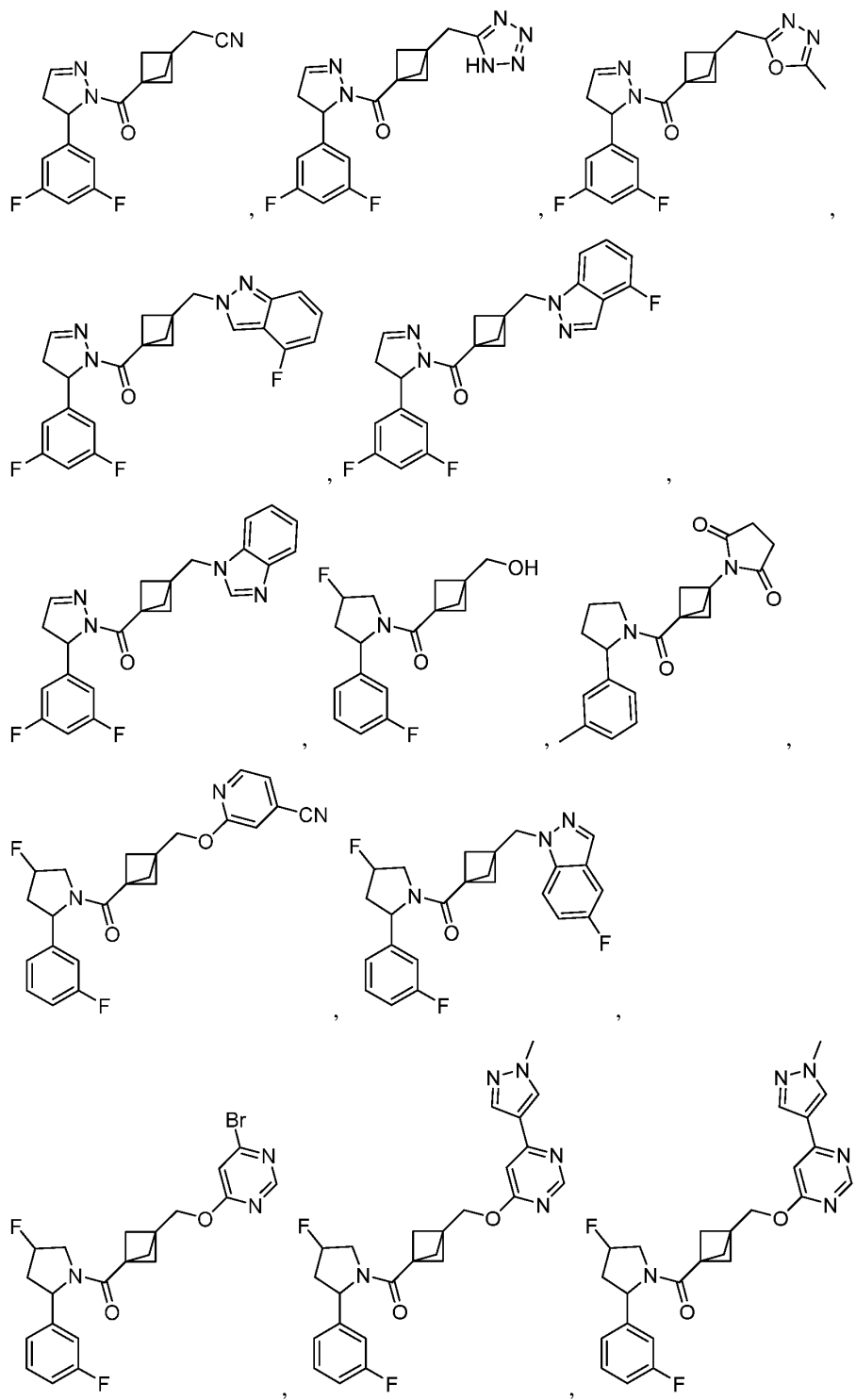
R^{7a} is chosen from H, alkyl, cyano, halo, and hydroxy.

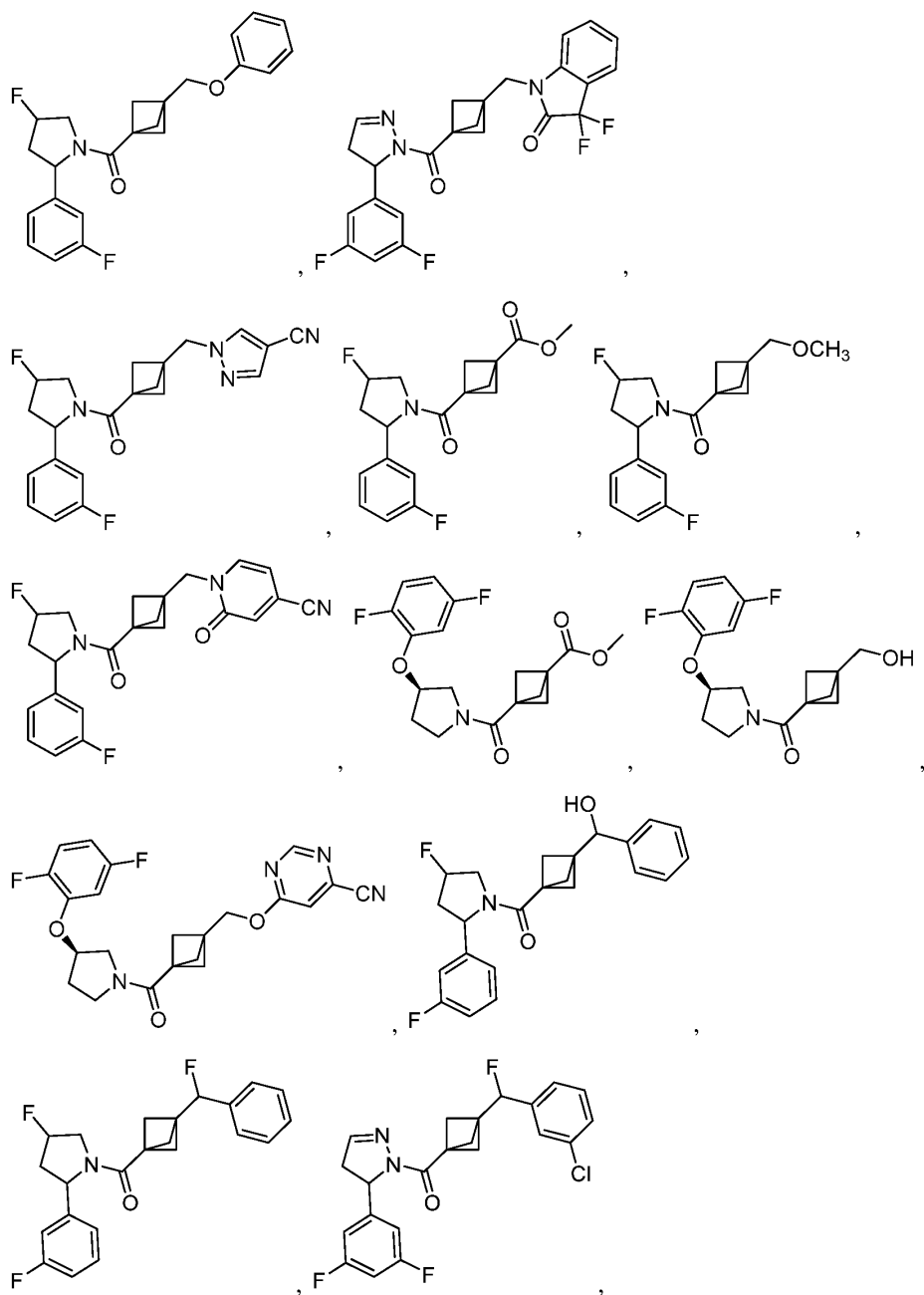
38. The compound as recited in claim 37, wherein the heterocycloalkyl formed by Y and the intervening carbons and nitrogen is chosen from pyrazoline and pyrrolidine.

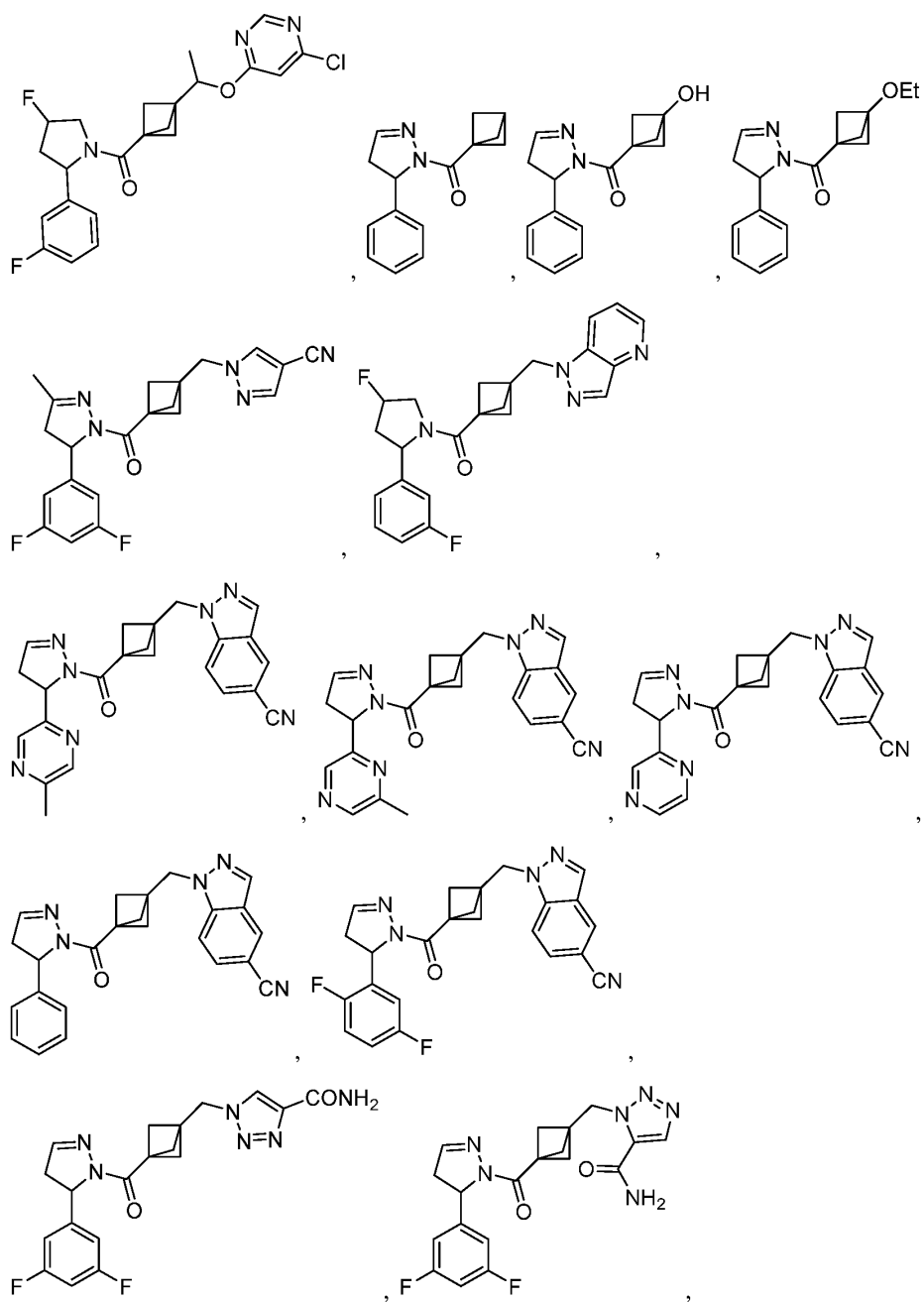
39. The compound as recited in claim 38, wherein R^{5a} , R^{5b} , R^{5c} , and R^{5d} are independently chosen from H, halo, cyano, $CONH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, cyano C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkoxy C_{1-6} alkyl, C_{3-7} cycloalkyl, halo C_{1-6} alkyl, $P(O)(CH_3)_2$, SO_2CH_3 , and 5- to 7-membered heteroaryl optionally substituted with methyl.
40. The compound as recited in claim 39, wherein at least one of R^{5a} and R^{5d} is H.
41. The compound as recited in any one of claims 37 – 40, wherein R^{6a} , R^{6b} , R^{6c} , R^{6d} , and R^{6e} are independently chosen from H, halo, methyl, cyclopropyl, cyano, and hydroxymethyl.
42. The compound as recited in claim 41, wherein at least one of R^{6a} , R^{6c} , and R^{6d} is H.
43. The compound as recited in any one of claims 37 – 42, wherein exactly one of Y^1 and Y^2 is N.
44. The compound as recited in any one of claims 37 – 43, wherein at most one of W^1 and W^2 is N.
45. The compound as recited in claim 44, wherein W^1 is chosen from CH and CF.
46. The compound as recited in claim 45, wherein W^2 is chosen from CH and CF.
47. The compound as recited in claim 1, chosen from:

