

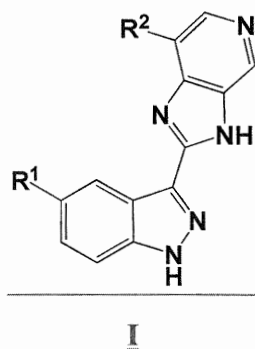
changes involving nuclear function. Recently, a link between neuronal activity, essential for the formation and refinement of neuronal connections, and Wnt signaling has been uncovered. Indeed, neuronal activity regulates the release of various Wnt proteins and the localization of their receptors. Wnt pathway mediates synaptic structural changes induced by neuronal activity or experience. Evidence suggests that dysfunction in Wnt signaling contributes to neurological disorders [*Brain Research Reviews* (2000), 33(1), 1–12; *Oncogene* (2006) 25(57), 7545-7553; *Molecular Neurodegeneration* (2008), 3, 9; *Neurobiology of Disease* (2010), 38(2), 148–153; *Journal of Neurodevelopmental Disorders* (2011), 3(2), 162–174 and *Cold Spring Harbor Perspectives in Biology* February (2012), 4(2)].

SUMMARY-OF-THE-INVENTION

[0009] The present ~~invention~~-disclosure makes available methods and reagents, involving contacting a cell with an agent, such as an aromatic compound, in a sufficient amount to antagonize a Wnt activity, e. g., to reverse or control an aberrant growth state or correct a genetic disorder due to mutations in Wnt signaling components.

[0010] Some embodiments disclosed herein include Wnt inhibitors containing an indazole core. Other embodiments disclosed herein include pharmaceutical compositions and methods of treatment using these compounds.

[0010a] In one aspect, there is provided a compound or pharmaceutically acceptable salt thereof having the structure of Formula I:



wherein:

R¹ is -heteroarylR³R⁴;

R² is selected from the group consisting of H, -heteroarylR⁵, -heterocyclylR⁶ and -arylR⁷;

R³ is selected from the group consisting of H, -heterocyclylR⁸, -NHC(=O)R⁹, -NHSO₂R¹⁰, -NR¹¹R¹² and -(C₁₋₆ alkyl)NR¹¹R¹²;

with the proviso that R² and R³ are not both H;

R⁴ is 1-3 substituents each selected from the group consisting of H, halide, -CF₃, -CN, OR¹³ and amino;

each R⁵ is independently 1-4 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, -C(=O)R¹¹, amino and -(C₁₋₆ alkyl)NR¹¹R¹²;

each R⁶ is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

each R⁷ is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, amino, -(C₁₋₆ alkyl)NHSO₂R¹¹, -NR¹²(C₁₋₆ alkyl)NR¹¹R¹² and -(C₁₋₆ alkyl)NR¹¹R¹²;

R⁸ is 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

R⁹ is selected from the group consisting of C₁₋₉ alkyl, -heteroarylR⁵, -heterocyclylR⁶, -arylR⁷ and -CH₂carbocyclyl;

R¹⁰ is selected from the group consisting of C₁₋₉ alkyl, -heteroarylR⁵, -heterocyclylR⁶, -arylR⁷, and -carbocyclylR¹⁴;

each R¹¹ is independently selected from C₁₋₆ alkyl;

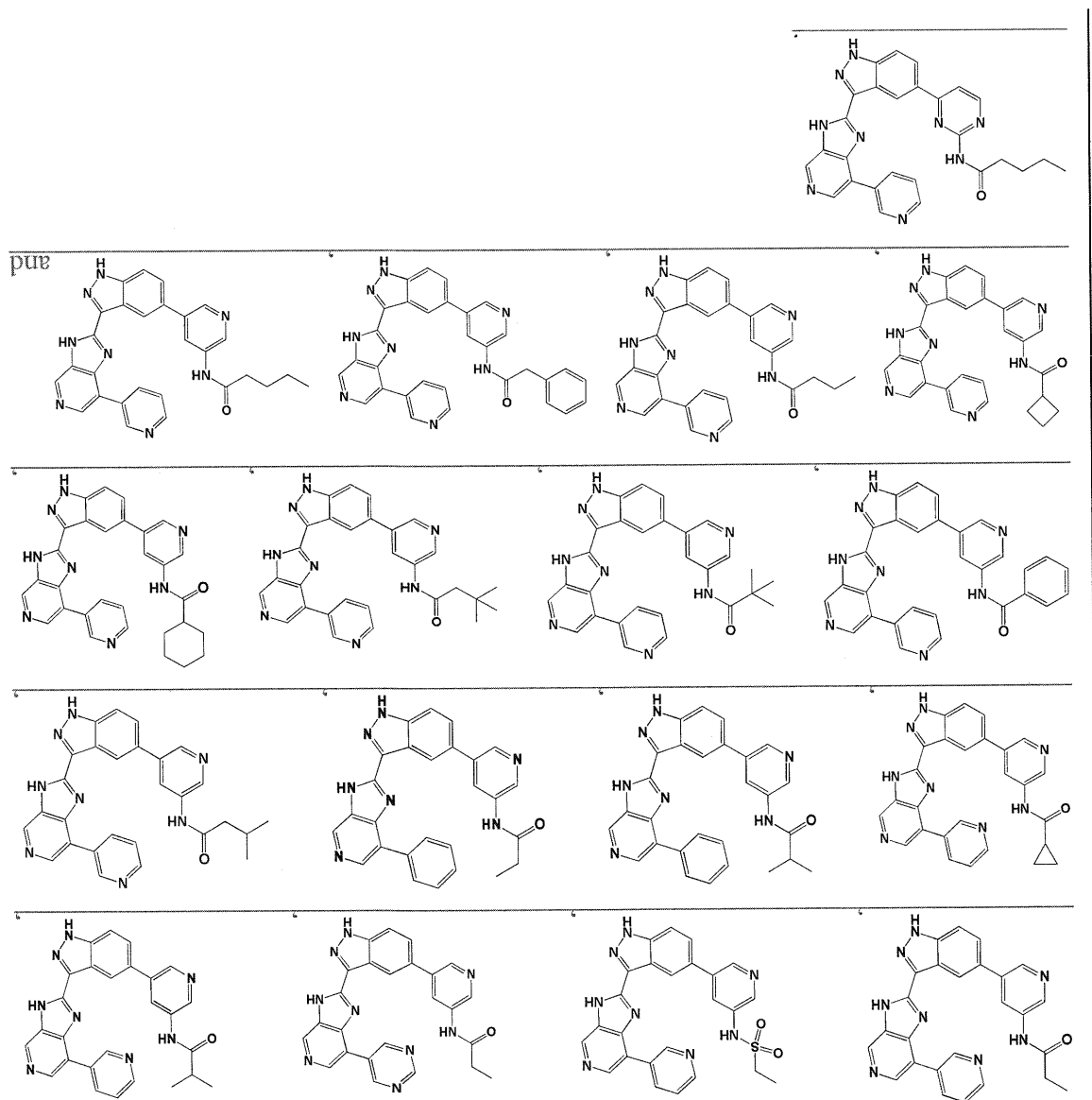
each R¹² is independently selected from the group consisting of H and C₁₋₆ alkyl;

each R¹¹ and R¹² are optionally linked to form a five or six membered heterocyclyl ring;

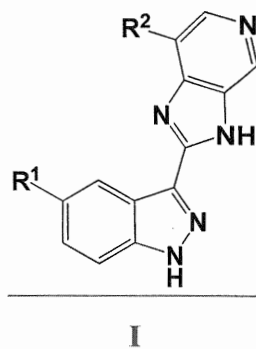
each R¹³ is independently selected from the group consisting of H and C₁₋₆ alkyl;

R¹⁴ is 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

with the proviso that Formula I is not a structure selected from the group consisting of:



[0010b] In one aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula I:



wherein:

R^1 is $\text{-heteroaryl}R^3R^4$;

R^2 is $\text{-aryl}R^7$;

R^3 is a $\text{-NHC(=O)}R^9$;

R^4 is H;

each R^7 is independently 1-2 substituents each selected from the group consisting of halide, -CF_3 , -CN , $\text{-(C}_{1-6}\text{ alkyl)NHSO}_2R^{11}$, $\text{-(C}_{1-6}\text{ alkyl)NR}^{11}R^{12}$, and $\text{-NR}^{12}(\text{C}_{1-6}\text{ alkyl)NR}^{11}R^{12}$;

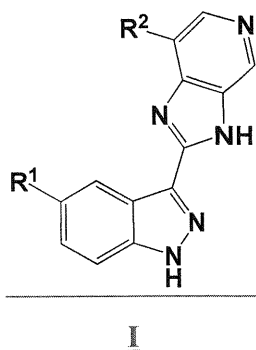
R^9 is selected from the group consisting of $\text{-(C}_{1-6}\text{ alkyl)}$, -aryl , -carbocyclyl , and $\text{-CH}_2\text{carbocyclyl}$;

each R^{11} is independently selected from $\text{-(C}_{1-6}\text{ alkyl)}$;

each R^{12} is independently selected from the group consisting of H and $\text{-(C}_{1-6}\text{ alkyl)}$; and

each R^{11} and R^{12} are optionally linked to form a four to six membered heterocyclyl ring.

[0010c] In one aspect, there is provided a compound, or pharmaceutically acceptable salt thereof, having the structure of Formula I:



wherein:

R^1 is $-\text{pyridin-3-yl}R^3R^4$;

R^2 is $-\text{phenyl}R^7$;

R^3 is a $-\text{NHC}(=\text{O})R^9$;

R^4 is H;

each R^7 is independently 1-2 substituents each selected from the group consisting of fluorine, $-\text{CH}_2\text{NHSO}_2R^{11}$, $-(\text{C}_{1-6}\text{ alkyl})\text{NR}^{11}R^{12}$, and $-\text{NHCH}_2\text{CH}_2\text{NR}^{11}R^{12}$;

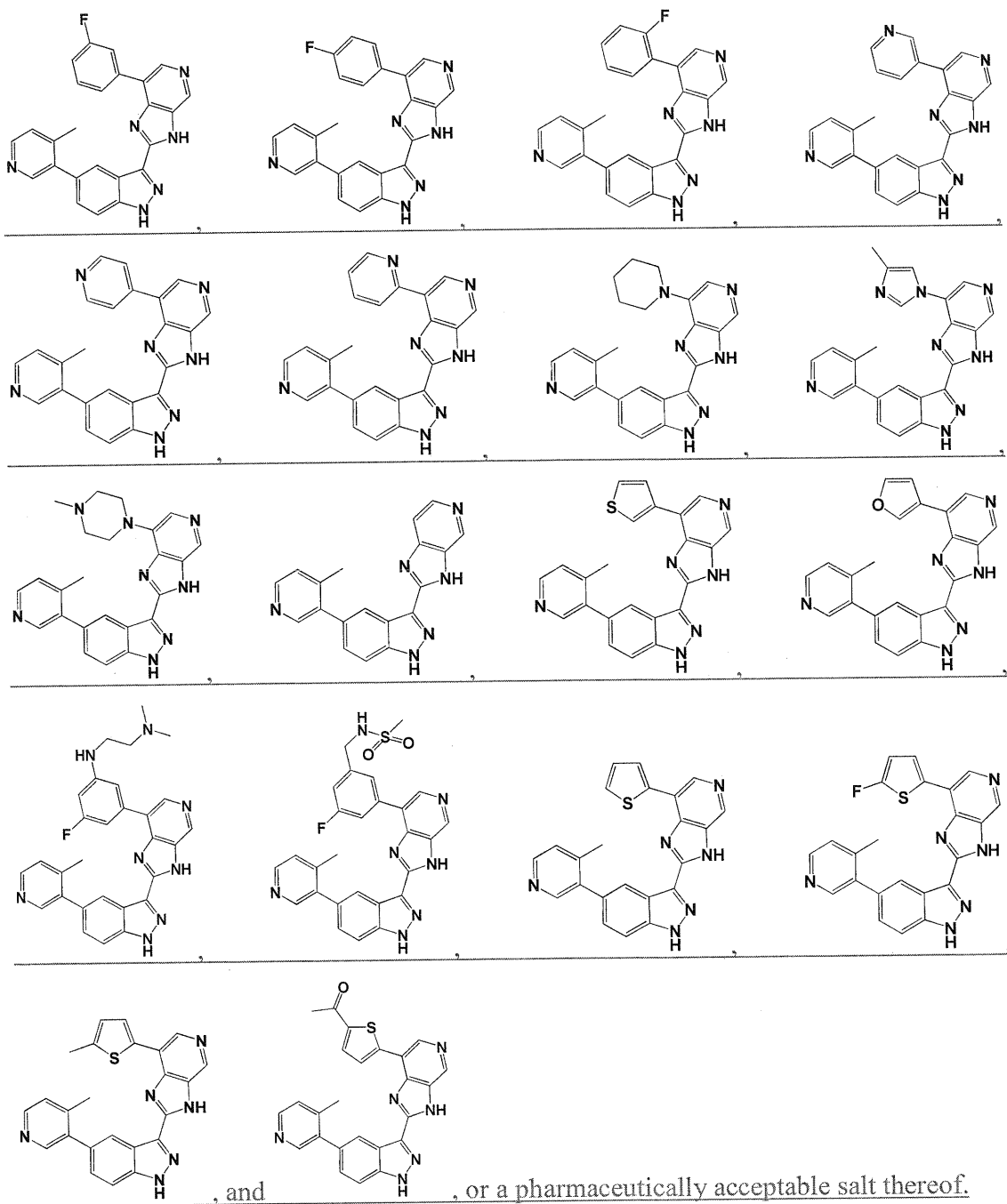
R^9 is selected from the group consisting of $-(\text{C}_{2-5}\text{ alkyl})$, $-\text{phenyl}$, $-\text{carbocyclyl}$, and $-\text{CH}_2\text{carbocyclyl}$;

each R^{11} is independently selected from $-(\text{C}_{1-2}\text{ alkyl})$;

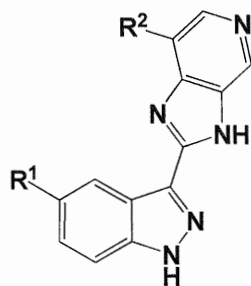
each R^{12} is independently selected from the group consisting of H and $-(\text{C}_{1-2}\text{ alkyl})$; and

each R^{11} and R^{12} are optionally linked to form a four to six membered heterocyclyl ring.

[0010d] In one aspect, there is provided a compound having a structure selected from the group consisting of:



[0011] One embodiment disclosed herein includes a compound having the structure of Formula I:

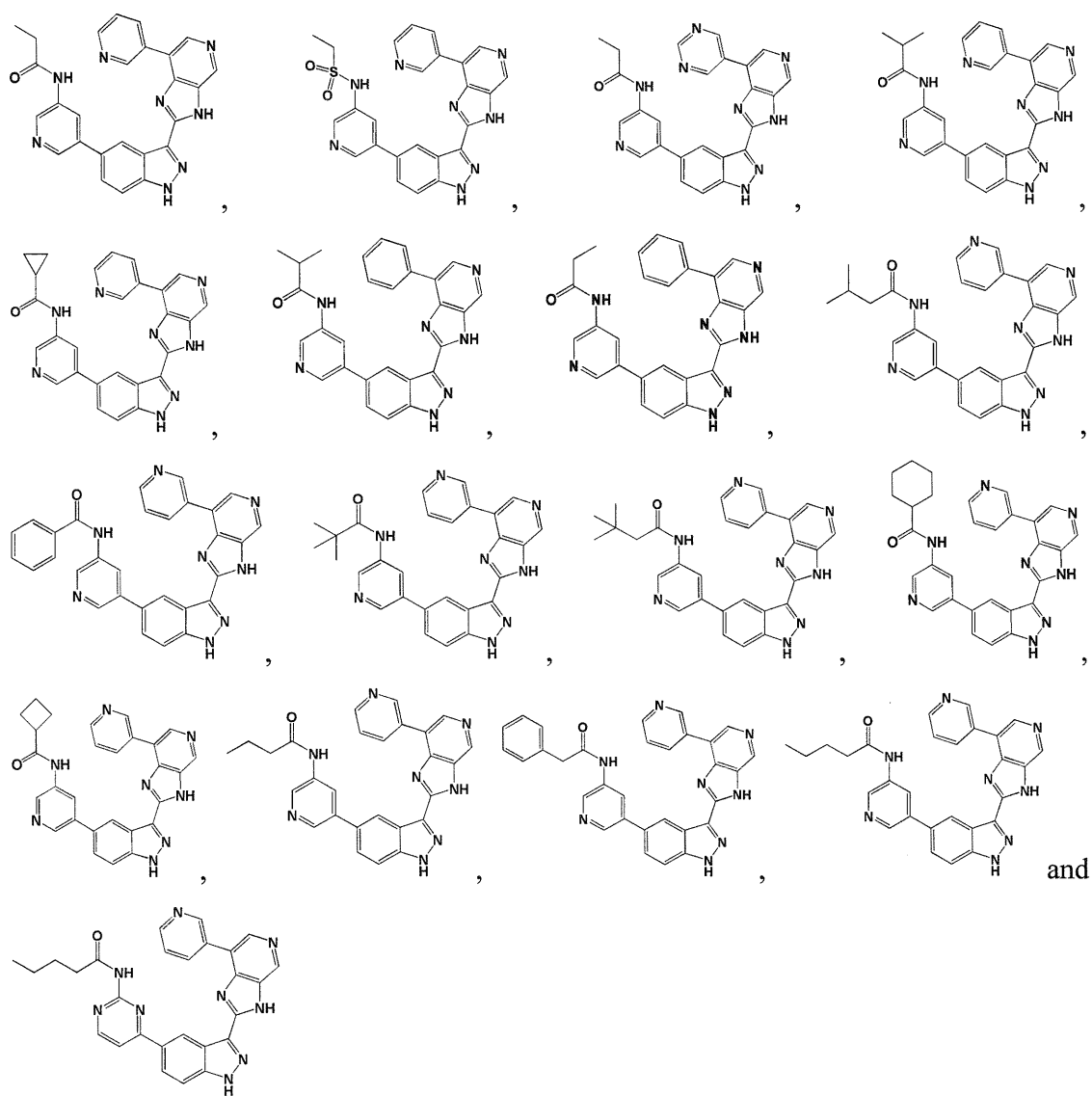


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as well as prodrugs and pharmaceutically acceptable salts thereof.

[0012] In some embodiments of Formula (I):

R¹ is -heteroarylR³R⁴;



[0013] Some embodiments include stereoisomers and pharmaceutically acceptable salts of a compound of general Formula (I).

[0014] Some embodiments include pro-drugs of a compound of general Formula (I).

[0014a] In one aspect, there is provided a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[0015] Some embodiments of the present ~~invention~~disclosure include pharmaceutical compositions comprising a compound of general Formula (I) and a pharmaceutically acceptable carrier.

[0015a] In another aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating a disorder or disease for preventing or reducing angiogenesis in a patient.

[0015b] In one aspect, there is provided a compound as defined herein, or a pharmaceutically acceptable salt thereof, for use in treating a disorder or disease in a patient, wherein the disorder or disease is selected from the group consisting of: diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, a mycotic or viral infection, a bone or cartilage disease, Alzheimer's disease, lung disease, and cancer.

[0016] Other embodiments disclosed herein include methods of inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins by administering to a subject affected by a disorder or disease in which aberrant Wnt

signaling is implicated, such as cancer and other diseases associated with abnormal angiogenesis, cellular proliferation, cell cycling and mutations in Wnt signaling components, a compound according to any of the above formulas. Accordingly, the compounds and compositions provided herein can be used to treat cancer, to reduce or inhibit angiogenesis, to reduce or inhibit cellular proliferation and correct an genetic disorder due to mutations in Wnt signaling components. Non-limiting examples of diseases which can be treated with the compounds and compositions provided herein include a variety of cancers, diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, mycotic and viral infections, osteochondrodysplasia, Alzheimer's disease, lung disease, osteoarthritis, polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

[0017] Another embodiment disclosed herein includes a pharmaceutical composition that has a compound according to any of the above formulas and a pharmaceutically acceptable carrier, diluent, or excipient.

[0018] Some embodiments of the present ~~invention~~disclosure include methods to prepare a compound of general Formula (I).

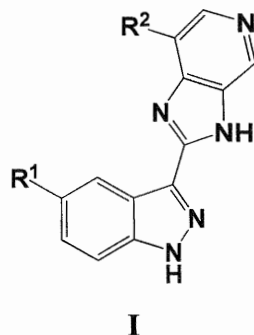
[0019] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed.

DETAILED DESCRIPTION OF THE INVENTION

[0020] Compositions and methods for inhibiting one or more members of the Wnt pathway, including one or more Wnt proteins would be of tremendous benefit. Certain embodiments provide such compositions and methods. Certain related

WHAT IS CLAIMED IS

1. A compound or pharmaceutically acceptable salt thereof having the structure of Formula I:



wherein:

R^1 is -heteroaryl R^3R^4 ;

R^2 is selected from the group consisting of H, -heteroaryl R^5 , -heterocyclyl R^6 and -aryl R^7 ;

R^3 is selected from the group consisting of H, -heterocyclyl R^8 , -NHC(=O) R^9 , -NHSO₂ R^{10} , -NR¹¹ R^{12} and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

with the proviso that R^2 and R^3 are not both H;

R^4 is 1-3 substituents each selected from the group consisting of H, halide, -CF₃, -CN, OR¹³ and amino;

each R^5 is independently 1-4 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, -C(=O) R^{11} , amino and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

each R^6 is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

each R^7 is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, amino, -(C₁₋₆ alkyl)NHSO₂ R^{11} , -NR¹²(C₁₋₆ alkyl)NR¹¹ R^{12} and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

R^8 is 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

R^9 is selected from the group consisting of C₁₋₉ alkyl, -heteroaryl R^5 , -heterocyclyl R^6 , -aryl R^7 and -CH₂carbocyclyl;

R^{10} is selected from the group consisting of C_{1-9} alkyl, -heteroaryl R^5 , -heterocyclyl R^6 , -aryl R^7 , and -carbocyclyl R^{14} ;

each R^{11} is independently selected from C_{1-6} alkyl;

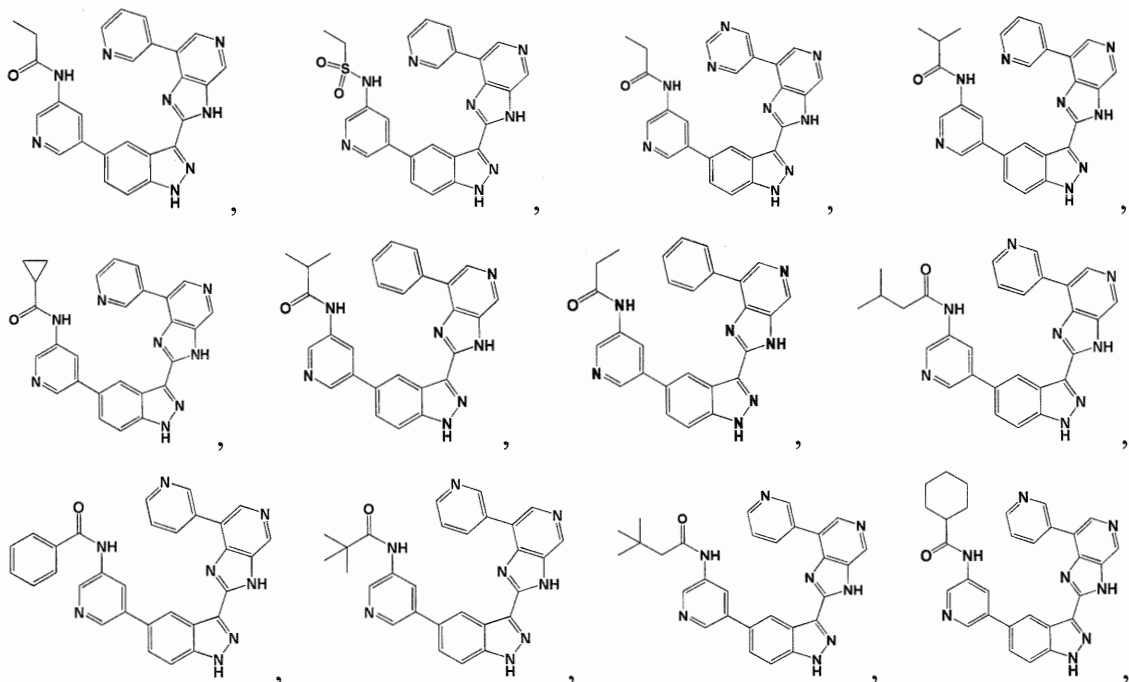
each R^{12} is independently selected from the group consisting of H and C_{1-6} alkyl;

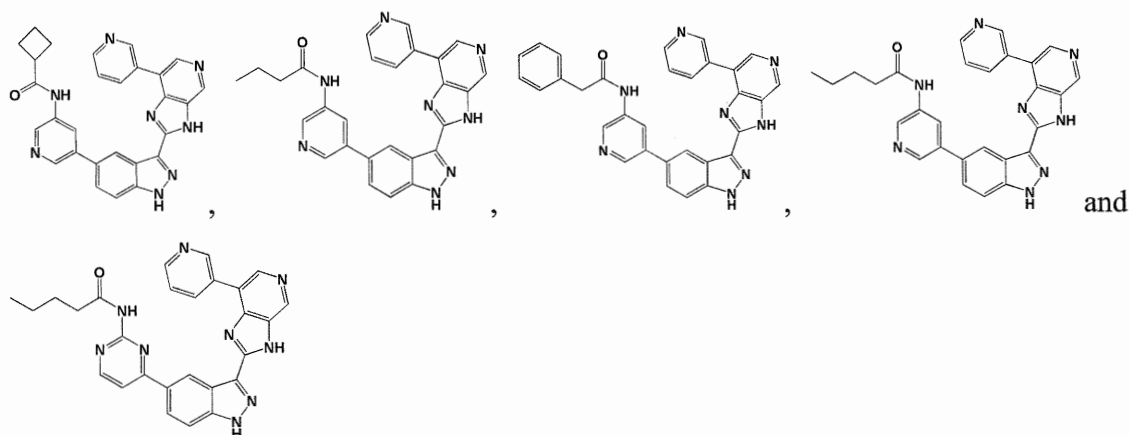
each R^{11} and R^{12} are optionally linked to form a five or six membered heterocyclyl ring;

each R^{13} is independently selected from the group consisting of H and C_{1-6} alkyl;