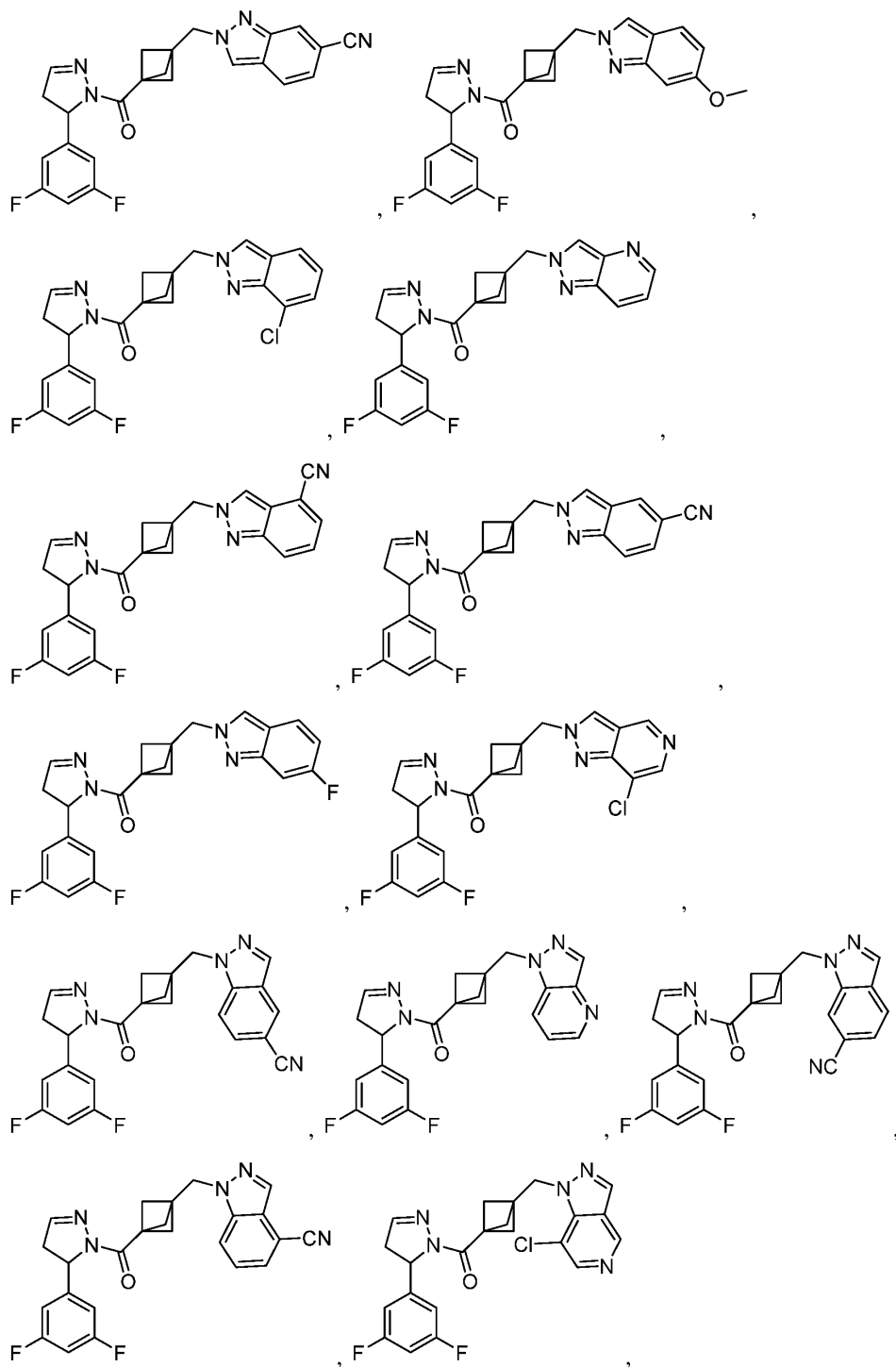


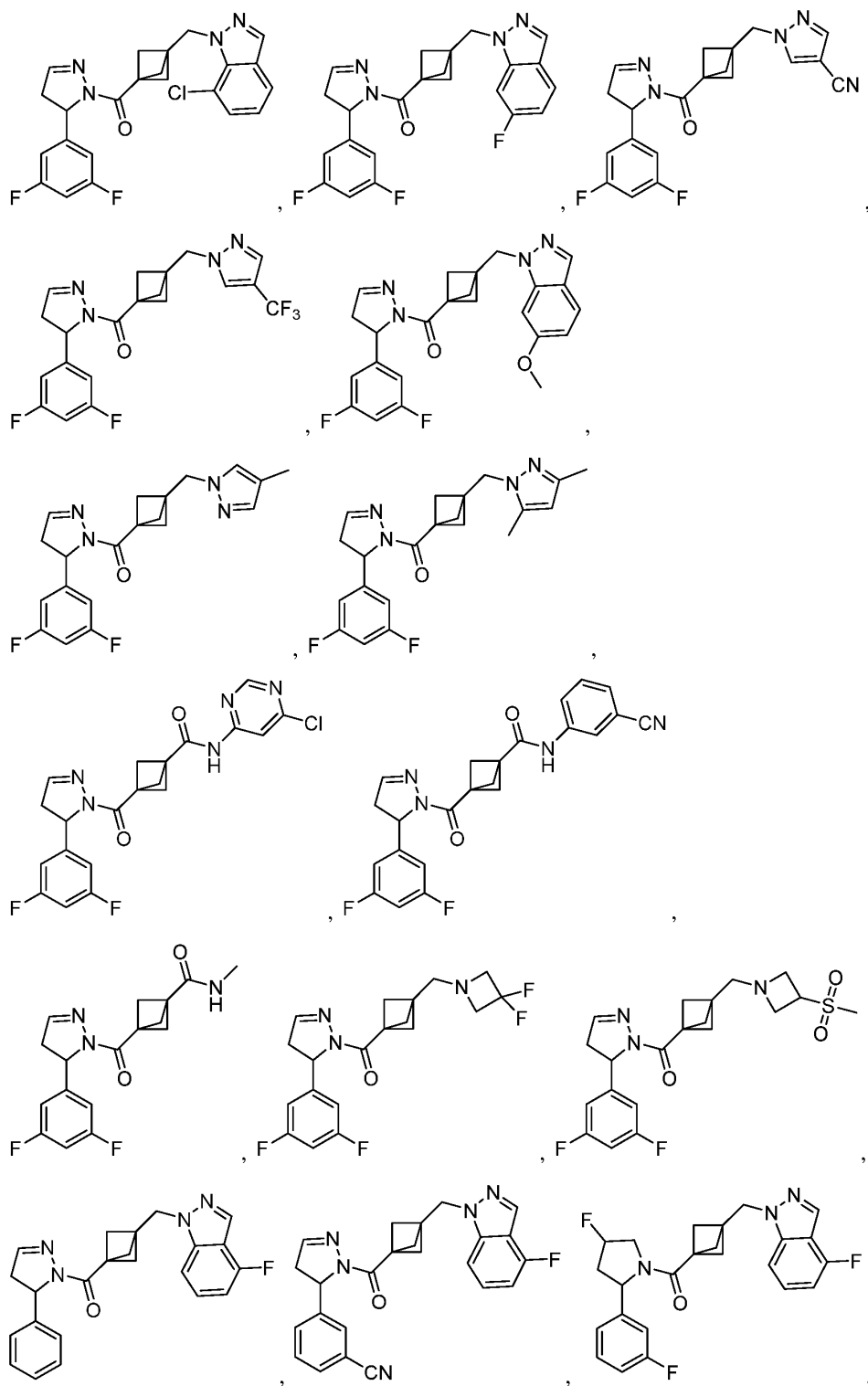


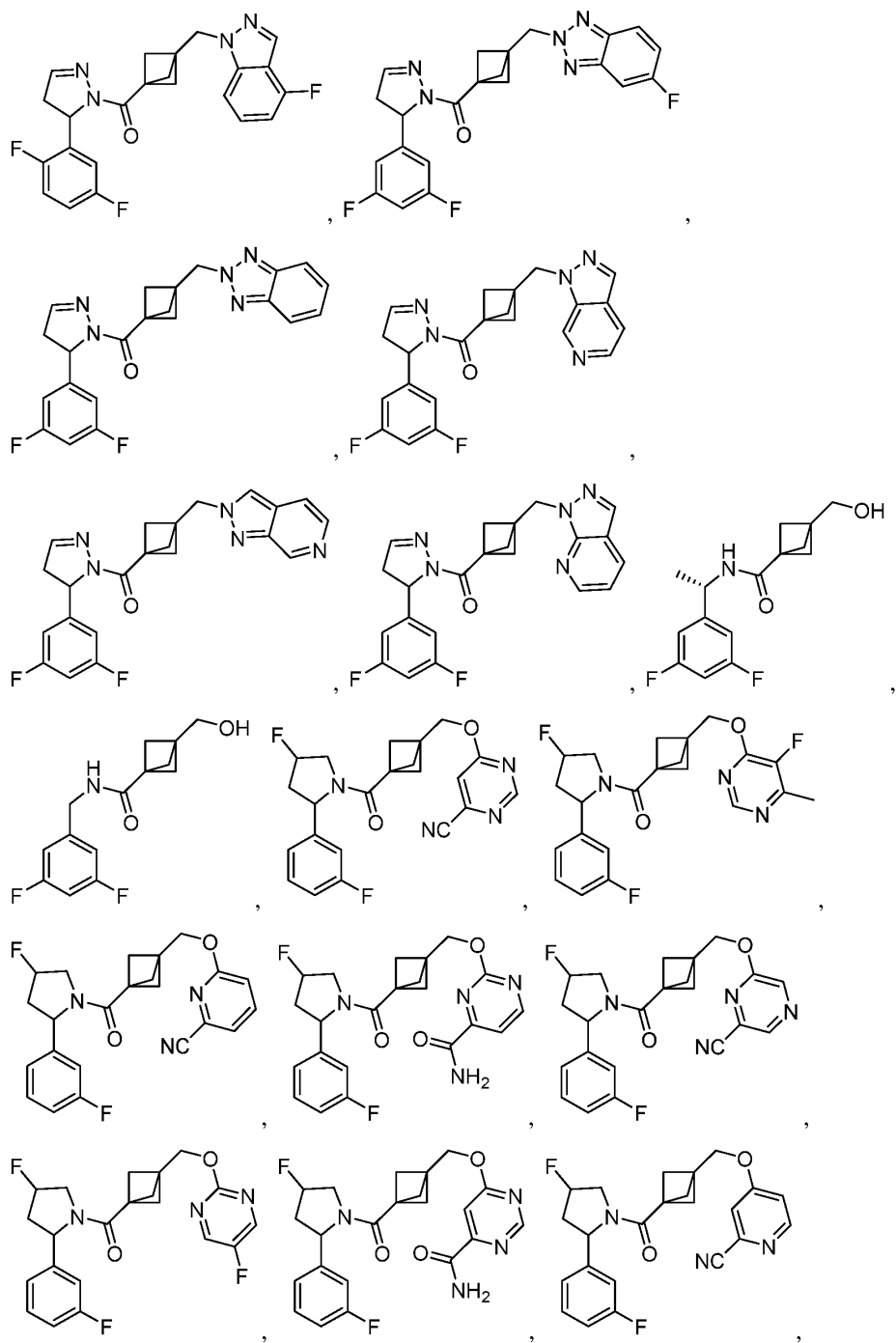


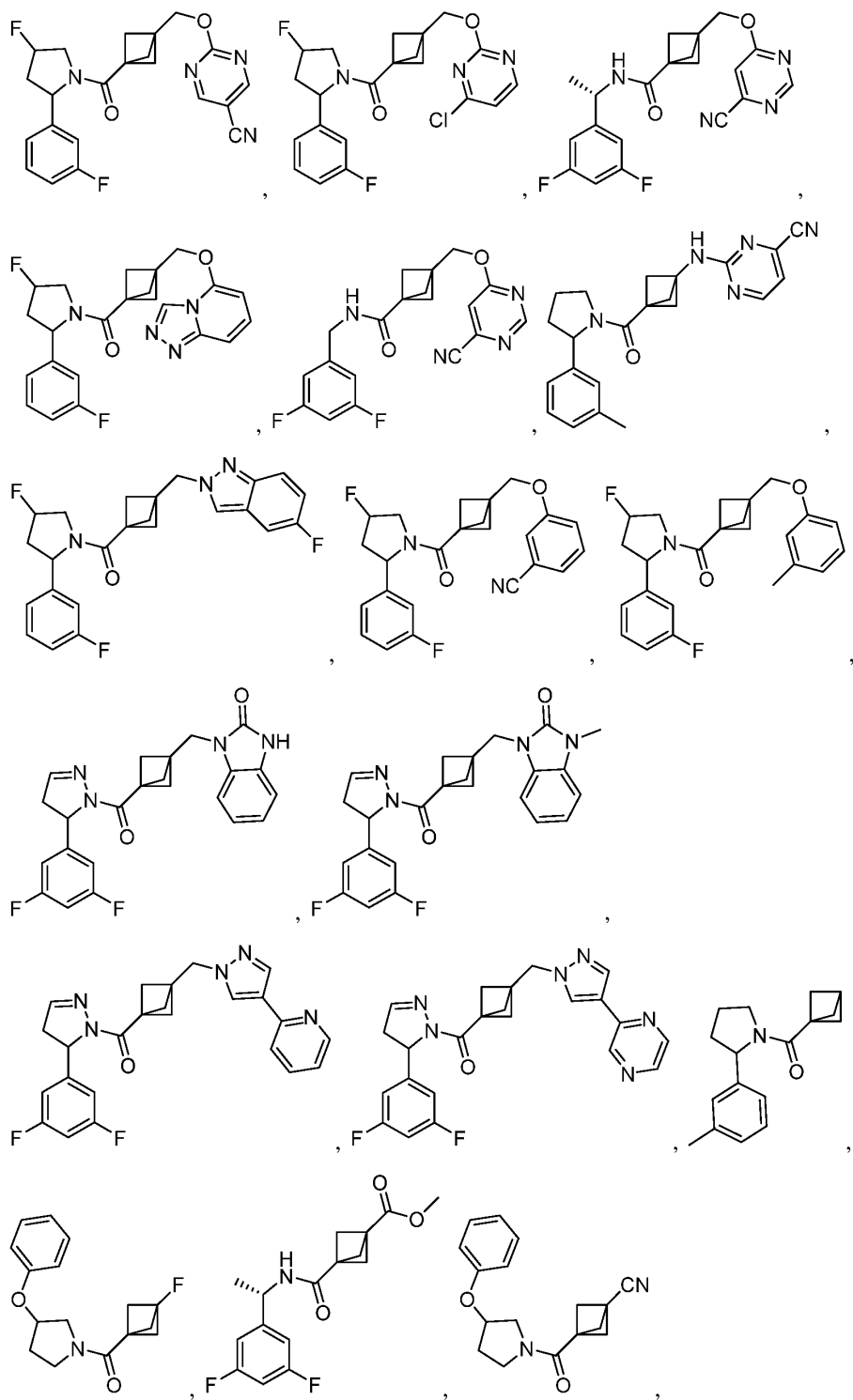


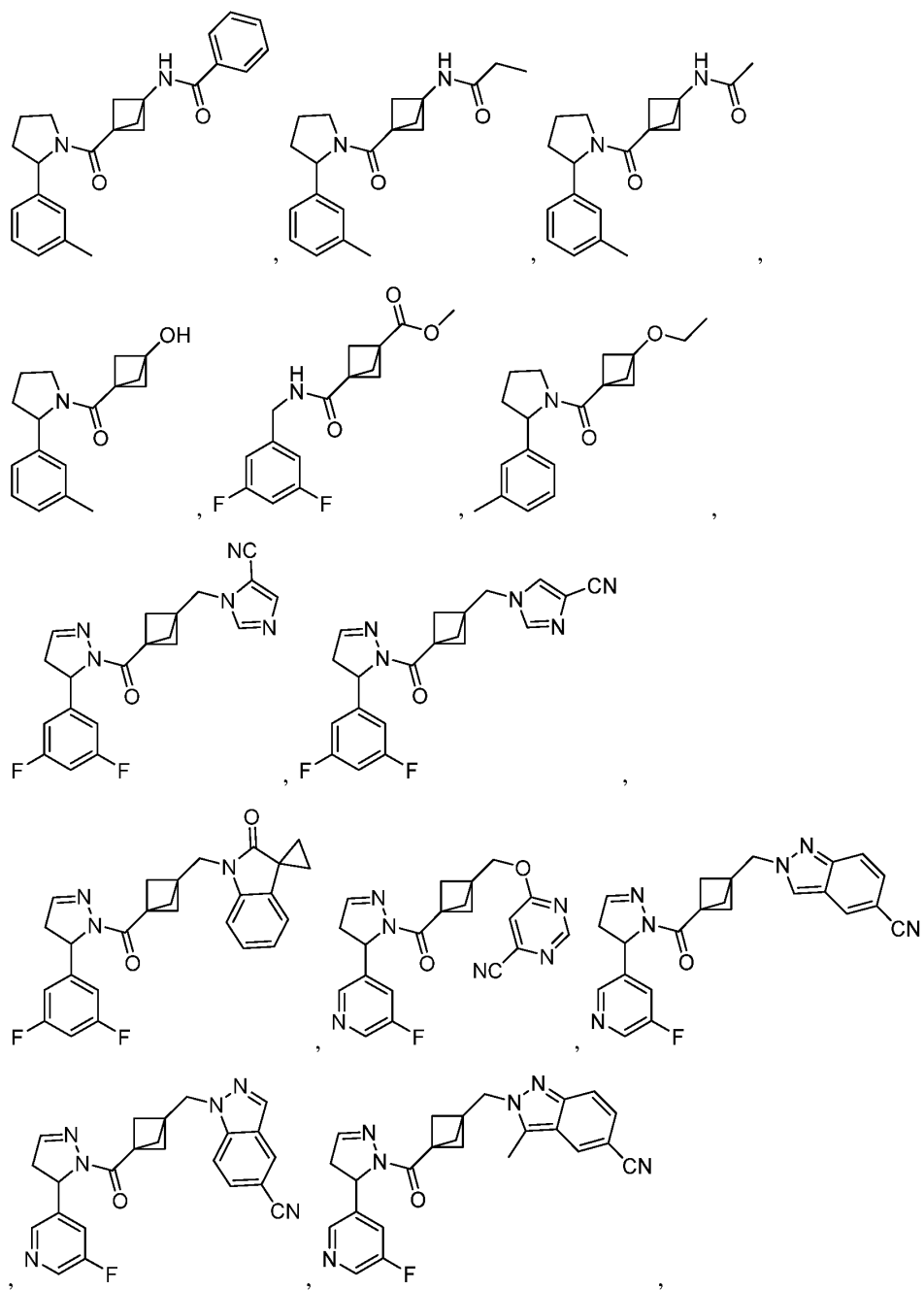


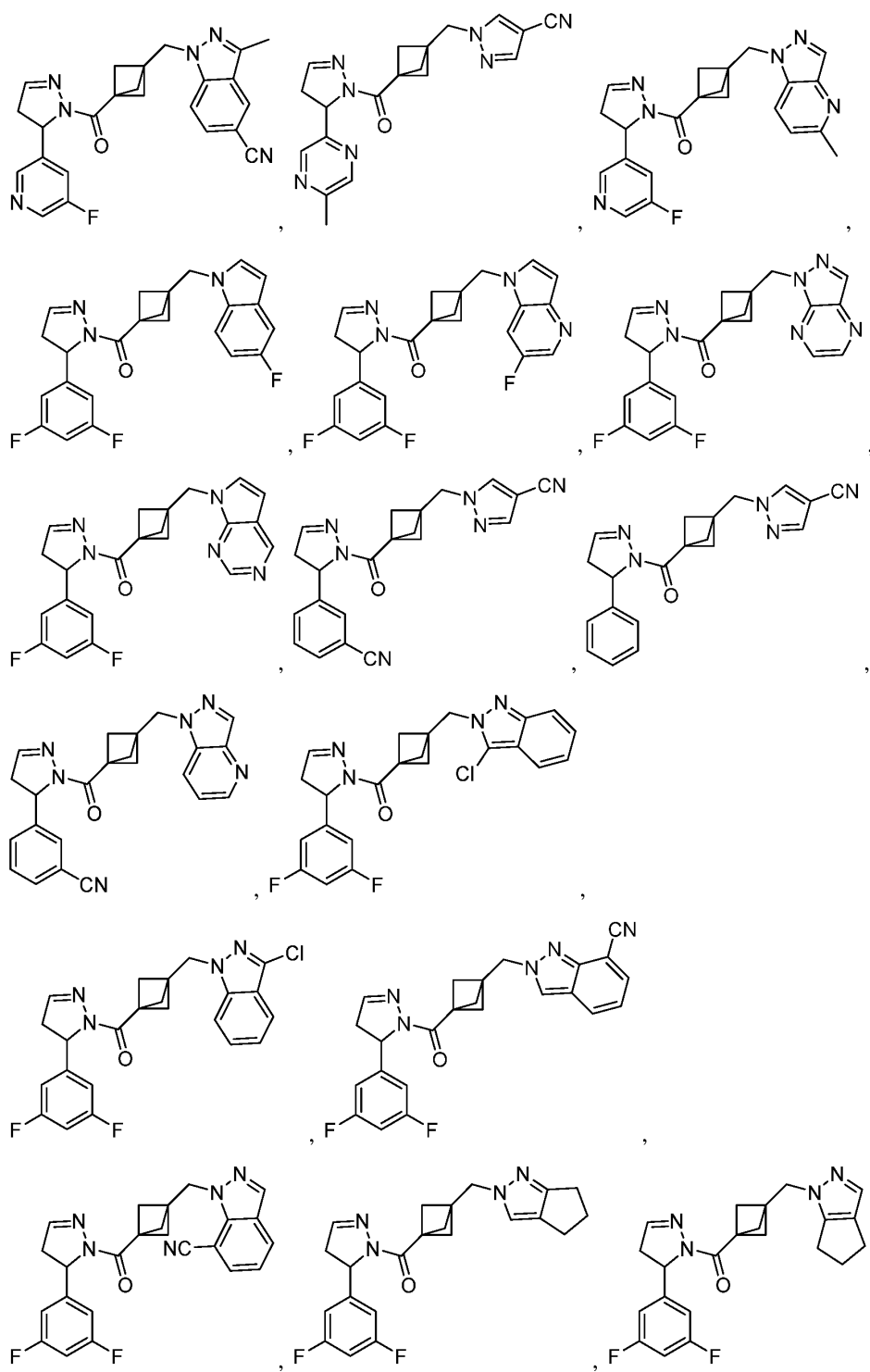


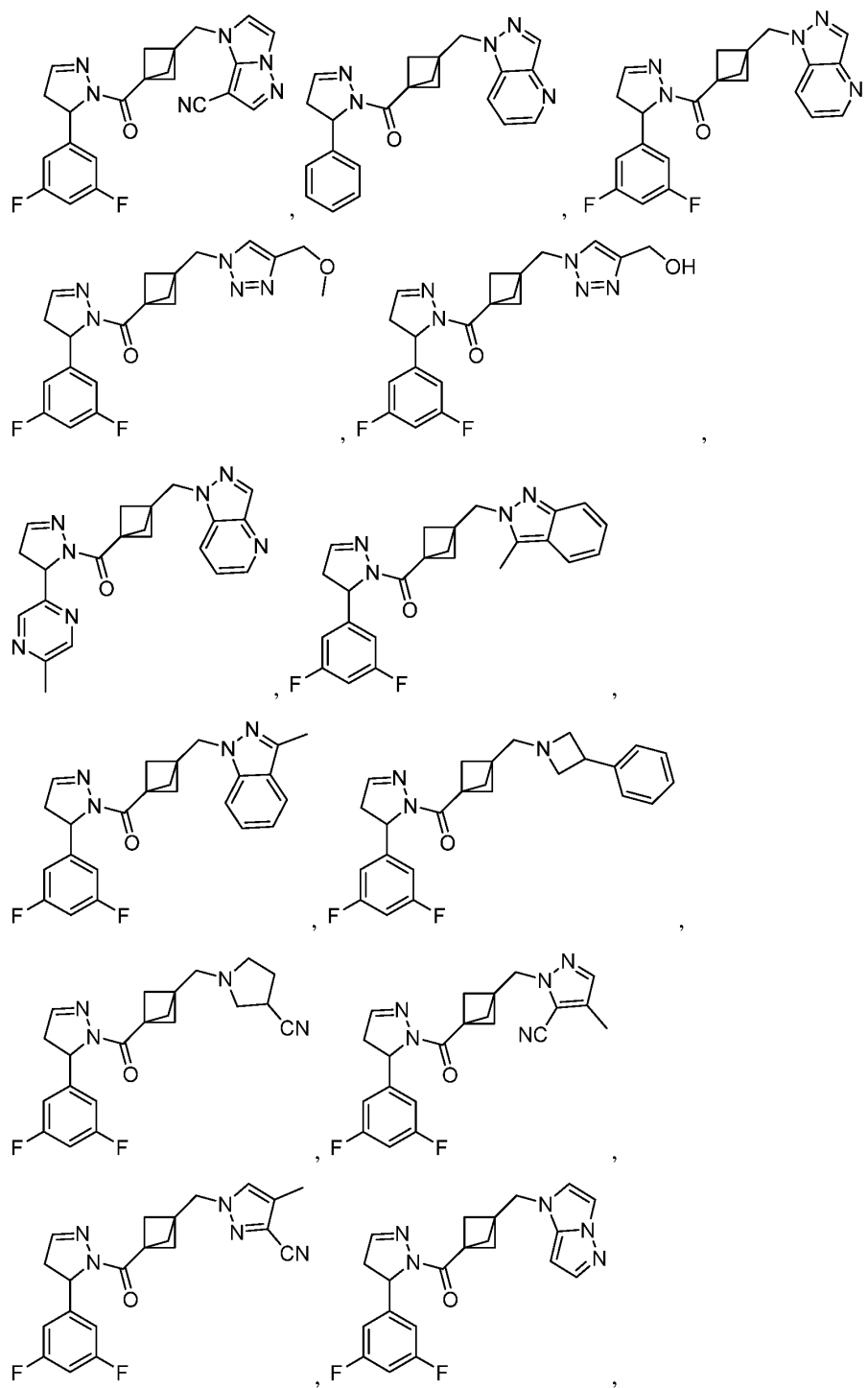


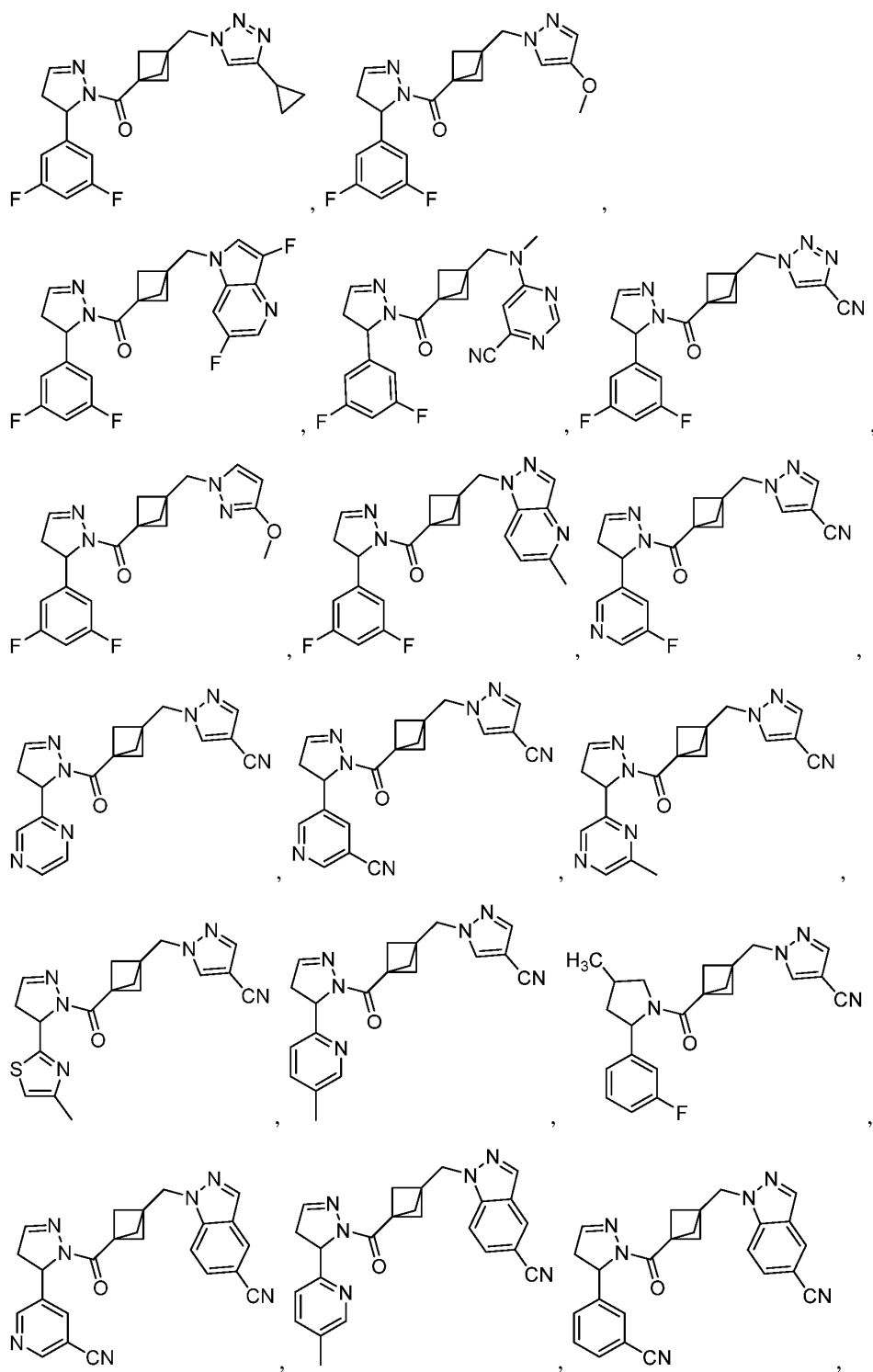


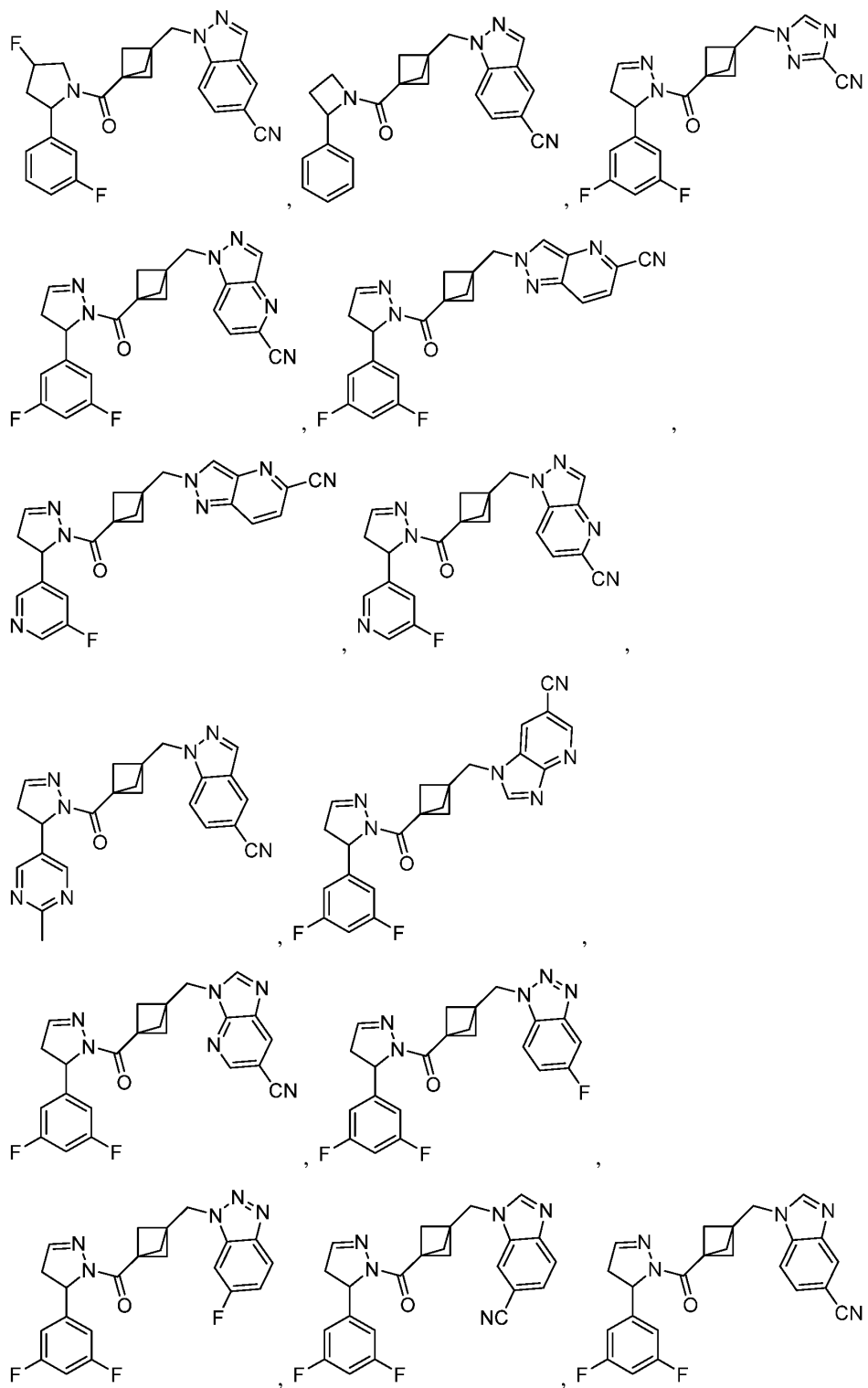


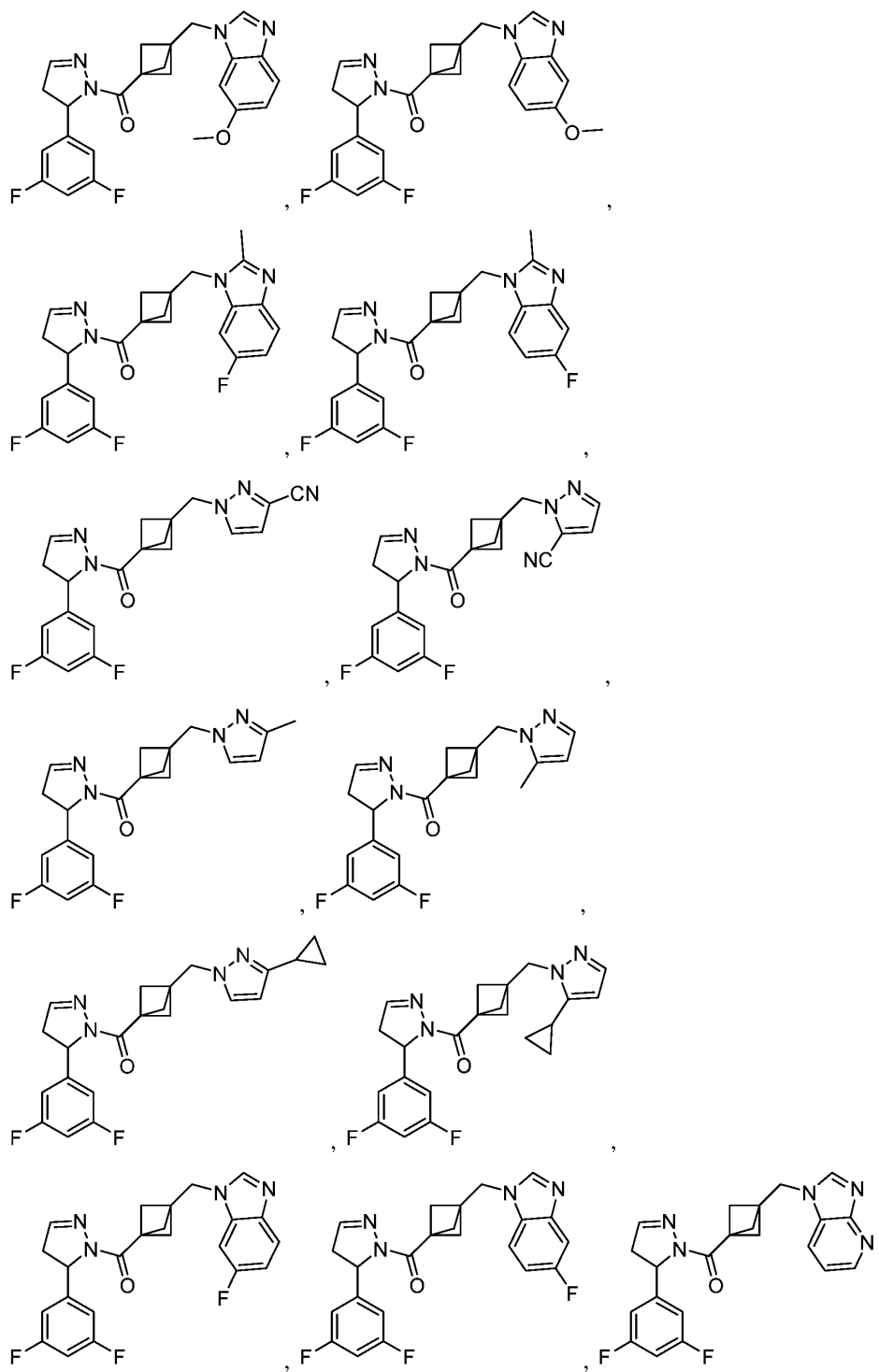


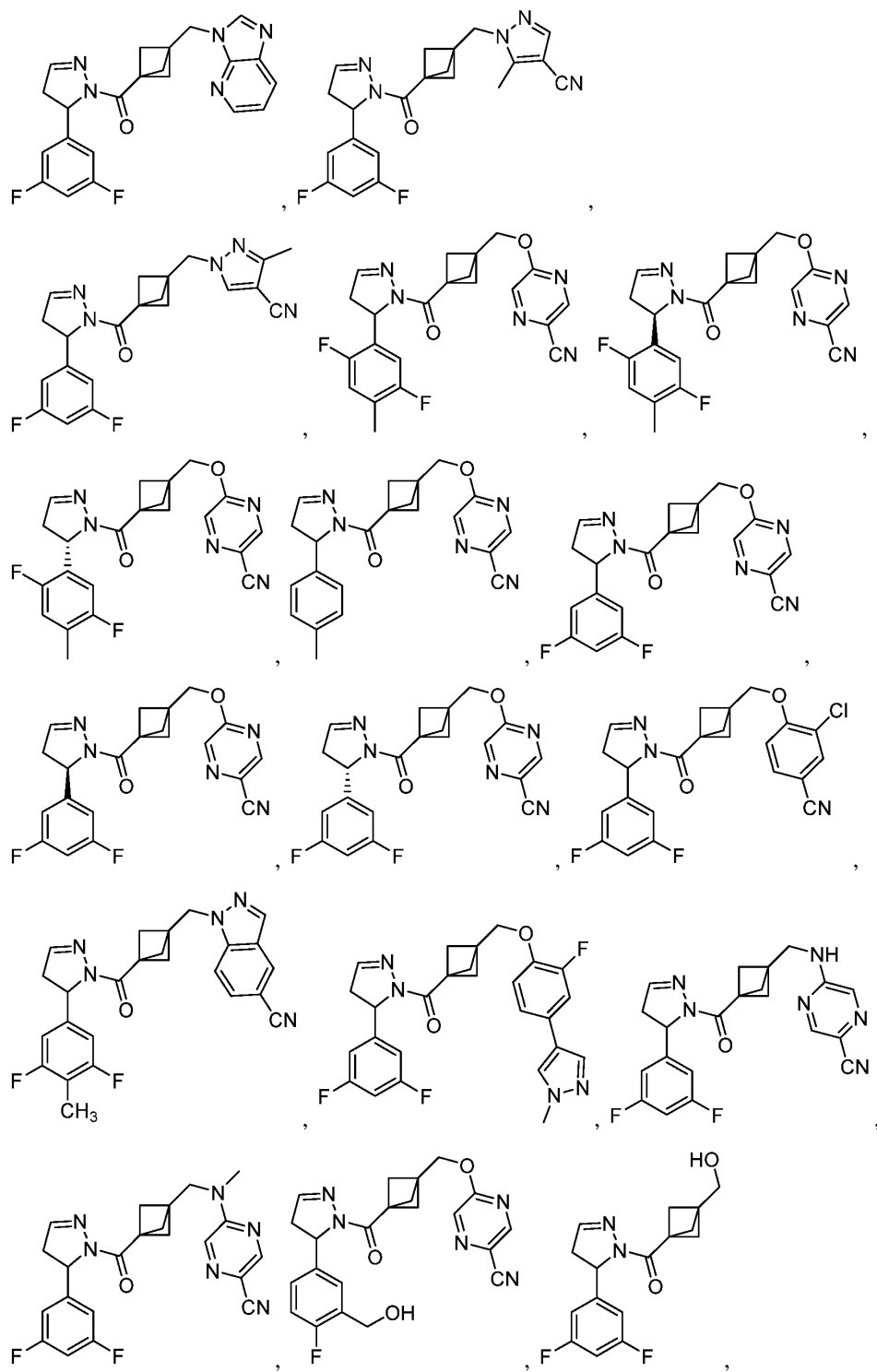


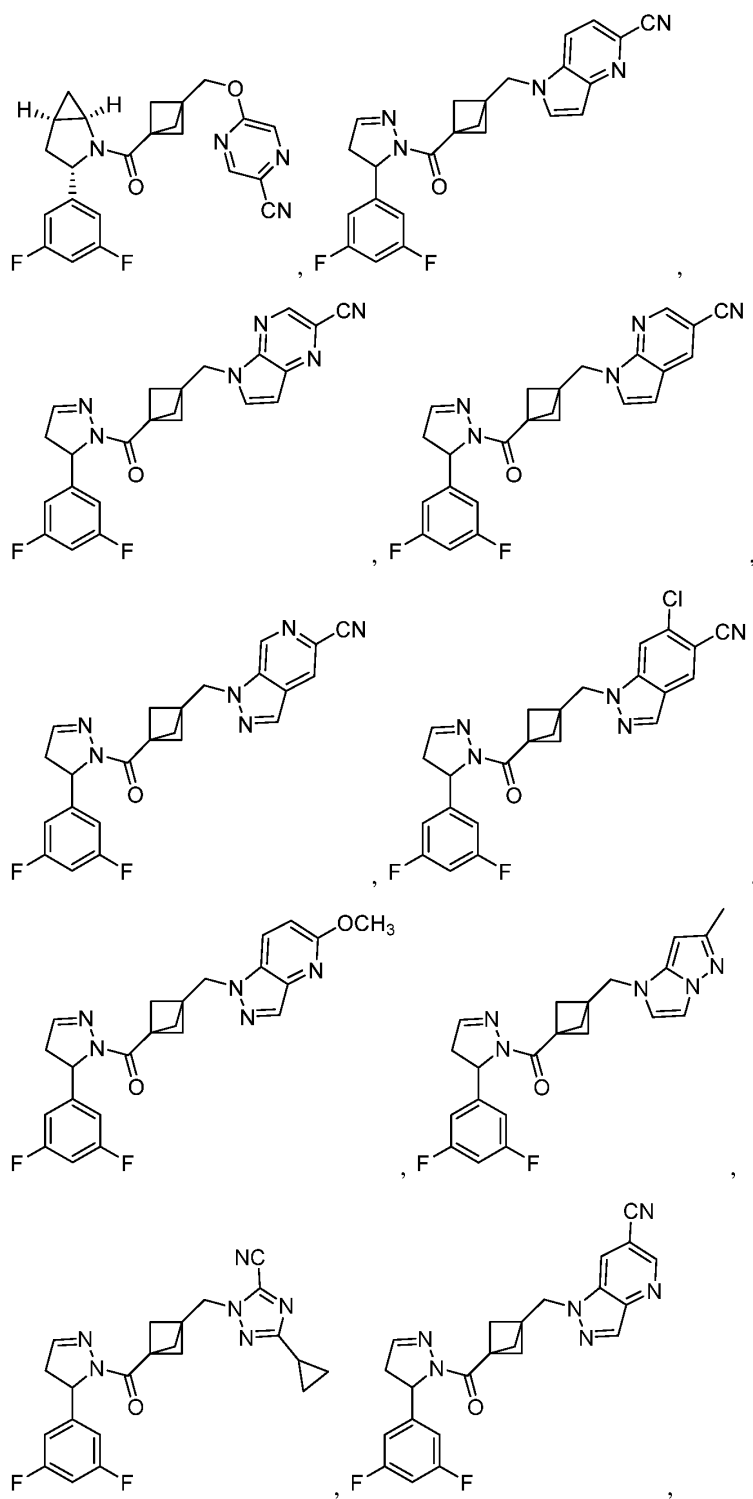


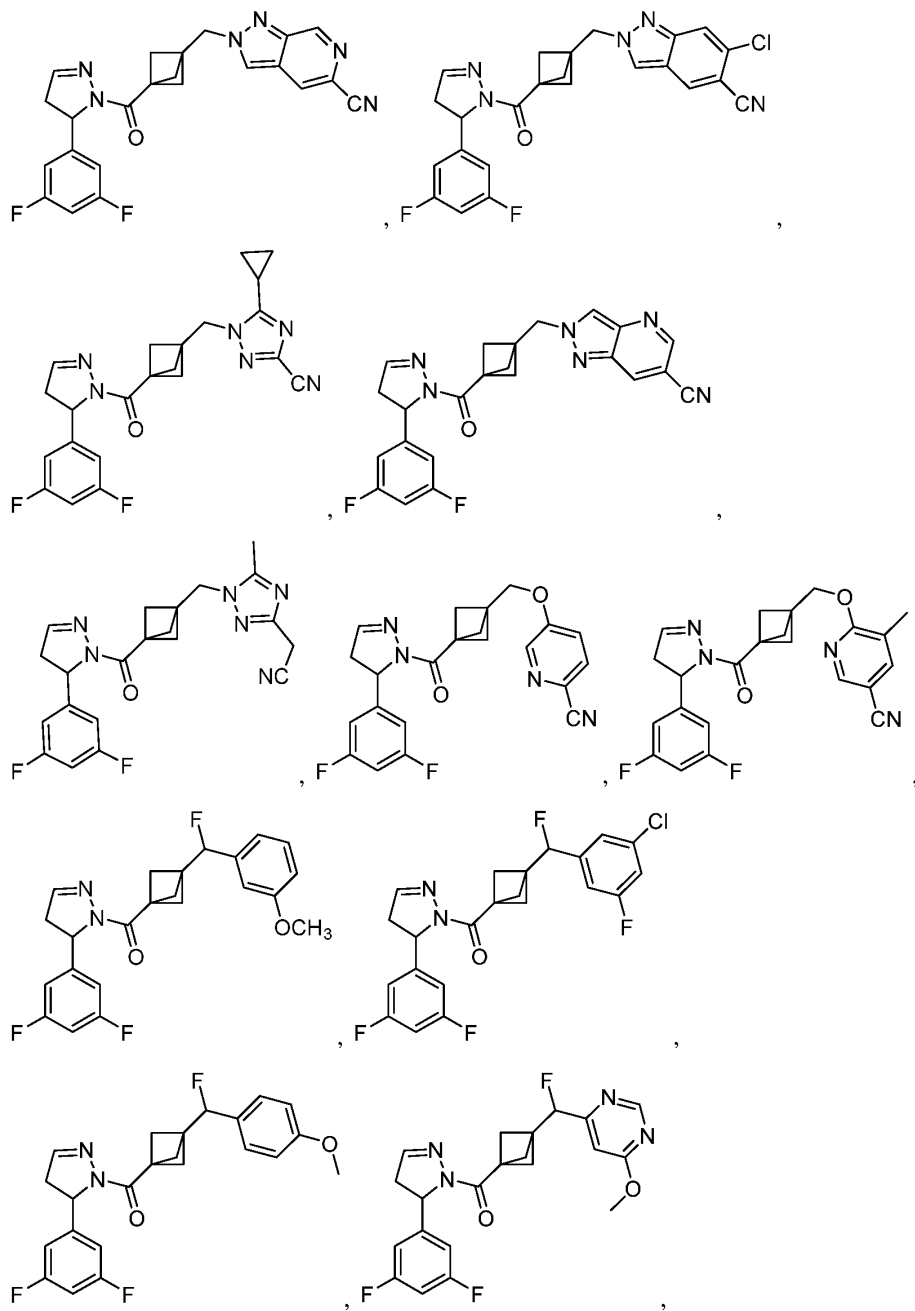


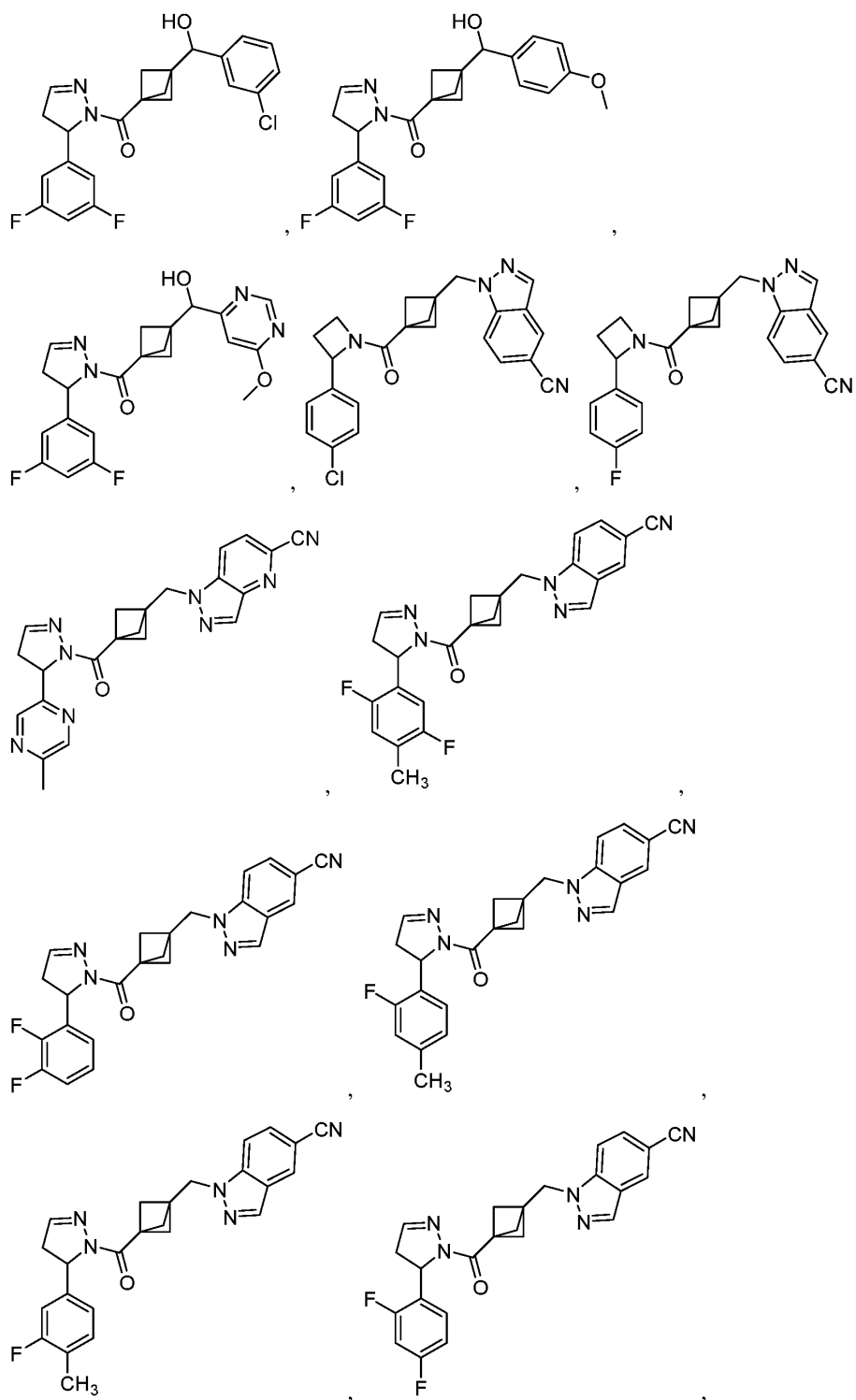


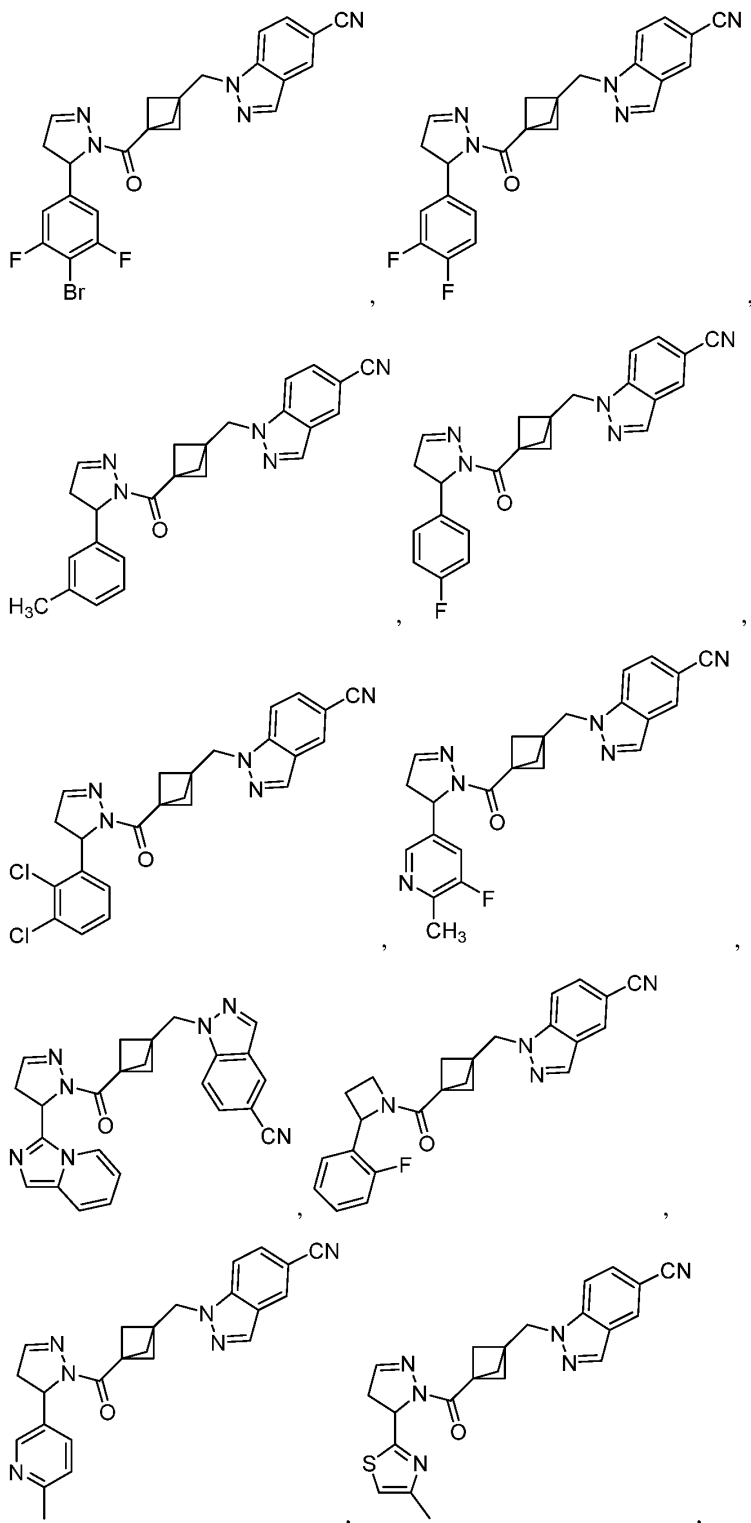


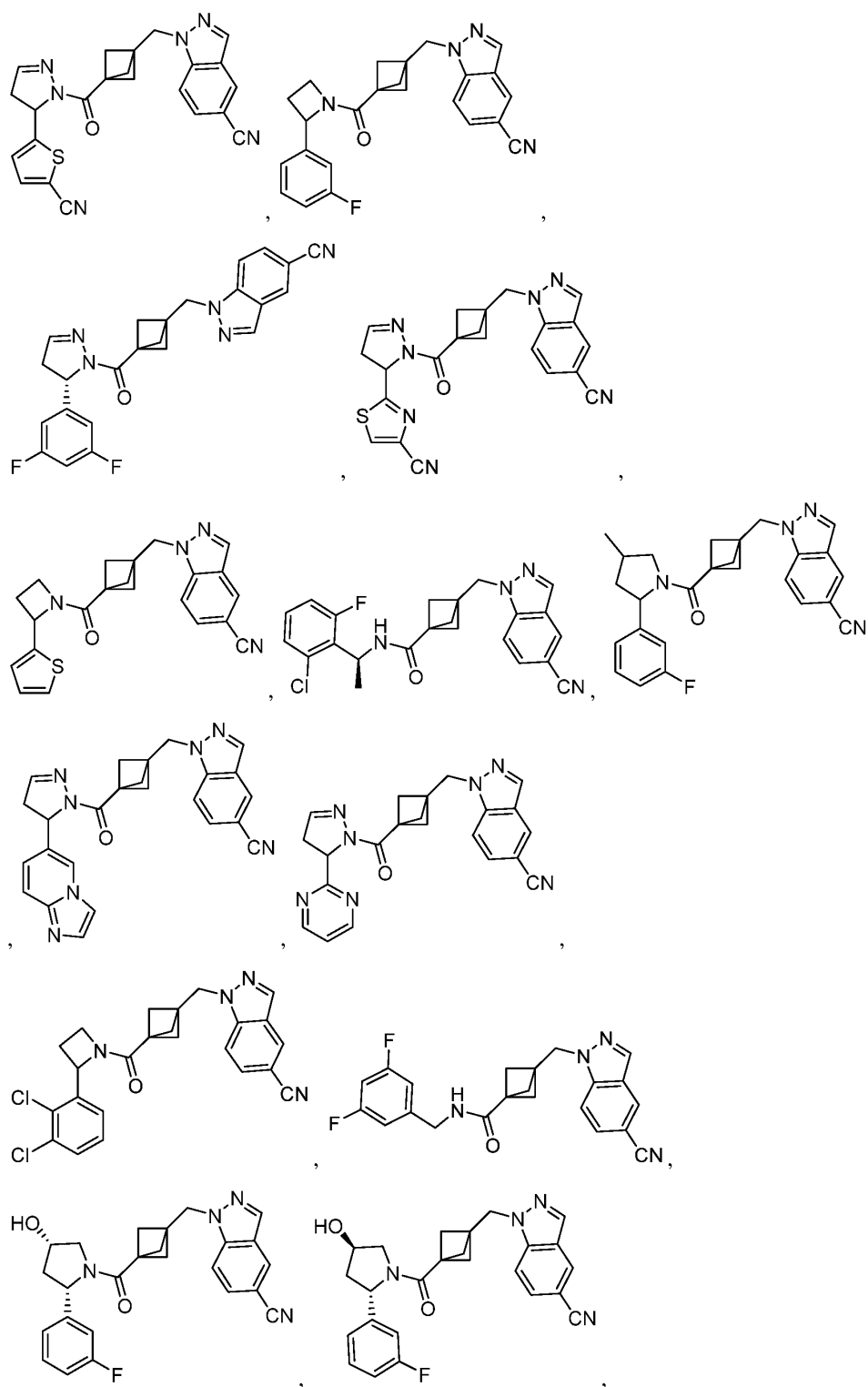


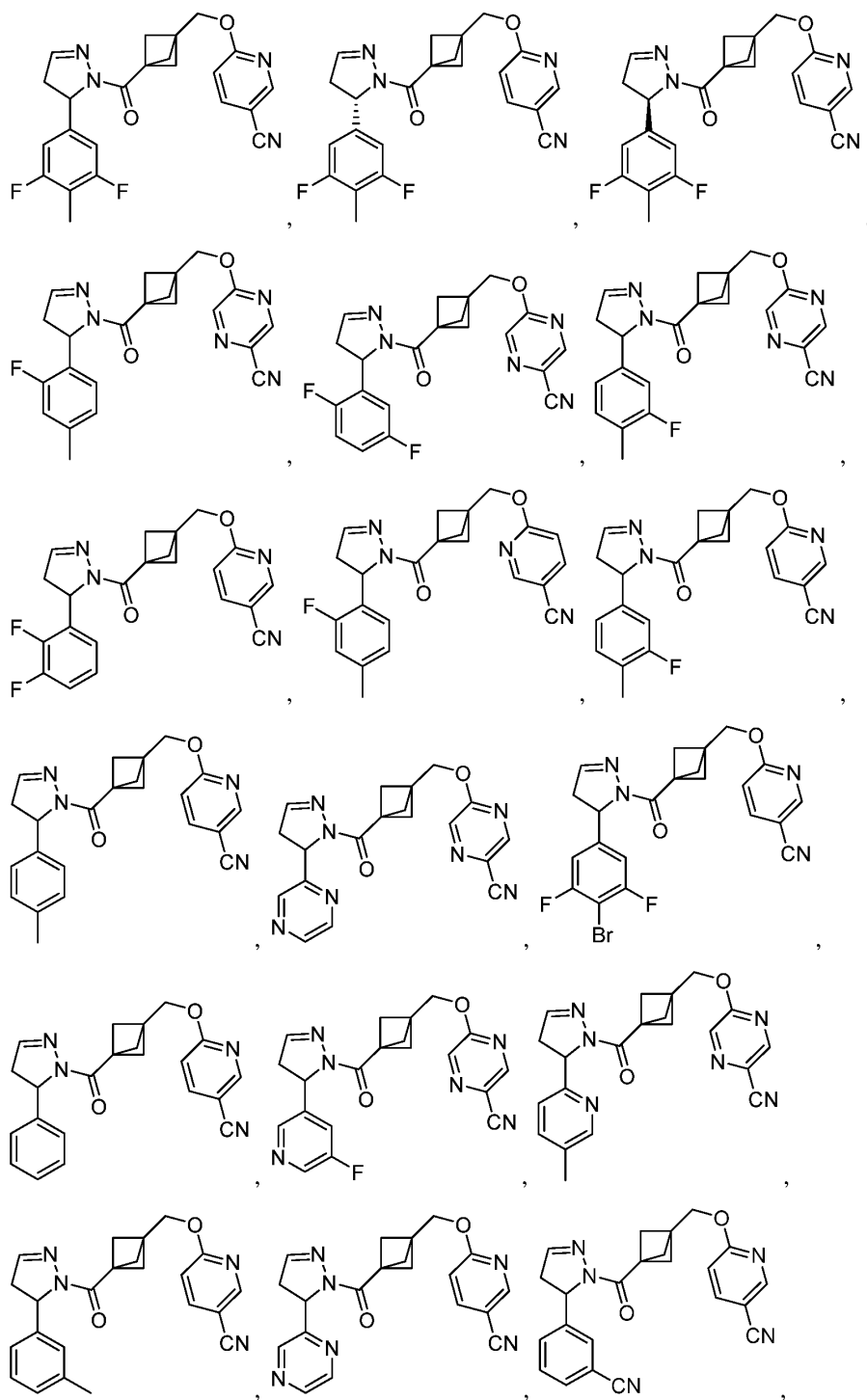


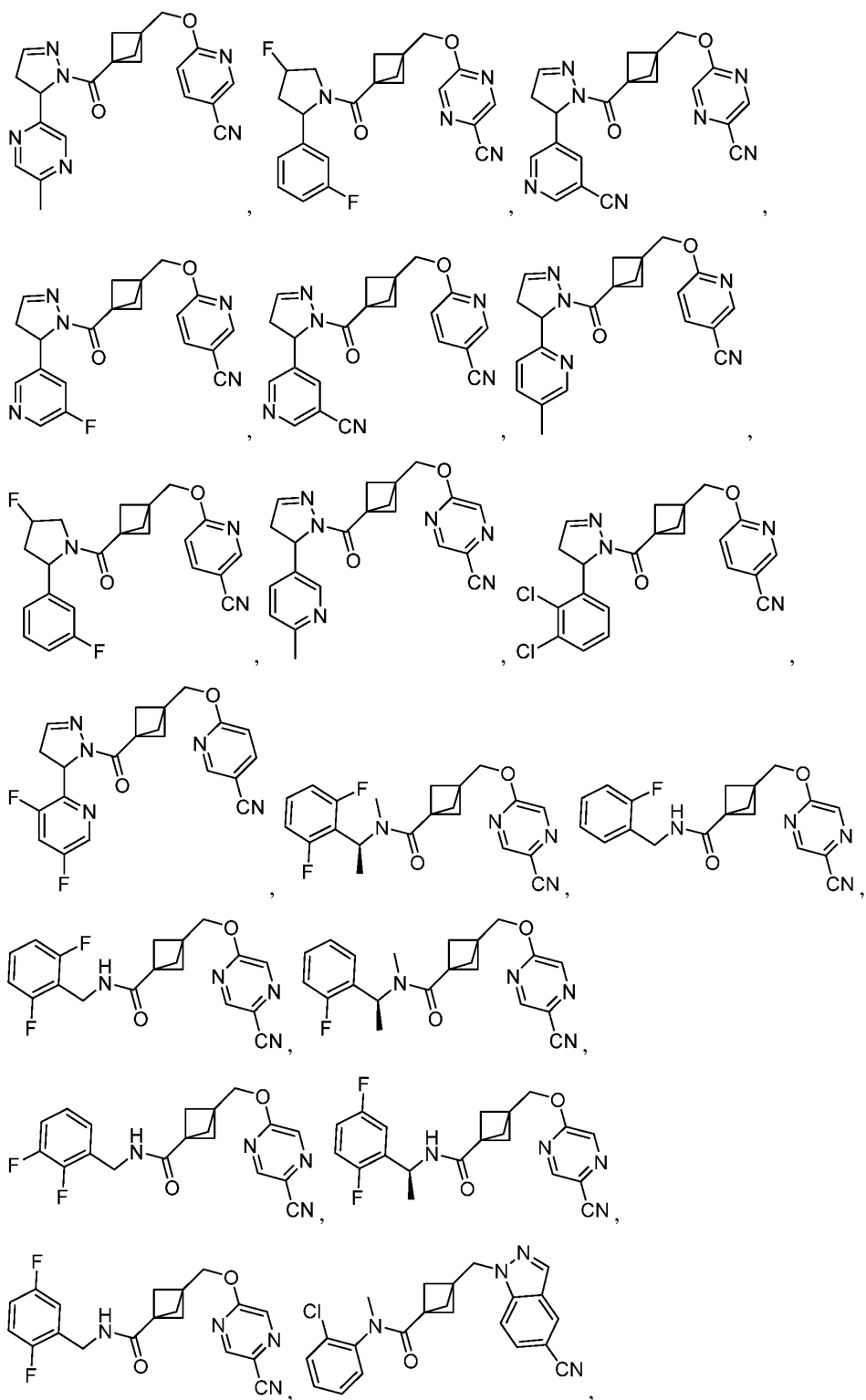


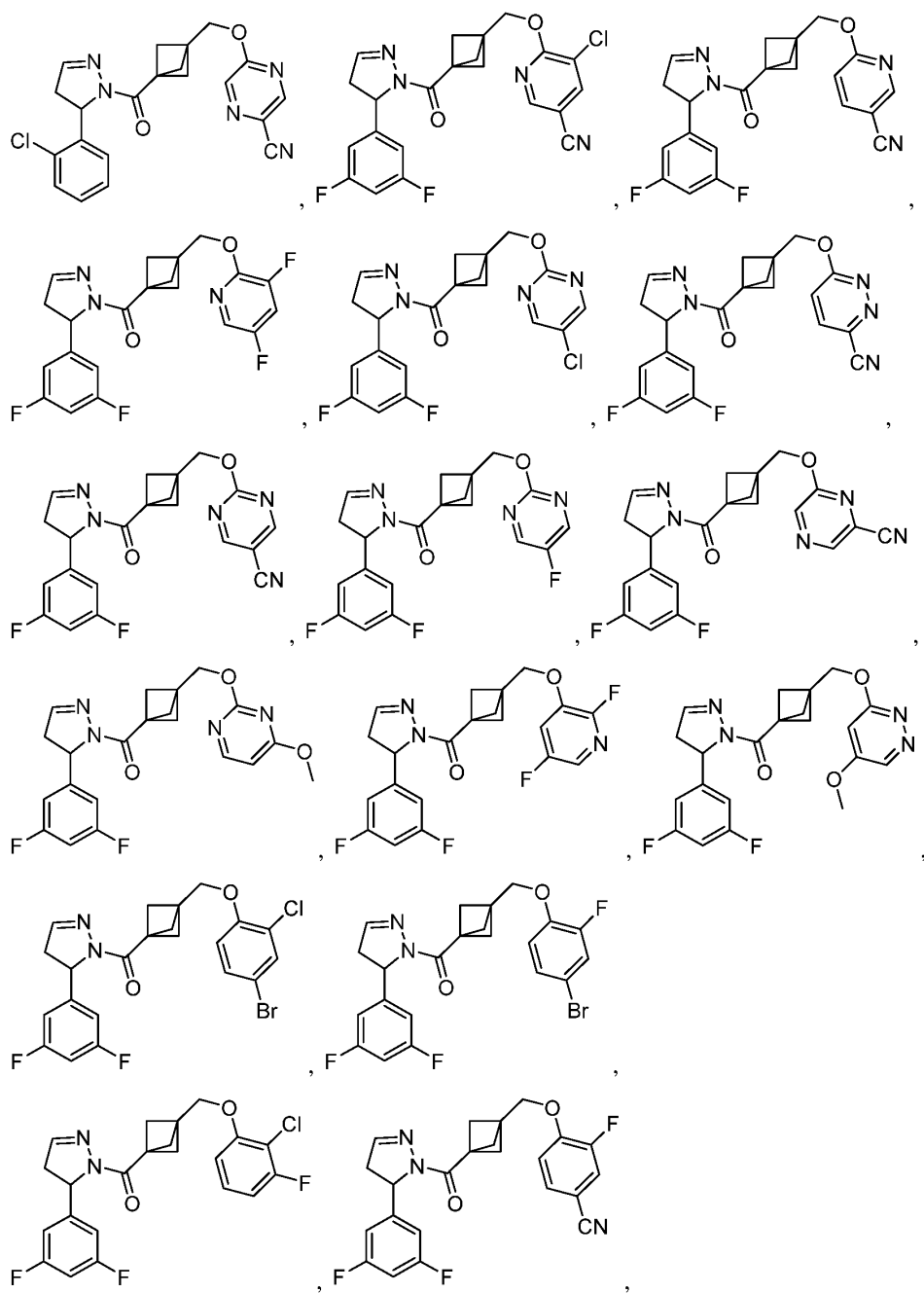


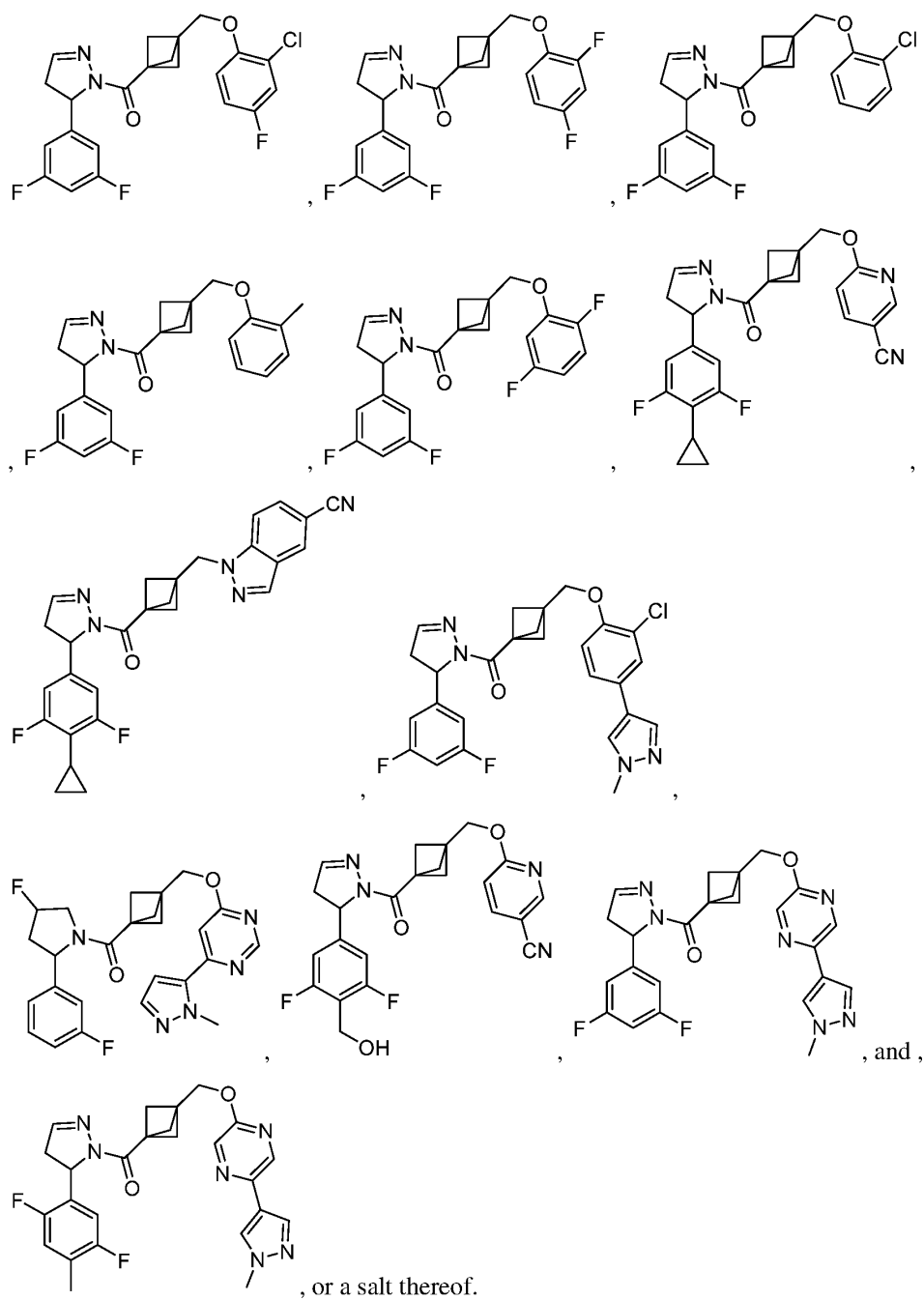












48. A compound as recited in any one of claims 1 – 47 for use as a medicament.

49. A compound as recited in any one of claims 1 – 47 for use in the manufacture of a medicament for the prevention or treatment of a disease ameliorated by the inhibition of RIPK1.