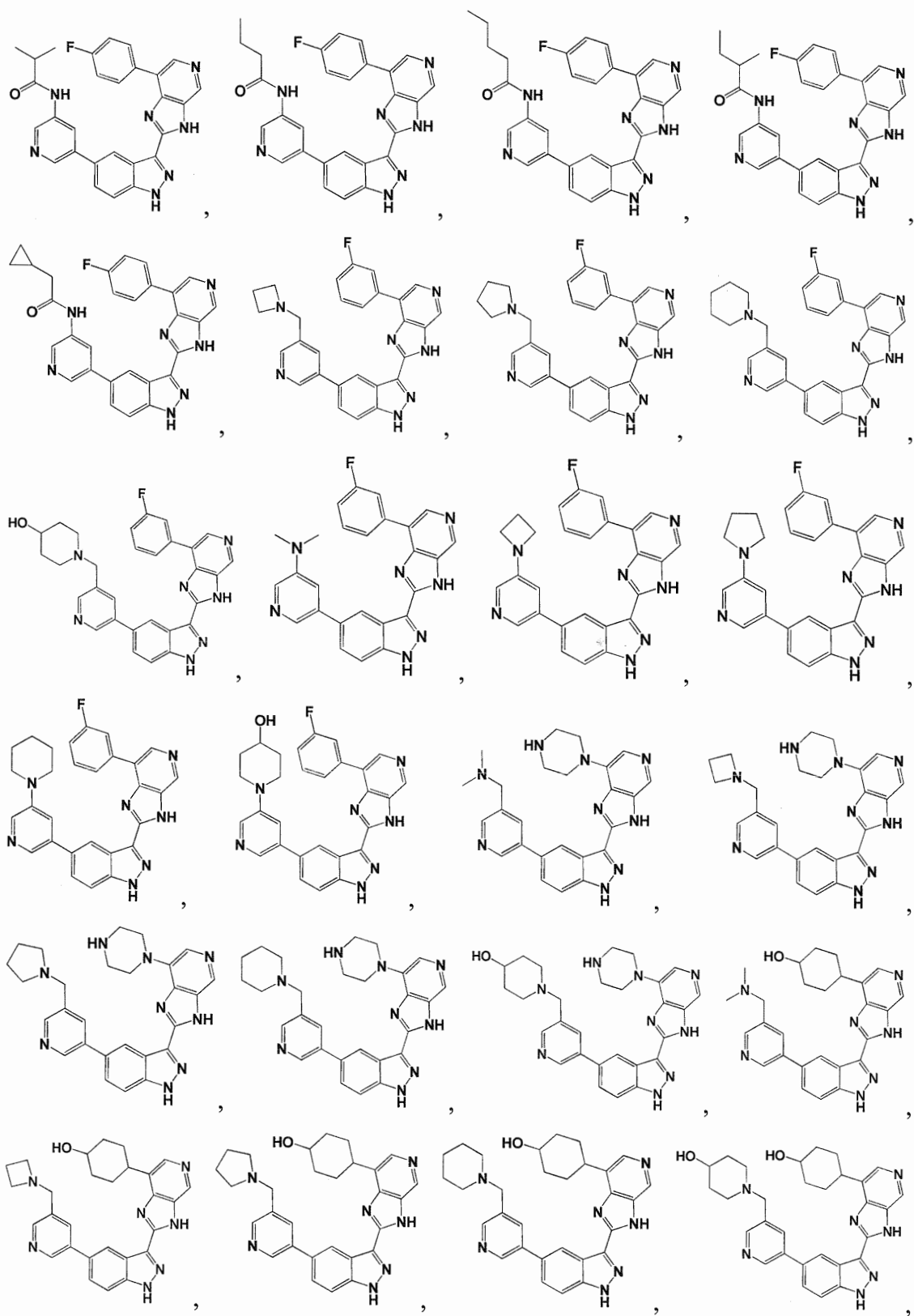
R^{14} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-CN$, OR^{13} and amino;

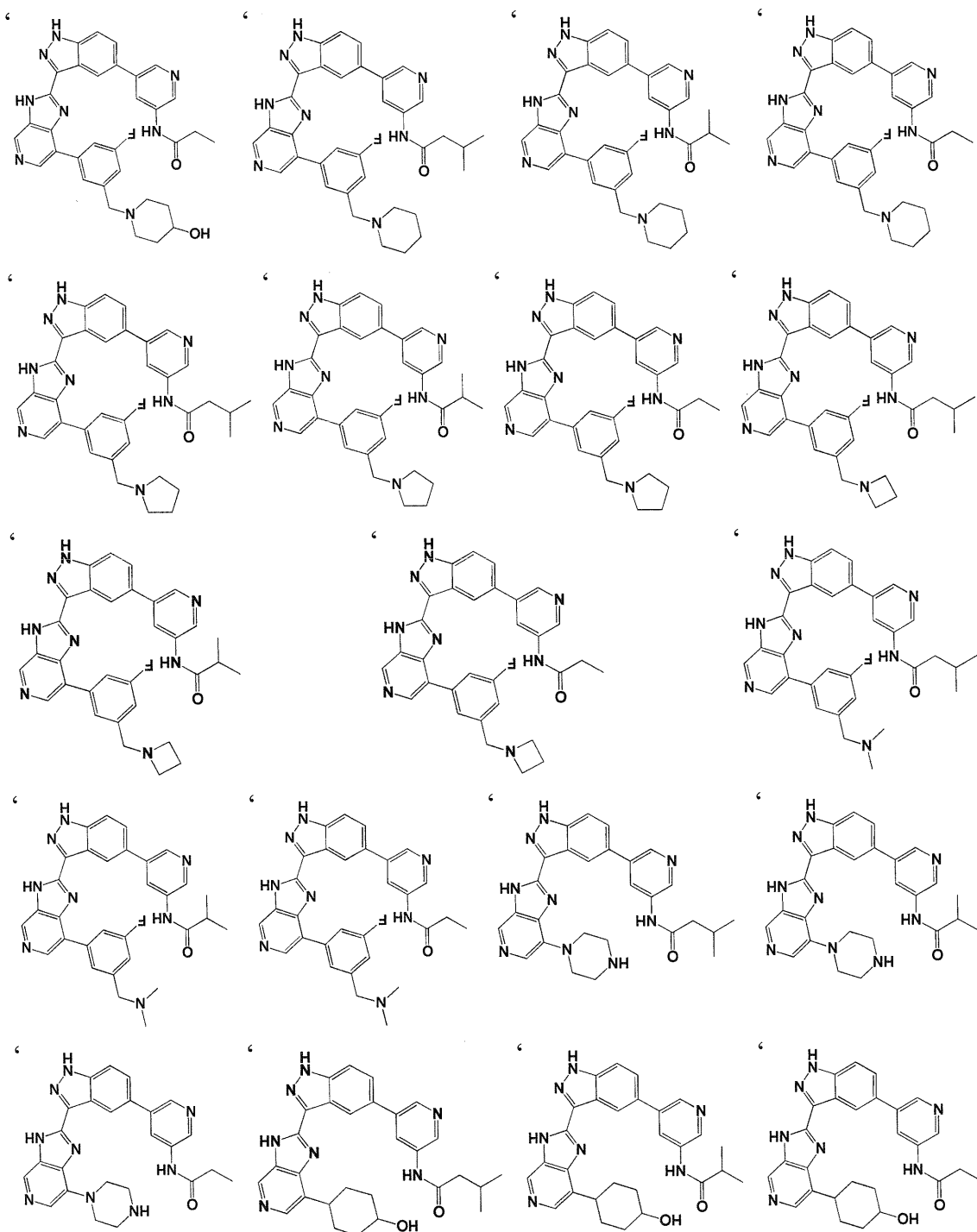
with the proviso that Formula I is not a structure selected from the group consisting of:

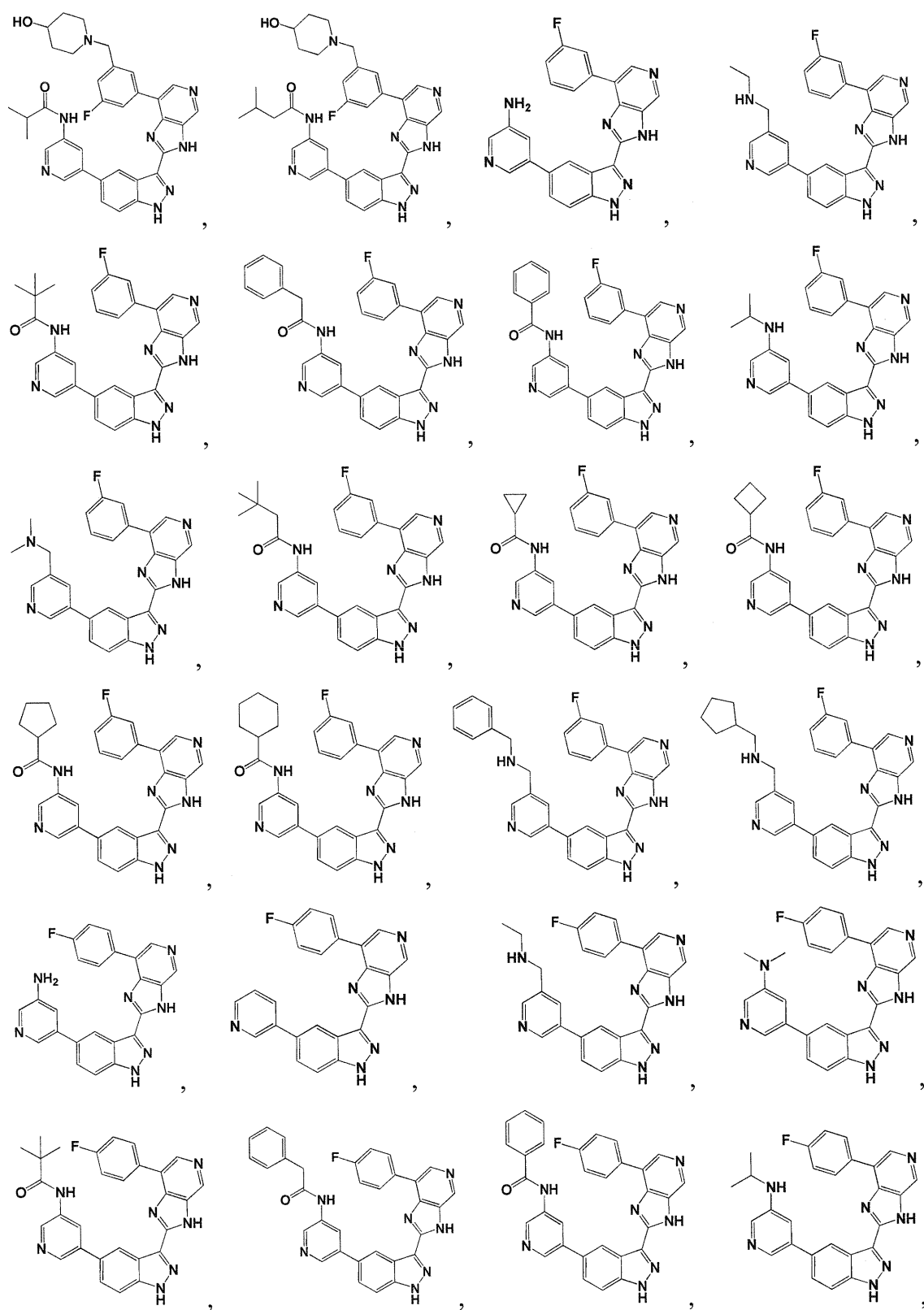


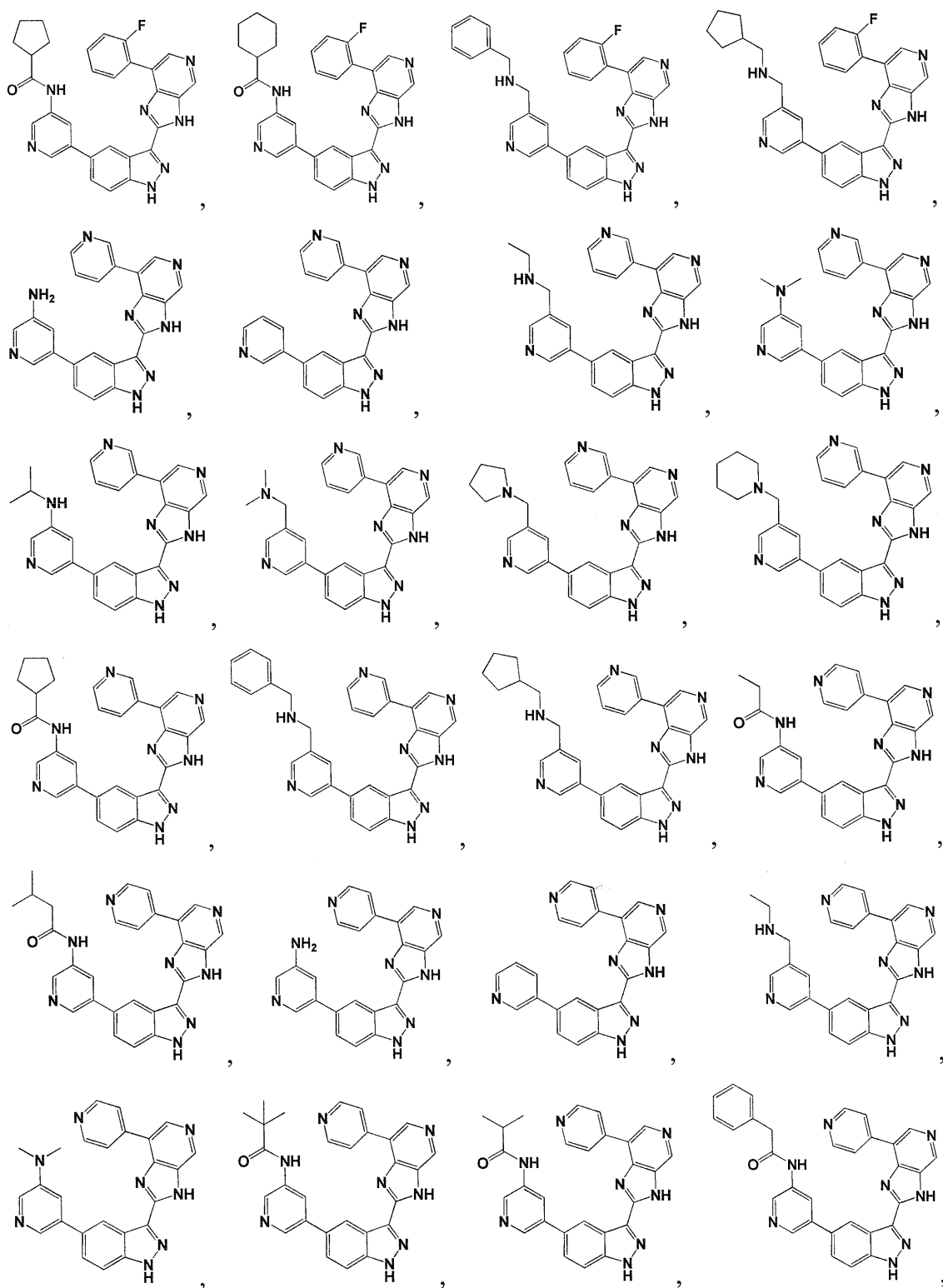


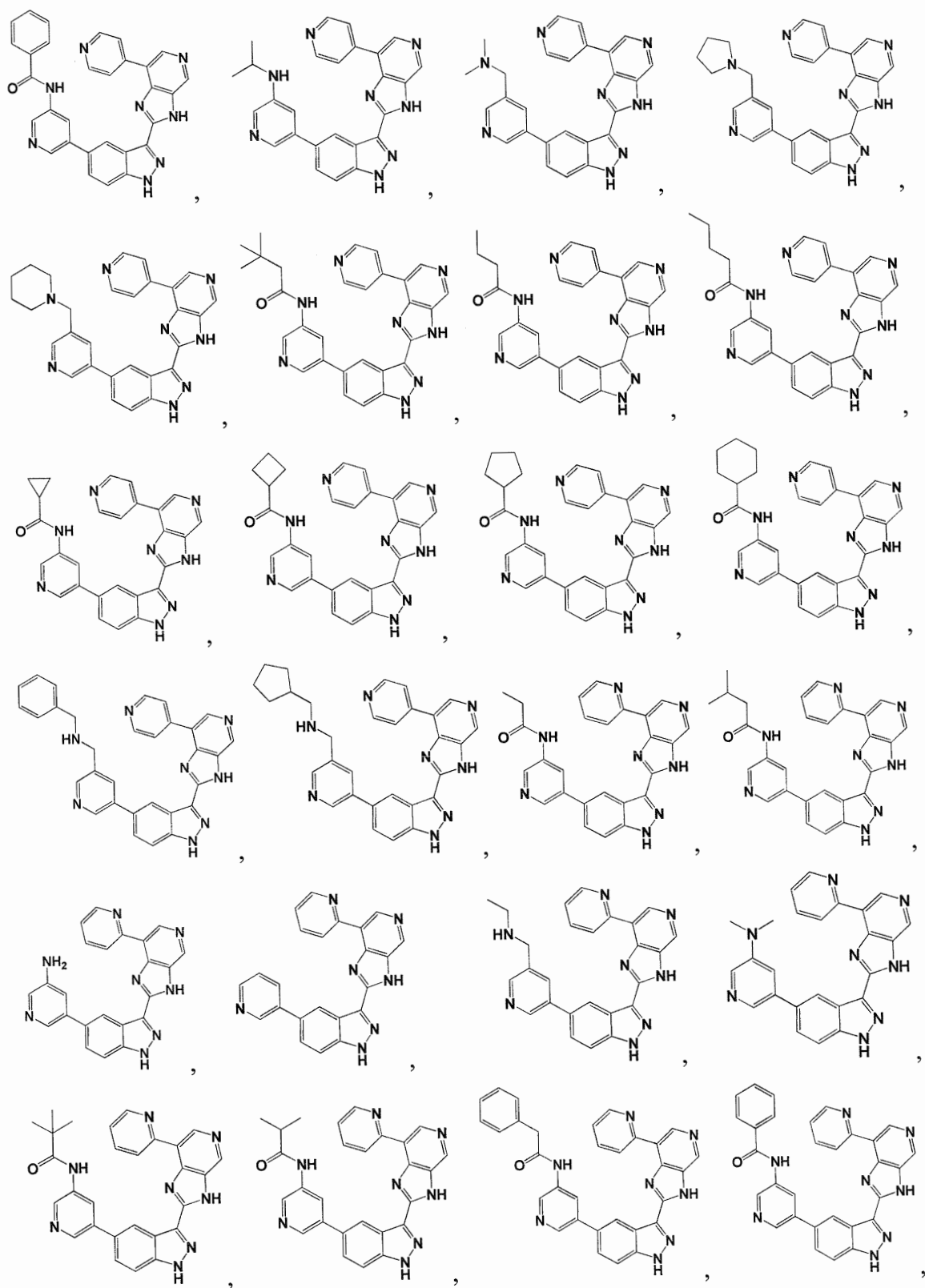
2. The compound of claim 1, wherein R^1 is pyridine- R^3R^4 .
3. The compound of claim 2, wherein R^1 is pyridin-3-yl- R^3R^4 .
4. The compound of claim 3, wherein R^3 is $-(C_{1-6} \text{ alkyl})NR^{11}R^{12}$.
5. The compound of claim 4, wherein R^3 is $-(C_{1-2} \text{ alkyl})NR^{11}R^{12}$, R^{11} is $-(C_{1-2} \text{ alkyl})$, R^{12} is $-(C_{1-2} \text{ alkyl})$ and R^4 is H.
6. The compound of claim 4, wherein R^{11} and R^{12} are optionally linked to form a five or six membered heterocyclyl ring and R^4 is H.
7. The compound of claim 6, wherein the five or six membered heterocyclyl ring is substituted with 1-2 fluorines.
8. The compound of claim 3, wherein R^3 is $-NHC(=O)R^9$.
9. The compound of claim 8, wherein R^4 is H and R^9 is selected from the group consisting of $-(C_{2-5} \text{ alkyl})$, phenyl, $-\text{carbocyclyl}$ and $-\text{CH}_2\text{carbocyclyl}$.
10. The compound of claim 3, wherein R^3 is $-NHSO_2R^{10}$.
11. The compound of claim 10, wherein R^4 is H and R^{10} is selected from the group consisting of $-(C_{1-4} \text{ alkyl})$ and phenyl.
12. The compound of claim 3, wherein R^3 is $-\text{heterocyclyl}R^8$.
13. The compound of claim 12, wherein R^4 is H and heterocyclyl is selected from the group consisting of morpholine, piperazine and piperidine.
14. The compound of claim 3, wherein R^3 is H and R^4 is amino.
15. The compound as in any one of claims 3-14, in which R^2 is $-\text{heteroaryl}R^5$.
16. The compound as in any one of claims 3-14, in which R^2 is $-\text{pyridin-3-yl}R^5$.
17. The compound as in any one of claims 3-14, in which R^2 is $-\text{pyridin-3-yl}R^5$ and R^5 is 1-2 fluorine atoms.