50. A compound as recited in any one of claims 1 – 47 for use in the treatment of a disease mediated by RIPK1.
51. The compound as recited in claim 50, wherein said disease is a neurological disease.
52. The compound as recited in claim 51, wherein said neurological disease is accompanied by an inflammatory component of cellular stress.
53. The compound as recited in claim 52, wherein said neurological disease is chosen from multiple sclerosis, Neimanm-Pick disease, Alzheimers disease, Parkinson's disease, amyotrophic lateral sclerosis, Lewy body dementia, frontotemporal dementia, and glutamine expansion diseases such as Huntington's disease, Kennedy's disease, and spinocerebellar ataxia.
54. The compound as recited in claim 50, wherein said disease is a neuropathy.
55. The compound as recited in claim 54, wherein said neuropathy is chosen from diabetic neuropathy and chemotherapy induced neuropathy.
56. The compound as recited in claim 50, wherein said disease is a retinal disease.
57. The compound as recited in claim 56, wherein said retinal disease is chosen from macular degeneration and retinitis.
58. The compound as recited in claim 50, wherein said disease is an auto-immune disorder.
59. The compound as recited in claim 58, wherein said auto-immune disorder is chosen from ulcerative colitis, rheumatoid arthritis, psoriasis, lupus, and inflammatory bowel disease.
60. The compound as recited in claim 50, wherein said disease is an inflammatory disease.
61. The compound as recited in claim 60, wherein said inflammatory disease is in one or more organs chosen from lung, heart, kidney, and liver.
62. The compound as recited in claim 50, wherein said disease is cancer.
63. The compound as recited in claim 62, wherein the cancer is treated by promoting an appropriate immune response to the tumor.
64. The compound as recited in claim 63, wherein the appropriate response to the tumor comprises, or results in, one or more of the following:
- an increase in the number or activity, or degree of tumor infiltration, of cytotoxic T-lymphocytes and/or natural killer cells;