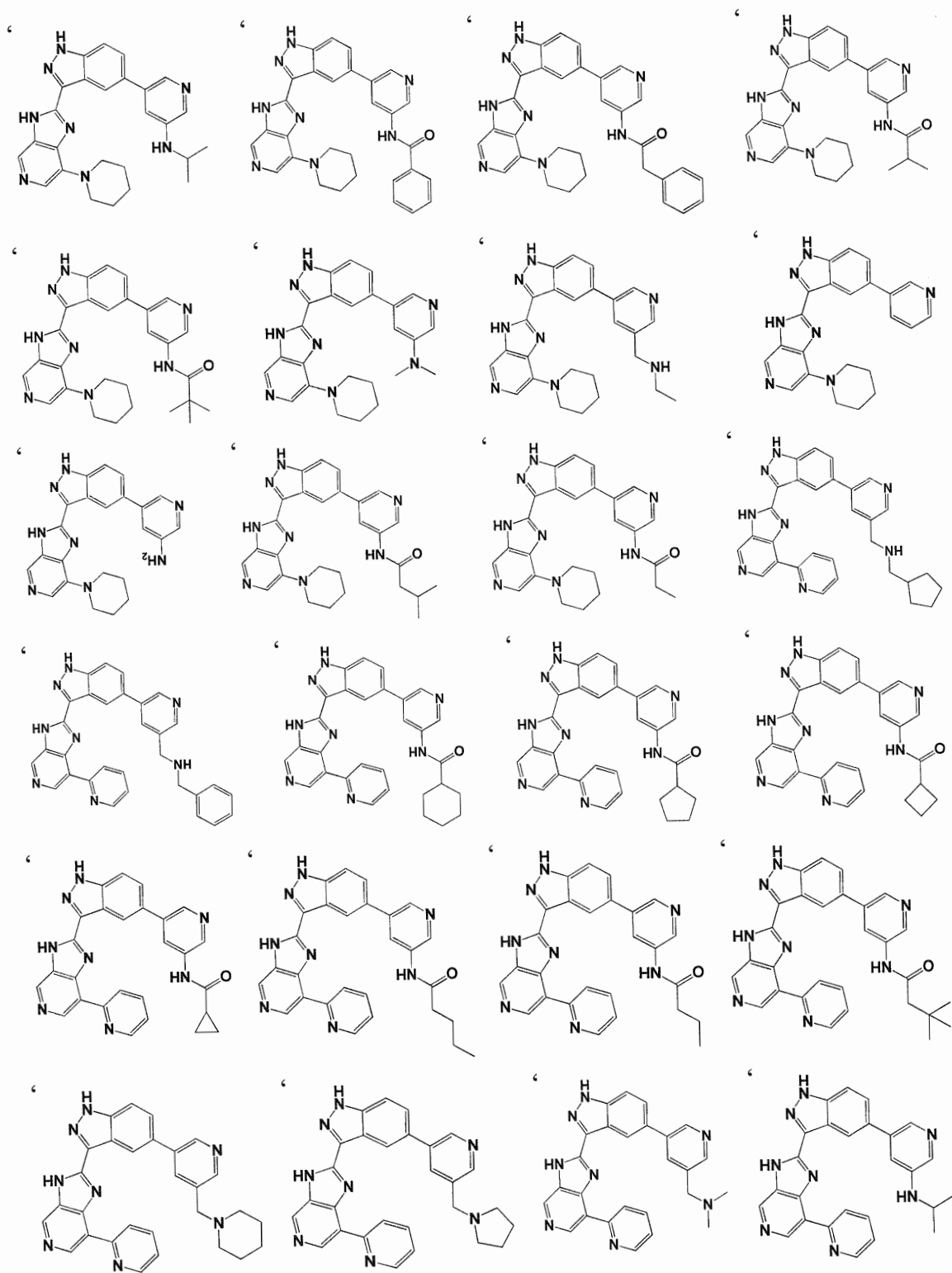


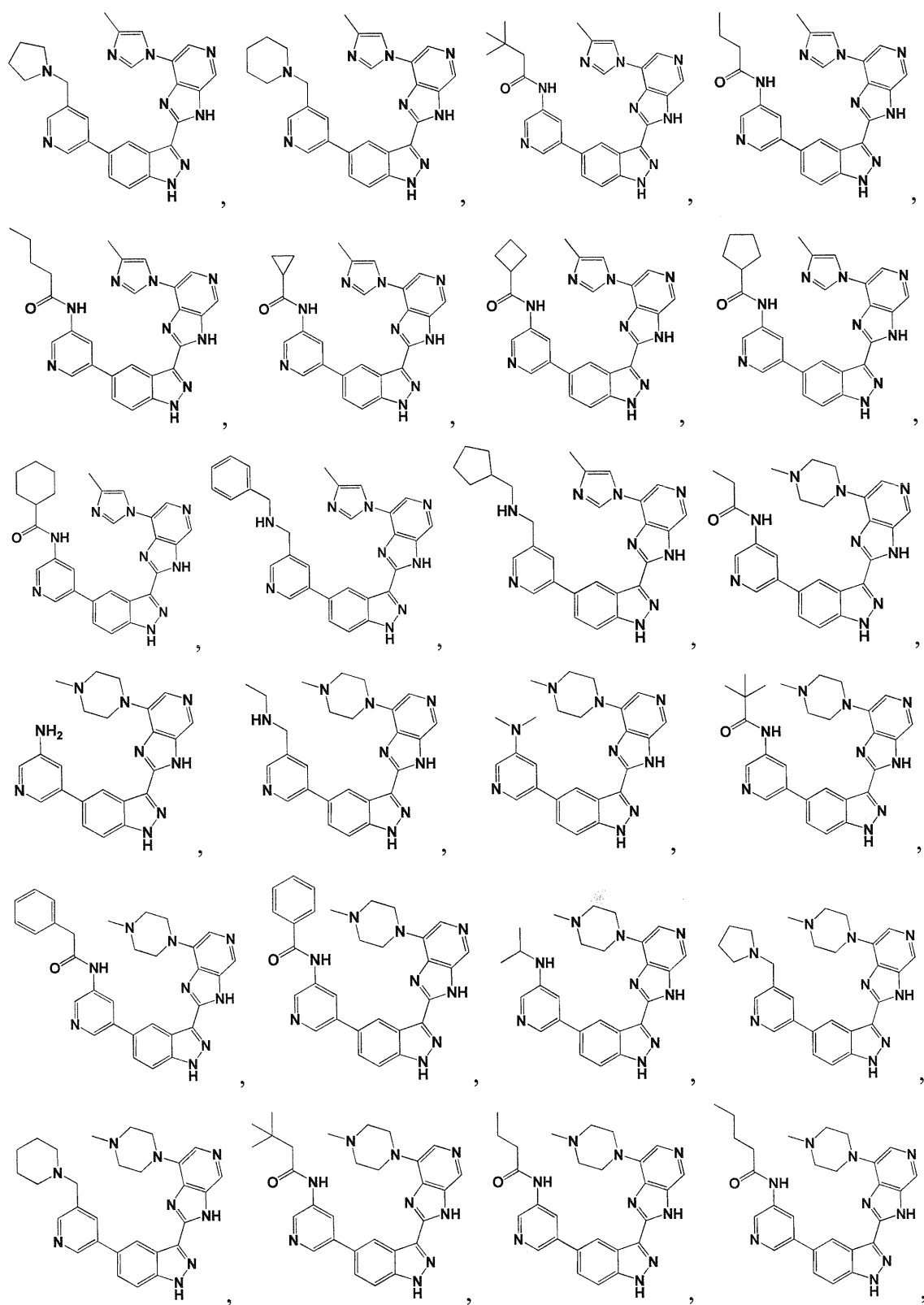


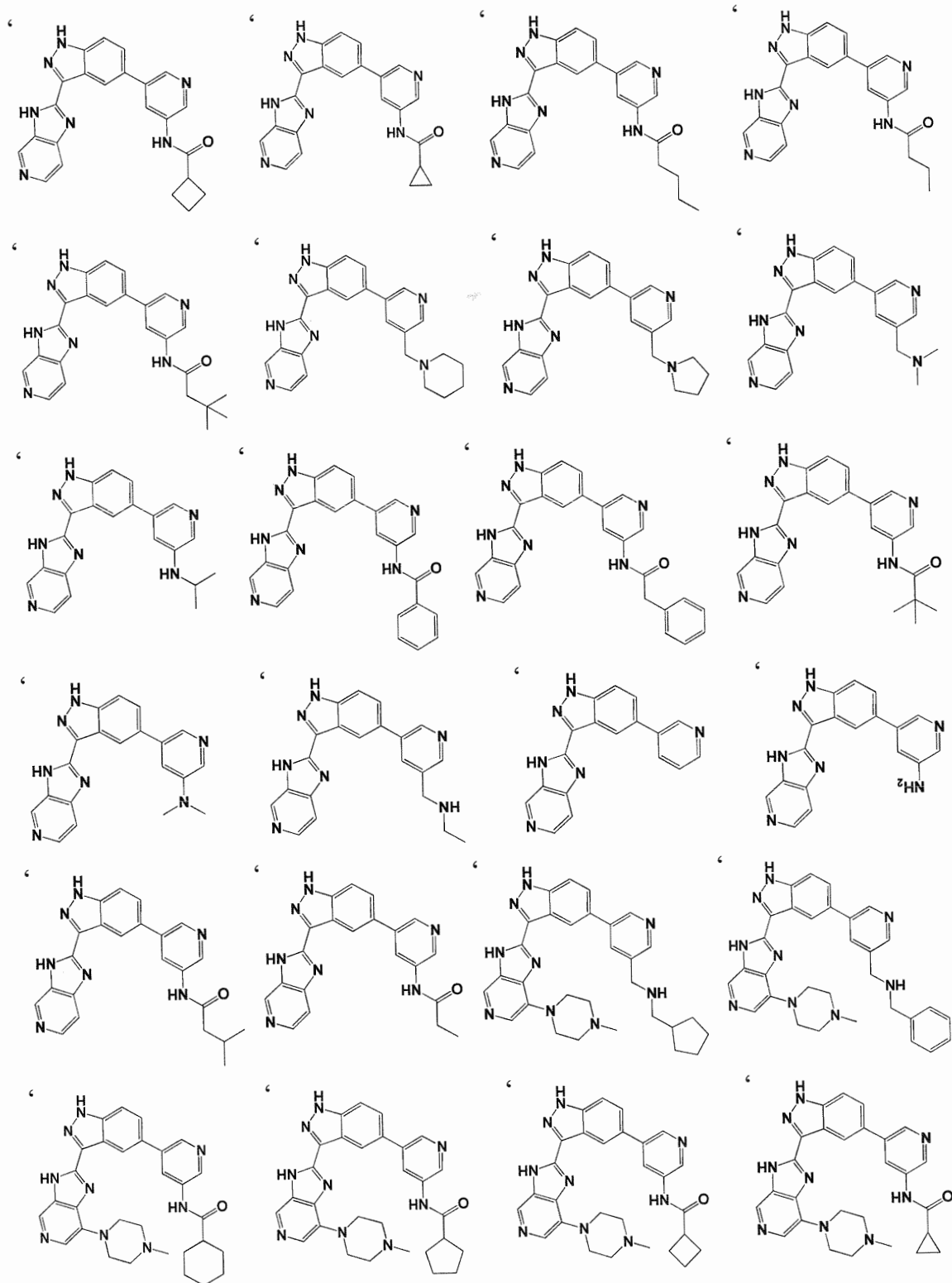


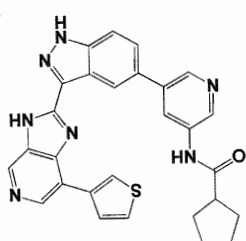
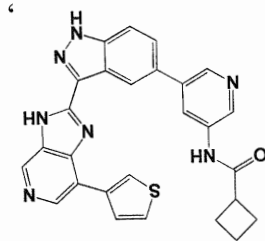
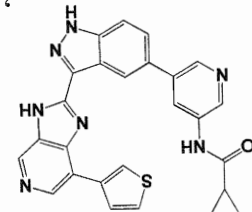
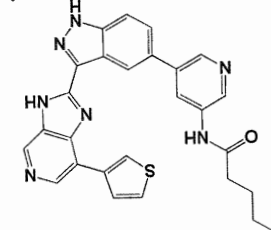
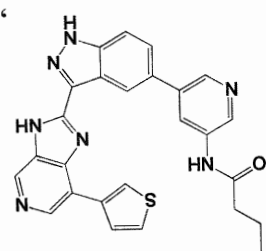
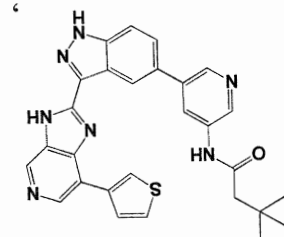
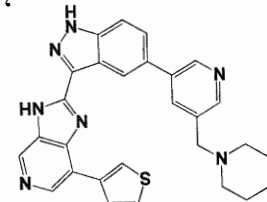
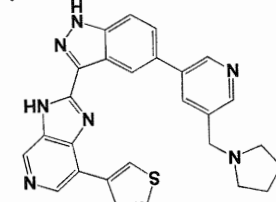
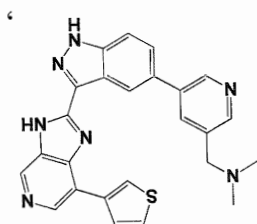
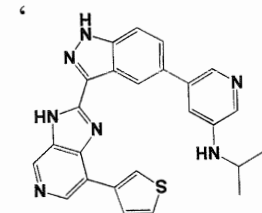
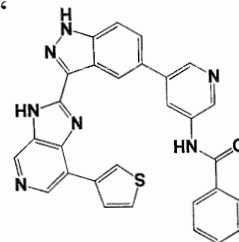
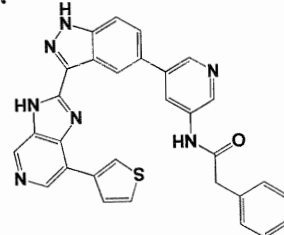
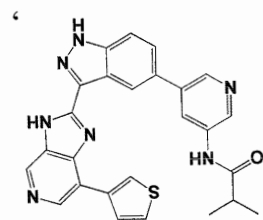
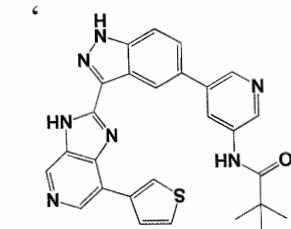
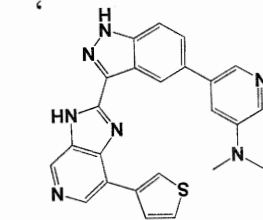
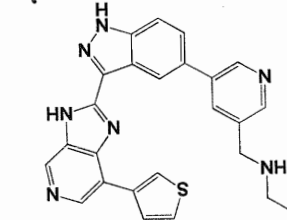
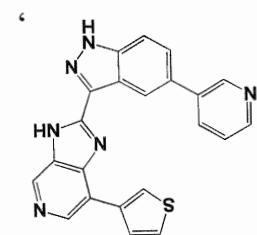
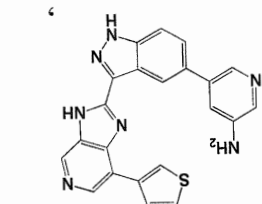
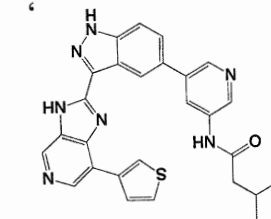
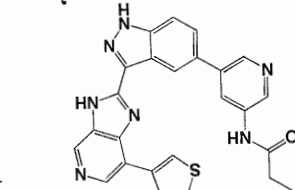
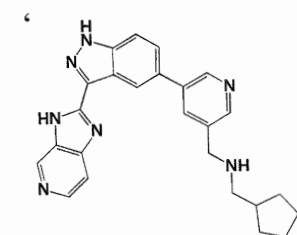
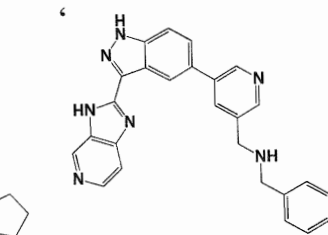
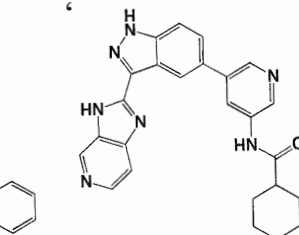
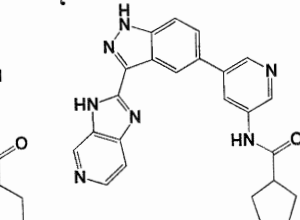


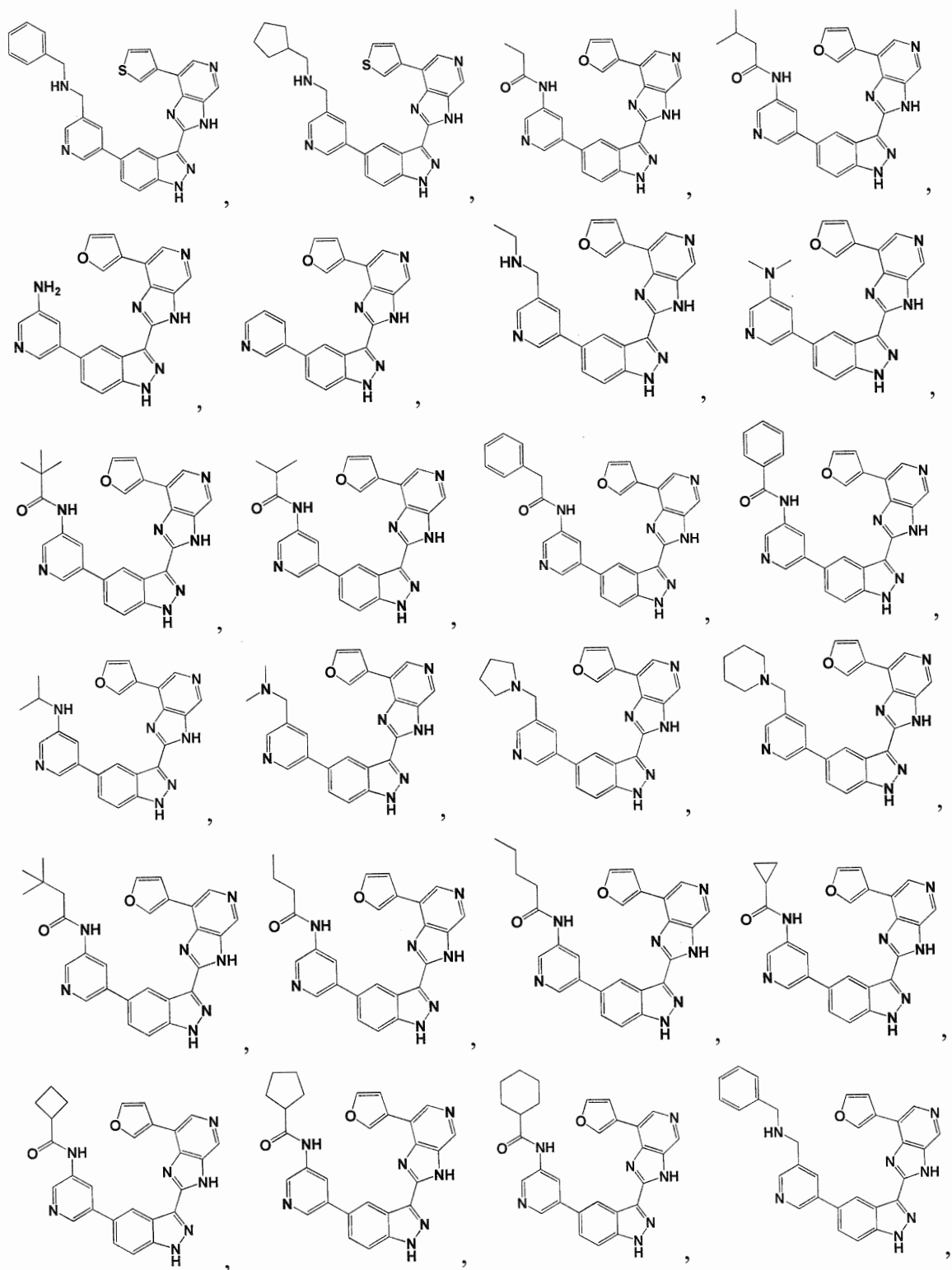


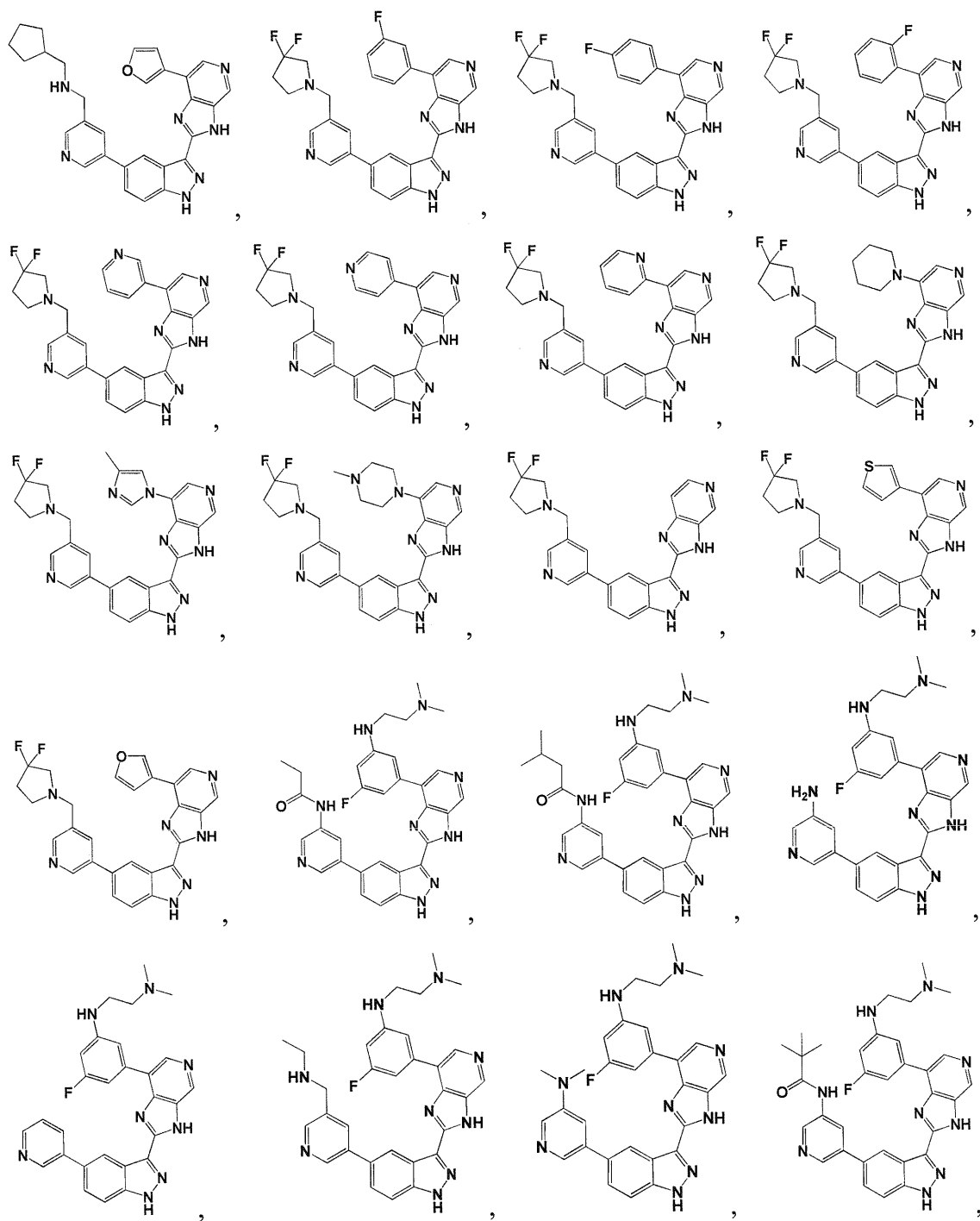




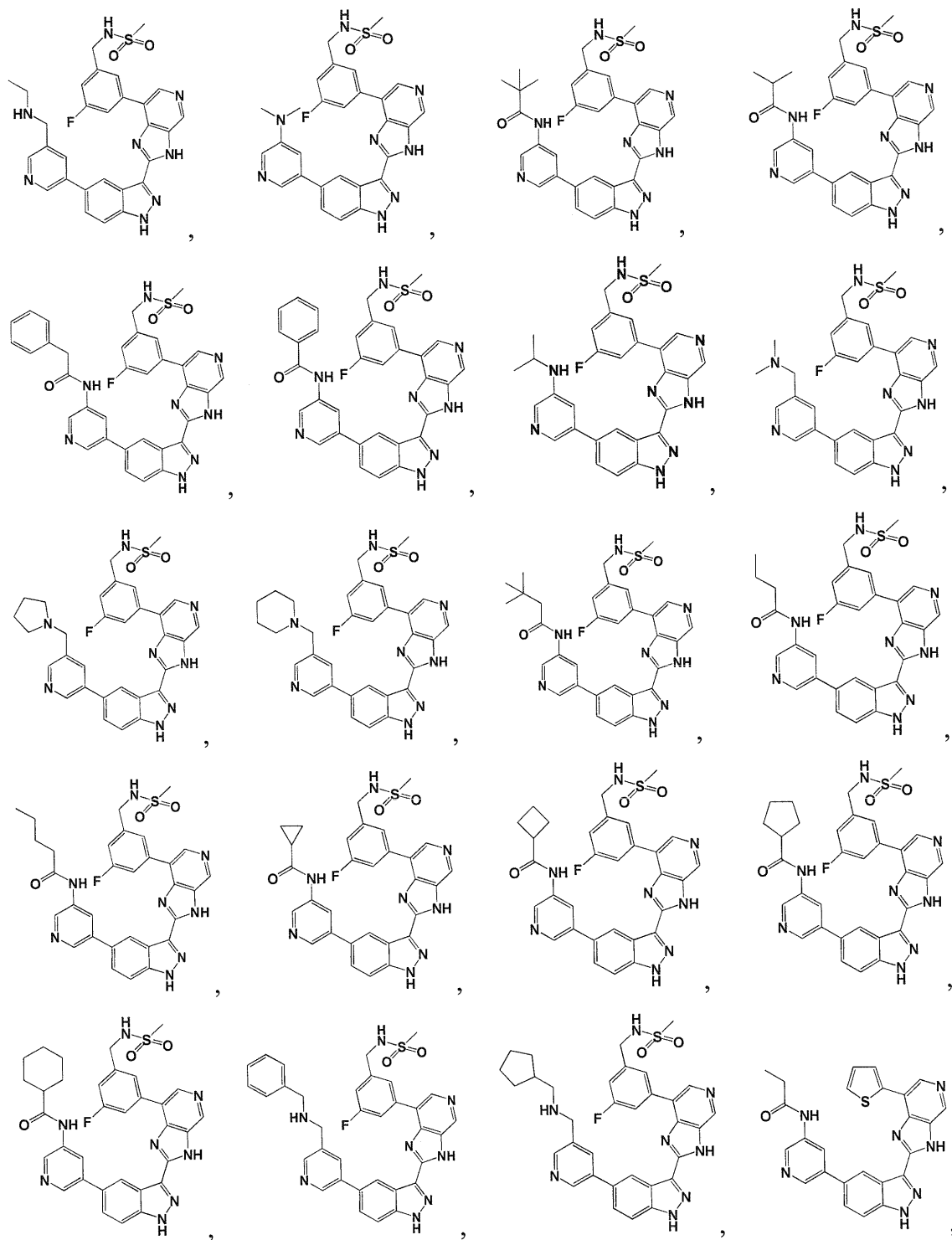


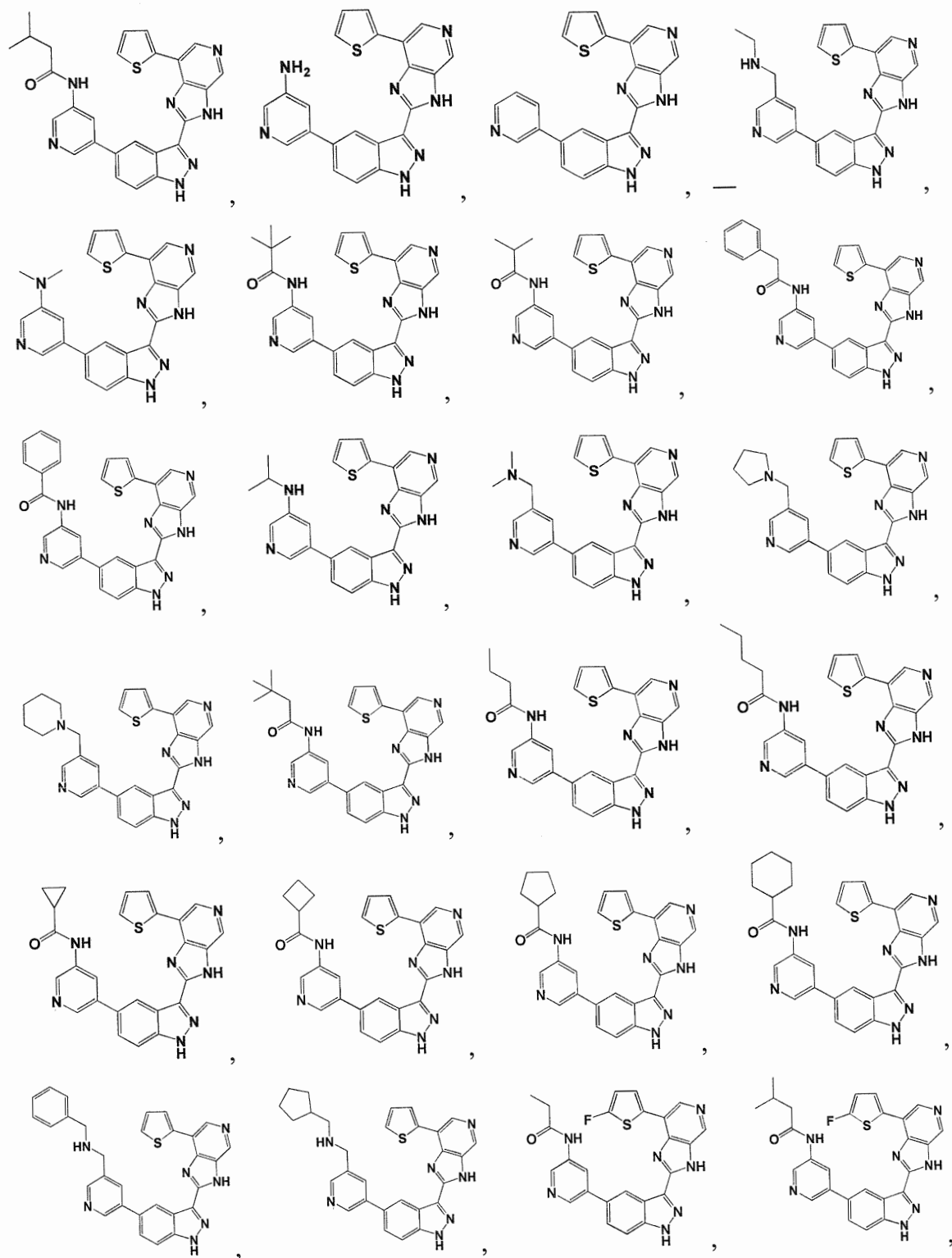


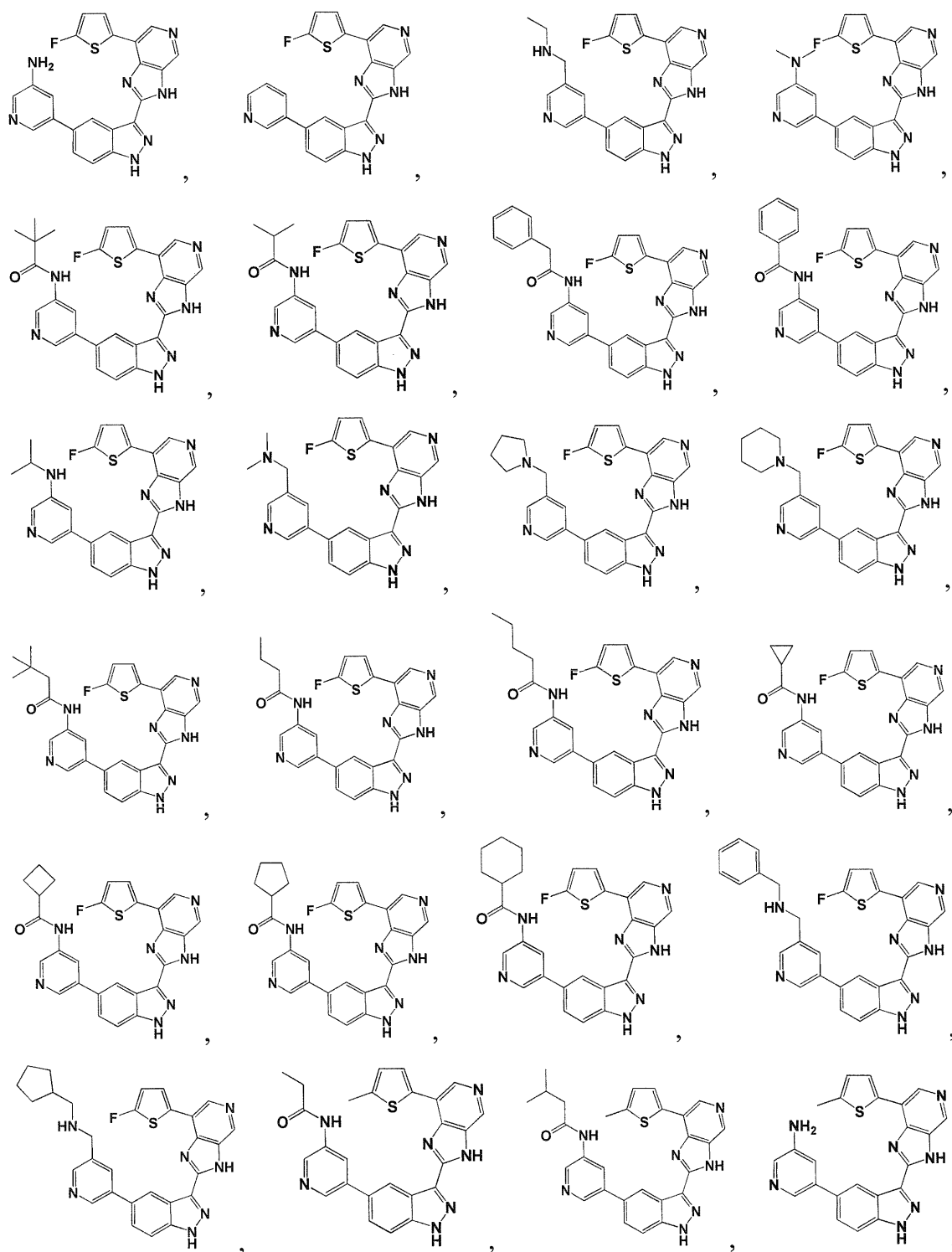


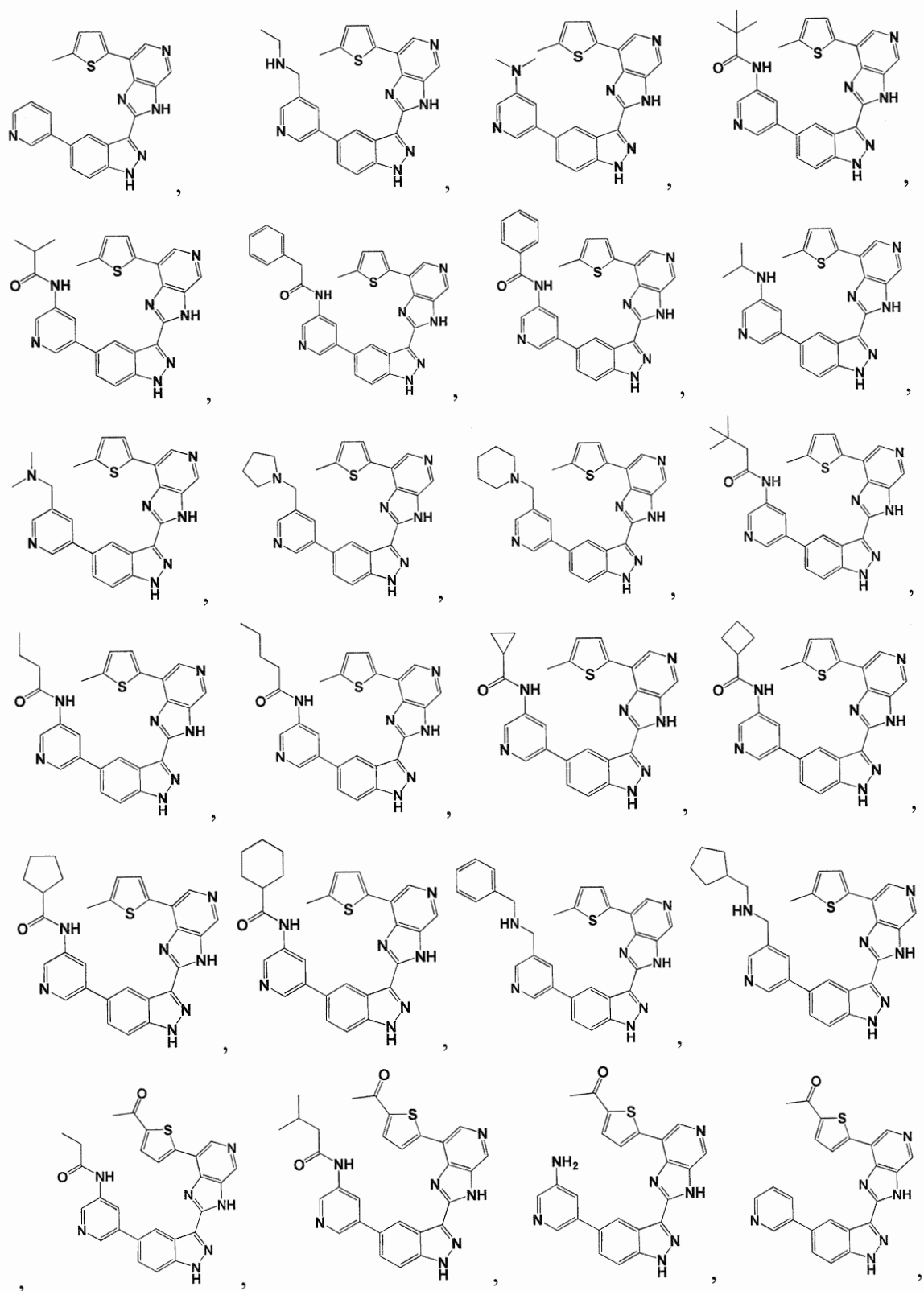


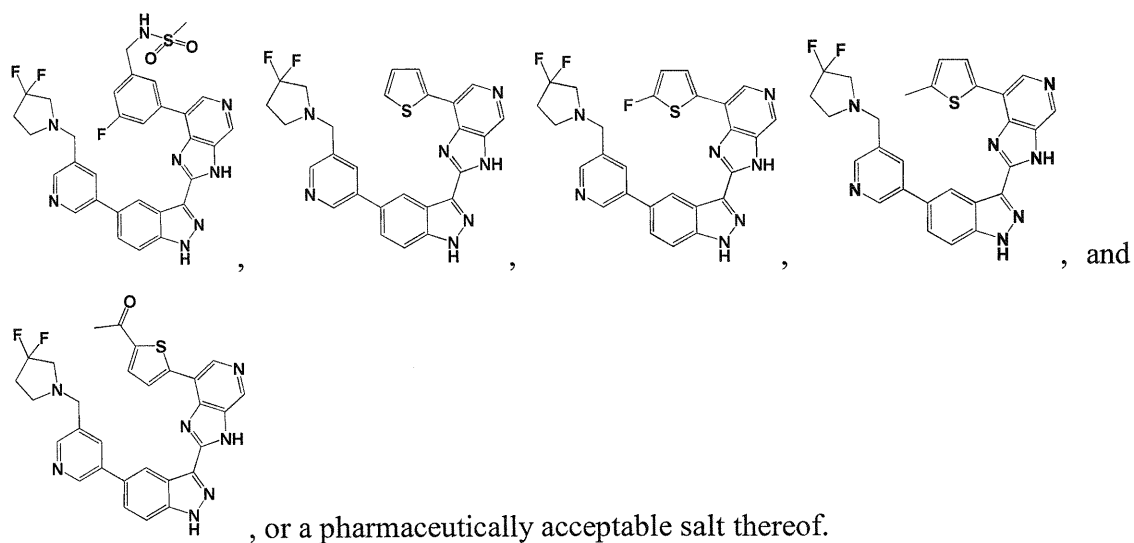




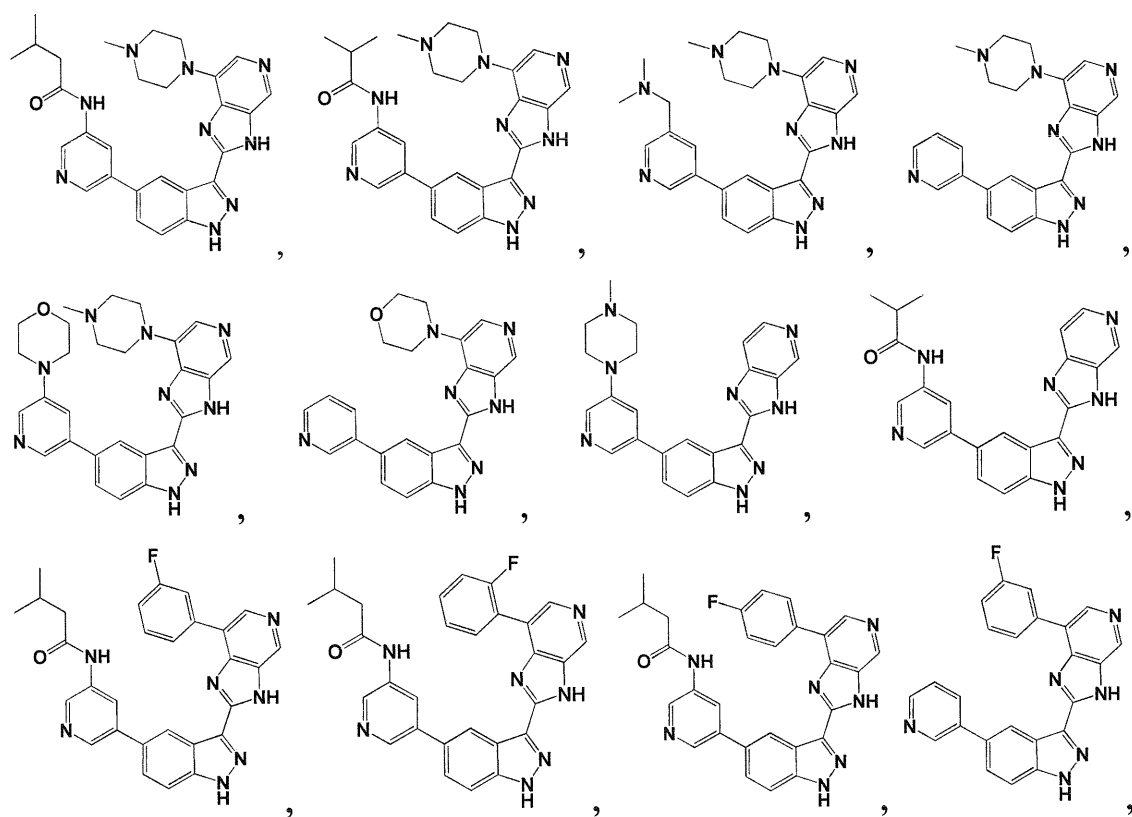


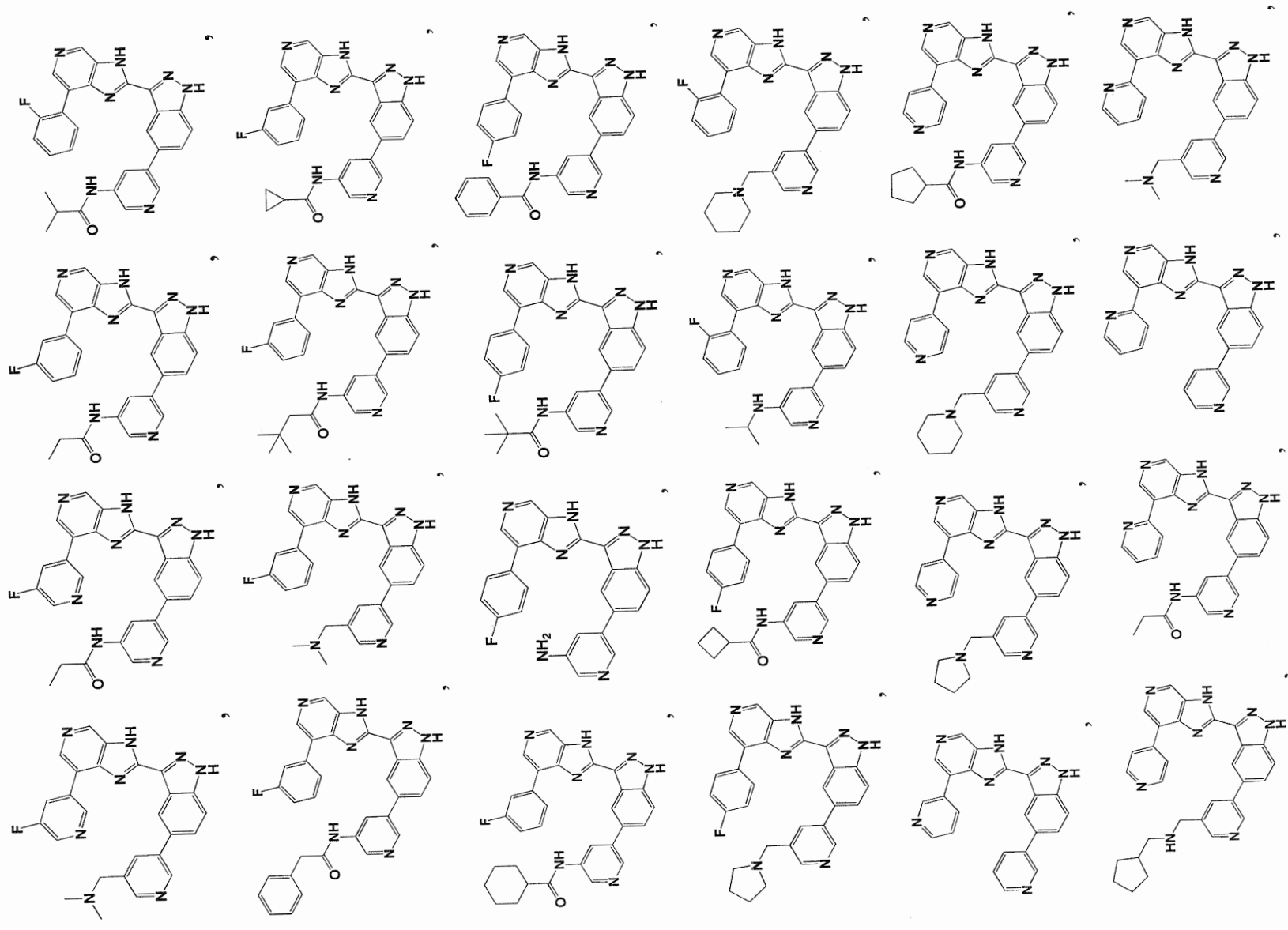


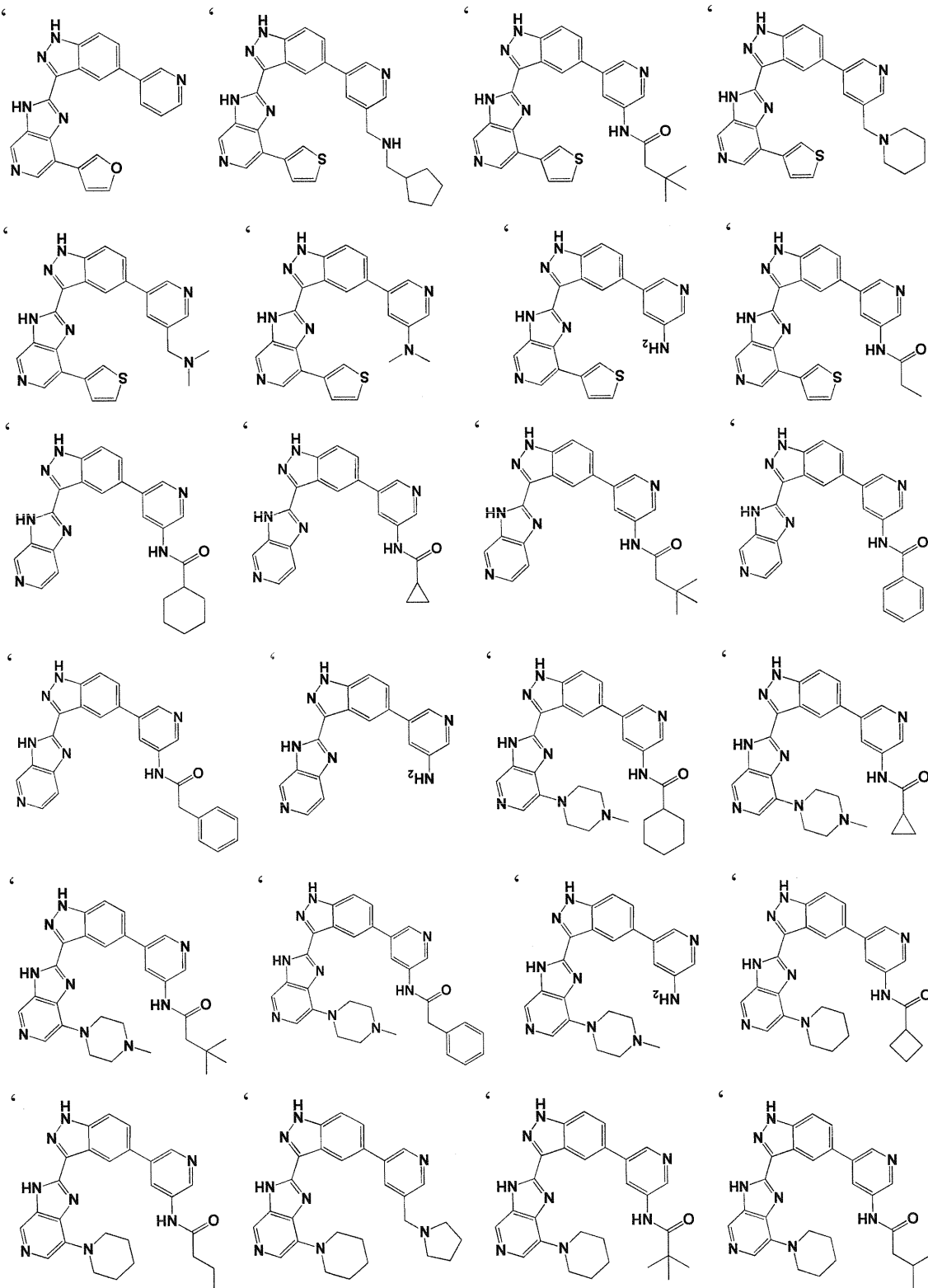


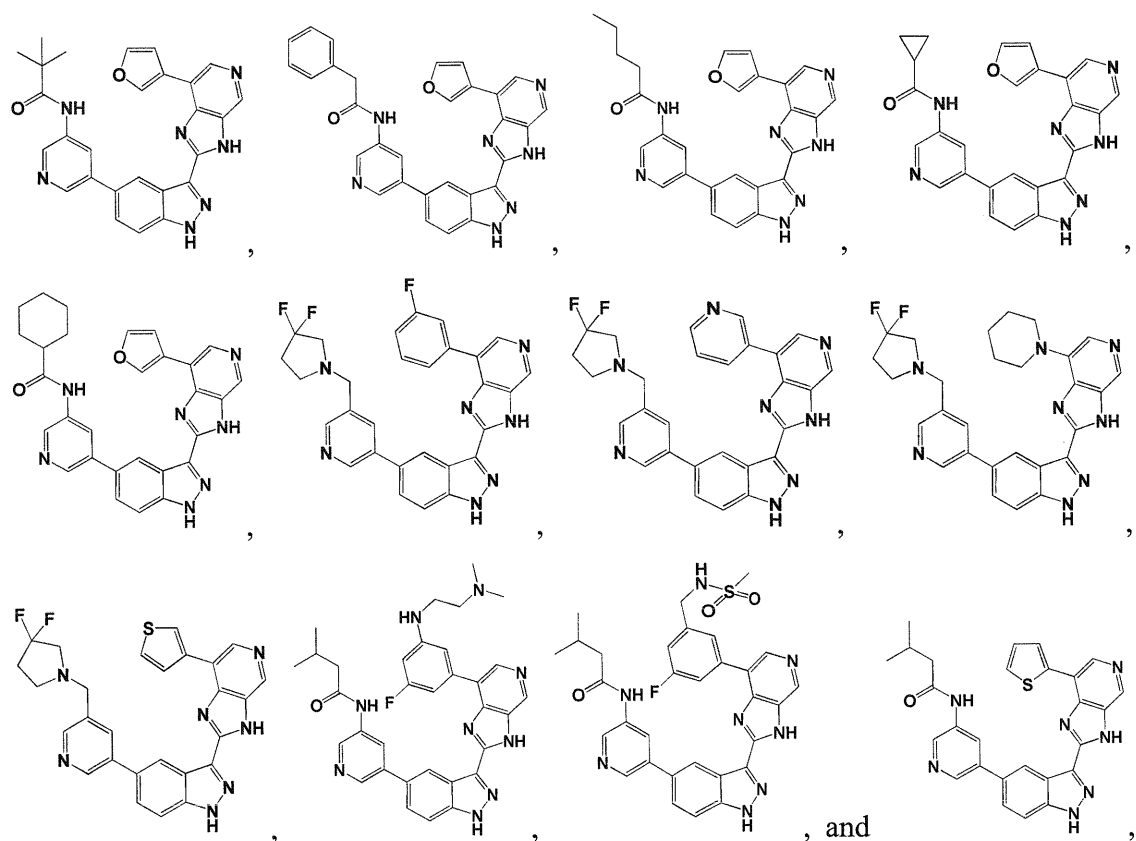


25. The compound of claim 1, having a structure selected from the group consisting of:



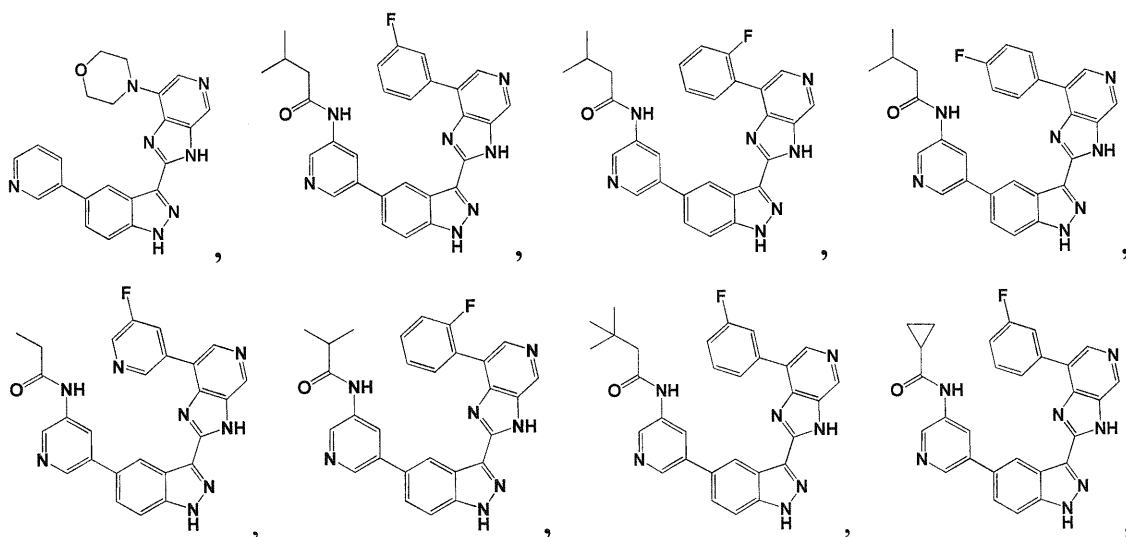


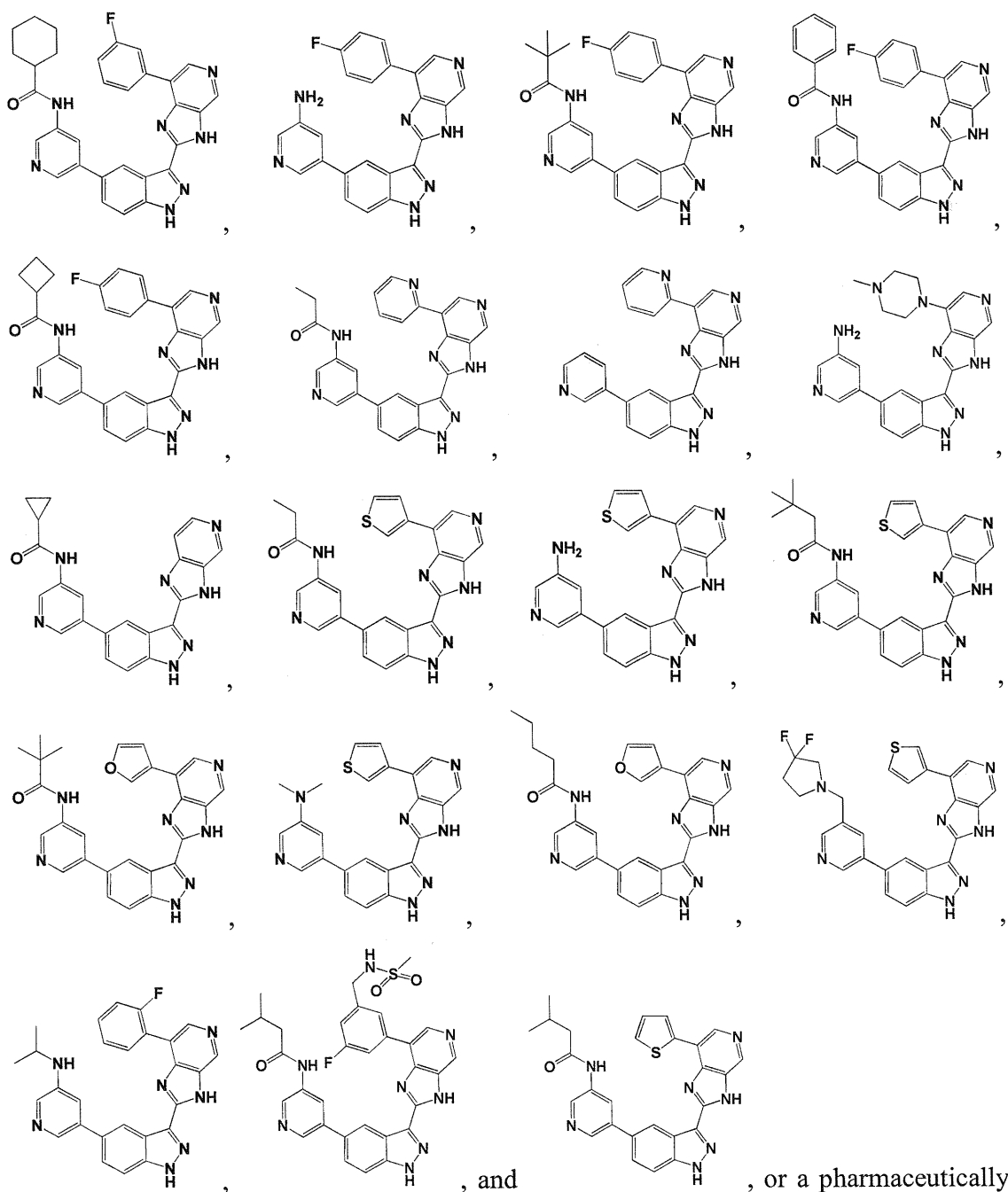




or a pharmaceutically acceptable salt thereof.

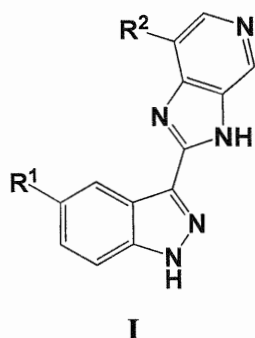
26. The compound of claim 1, having a structure selected from the group consisting of:





acceptable salt thereof.

27. A compound, or pharmaceutically acceptable salt thereof, having the structure of Formula I:



wherein:

R^1 is -heteroaryl R^3R^4 ;

R^2 is -aryl R^7 ;

R^3 is a -NHC(=O) R^9 ;

R^4 is H;

each R^7 is independently 1-2 substituents each selected from the group consisting of halide, -CF₃, -CN, -(C₁₋₆ alkyl)NHSO₂ R^{11} , -(C₁₋₆ alkyl)NR¹¹ R^{12} , and -NR¹²(C₁₋₆ alkyl)NR¹¹ R^{12} ;

R^9 is selected from the group consisting of -(C₁₋₆ alkyl), -aryl, -carbocyclyl, and -CH₂carbocyclyl;

each R^{11} is independently selected from -(C₁₋₆ alkyl);

each R^{12} is independently selected from the group consisting of H and -(C₁₋₆ alkyl); and

each R^{11} and R^{12} are optionally linked to form a four to six membered heterocyclyl ring.