 - an increase in the number or activity of M1 macrophages in the tumor microenvironment and/or a decrease in the in the number or activity of M2 macrophages in the tumor microenvironment;
 - a decrease in the number or activity of regulatory T cells; and

- a decrease in the number or activity of myeloid-derived suppressor cells.
 - a decrease in the number or activity of myeloid-derived suppressor cells.
65. A compound as recited in any one of claims 1 – 47 for use in the treatment of an injury to the CNS.
66. The compound as recited in claim 65, wherein said injury is chosen from traumatic brain injury and stroke.
67. A pharmaceutical composition comprising a compound as recited in claim 1 together with a pharmaceutically acceptable carrier.
68. A method of inhibition of RIPK1 comprising contacting RIPK1 with a compound as recited in claim 1.
69. A method of treatment of a RIPK1-mediated disease comprising the administration of a therapeutically effective amount of a compound as recited in claim 1 to a patient in need thereof.
70. The method as recited in claim 69, wherein said disease is a neurological disease.
71. The method as recited in claim 70, wherein said neurological disease is accompanied by an inflammatory component of cellular stress.
72. The method as recited in claim 71, wherein said neurological disease is chosen from Multiple Sclerosis, Neimanm-Pick disease, Alzheimers disease, Parkinson's disease, amyotrophic lateral sclerosis, Lewy body dementia, frontotemporal dementia, and glutamine expansion diseases such as Huntington's disease, Kennedy's disease, spinocerebellar ataxia.
73. The method as recited in claim 69, wherein said disease is a neuropathy.
74. The method as recited in claim 73, wherein said neuropathy is chosen from diabetic neuropathy and chemotherapy induced neuropathy.
75. The method as recited in claim 69, wherein said disease is a retinal disease.
76. The method as recited in claim 75, wherein said retinal disease is chosen from macular degeneration and retinitis.
77. The method as recited in claim 69, wherein said disease is an autoimmune disorder.