28. The compound of claim 27, wherein R^1 is pyridinyl R^3R^4 .

29. The compound of claim 28, wherein R^1 is pyridin-3-yl R^3R^4 .

30. The compound of claim 28, wherein R^9 is -(C₁₋₆ alkyl).

31. The compound of claim 28, wherein R^9 is -(C₂₋₅ alkyl).

32. The compound of claim 28, wherein R^9 is carbocyclyl.

33. The compound of claim 28, wherein R^9 is -CH₂carbocyclyl.

34. The compound of claim 28, wherein R^9 is phenyl.

35. The compound of claim 31, wherein R^7 is halide.

36. The compound of claim 35, wherein R^7 is fluorine.

37. The compound of claim 31, wherein R^7 is 2 substituents consisting of a fluorine atom and $-(C_{1-6} \text{ alkyl})NR^{11}R^{12}$.

38. The compound of claim 37, wherein R^{11} and R^{12} are both $-(C_{1-2} \text{ alkyl})$.

39. The compound of claim 37, wherein R^{11} and R^{12} are linked to form an azetidine ring.

40. The compound of claim 37, wherein R^{11} and R^{12} are linked to form a pyrrolidine ring.

41. The compound of claim 37, wherein R^{11} and R^{12} are linked to form a piperidine ring.

42. The compound of claim 31, wherein R^7 is 2 substituents consisting of a fluorine atom and $-NR^{12}(C_{1-6} \text{ alkyl})NR^{11}R^{12}$.

43. The compound of claim 42, wherein R^7 is 2 substituents consisting of a fluorine atom and $-NHCH_2CH_2NR^{11}R^{12}$.

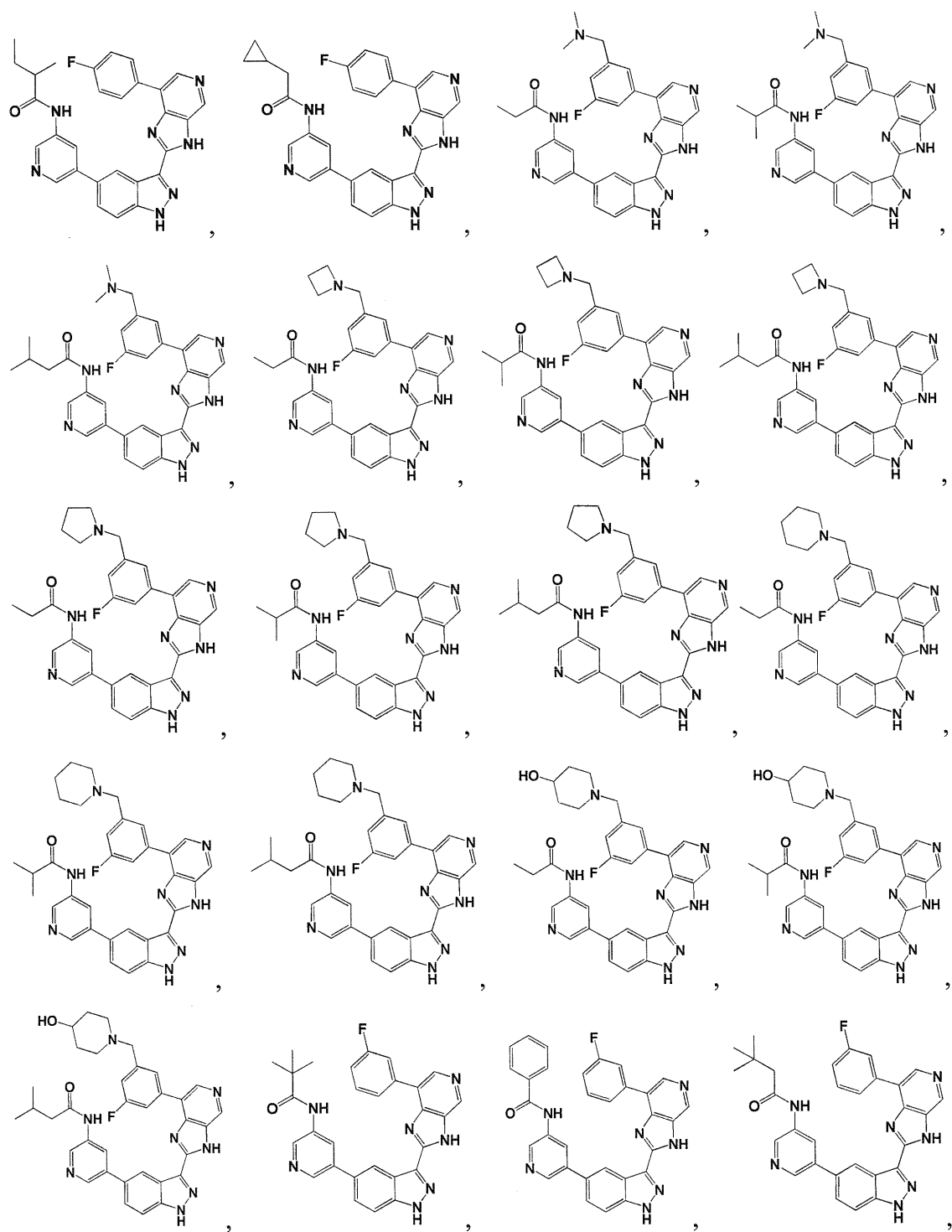
44. The compound of claim 43, wherein R^{11} and R^{12} are both $-(C_{1-2} \text{ alkyl})$.

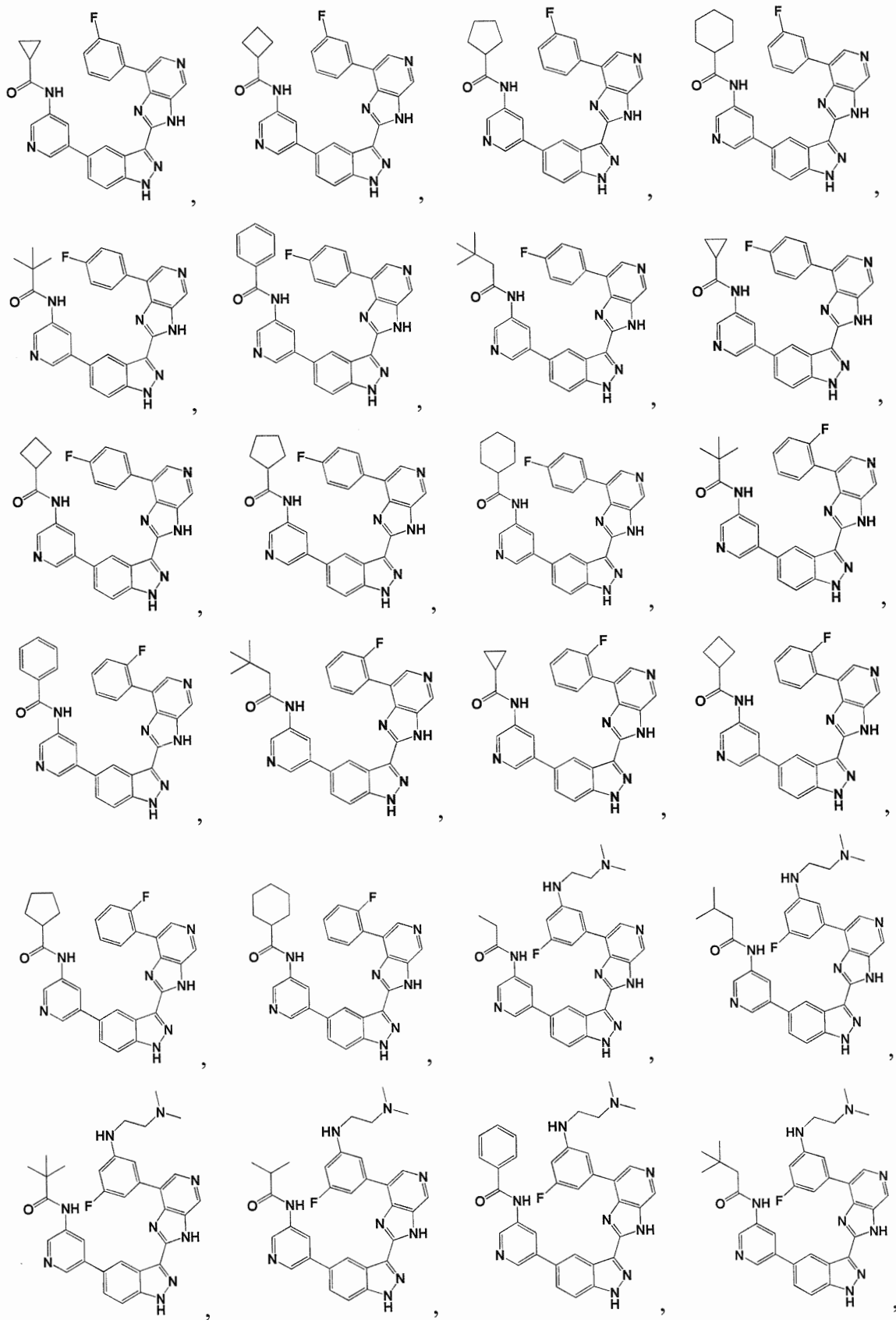
45. The compound of claim 31, wherein R^7 is 2 substituents consisting of a fluorine atom and $-(C_{1-6} \text{ alkyl})NHSO_2R^{11}$.

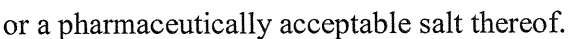
46. The compound of claim 45, wherein R^7 is 2 substituents consisting of a fluorine atom and $-CH_2NHSO_2R^{11}$.

47. The compound of claim 46, wherein R^{11} is $-(C_{1-2} \text{ alkyl})$.

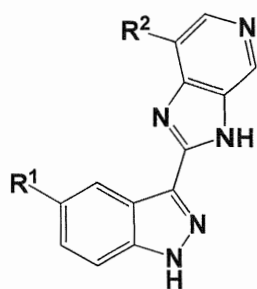
48. The compound of claim 27, having a structure selected from the group consisting of:







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I

wherein:

R^1 is $-\text{pyridin-3-yl}R^3R^4$;

R^2 is $-\text{phenyl}R^7$;

R^3 is a $-\text{NHC}(=\text{O})R^9$;

R^4 is H;

each R^7 is independently 1-2 substituents each selected from the group consisting of fluorine, $-\text{CH}_2\text{NHSO}_2R^{11}$, $-(\text{C}_{1-6} \text{ alkyl})\text{NR}^{11}R^{12}$, and $-\text{NHCH}_2\text{CH}_2\text{NR}^{11}R^{12}$;

R^9 is selected from the group consisting of $-(\text{C}_{2-5} \text{ alkyl})$, $-\text{phenyl}$, $-\text{carbocyclyl}$, and $-\text{CH}_2\text{carbocyclyl}$;

each R^{11} is independently selected from $-(\text{C}_{1-2} \text{ alkyl})$;

each R^{12} is independently selected from the group consisting of H and $-(\text{C}_{1-2} \text{ alkyl})$; and

each R^{11} and R^{12} are optionally linked to form a four to six membered heterocyclyl ring.

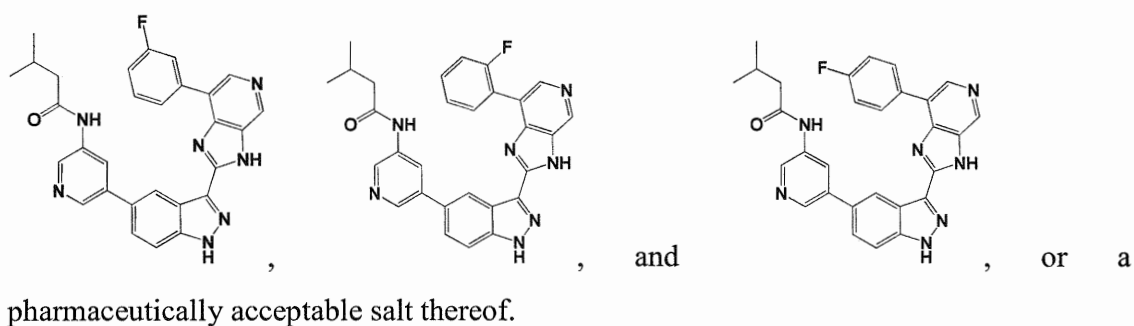
50. The compound of claim 49, wherein R^9 is $-(\text{C}_{2-5} \text{ alkyl})$.

51. The compound of claim 49, wherein R^9 is carbocyclyl.

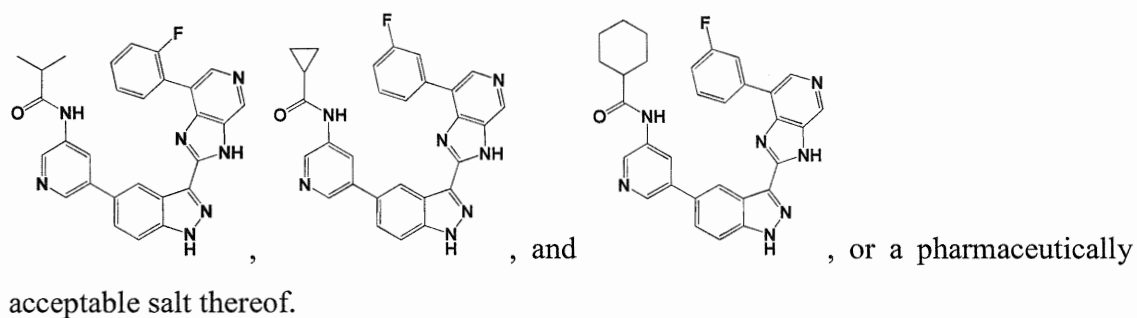
52. The compound of claim 50, wherein R^7 is one fluorine.

53. The compound of claim 50, wherein R^7 is 2 substituents consisting of a fluorine atom and $-\text{CH}_2\text{NHSO}_2R^{11}$, and R^{11} is $-(\text{C}_{1-2} \text{ alkyl})$.

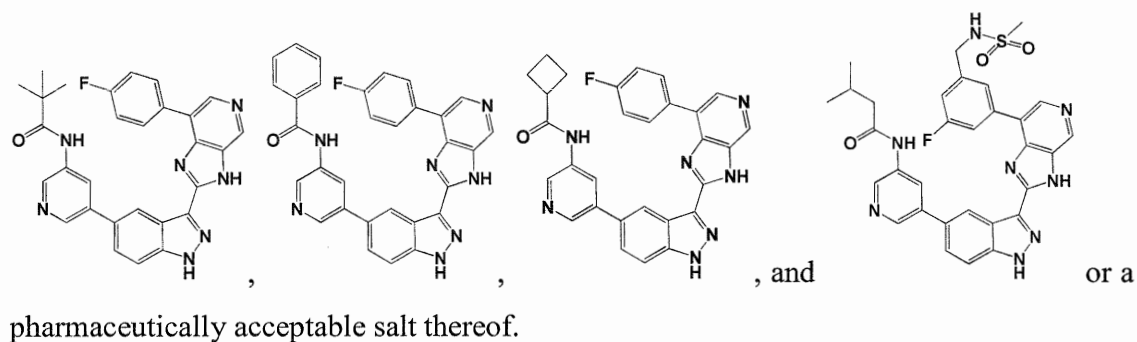
54. The compound of claim 49, having a structure selected from the group consisting of:



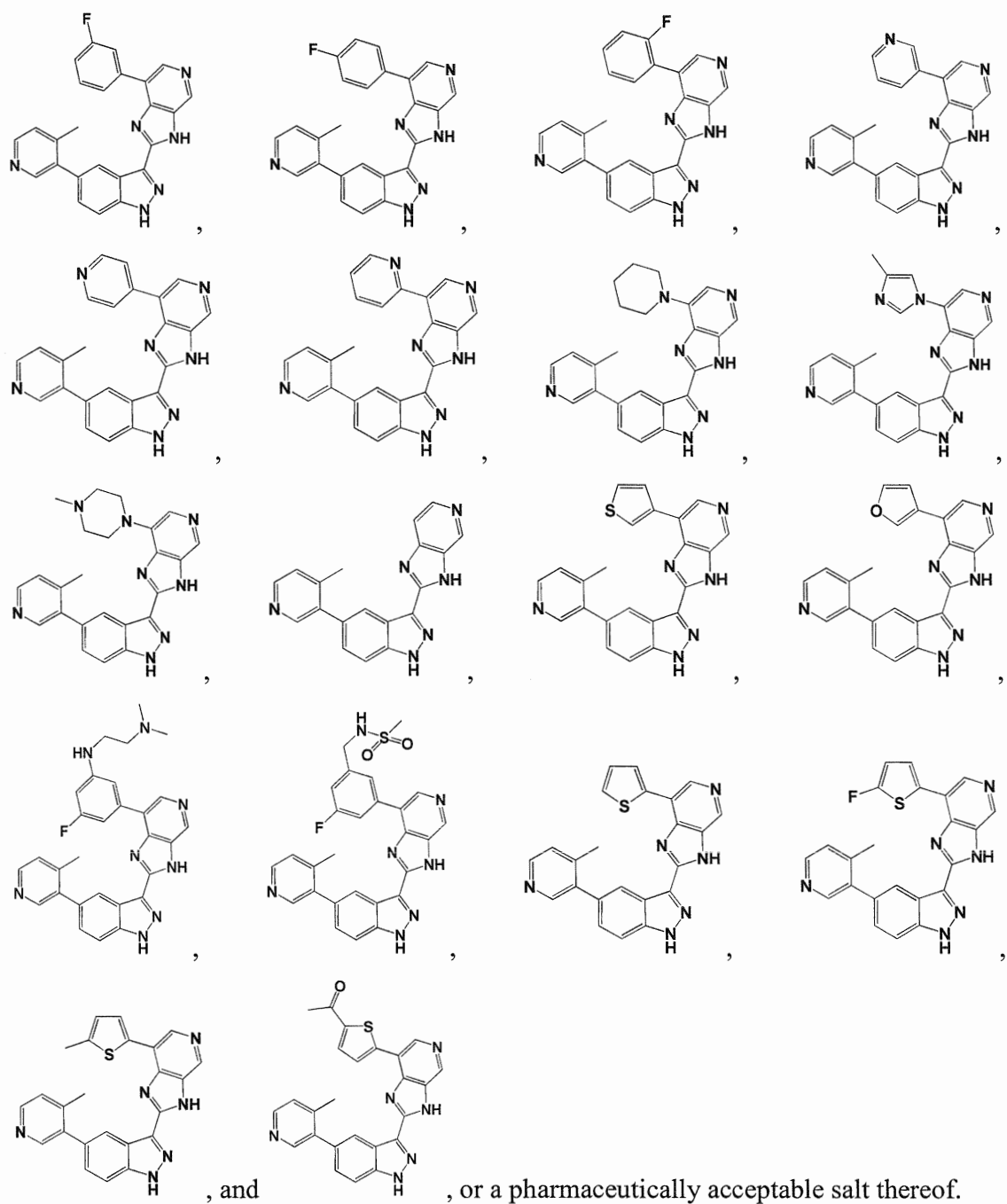
55. The compound of claim 49, having a structure selected from the group consisting of:



56. The compound of claim 49, having a structure selected from the group consisting of:



57. A compound having a structure selected from the group consisting of:



58. A compound according to any one of claims 1-57, or a pharmaceutically acceptable salt thereof, for use in treating a disorder or disease in a patient, wherein the disorder or disease is selected from the group consisting of: diabetic retinopathy, pulmonary fibrosis, rheumatoid arthritis, scleroderma, a mycotic or viral infection, a bone or cartilage disease, Alzheimer's disease, lung disease, and cancer.

59. The compound of claim 58, wherein the disorder or disease is osteoarthritis.

60. The compound of claim 58, wherein the disorder or disease is diabetic retinopathy.

61. The compound of claim 58, wherein the disorder or disease is pulmonary fibrosis.

62. The compound of claim 58, wherein the disorder or disease is rheumatoid arthritis.

63. The compound of claim 58, wherein the disorder or disease is scleroderma.

64. The compound of claim 58, wherein the disorder or disease is Alzheimer's disease.

65. The compound of claim 58, wherein the disorder or disease is lung disease.

66. The compound of claim 58, wherein the cancer is selected from the group consisting of: hepatocellular carcinoma, colorectal cancer, colon cancer, cancers of the stomach, liver cancers, breast cancer, pancreatic cancer, leukemia, lymphoma, sarcoma, and ovarian cancer.

67. The compound of claim 66, wherein the cancer is hepatocellular carcinoma.

68. The compound of claim 66, wherein the cancer is colorectal cancer.

69. The compound of claim 66, wherein the cancer is colon cancer.

70. The compound of claim 66, wherein the cancer is a cancer of the stomach.

71. The compound of claim 66, wherein the cancer is a liver cancer.

72. The compound of claim 66, wherein the cancer is breast cancer.

73. The compound of claim 66, wherein the cancer is pancreatic cancer.

74. The compound of claim 66, wherein the cancer is leukemia.

75. The compound of claim 66, wherein the cancer is lymphoma.

76. The compound of claim 66, wherein the cancer is sarcoma.

77. The compound of claim 66, wherein the cancer is ovarian cancer.

78. The compound of claim 58, wherein the compound inhibits one or more proteins in the Wnt pathway.

79. The compound of claim 58, wherein the compound inhibits signaling induced by one or more Wnt proteins.

80. The compound of either claim 78 or 79, wherein the Wnt proteins are selected from the group consisting of: WNT1, WNT2, WNT2B, WNT3, WNT3A,

WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, and WNT16.

81. The compound of claim 58, wherein the compound inhibits a kinase activity.

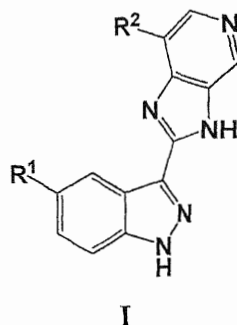
82. A compound of any one of claims 1-57, or a pharmaceutically acceptable salt thereof, for use in treating a disorder or disease for preventing or reducing angiogenesis in a patient.

83. The compound of claim 58 or 82, wherein the patient is human.

84. A pharmaceutical composition comprising a compound according to any one of the claims 1-57, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

WHAT IS CLAIMED IS:

1. A compound or pharmaceutically acceptable salt thereof having the structure of Formula I:



wherein:

R^1 is -heteroaryl R^3R^4 ;

R^2 is selected from the group consisting of H, -heteroaryl R^5 , -heterocyclyl R^6 and -aryl R^7 ;

R^3 is selected from the group consisting of H, -heterocyclyl R^8 , -NHC(=O) R^9 , -NHSO₂ R^{10} , -NR¹¹ R^{12} and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

with the proviso that R^2 and R^3 are not both H;

R^4 is 1-3 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

each R^5 is independently 1-4 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, -C(=O) R^{11} , amino and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

each R^6 is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

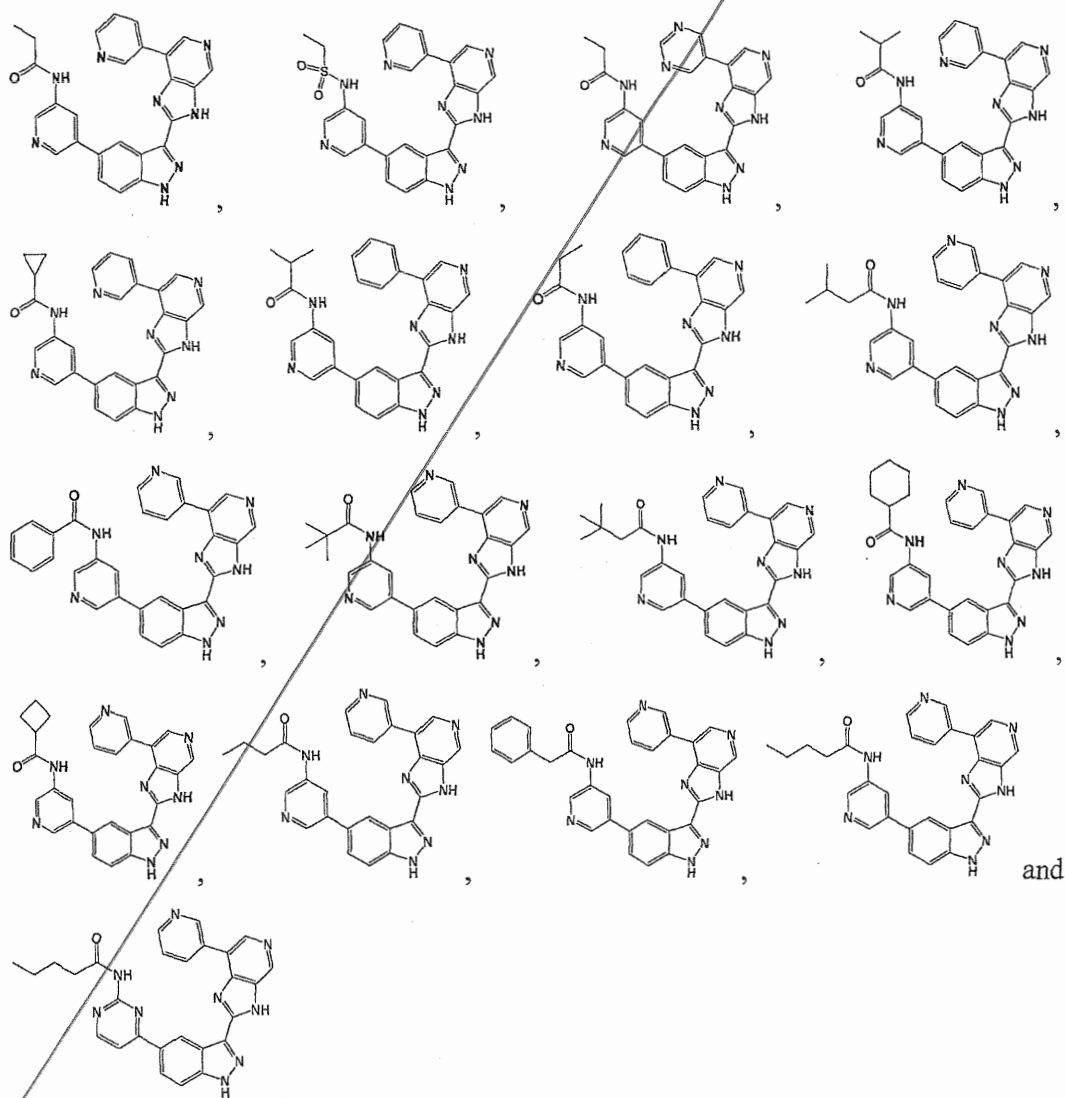
each R^7 is independently 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³, amino, -(C₁₋₆ alkyl)NHSO₂ R^{11} , -NR¹²(C₁₋₆ alkyl)NR¹¹ R^{12} and -(C₁₋₆ alkyl)NR¹¹ R^{12} ;

R^8 is 1-5 substituents each selected from the group consisting of H, C₁₋₉ alkyl, halide, -CF₃, -CN, OR¹³ and amino;

R^9 is selected from the group consisting of C₁₋₉ alkyl, -heteroaryl R^5 , -heterocyclyl R^6 , -aryl R^7 and -CH₂carbocyclyl;