78. The method as recited in claim 77, wherein said autoimmune disorder is chosen from ulcerative colitis, rheumatoid arthritis, psoriasis, lupus, and inflammatory bowel disease.
79. The method as recited in claim 69, wherein said disease is an inflammatory disease.
80. The method as recited in claim 79, wherein said inflammatory disease is in one or more organs chosen from lung, heart, kidney, and liver.

81. The method as recited in claim 69, wherein said disease is cancer.
82. The method as recited in claim 81, wherein the cancer is treated by promoting an appropriate immune response to the tumor.
83. The method as recited in claim 82, wherein the appropriate immune response to the tumor comprises, or results in, one or more of the following:
- an increase in the number or activity, or degree of tumor infiltration, of cytotoxic T-lymphocytes and/or natural killer cells;
 - an increase in the number or activity of M1 macrophages in the tumor microenvironment and/or a decrease in the in the number or activity of M2 macrophages in the tumor microenvironment;
 - a decrease in the number or activity of regulatory T cells; and
 - a decrease in the number or activity of myeloid-derived suppressor cells.
84. A method of treatment of injury to the CNS comprising the administration of a therapeutically effective amount of a compound as recited in claim 1 to a patient in need thereof.
85. The method as recited in claim 84, wherein said injury is chosen from traumatic brain injury and stroke.
86. A method of treatment of a RIPK1-mediated disease comprising the administration of:
- (a) a therapeutically effective amount of a compound as recited in claim 1; and
 - (b) another therapeutic agent.
87. The method as recited in claim 86, wherein the disease is cancer.
88. The method as recited in claim 87, wherein the other therapeutic agent is a checkpoint inhibitor.
89. The method as recited in claim 87, wherein the checkpoint inhibitor is chosen from an anti-PD1 inhibitor, an anti-PDL1 inhibitor, an anti-CTLA4 inhibitor, an anti-OX50 inhibitor, an anti-TIM3 inhibitor, and an anti-LAG3 inhibitor.