R^{10} is selected from the group consisting of C₁₋₉ alkyl, -heteroaryl R^5 , -heterocyclyl R^6 , -aryl R^7 , and -carbocyclyl R^{14} ;

each R^{11} is independently selected from C_{1-6} alkyl;
each R^{12} is independently selected from the group consisting of H and C_{1-6} alkyl;
each R^{11} and R^{12} are optionally linked to form a five or six membered heterocyclyl ring;
each R^{13} is independently selected from the group consisting of H and C_{1-6} alkyl;
 R^{14} is 1-5 substituents each selected from the group consisting of H, C_{1-9} alkyl, halide, $-CF_3$, $-CN$, OR^{13} and amino;
with the proviso that Formula I is not a structure selected from the group consisting of:

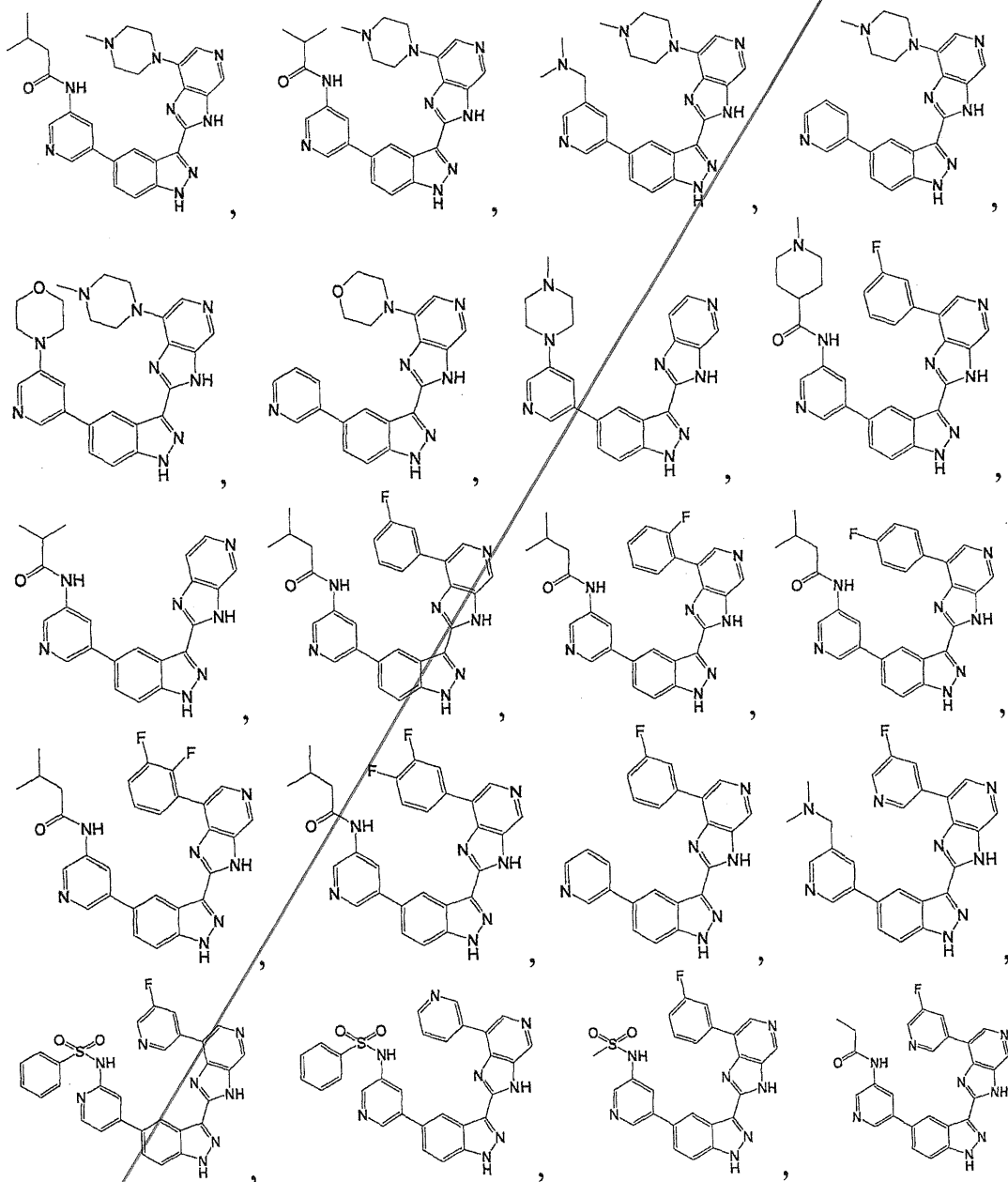


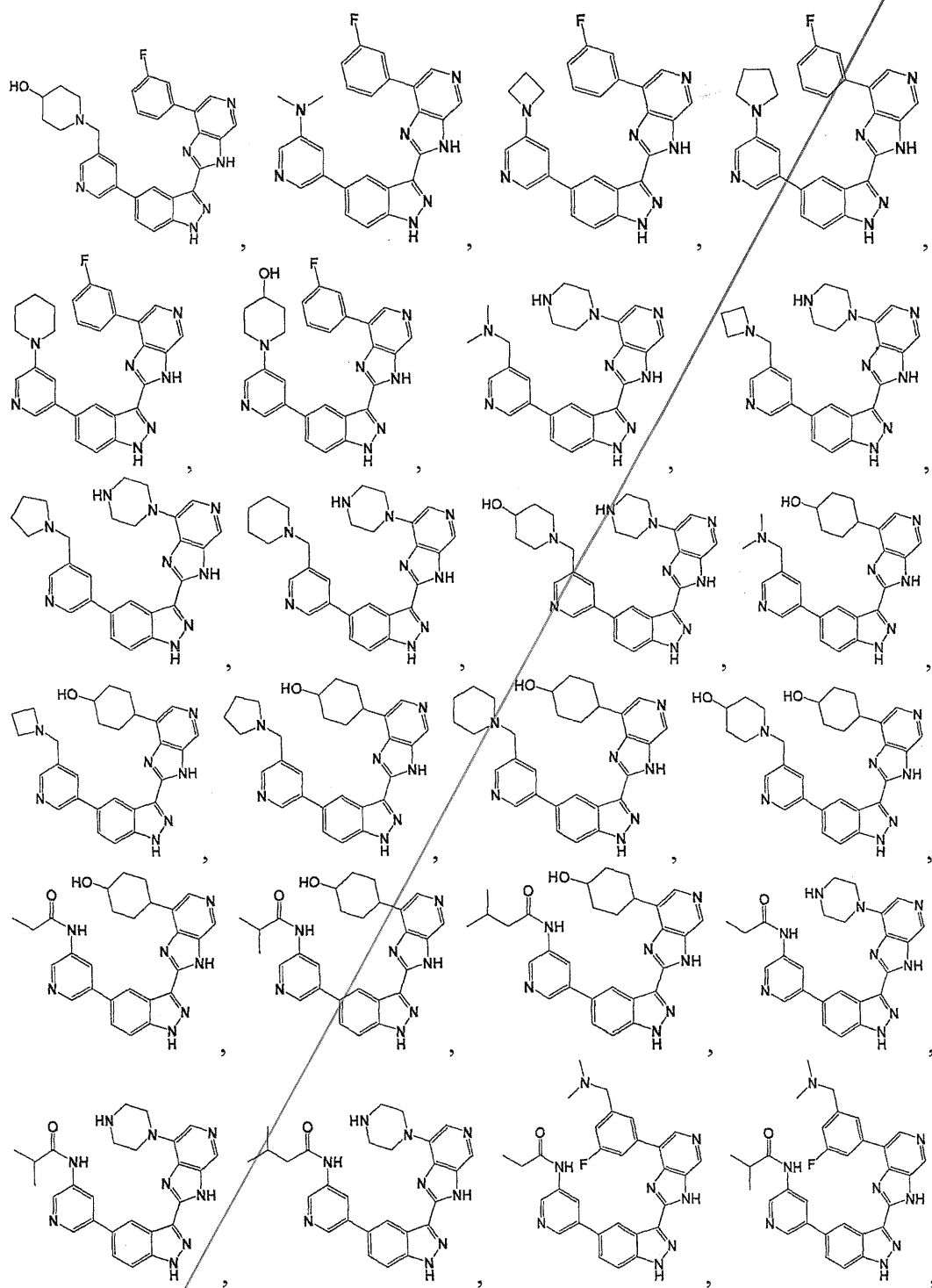
2. The compound of claim 1 wherein R^1 is pyridine R^3R^4 .

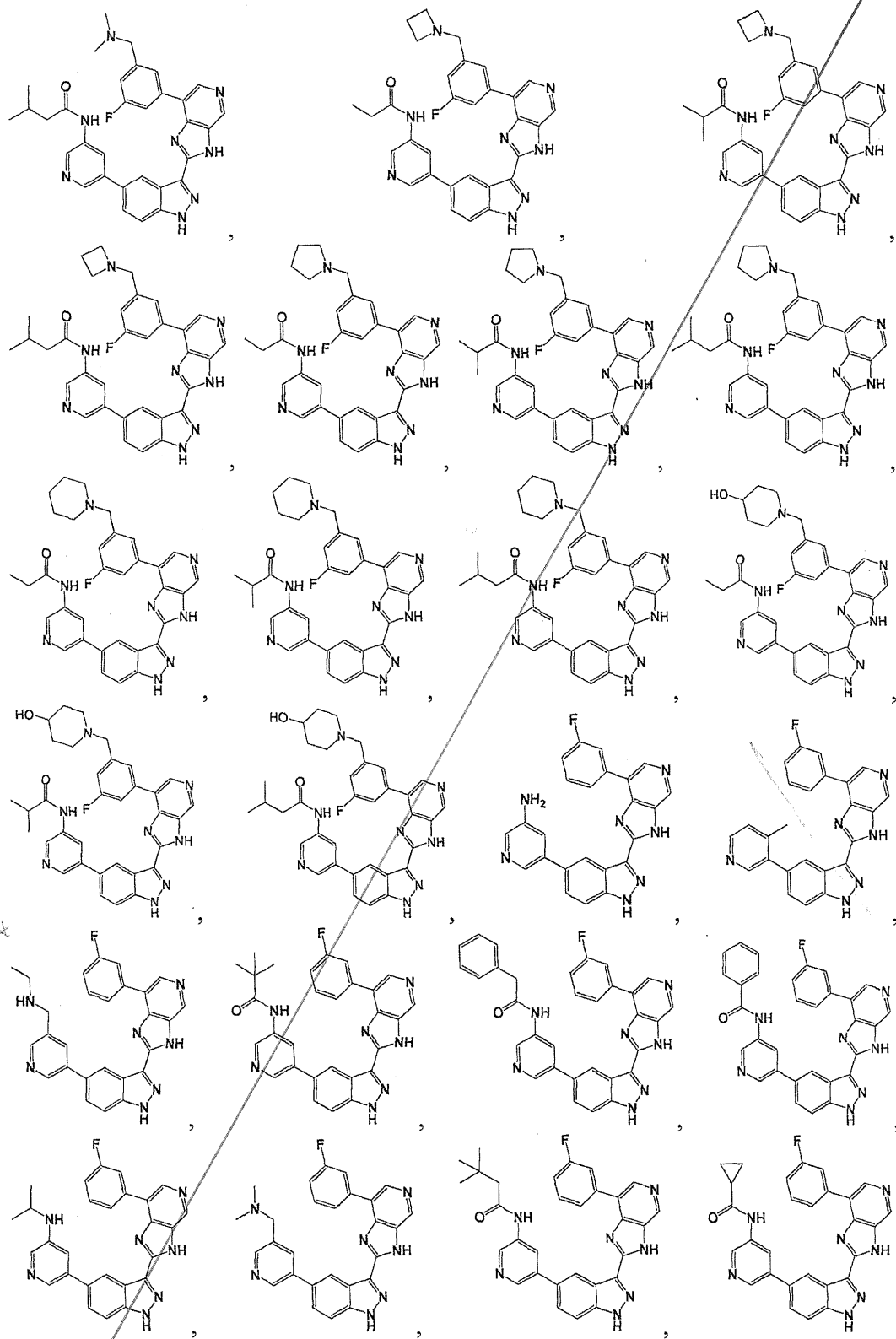
3. The compound of claim 2 wherein R^1 is pyridin-3-yl R^3R^4 .
4. The compound of claim 3 wherein R^3 is $-(C_{1-6} \text{ alkyl})NR^{11}R^{12}$.
5. The compound of claim 4 wherein R^3 is $-(C_{1-2} \text{ alkyl})NR^{11}R^{12}$, R^{11} is $-(C_{1-2} \text{ alkyl})$, R^{12} is $-(C_{1-2} \text{ alkyl})$ and R^4 is H.
6. The compound of claim 4 wherein R^{11} and R^{12} are optionally linked to form a five or six membered heterocyclyl ring and R^4 is H.
7. The compound of claim 6 wherein the five or six membered heterocyclyl ring is substituted with 1-2 fluorines.
8. The compound of claim 3 wherein R^3 is $-NHC(=O)R^9$.
9. The compound of claim 8 wherein R^4 is H and R^9 is selected from the group consisting of $-(C_{2-5} \text{ alkyl})$, phenyl, $-\text{carbocyclyl}$ and $-\text{CH}_2\text{carbocyclyl}$.
10. The compound of claim 3 wherein R^3 is $-NHSO_2R^{10}$.
11. The compound of claim 10 wherein R^4 is H and R^{10} is selected from the group consisting of $-(C_{1-4} \text{ alkyl})$ and phenyl.
12. The compound of claim 3 wherein R^3 is $-\text{heterocyclyl}R^8$.
13. The compound of claim 12 wherein R^4 is H and heterocyclyl is selected from the group consisting of morpholine, piperazine and piperidine.
14. The compound of claim 3 wherein R^3 is H and R^4 is amino.
15. The compound as in any of claims 3-14, in which R^2 is $-\text{heteroaryl}R^5$.
16. The compound as in any of claims 3-14, in which R^2 is $-\text{pyridin-3-yl}R^5$.
17. The compound as in any of claims 3-14, in which R^2 is $-\text{pyridin-3-yl}R^5$ and R^5 is 1-2 fluorine atoms.
18. The compound as in any of claims 3-14, in which R^2 is $\text{thiophene}R^5$.
19. The compound as in any of claims 3-14, in which R^2 is $-\text{heterocyclyl}R^6$.
20. The compound as in any of claims 3-14, in which R^2 is $-\text{heterocyclyl}R^6$, in which R^6 is selected from the group consisting of H, F and $-(C_{1-4} \text{ alkyl})$, and heterocyclyl is selected from the group consisting of morpholine, piperazine and piperidine.
21. The compound as in any of claims 3-14, in which R^2 is $-\text{aryl}R^7$.
22. The compound as in any of claims 3-14, in which R^2 is $-\text{phenyl}R^7$ and R^7 is 1-2 fluorine atoms.

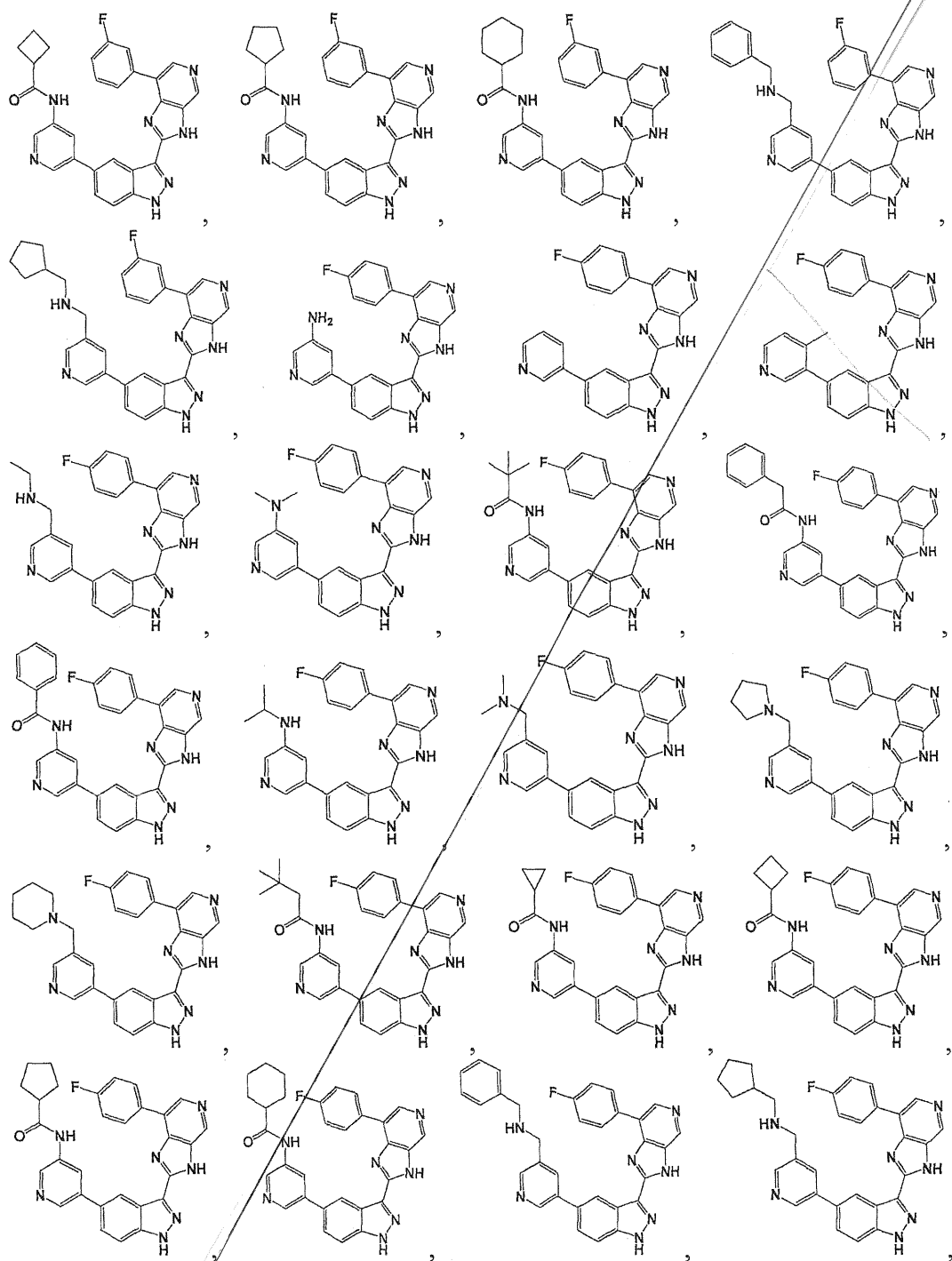
23. The compound as in any of claims 3-14, in which R^2 is -phenyl R^7 and R^7 is 2 substituents consisting of 1 fluorine atom and either $-NR^{12}(C_{1-6} \text{ alkyl})NR^{11}R^{12}$ or $-(C_{1-6} \text{ alkyl})NHSO_2R^{11}$.

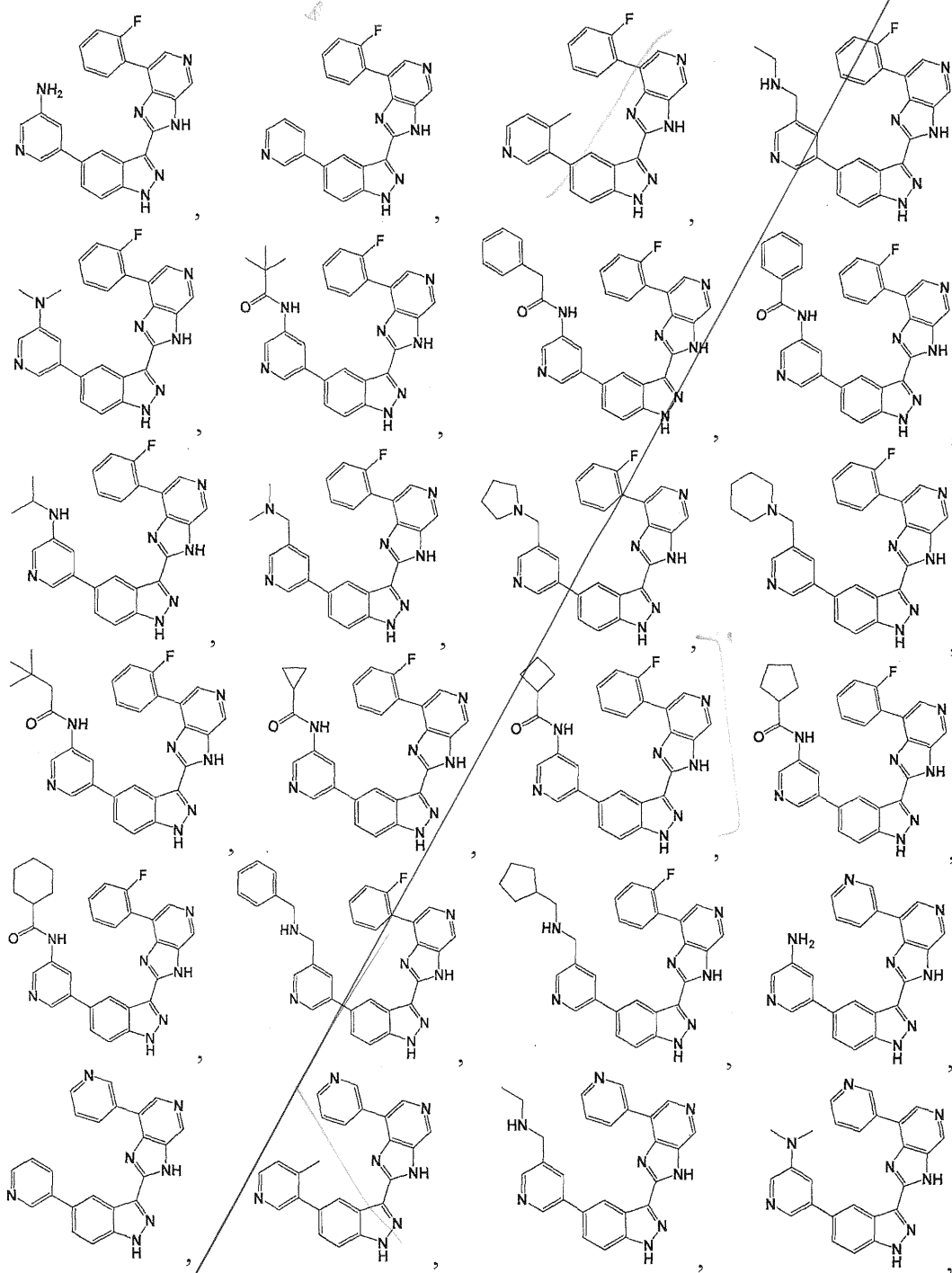
24. The compound of claim 1 having a structure selected from the group consisting of:

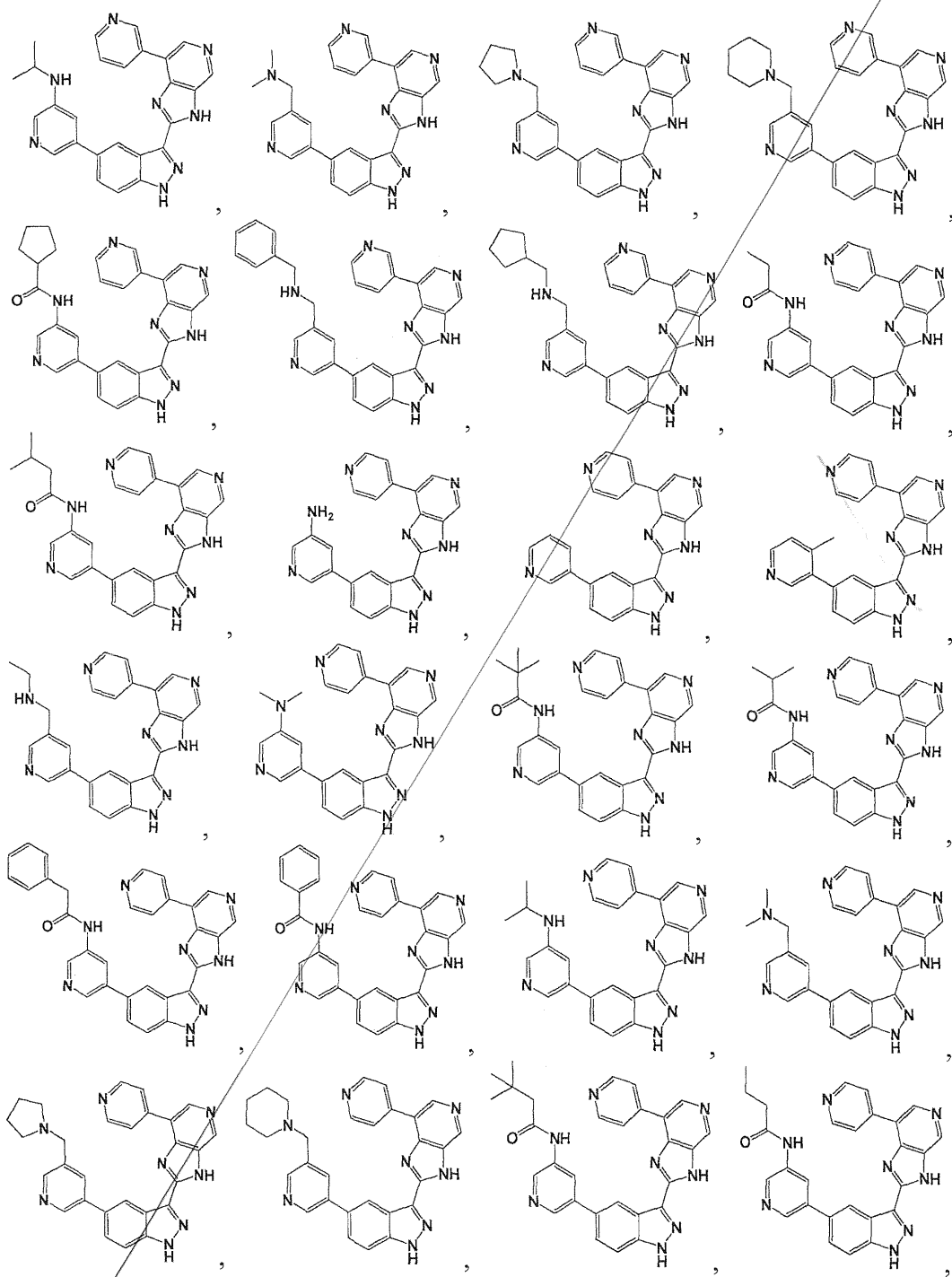


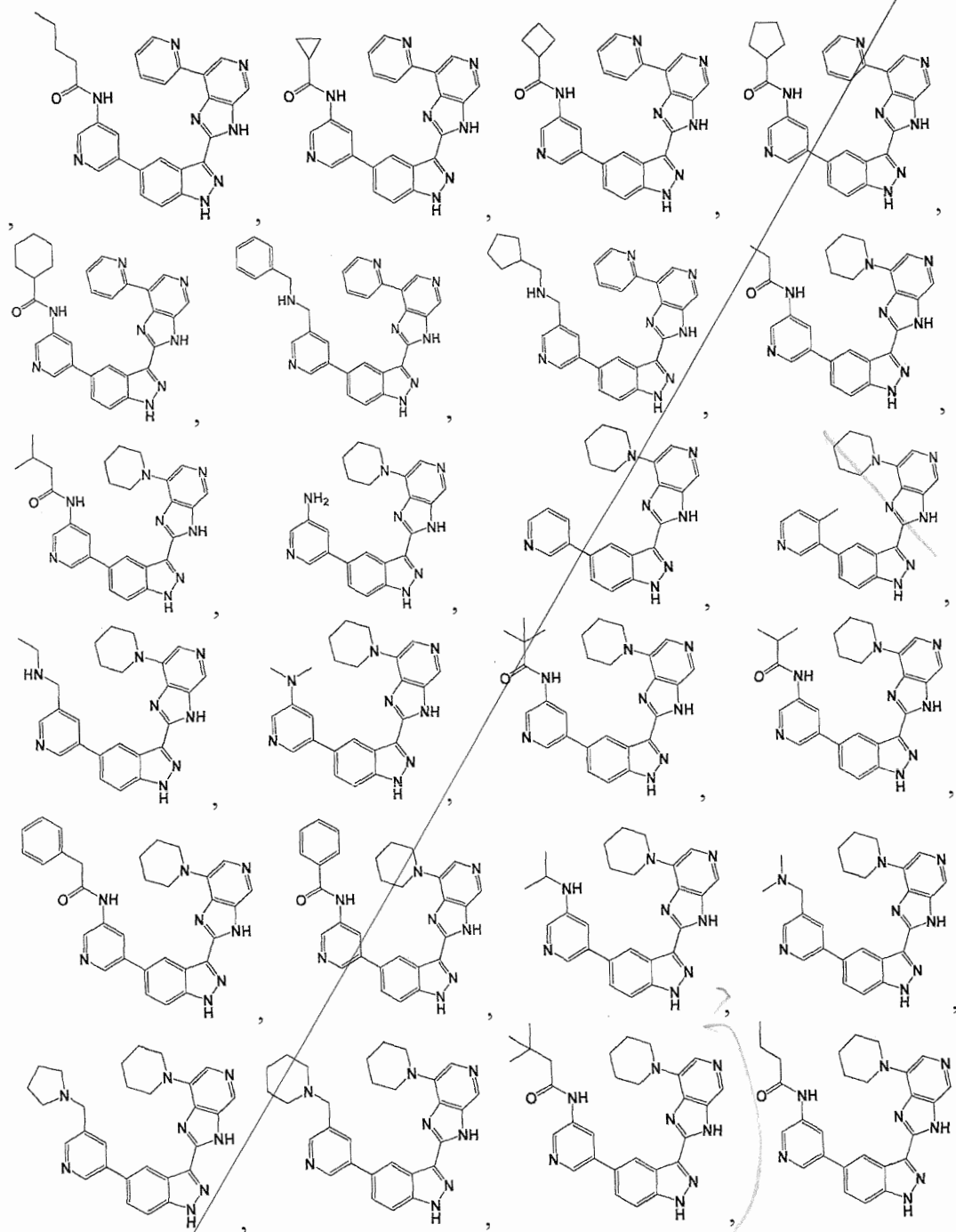


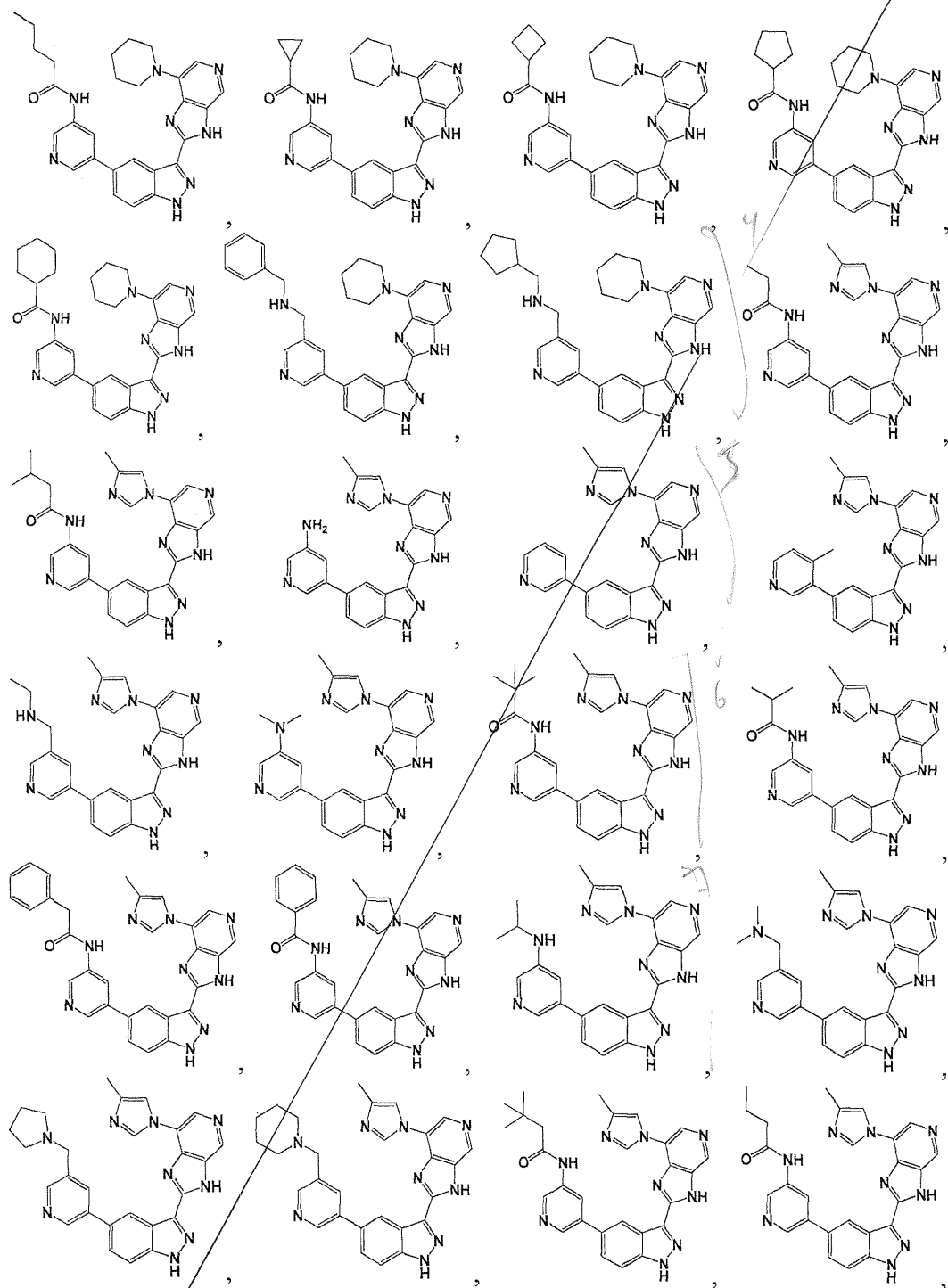


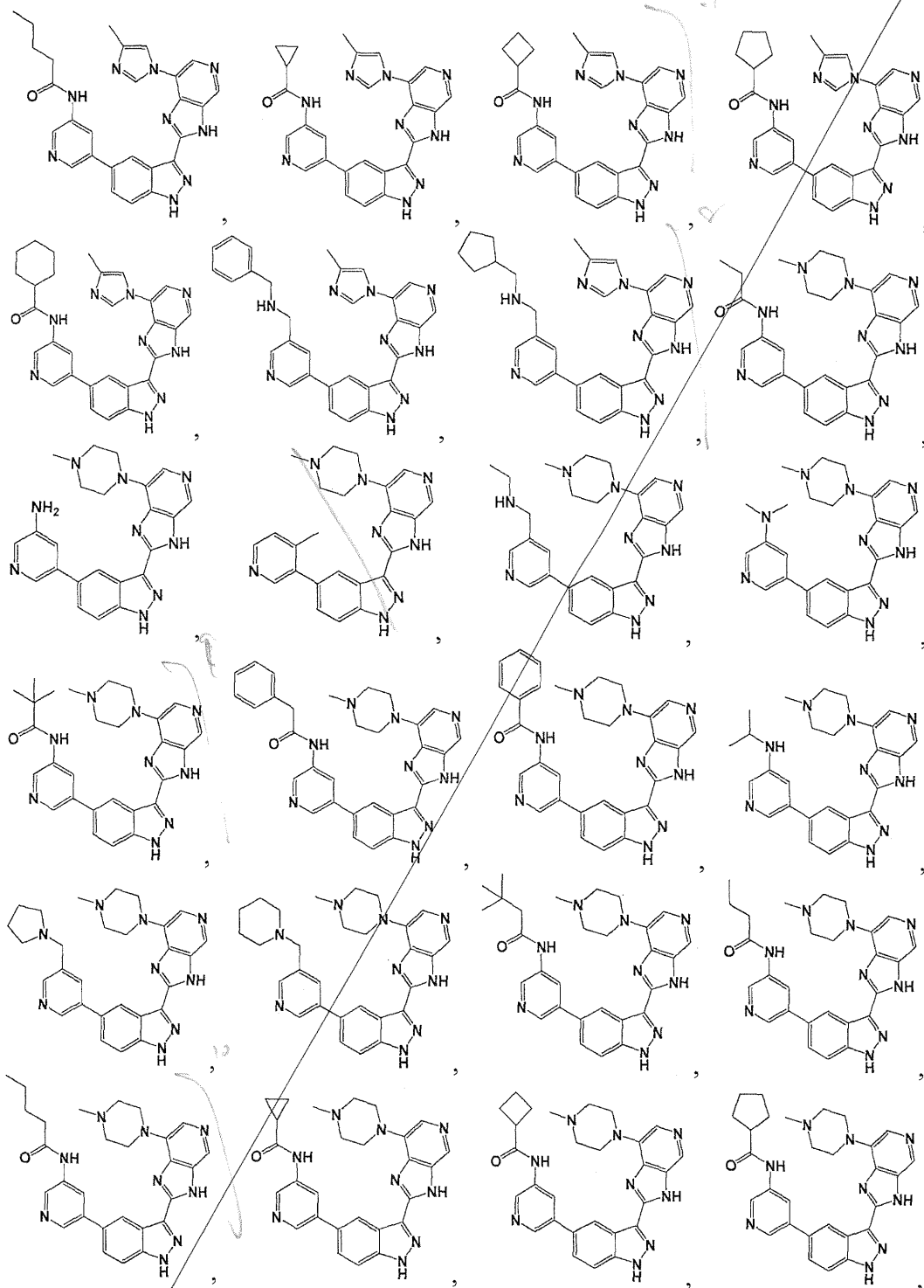


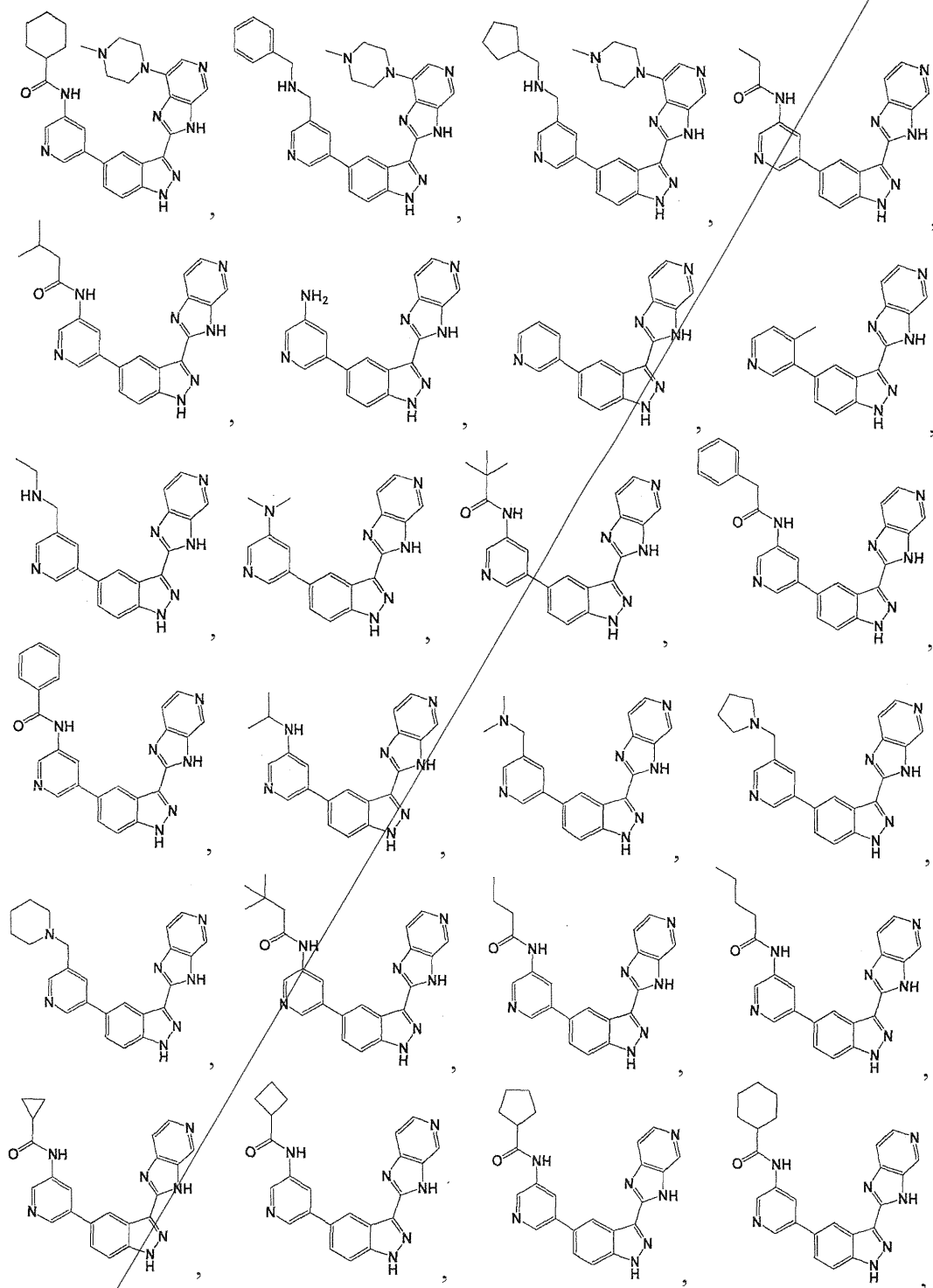


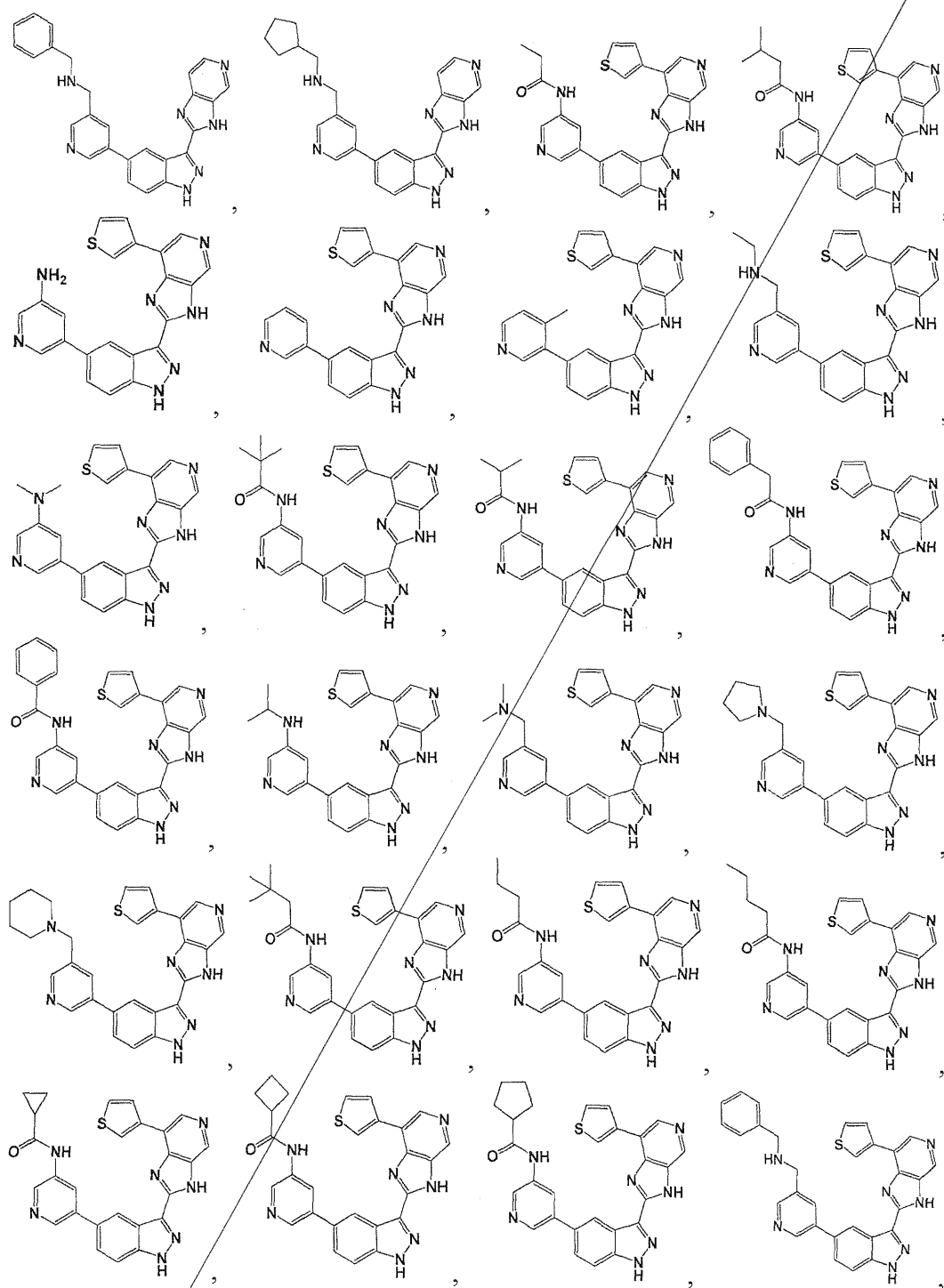


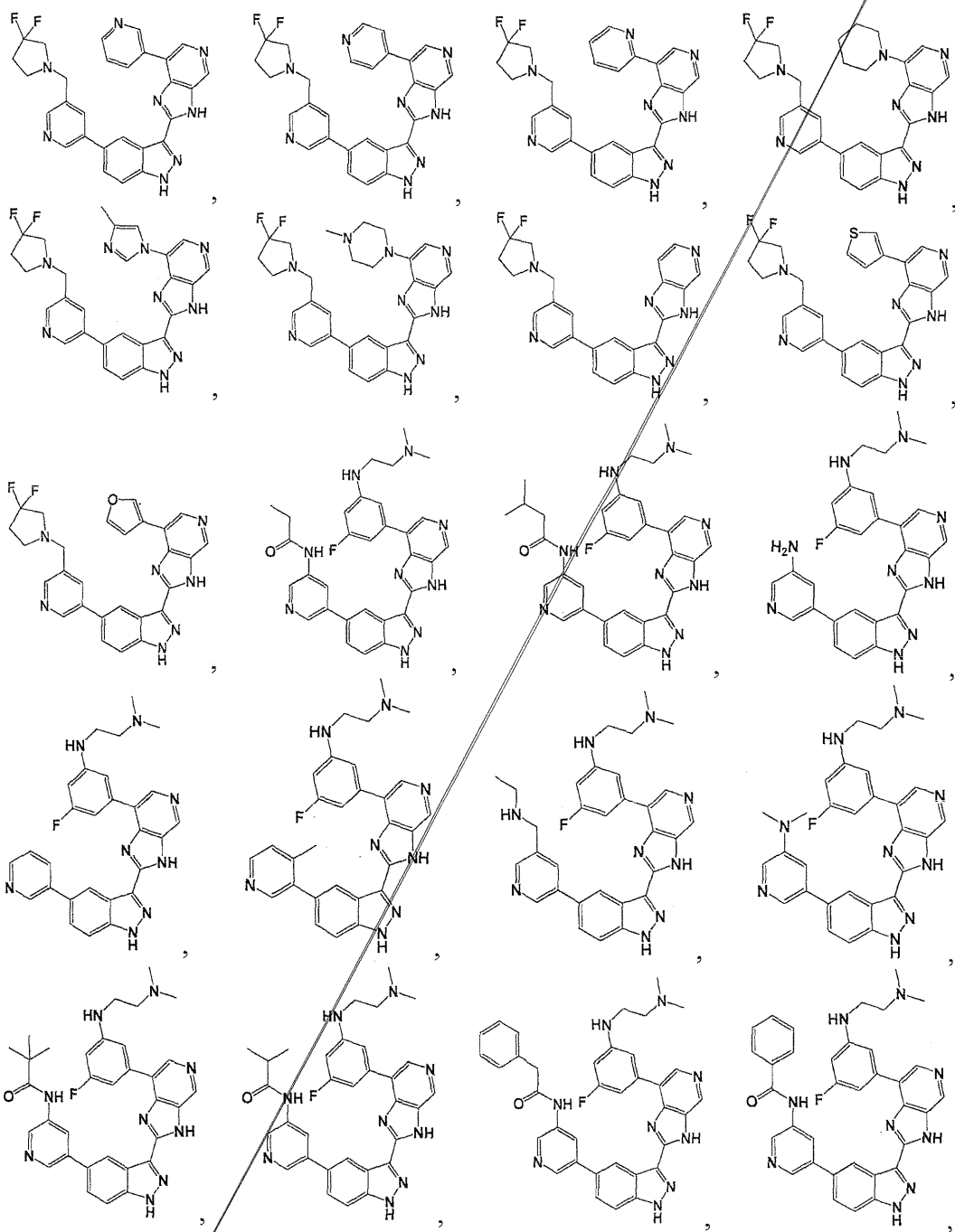


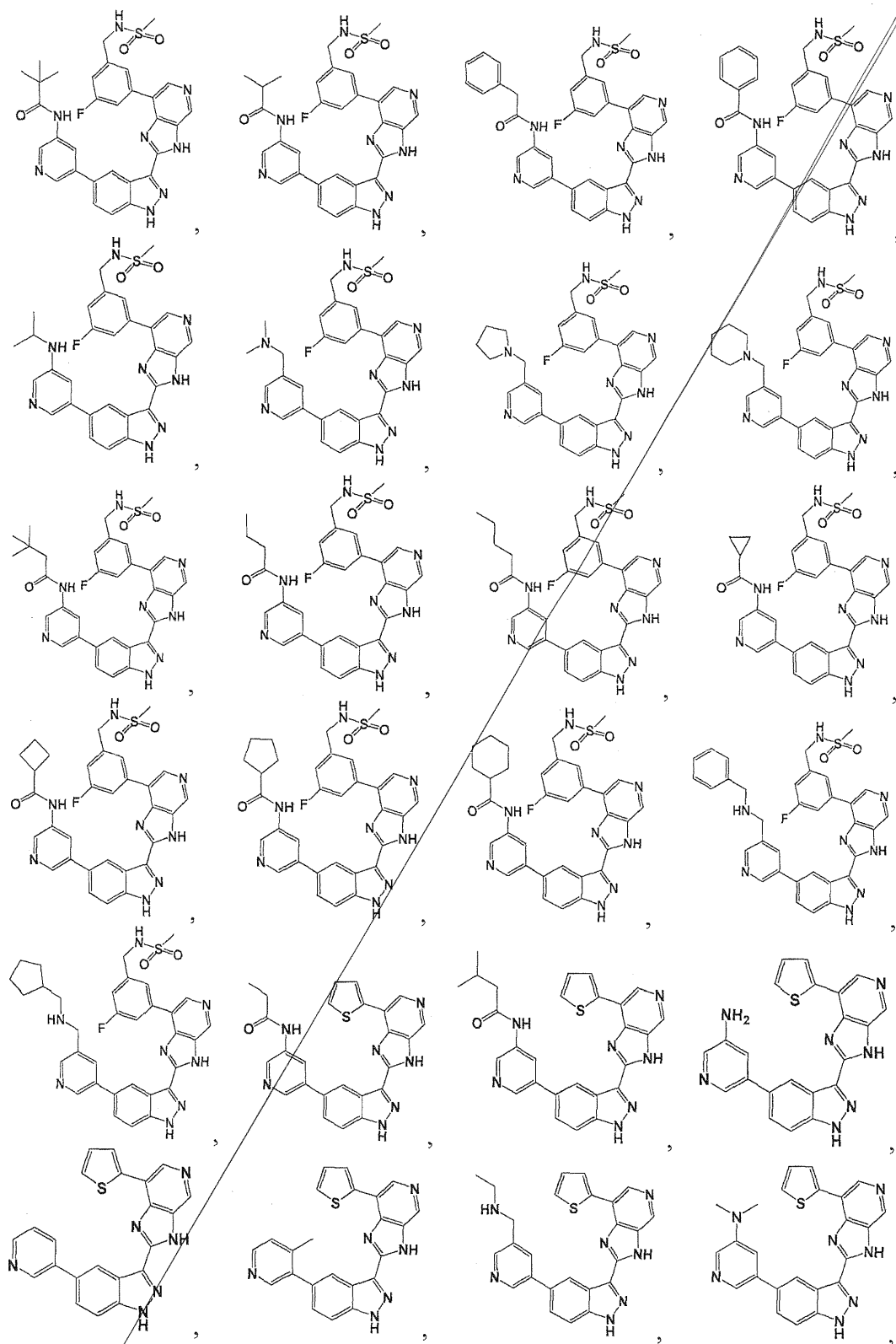


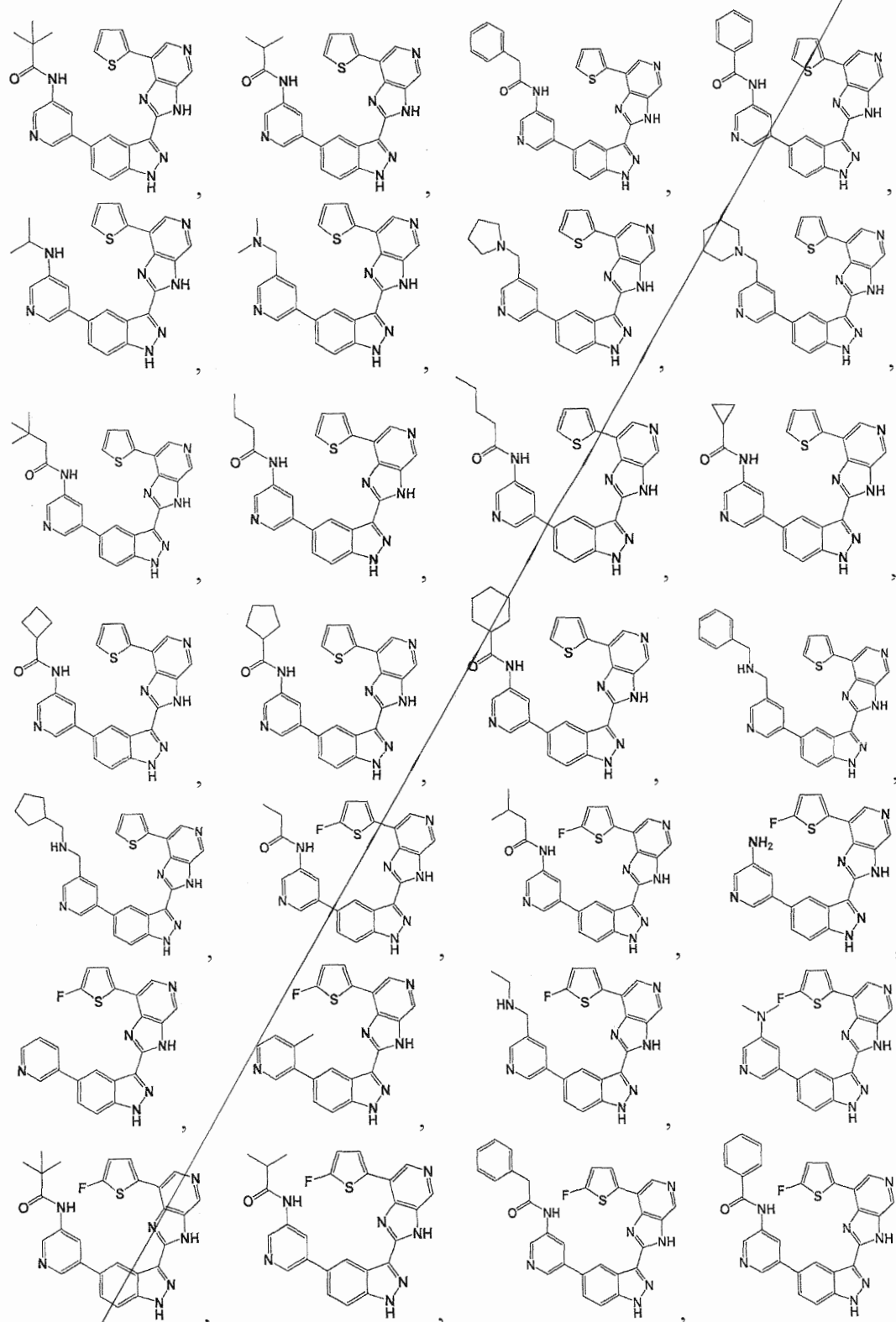


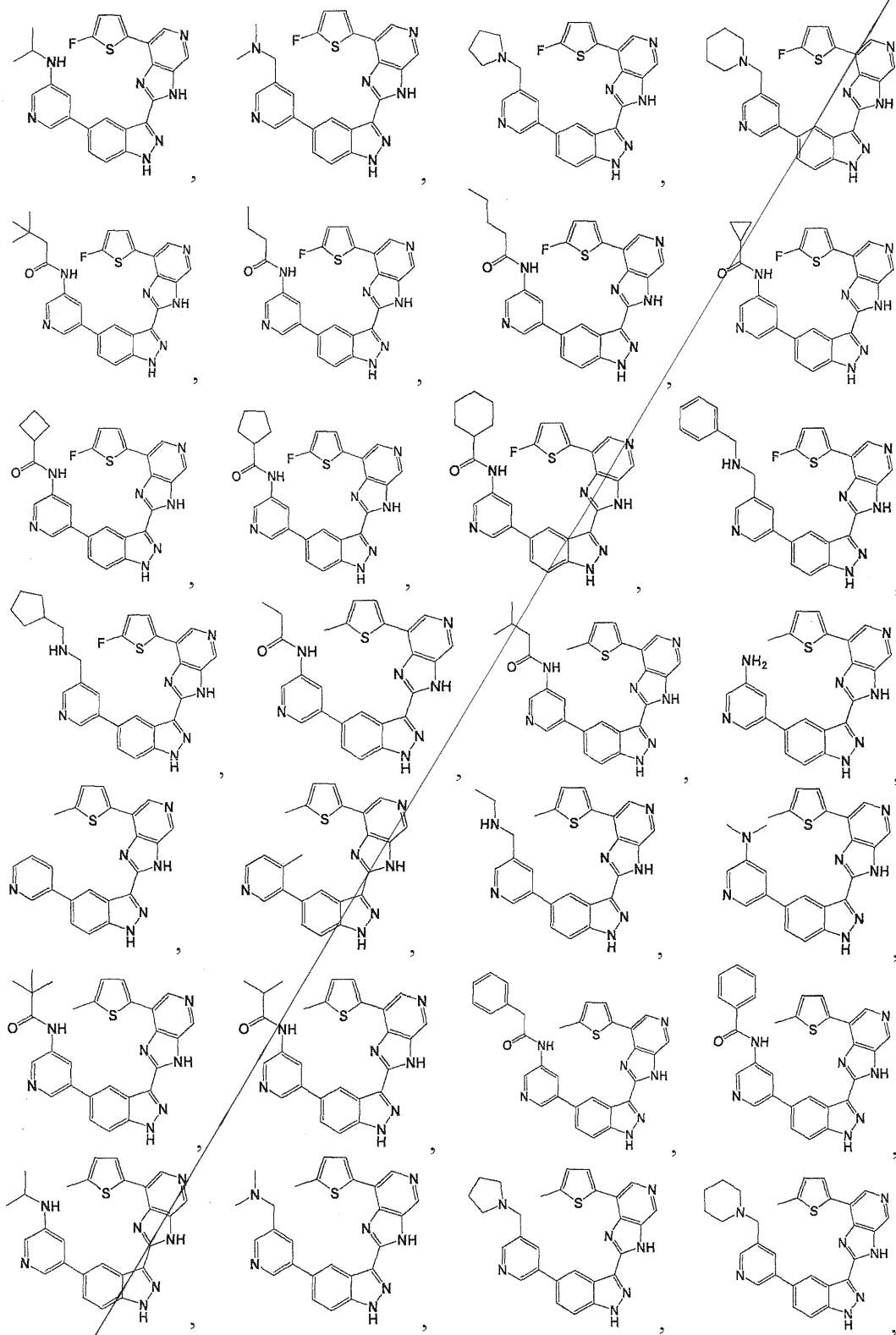


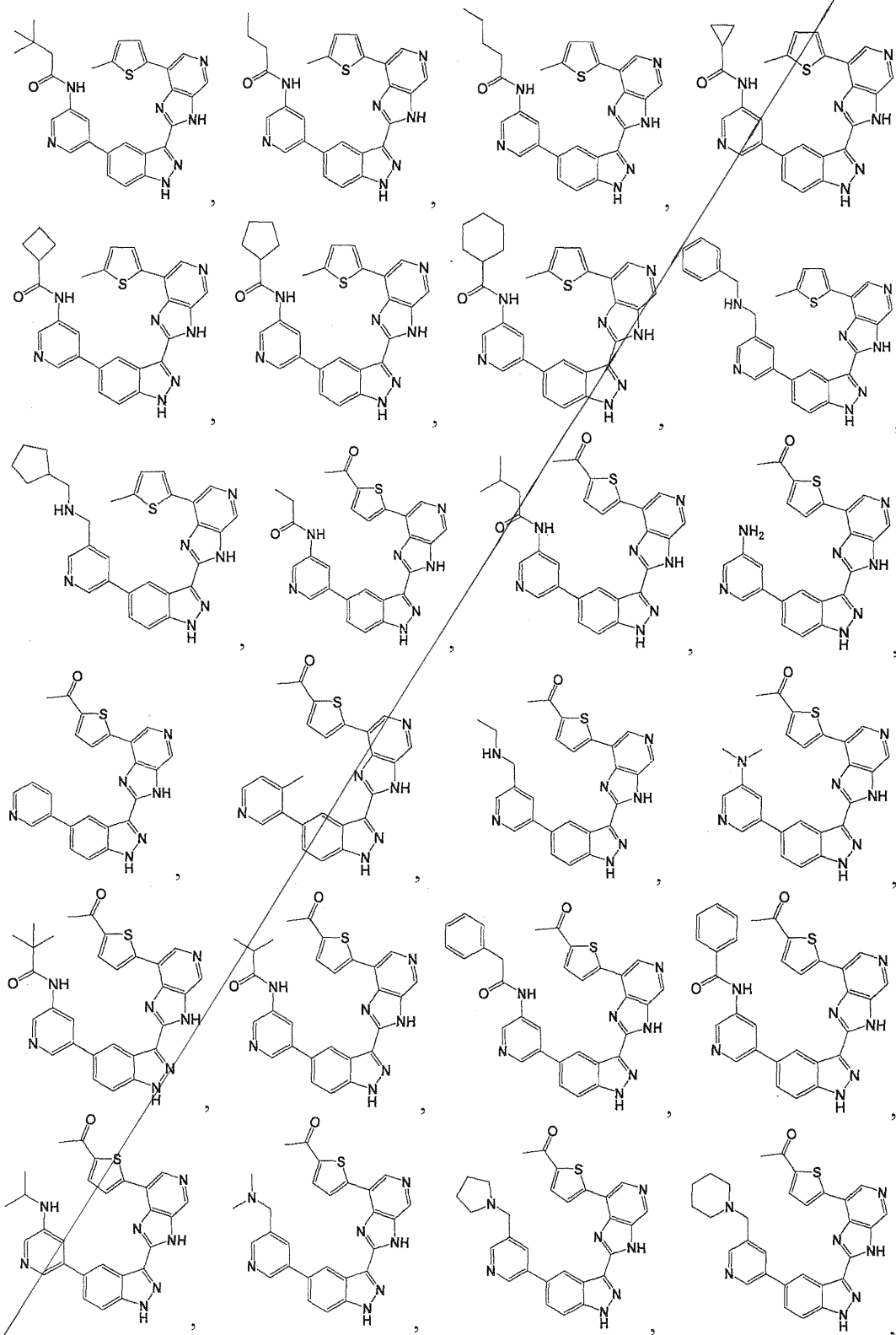


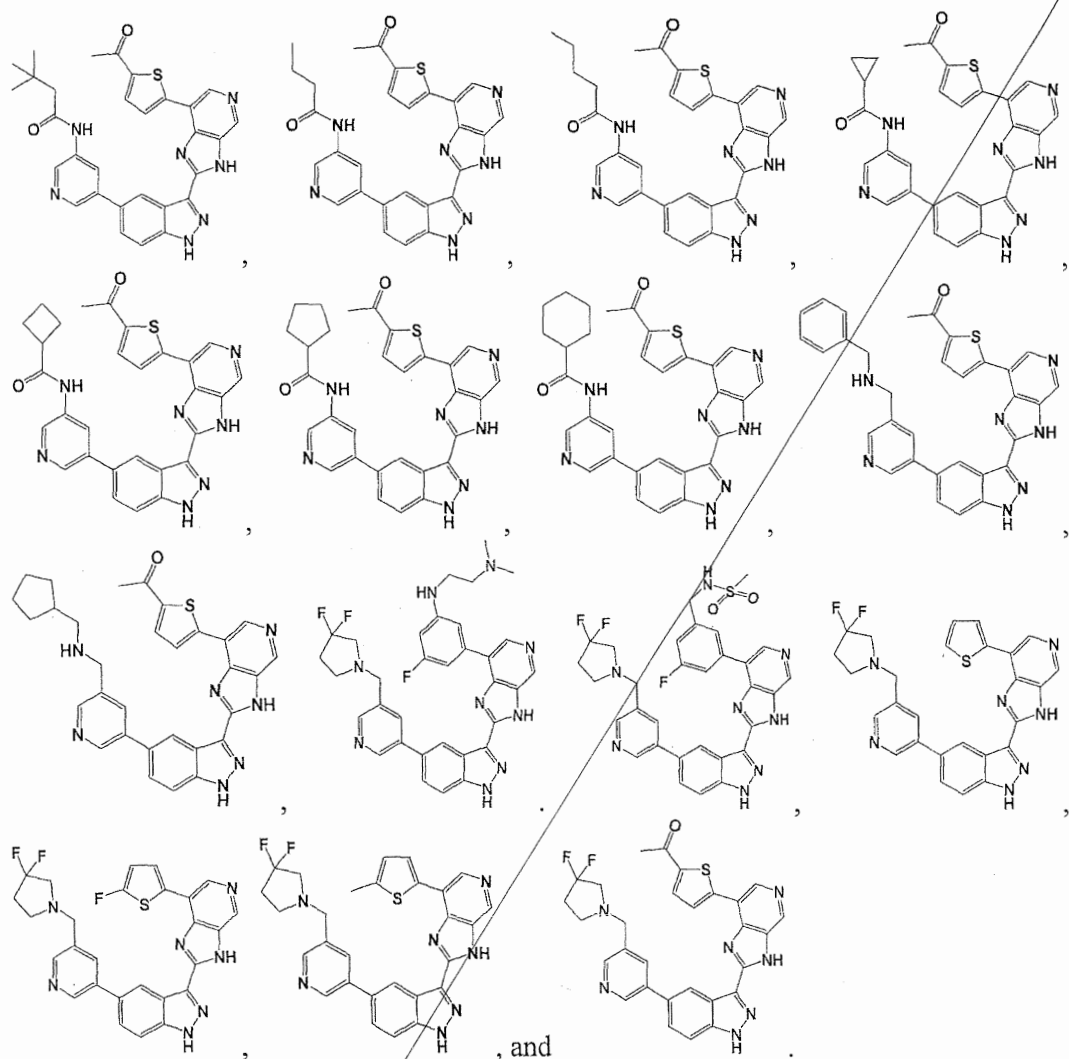




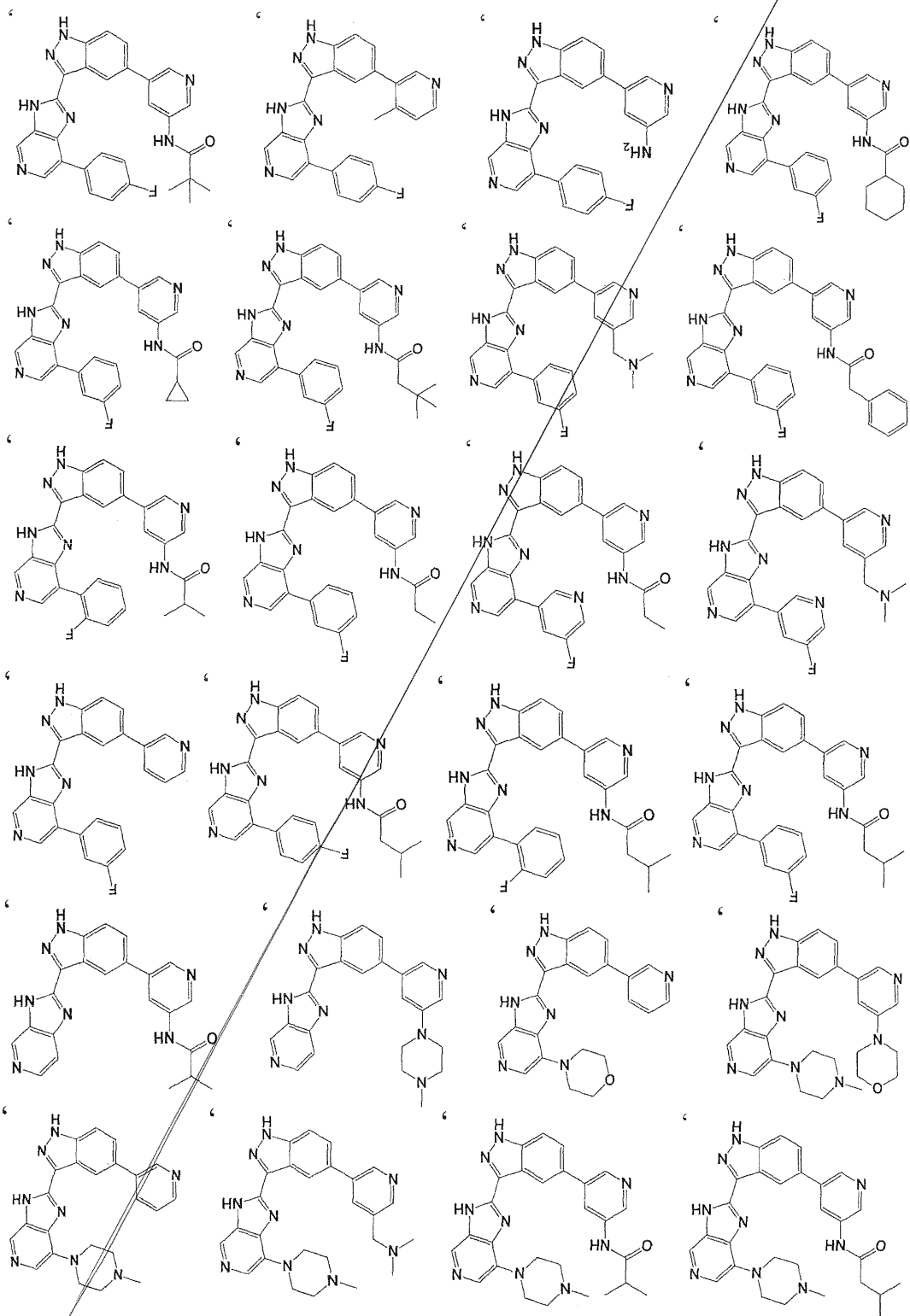


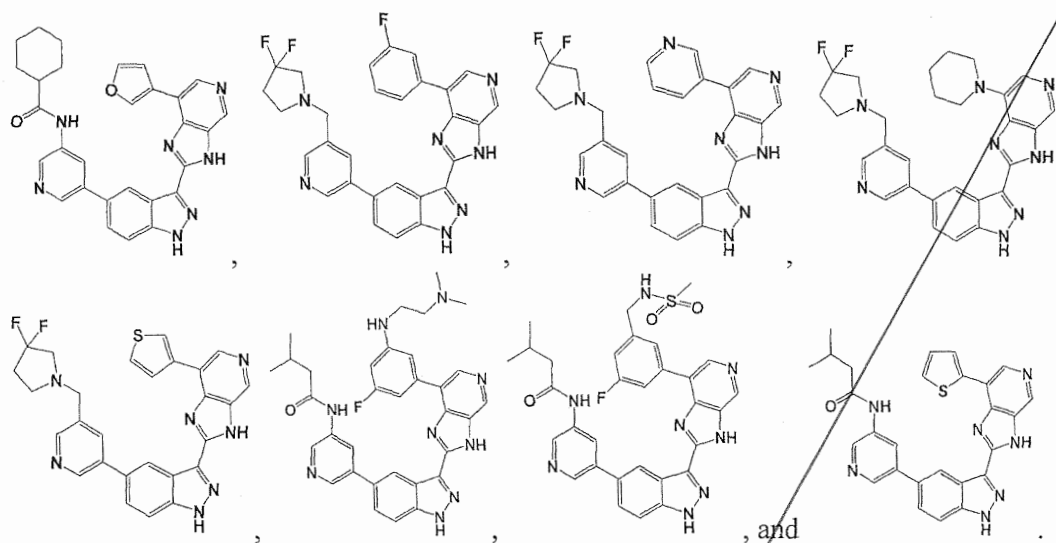
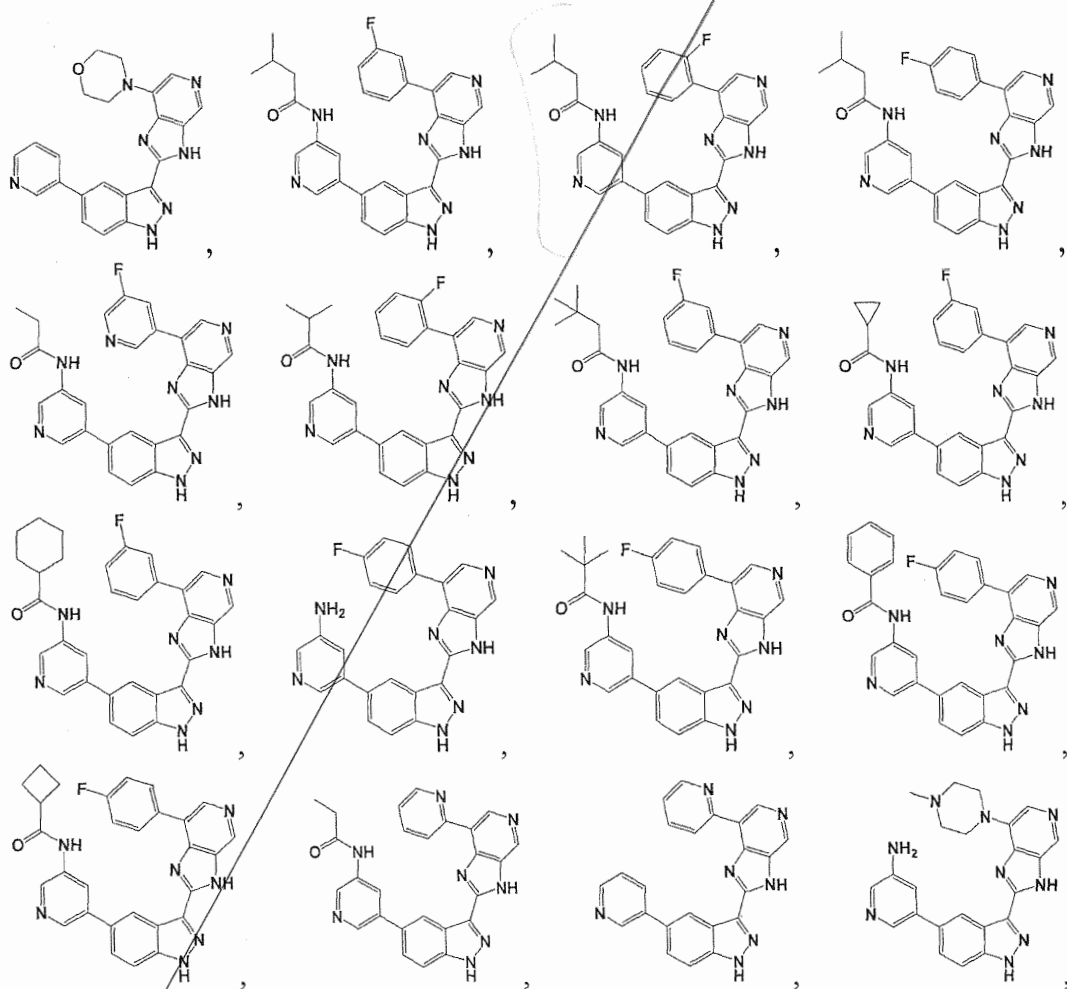


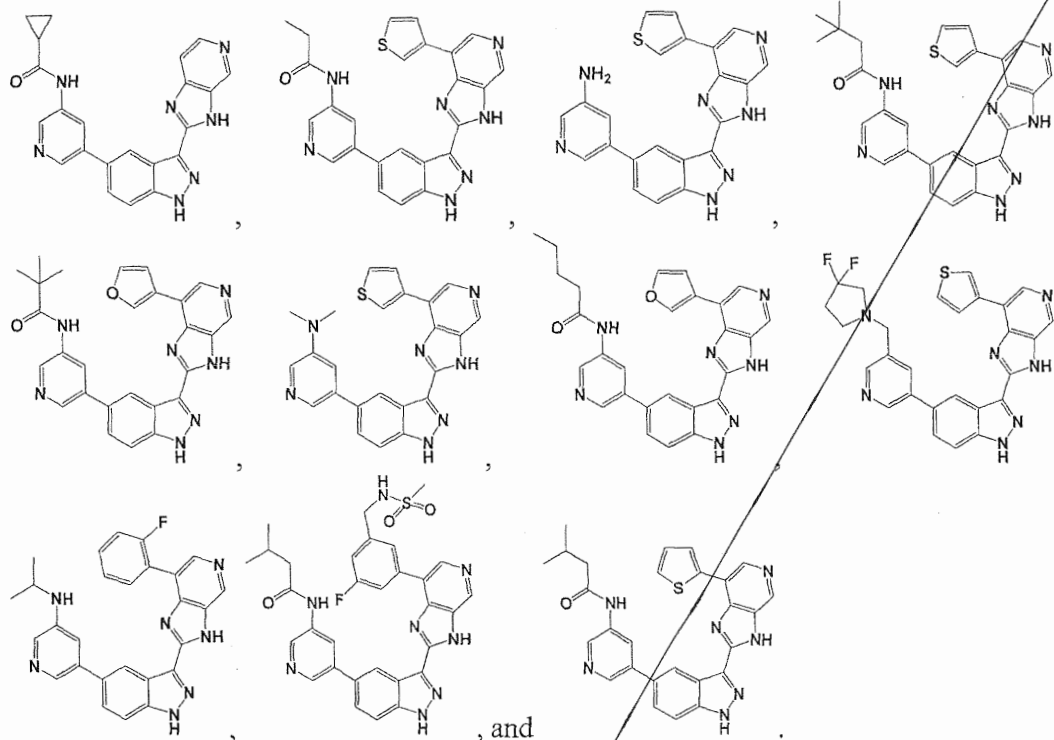




25. The compound of claim 1 having a structure selected from the group consisting of:







27. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

28. A method of treating a disorder or disease in which aberrant Wnt signaling is implicated in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

29. A method of claim 28, wherein the disorder or disease is cancer.

30. A method of claim 28, wherein the disorder or disease is diabetic retinopathy.

31. A method of claim 28, wherein the disorder or disease is pulmonary fibrosis.

32. A method of claim 28, wherein the disorder or disease is rheumatoid arthritis.

33. A method of claim 28, wherein the disorder or disease is scleroderma.

34. A method of claim 28, wherein the disorder or disease is a mycotic or viral infection.

35. A method of claim 28, wherein the disorder or disease is a bone or cartilage disease.

36. A method of claim 28, wherein the disorder or disease is Alzheimer's disease.

37. A method of claim 28, wherein the disorder or disease is osteoarthritis.

38. A method of claim 28, wherein the disorder or disease is lung disease.

39. A method of claim 28, wherein the disorder or disease is a genetic disease caused by mutations in Wnt signaling components, wherein the genetic disease is selected from: polyposis coli, osteoporosis-pseudoglioma syndrome, familial exudative vitreoretinopathy, retinal angiogenesis, early coronary disease, tetra-amelia syndrome, Müllerian-duct regression and virilization, SERKAL syndrome, diabetes mellitus type 2, Fuhrmann syndrome, Al-Awadi/Raas-Rothschild/Schinzel phocomelia syndrome, odonto-onycho-dermal dysplasia, obesity, split-hand/foot malformation, caudal duplication syndrome, tooth agenesis, Wilms tumor, skeletal dysplasia, focal dermal hypoplasia, autosomal recessive anonychia, neural tube defects, alpha-thalassemia (ATRX) syndrome, fragile X syndrome, ICF syndrome, Angelman syndrome, Prader-Willi syndrome, Beckwith-Wiedemann Syndrome and Rett syndrome.

40. The method of claim 28, wherein the patient is a human.

41. The method of claim 29, wherein the cancer is chosen from: hepatocellular carcinoma, colon cancer, breast cancer, pancreatic cancer leukemia, lymphoma, sarcoma and ovarian cancer.

42. The method of claim 28, wherein the compound inhibits one or more proteins in the Wnt pathway.

43. The method of claim 28, wherein the compound inhibits signaling induced by one or more Wnt proteins.

44. The method of either claim 42 or 43, wherein the Wnt proteins are chosen from: WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, and WNT16.

45. The method of claim 28, wherein the compound inhibits a kinase activity.

46. A method of treating a disease or disorder mediated by the Wnt pathway in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

47. The method of claim 44, wherein the compound inhibits one or more Wnt proteins.

48. A method of treating a disease or disorder mediated by kinase activity in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

49. The method of claim 46, wherein the disease or disorder comprises tumor growth, cell proliferation, or angiogenesis.

50. A method of inhibiting the activity of a protein kinase receptor, the method comprising contacting the receptor with an effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

51. A method of treating a disease or disorder associated with aberrant cellular proliferation in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

52. A method of preventing or reducing angiogenesis in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

53. A method of preventing or reducing abnormal cellular proliferation in a patient, the method comprising administering to the patient a therapeutically effective amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof.