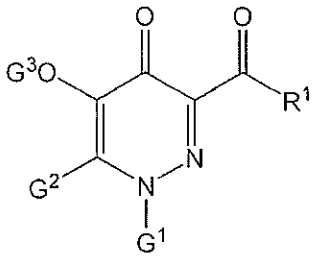
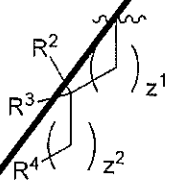
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:



G^1 is selected from the group consisting of [redacted] and R^5;

G^2 is hydrogen, halogen, -CN, an optionally substituted C_{1-6} alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, $-CH_2OH$, $-CH(Y^1)(OH)$ or $-C(O)Y^1$,;

G^3 is selected from the group consisting of hydrogen, $-C(O)Y^2$, $-C(O)O-Y^2$, $-(CH_2)-O(CO)Y^2$, $-(CH_2)-O(CO)OY^2$, $-(CHCH_3)-O(CO)Y^2$, and $-(CHCH_3)-O(CO)OY^2$;

Y^1 and Y^2 are independently an optionally substituted C_{1-6} alkyl or an optionally substituted aryl;

R^1 is selected from the group consisting of OR^6, NH_2, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted mono-substituted amine, an optionally substituted di-substituted amine, an optionally substituted heterocyclyl, an optionally substituted N-sulfonamido and an optionally substituted alkoxyamine, or R^{10};

R^2 is hydrogen, C_{1-6} alkyl, an optionally substituted C_{3-6} cycloalkyl, an optionally substituted aryl, an optionally substituted aryl(C_{1-6} alkyl) or an optionally substituted C-amido;

R^3 is hydrogen or C_{1-6} alkyl;

or R^2 and R^3 are taken together to form an optionally substituted C_{3-6} cycloalkyl, an optionally substituted 5 to 6 membered heterocyclyl or =O;

R^4 is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

or R^4 is $A^1R^{A4}R^{B4}$, wherein A^1 is CH or N; and R^{A4} and R^{B4} are each independently an optionally substituted phenyl;

R^5 is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

R^6 is selected from the group consisting of hydrogen, C_{1-6} alkyl, $-C(O)R^7$ and $-C(O)NR^8R^9$;

R^7 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

R^8 and R^9 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

or R^8 and R^9 are taken together to form an optionally substituted heterocyclyl;

wherein when R^1 is R^{10}, then R^{10} and R^4 are taken together and include L^1, where L^1 connects R^{10} and R^4 to form an 11- to 20-membered ring, or wherein when R^1 is R^{10}, then R^{10} and R^5 are taken together and include L^1, where L^1 connects R^1 and R^5 to form an 11- to 20-membered ring;

wherein R^{10} is optionally substituted $-CH_2-$, optionally substituted -CH=CH-, O (oxygen), S (sulfur), or NR^{11};

wherein R^{11} is hydrogen or C_{1-6} alkyl; and

Z^1 and Z^2 are independently 0, 1, 2, 3 or 4.

2. The compound of Claim 1,

wherein:

G^2 is hydrogen or C_{1-6} alkyl;

$\mathbf{G^3}$ is selected from the group consisting of hydrogen, -C(O)$\mathbf{Y^2}$, -C(O)O-$\mathbf{Y^2}$, -(CH_2)-O(CO)$\mathbf{Y^2}$, –(CH_2)-O(CO)O$\mathbf{Y^2}$, –$(CHCH_3)$-O(CO)$\mathbf{Y^2}$, and –$(CHCH_3)$-O(CO)O$\mathbf{Y^2}$;

$\mathbf{Y^2}$ is $C_{1\text{-}6}$ alkyl;

$\mathbf{R^1}$ is selected from the group consisting of OR^6, NH_2, mono-substituted amine, di-substituted amine, heterocyclyl and N-sulfonamido, said mono-substituted amine, an di-substituted amine, heterocyclyl and N-sulfonamido are each optionally substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino;

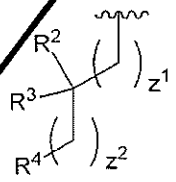
$\mathbf{R^2}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

$\mathbf{R^3}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

or $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted $C_{3\text{-}6}$ cycloalkyl or an optionally substituted 5 to 6 membered heterocyclyl:

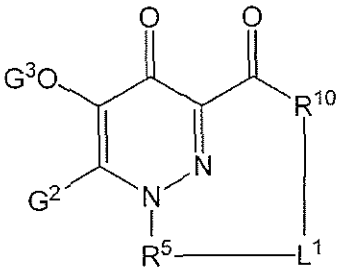
3. The compound of Claim 1,

wherein:

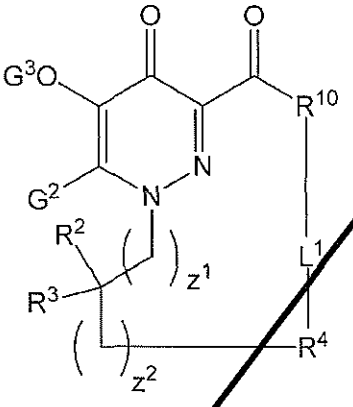
$\mathbf{G^1}$ is  : and

$\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted piperidino or an optionally substituted pyrrolidino.

4. The compound of Claim 1, having the structure of Formula (**Ih**) or Formula (**Ij**), or a pharmaceutically acceptable salt thereof:



(**Ih**) or



(**Ij**),

wherein:

$\mathbf{L^1}$ is $-\mathbf{L^2}-$, or $-\mathbf{L^3}-\mathbf{L^4}-\mathbf{L^5}-$;

$\mathbf{L^2}$ is selected from the group consisting of an optionally substituted alkylene, an optionally substituted alkenylene, an optionally substituted heteroalkylene and an optionally substituted heteroalkenylene;

$\mathbf{L^3}$ is an optionally substituted C_{1-6} alkylene;

$\mathbf{L^4}$ is an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, O (oxygen), S (sulfur), or $N\mathbf{R^{11}}$; and

$\mathbf{L^5}$ is an optionally substituted C_{1-6} alkylene or an optionally substituted heteroalkylene.

5. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted alkylene.

6. The compound of Claim 5, wherein $\mathbf{L^2}$ is an optionally substituted C_{4-7} alkylene.

7. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted alkenylene.

8. The compound of Claim 7, wherein $\mathbf{L^2}$ is an optionally substituted C_{4-7} alkenylene.

9. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted heteroalkylene.

10. The compound of Claim 9, wherein $\mathbf{L^2}$ is an optionally substituted $-(CH_2)_3-O-$, an optionally substituted $-(CH_2)_4-O-$, an optionally substituted $-(CH_2)_5-O-$, an optionally substituted $-(CH_2)_3-S-$, an optionally substituted $-(CH_2)_4-S-$, an optionally substituted

-$(CH_2)_5$-S–, an optionally substituted –$(CH_2)_3$-NH–, an optionally substituted –$(CH_2)_4$-NH– or an optionally substituted -$(CH_2)_5$-NH–.

11. The compound of Claim 9, wherein $\mathbf{L^2}$ is an optionally substituted -$(CH_2)_3$-O-, an optionally substituted –$(CH_2)_4$-O–, or an optionally substituted -$(CH_2)_5$-O–.

12. The compound of Claim 4, wherein $\mathbf{L^2}$ is optionally substituted heteroalkenylene.

13. The compound of Claim 12, wherein $\mathbf{L^2}$ is an optionally substituted -$(CH_2)(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-S–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-S–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-S an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-NH–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-NH– or an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-NH .

14. The compound of Claim 13, wherein $\mathbf{L^2}$ is an optionally substituted C_3 oxygen containing heteroalkenylene, an optionally substituted C_4 oxygen containing heteroalkenylene, or an optionally substituted C_5 oxygen containing heteroalkenylene.

15. The compound of Claim 4,

wherein:

$\mathbf{L^1}$ is $\mathbf{-L^3\text{-}L^4\text{-}L^5}$-:

$\mathbf{L^3}$ is an optionally substituted $C_{1\text{-}4}$ alkylene;

$\mathbf{L^4}$ is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

$\mathbf{L^5}$ is an optionally substituted $C_{1\text{-}4}$ alkylene.

16. The compound of Claim 4,

wherein:

$\mathbf{L^1}$ is $\mathbf{-L^3\text{-}L^4\text{-}L^5}$-:

$\mathbf{L^3}$ is an optionally substituted $C_{1\text{-}4}$ alkylene;

$\mathbf{L^4}$ is O (oxygen), S (sulfur), or $\mathbf{NR^{11}}$; and

$\mathbf{L^5}$ is an optionally substituted $C_{1\text{-}4}$ alkylene.

17. The compound of Claim 4,

wherein:

L^1 is $-L^3-L^4-L^5-$;

L^3 is optionally substituted C_{2-4} alkylene;

L^4 is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, O (oxygen), S (sulfur), or NR^{11}; and

L^5 is optionally substituted C_{2-4} alkylene.

18. The compound of any one of Claims 4 or 16-17,

wherein:

R^1 is R^{10} where R^{10} is NR^{11}; and

R^{11} is H (hydrogen).

19. The compound of Claim 1, wherein R^1 is OR^6.

20. The compound of Claim 19, wherein R^6 is hydrogen.

21. The compound of Claim 19, wherein R^6 is C_{1-6} alkyl.

22. The compound of Claim 19, wherein R^6 is $-C(O)R^7$.

23. The compound of Claim 19, wherein R^6 is $-C(O)NR^8R^9$.

24. The compound of Claim 1, wherein R^1 is NH_2.

25. The compound of Claim 1, wherein R^1 is an optionally substituted mono-substituted amine.

26. The compound of Claim 1, wherein R^1 is an optionally substituted di-substituted amine.

27. The compound of Claim 1, wherein R^1 is an optionally substituted heterocyclyl.

28. The compound of Claim 27, wherein the heterocyclyl is a 5 to 6 membered heterocyclyl.

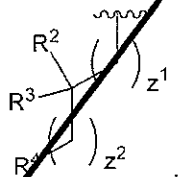
29. The compound of Claim 27 or 28, wherein the heterocyclyl contains at least one nitrogen in the ring and is an N-linked heterocyclyl.

30. The compound of Claim 1, wherein R^1 is an optionally substituted N-sulfonamido.

31. The compound of Claim 1, wherein $\mathbf{R^1}$ is $\mathbf{R^{10}}$.

32. The compound of Claim 1, wherein $\mathbf{R^{10}}$ is CH_2.

33. The compound of Claim 1, wherein $\mathbf{R^{10}}$ is $\mathbf{NR^{11}}$.

34. The compound of any one of Claims 1-18, wherein $\mathbf{G^1}$ is 

.

35. The compound of Claim 34, wherein $\mathbf{R^2}$ is hydrogen.

36. The compound of Claim 34, wherein $\mathbf{R^2}$ is C_{1-6} alkyl.

37. The compound of any one of Claims 34-36, wherein $\mathbf{R^3}$ is hydrogen.

38. The compound of any one of Claims 34-36, wherein $\mathbf{R^3}$ is C_{1-6} alkyl.

39. The compound of Claim 34, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted C_{3-6} cycloalkyl.

40. The compound of Claim 39, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an unsubstituted C_{3-6} cycloalkyl.

41. The compound of Claim 39 or 40, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form a C_5 cycloalkyl.

42. The compound of Claim 34, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted 5 to 6 membered heterocyclyl.

43. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

44. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is an optionally substituted aryl.

45. The compound of Claim 44, wherein the optionally substituted aryl is an optionally substituted phenyl.

46. The compound of Claim 45, wherein the optionally substituted phenyl is a substituted phenyl.

47. The compound of Claim 46, wherein the substituted phenyl is a mono-substituted phenyl.

48. The compound of Claim 47, wherein the substituted phenyl is an ortho-substituted phenyl.

49. The compound of Claim 47, wherein the substituted phenyl is a meta-substituted phenyl.

50. The compound of Claim 47, wherein the substituted phenyl is a para-substituted phenyl.

51. The compound of Claim 46, wherein the substituted phenyl is a di-substituted phenyl.

52. The compound of Claim 46, wherein the substituted phenyl is substituted with 3 or more substituents.

53. The compound of any one of Claims 32-42, wherein R^4 is an optionally substituted cycloalkyl.

54. The compound of any one of Claims 32-42, wherein R^4 is an optionally substituted heteroaryl.

55. The compound of any one of Claims 32-42, wherein R^4 is an optionally substituted heterocyclyl.

56. The compound of any one of Claims 32-55, wherein R^4 is substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, alkoxy, aryloxy, haloalkyl, haloalkoxy, hydroxyalkyl, N-sulfonamido, S–sulfonamido, sulfonyl, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, carbonyl, C-carboxy, $-CH_2-$(mono-substituted amine) and CH_2-(di-substituted amine).

57. The compound of Claim 56, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, aryl, cyano, halogen, haloalkyl and haloalkoxy.

58. The compound of Claim 56, wherein the optionally substituted cycloalkyl is a substituted cycloalkyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen and haloalkyl.

59. The compound of Claim 56, wherein the optionally substituted heterocyclyl is a substituted heterocyclyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen, haloalkyl, aryl(C_{1-6} alkyl) and C-carboxy.

60. The compound of any one of Claims 34-59, wherein Z^1 is 0.

61. The compound of any one of Claims 34-59, wherein Z^1 is 1.

62. The compound of any one of Claims 34-59, wherein Z^1 is 2.

63. The compound of any one of Claims 34-59, wherein Z^1 is 3.

64. The compound of any one of Claims 34-59, wherein Z^1 is 4.

65. The compound of any one of Claims 34-64, wherein Z^2 is 0.

66. The compound of any one of Claims 34-64, wherein Z^2 is 1.

67. The compound of any one of Claims 34-64, wherein Z^2 is 2.

68. The compound of any one of Claims 34-64, wherein Z^2 is 3.

69. The compound of any one of Claims 34-64, wherein Z^2 is 4.

70. The compound of any one of Claims 1-18, wherein G^1 is R^5.

71. The compound of Claim 70, wherein R^5 is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

72. The compound of Claim 70, wherein R^5 is an optionally substituted aryl.

73. The compound of Claim 72, wherein the optionally substituted aryl is an optionally substituted phenyl.

74. The compound of Claim 73, wherein the optionally substituted phenyl is a substituted phenyl.

75. The compound of Claim 74, wherein the substituted phenyl is a mono-substituted phenyl.

76. The compound of Claim 75, wherein the substituted phenyl is an ortho-substituted phenyl.

77. The compound of Claim 75, wherein the substituted phenyl is a meta-substituted phenyl.

78. The compound of Claim 75, wherein the substituted phenyl is a para-substituted phenyl.

79. The compound of Claim 74, wherein the substituted phenyl is a di-substituted phenyl.

80. The compound of Claim 74, wherein the substituted phenyl is substituted with 3 or more substituents.

81. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted cycloalkyl.

82. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted heteroaryl.

83. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted heterocyclyl.

84. The compound of any one of Claims 70-83, wherein $\mathbf{R^5}$ is substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, alkoxy, aryloxy, haloalkyl, haloalkoxy, hydroxyalkyl, N-sulfonamido, S–sulfonamido, sulfonyl, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, carbonyl, C–carboxy, $-CH_2-$(mono-substituted amine) and CH_2-(di-substituted amine).

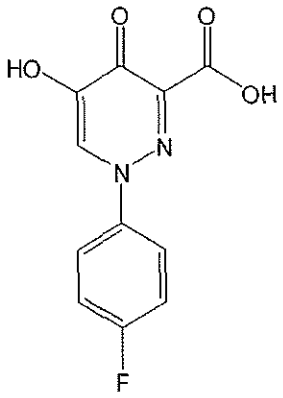
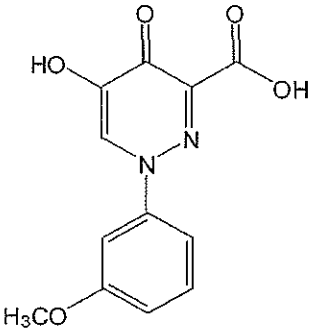
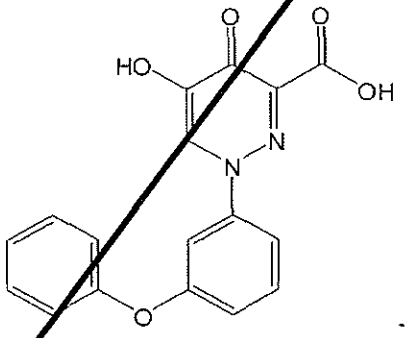
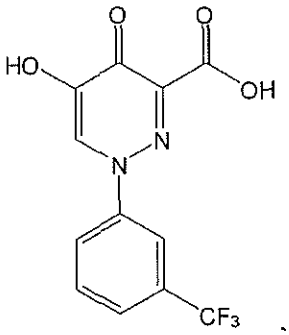
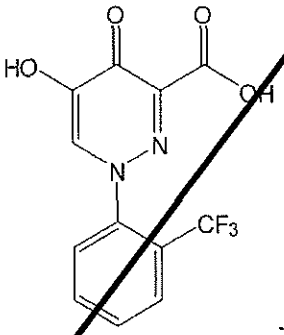
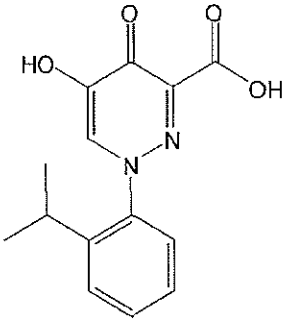
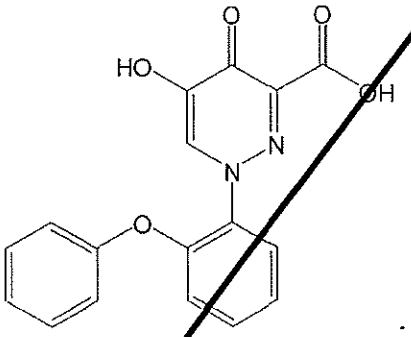
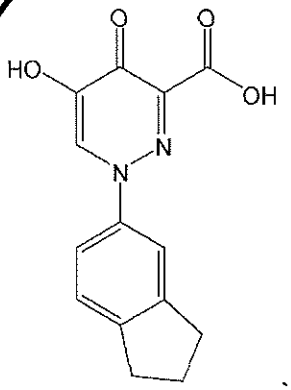
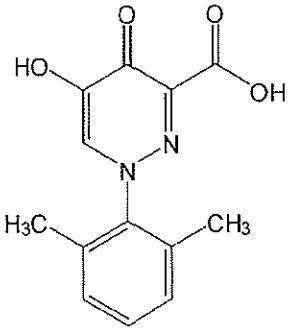
85. The compound of Claim 84, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen and haloalkyl.

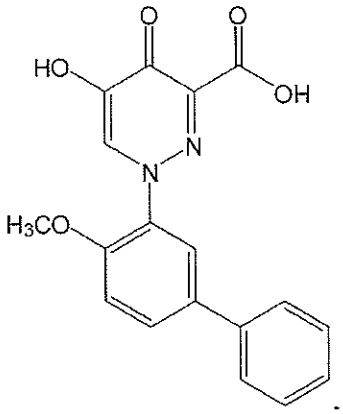
86. The compound of Claim 84, wherein the optionally substituted cycloalkyl is a substituted cycloalkyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen and haloalkyl.

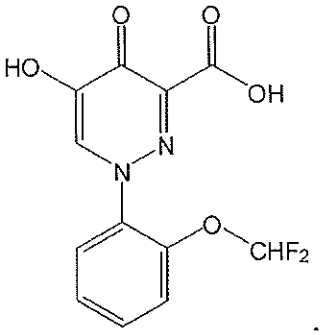
87. The compound of Claim 84, wherein the optionally substituted heterocyclyl is a substituted heterocyclyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen, haloalkyl, aryl(C_{1-6} alkyl) and C-carboxy.

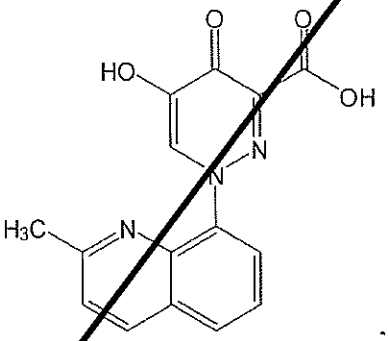
88. The compound of any one of Claims 1-87, wherein $\mathbf{G^3}$ is hydrogen.

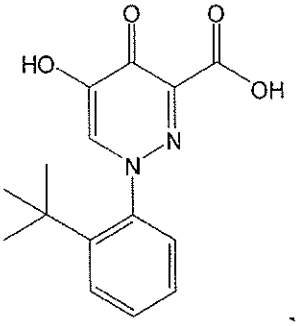
89. The compound of Claim 1, wherein the compound is selected from the group consisting of:

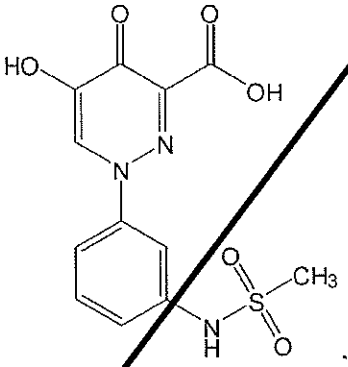










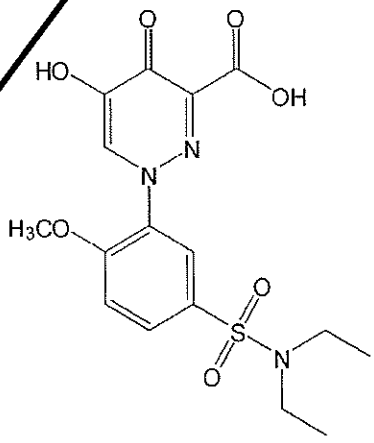


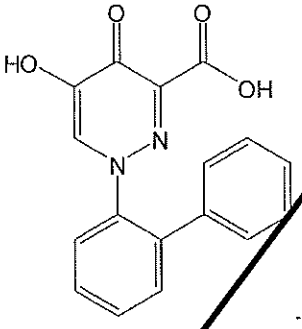


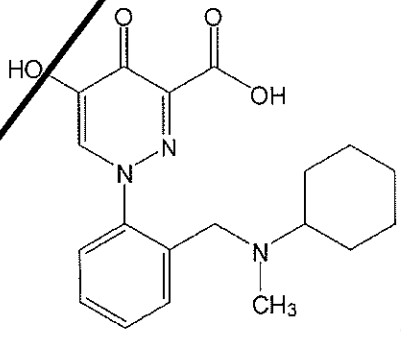


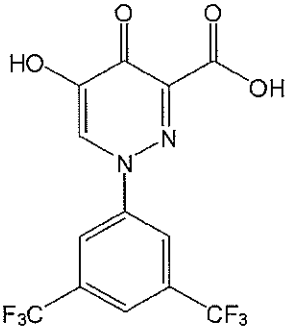


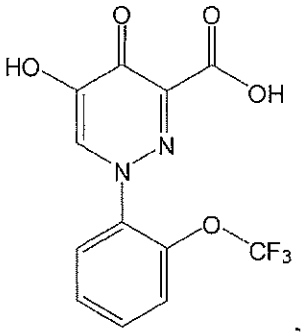


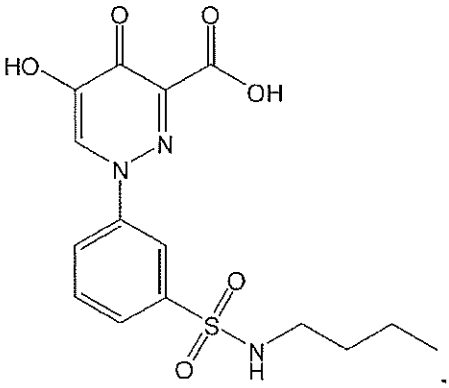


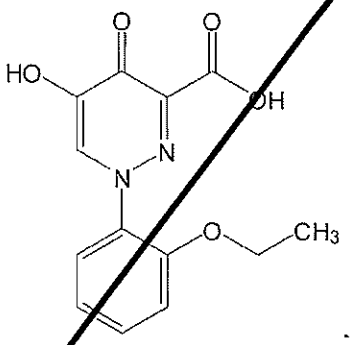


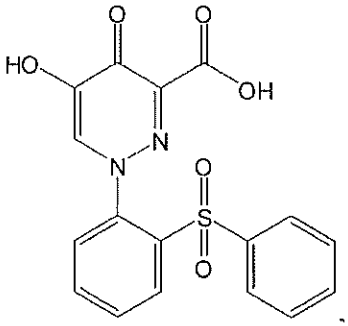


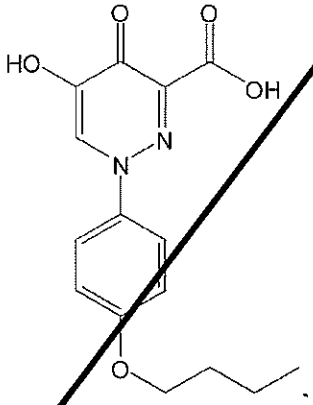


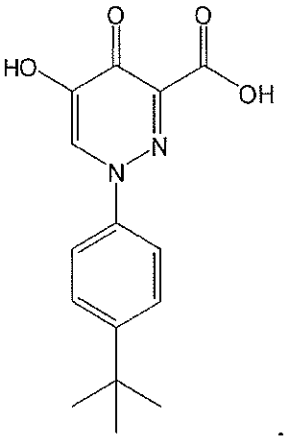


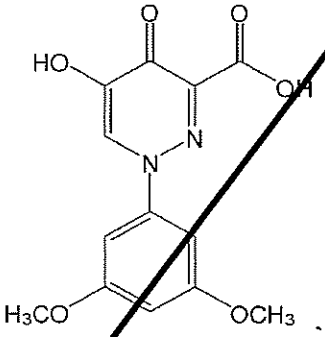


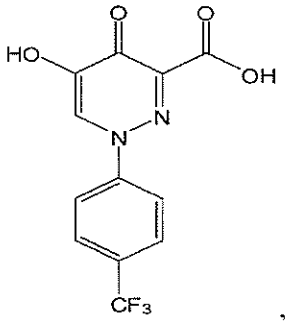


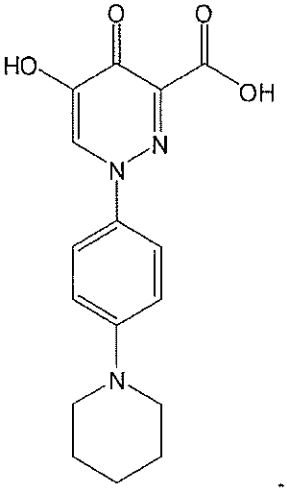


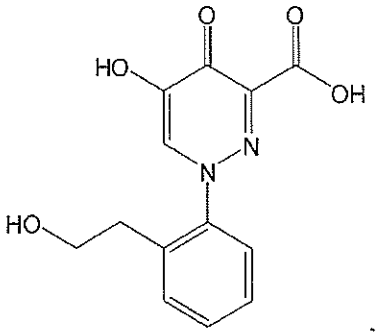


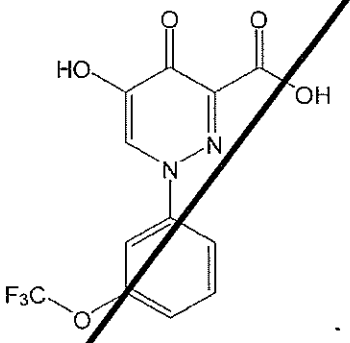


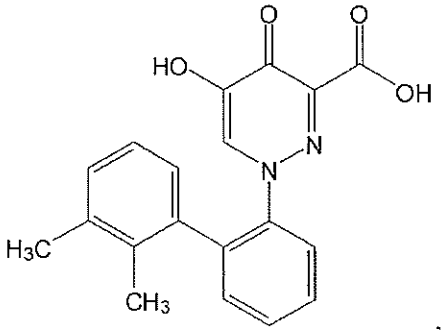


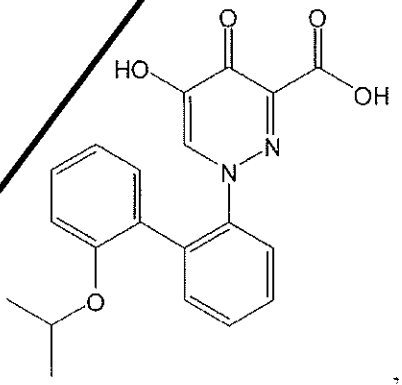


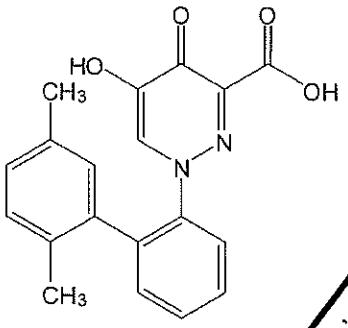


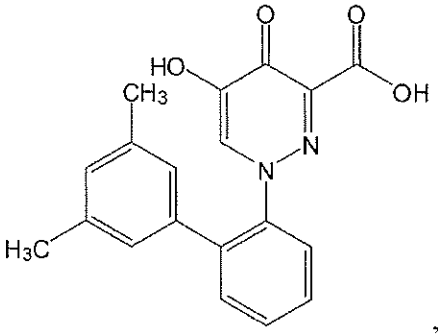


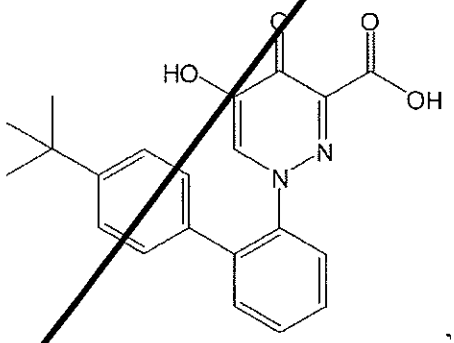


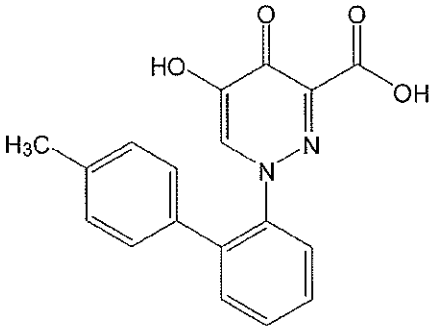


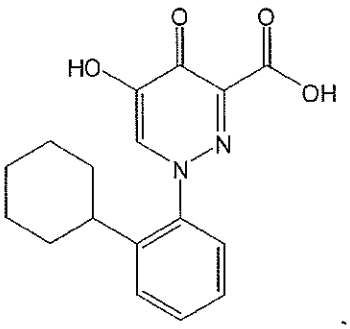


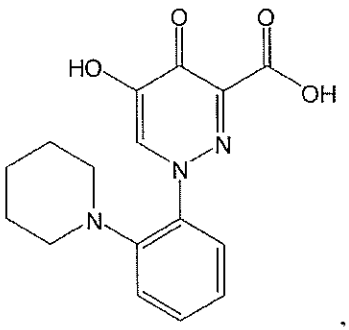


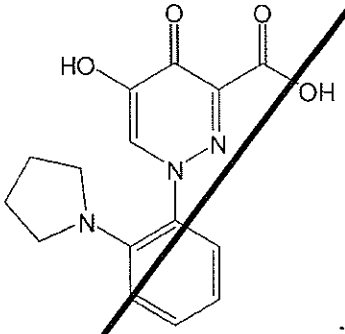


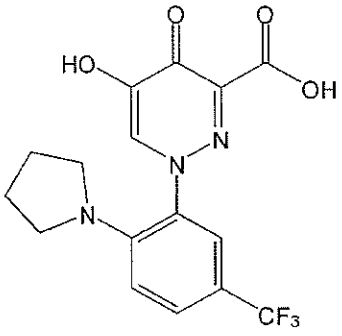


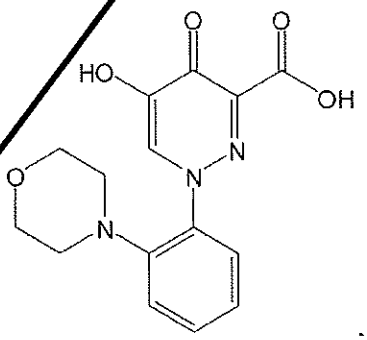


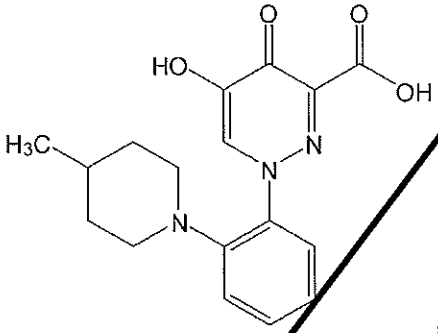


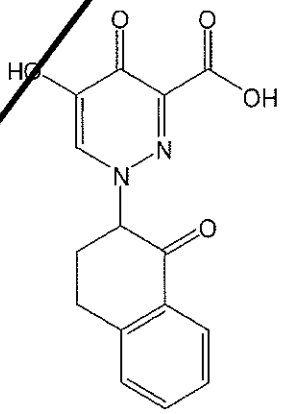


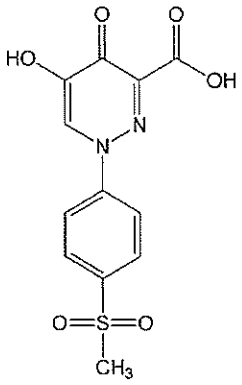


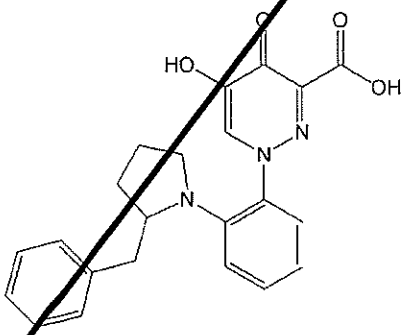


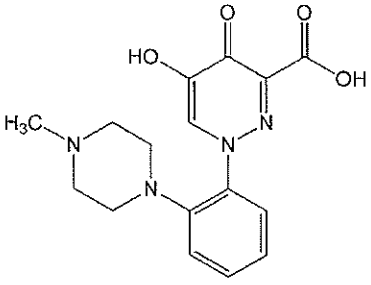


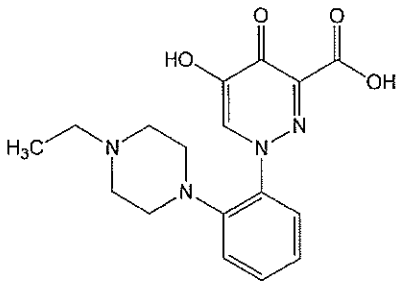


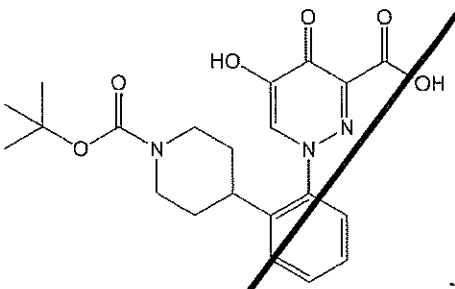


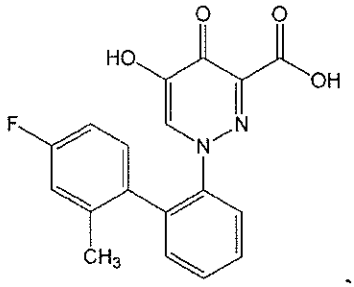


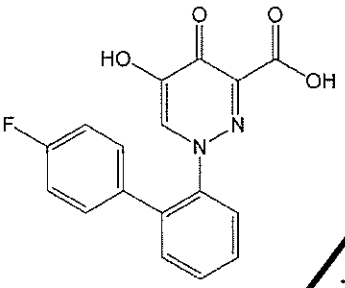


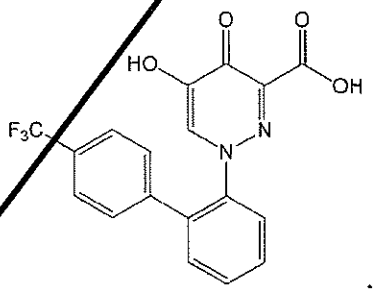


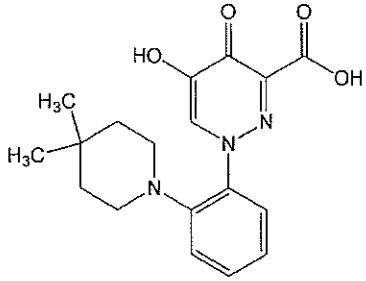


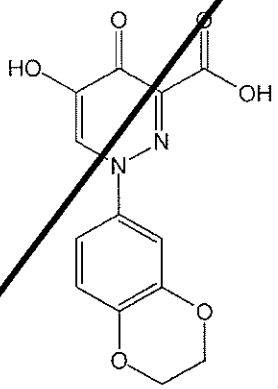


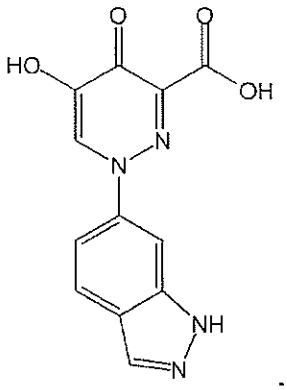


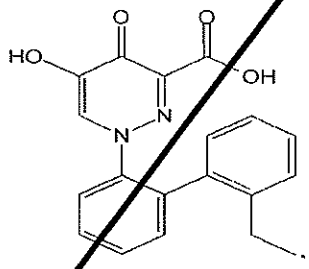


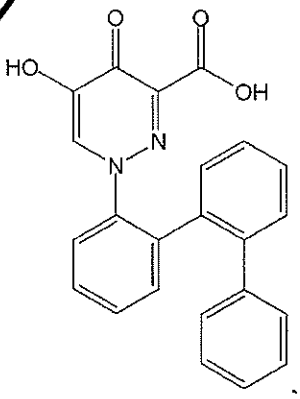


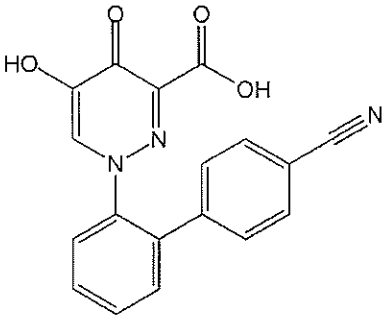


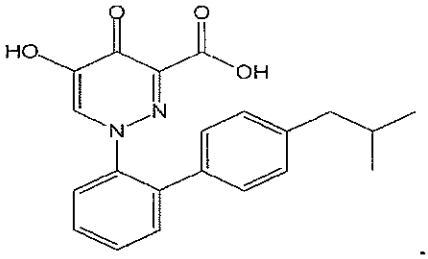
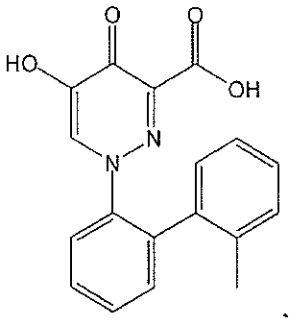
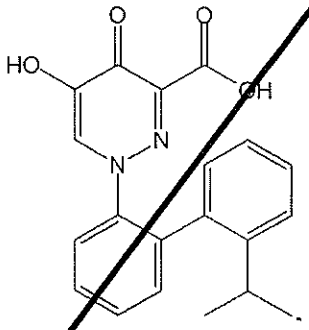
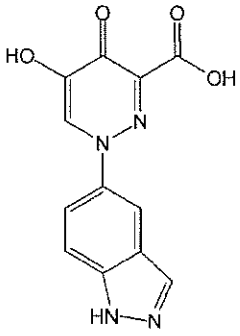
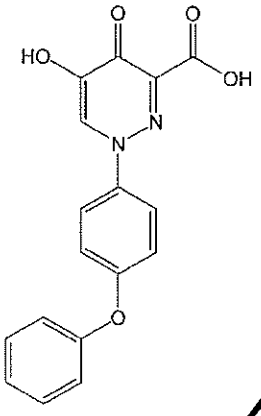
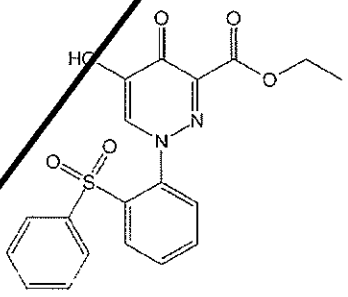
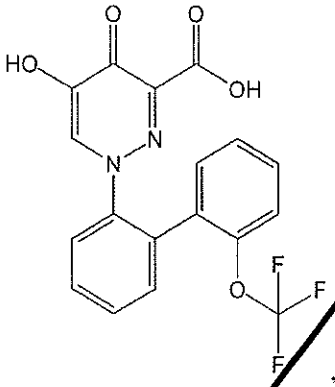




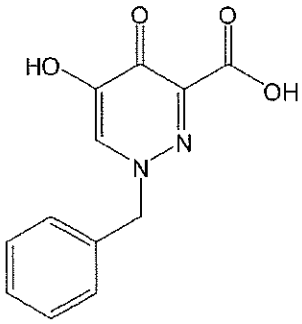


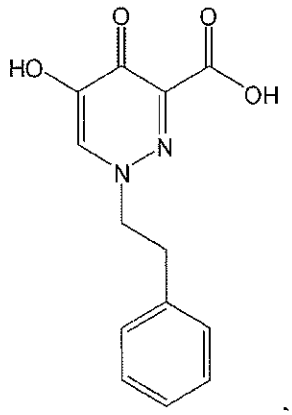


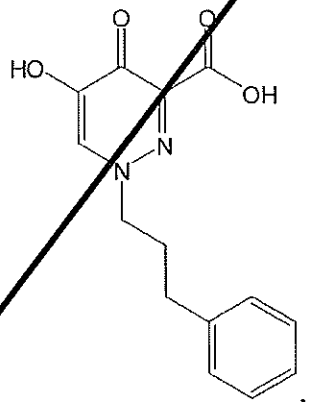


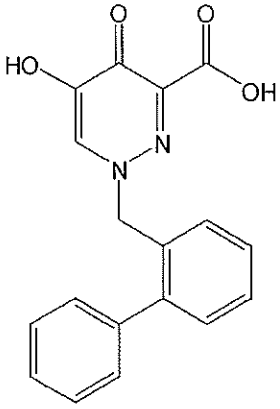






and

, or a pharmaceutically acceptable salt of any of the foregoing.

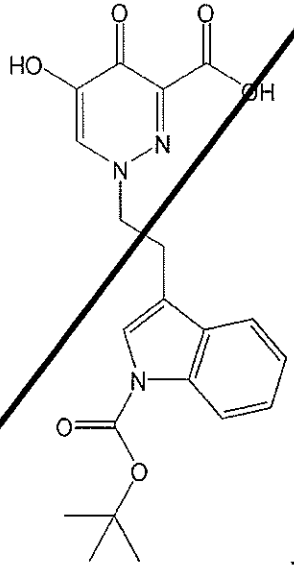
90. The compound of Claim 1, wherein the compound is selected from the group consisting of:

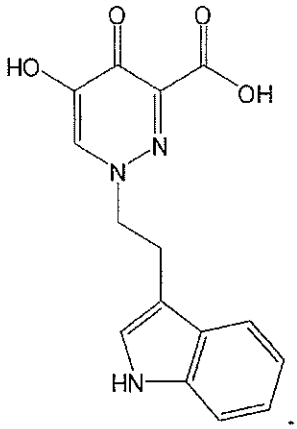


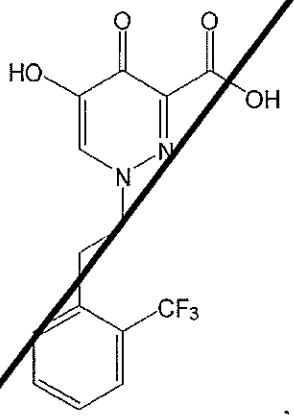


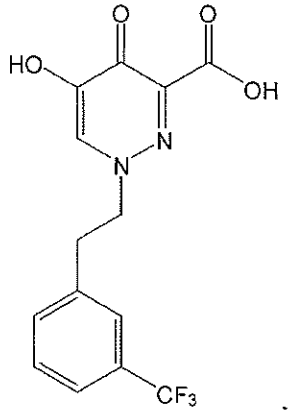


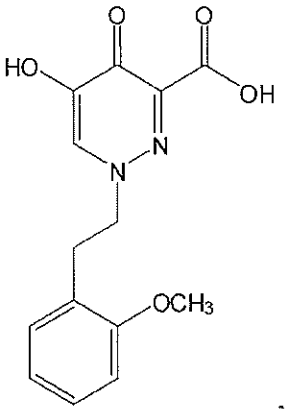


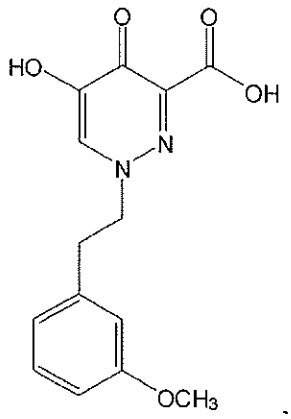


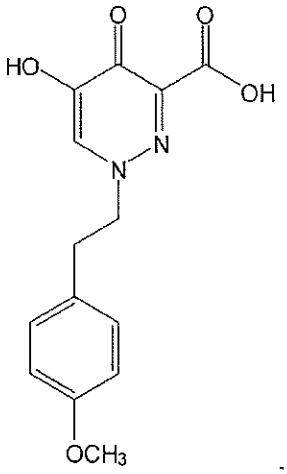


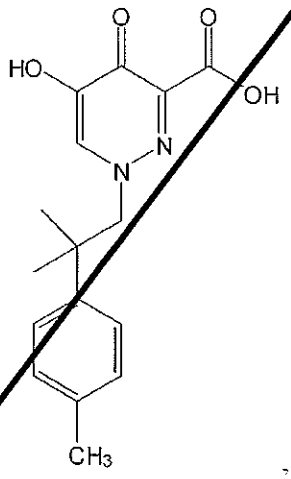


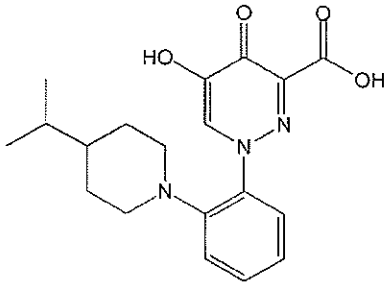


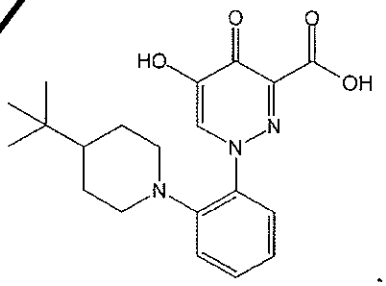


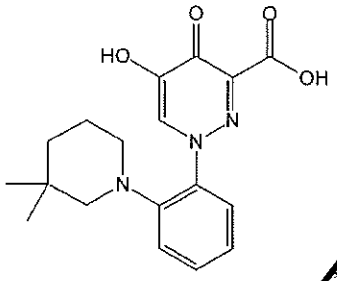


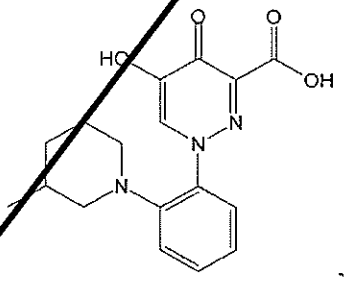


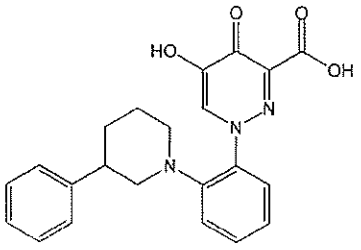


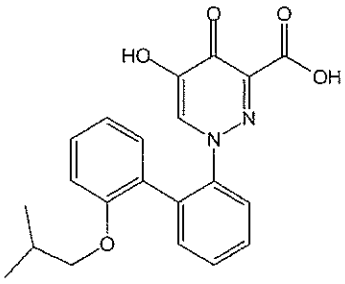
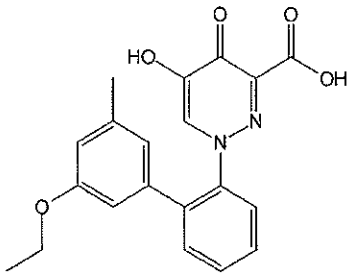
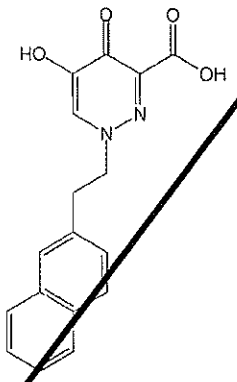


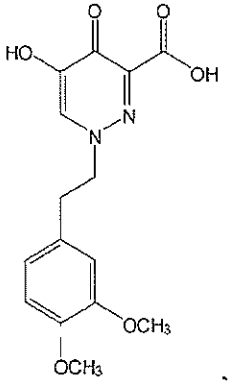




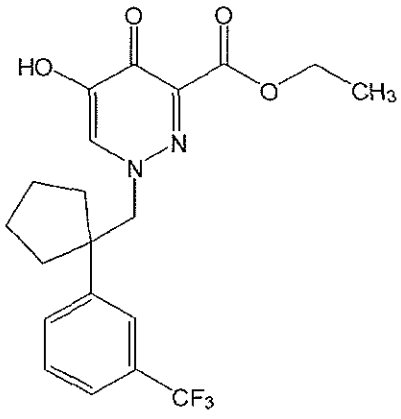
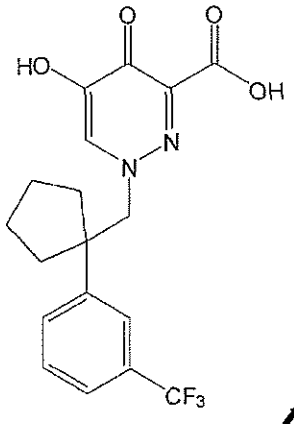
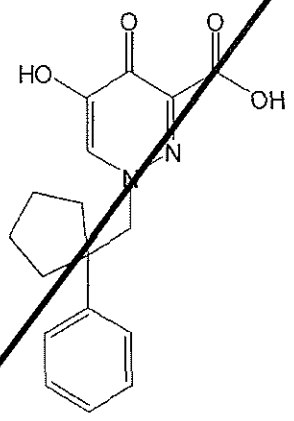
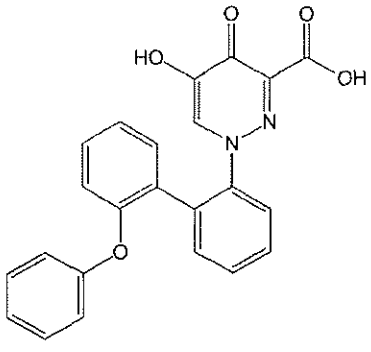
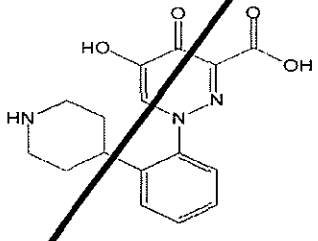
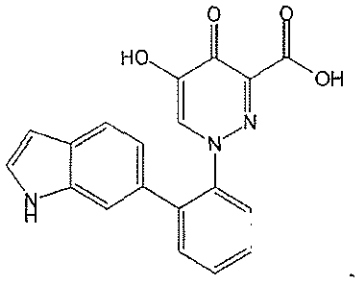
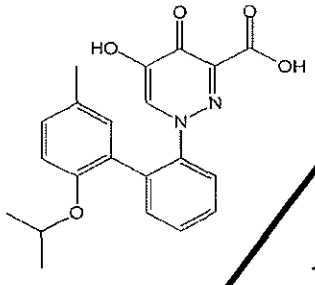
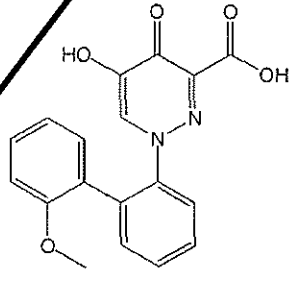
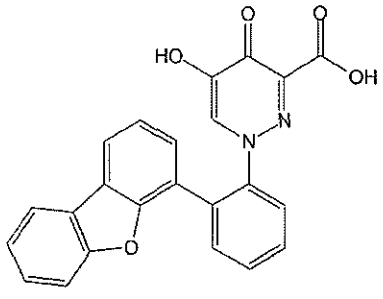
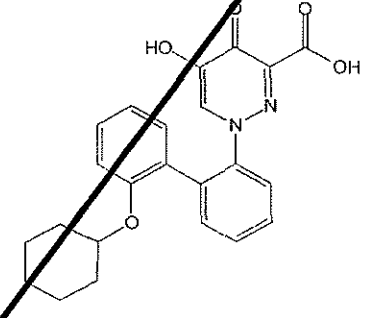
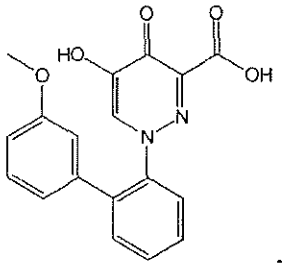
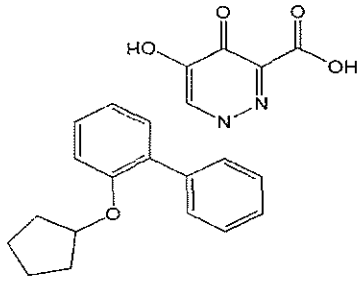


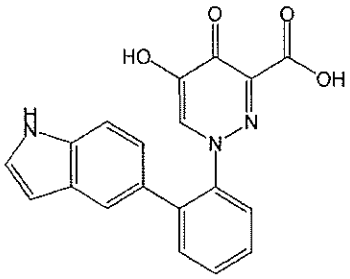
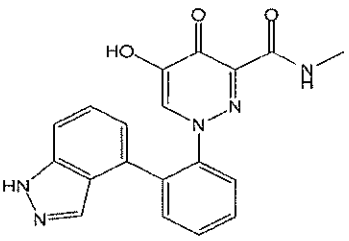
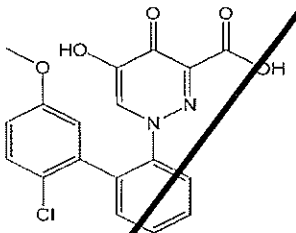
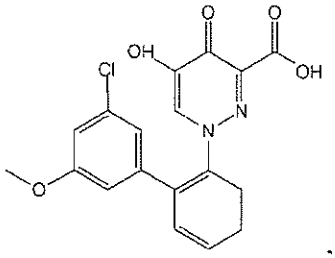
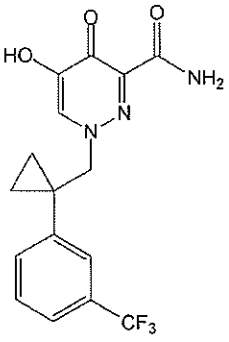
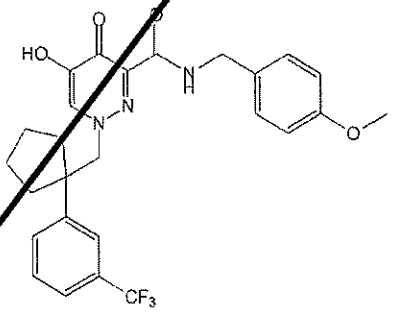
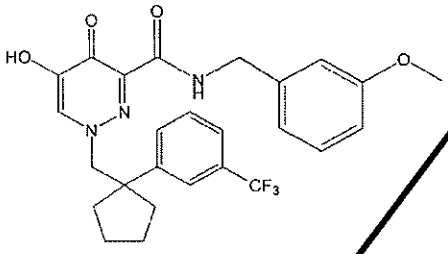
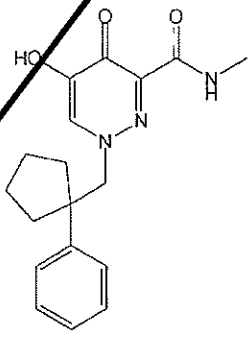
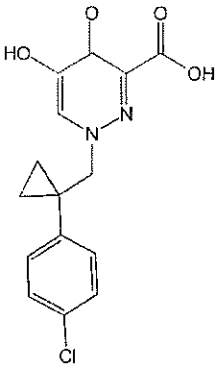
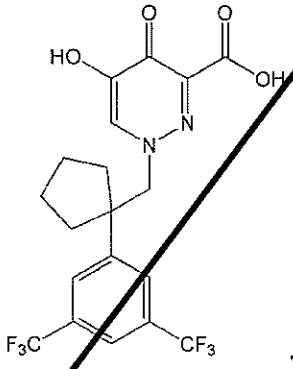





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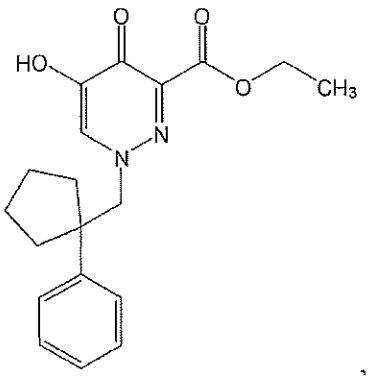

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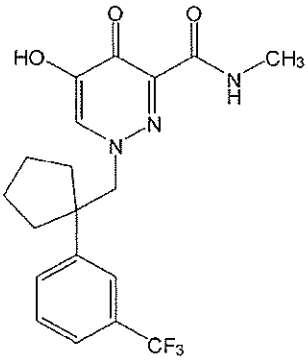
91. The compound of Claim 1, wherein the compound is selected from the group consisting of:

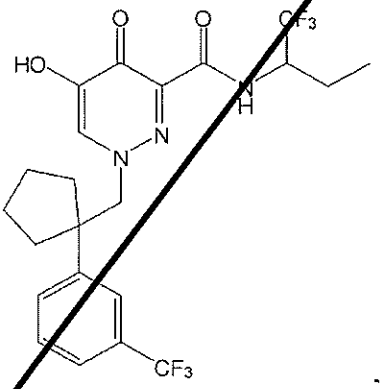













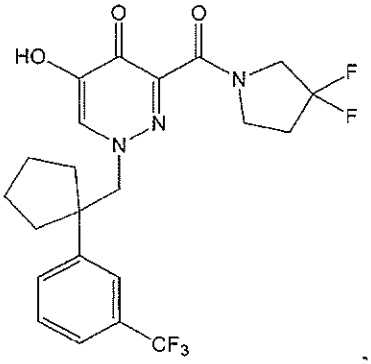









and

, or a pharmaceutically acceptable salt of any of the foregoing.

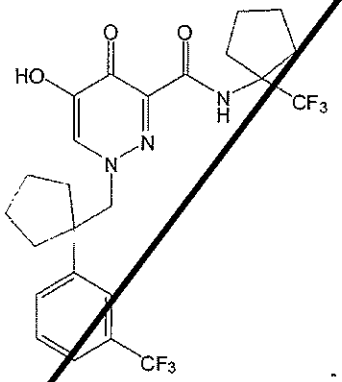
92. The compound of Claim 1, wherein the compound is selected from the group consisting of:

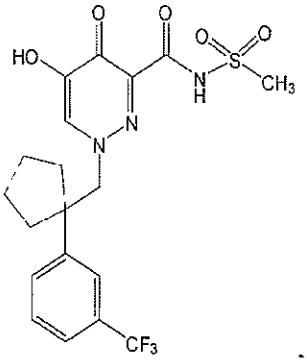


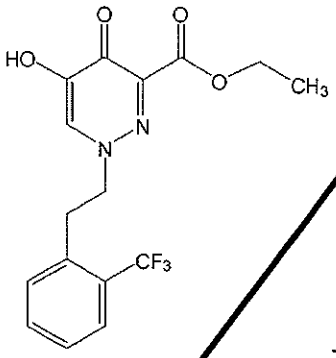


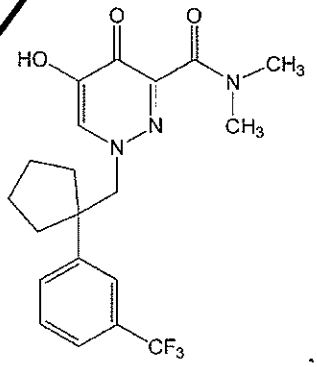


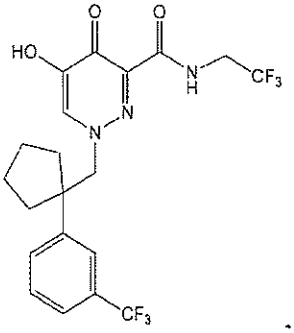


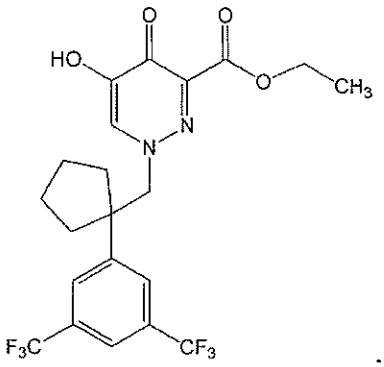


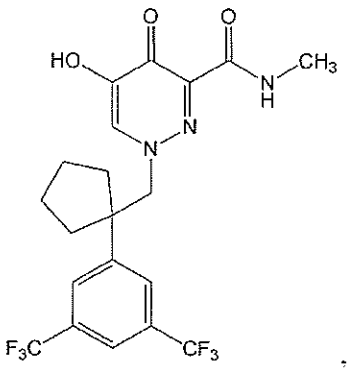


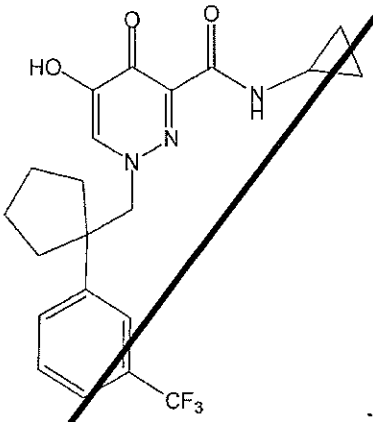


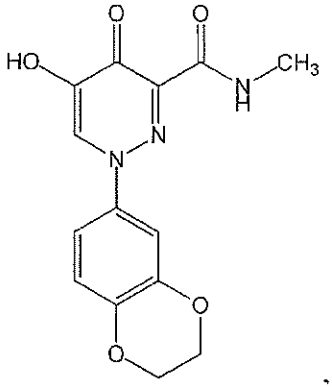


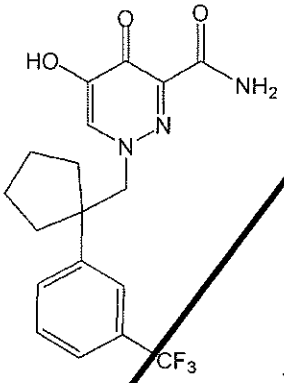


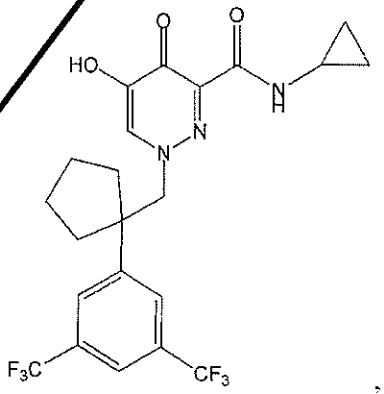


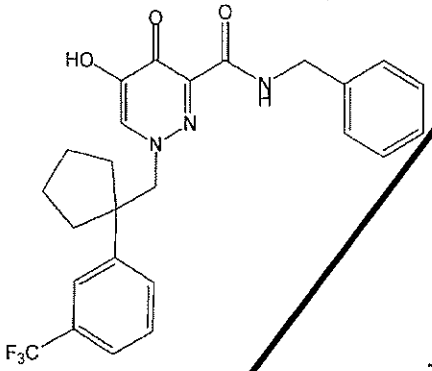


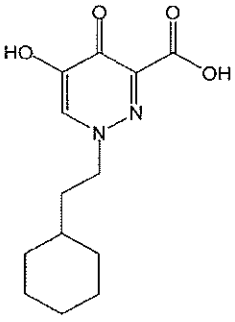


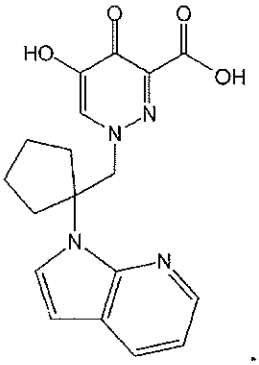


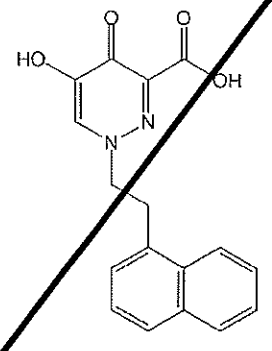


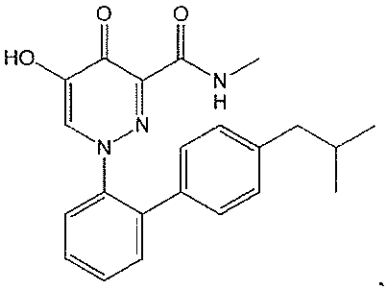


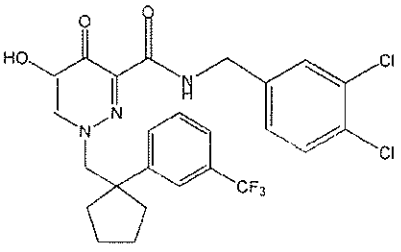


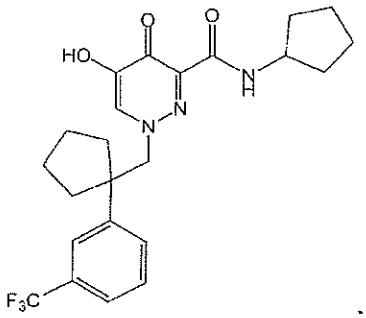
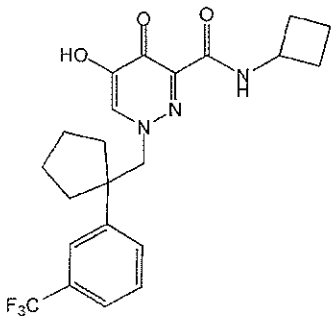
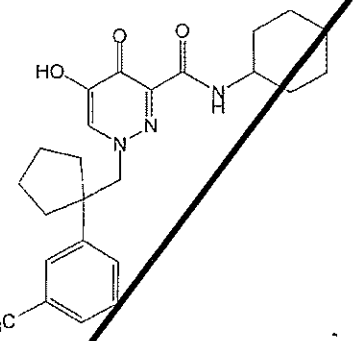
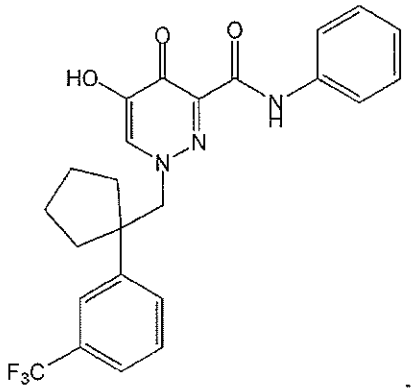
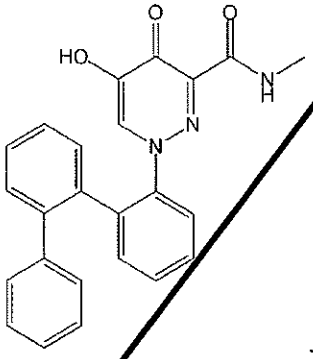
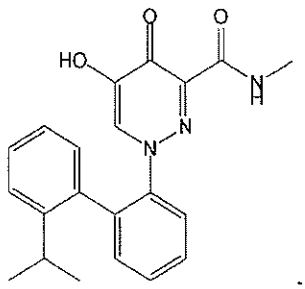
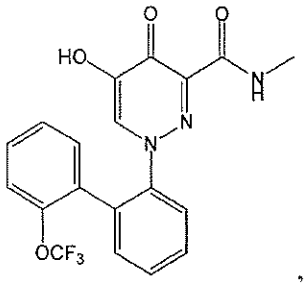
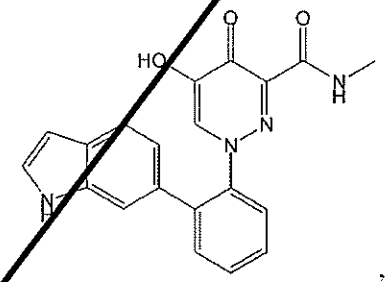
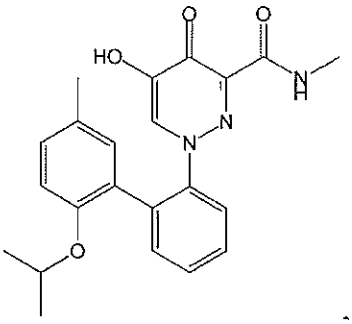
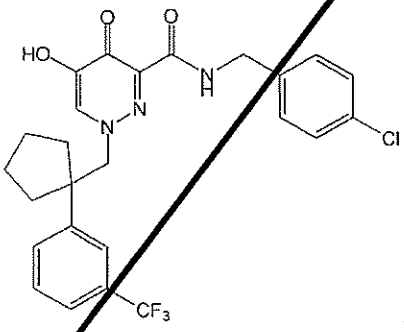
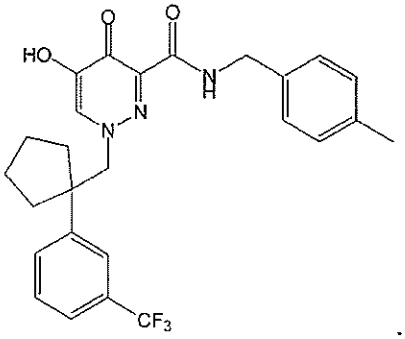
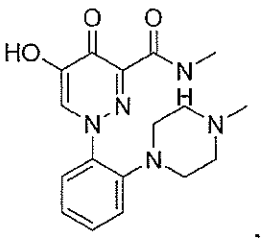


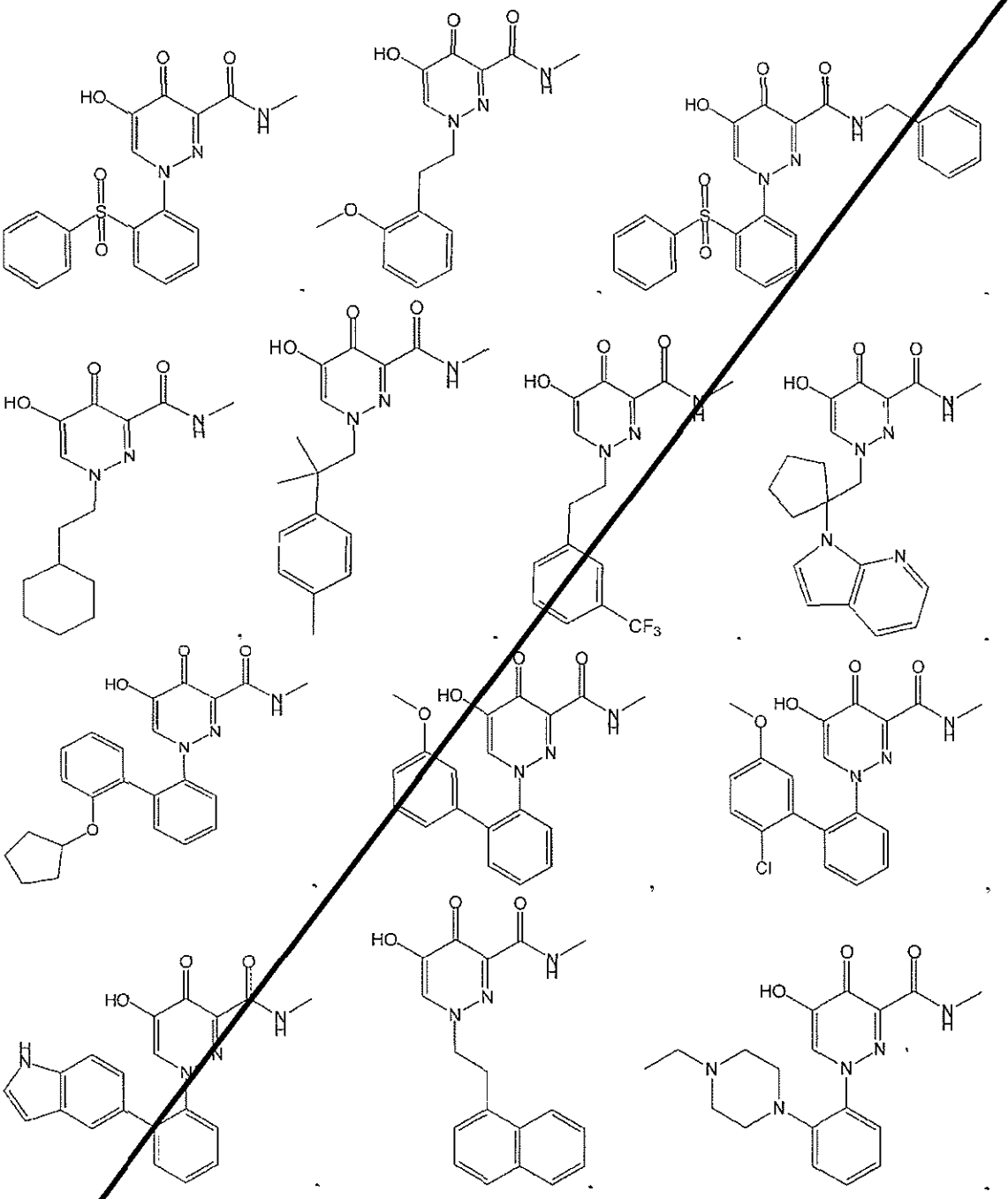


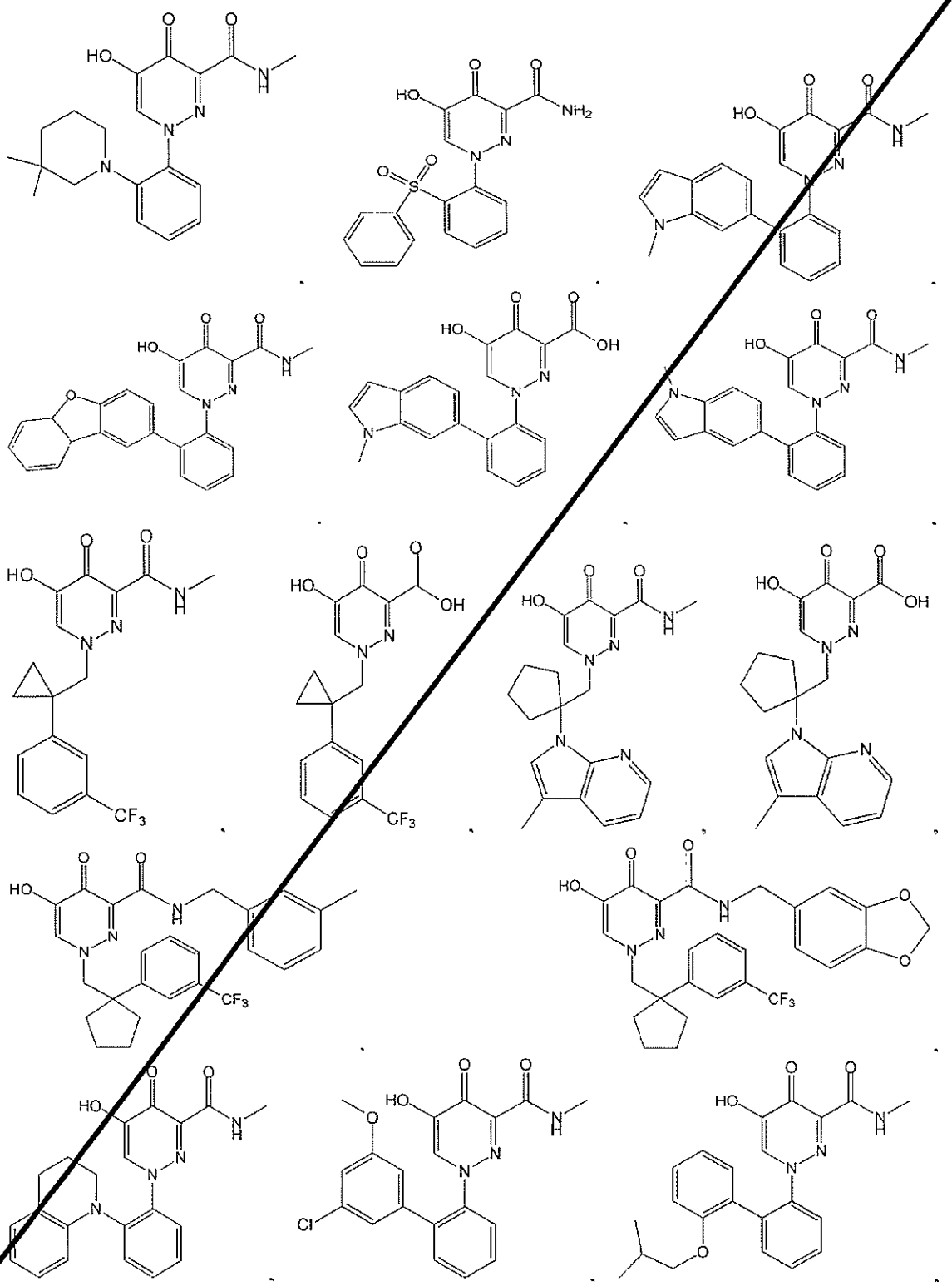


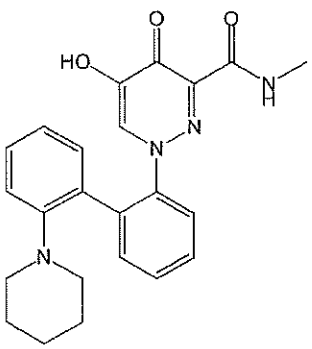
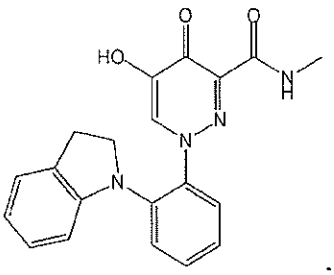
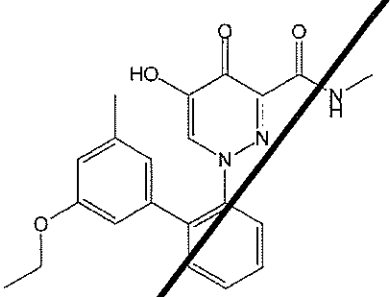
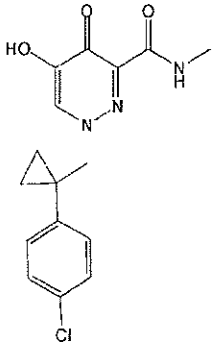
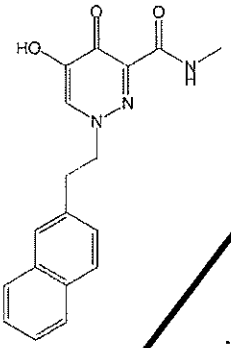
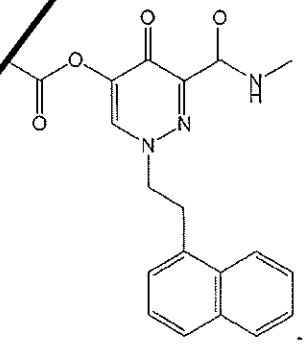
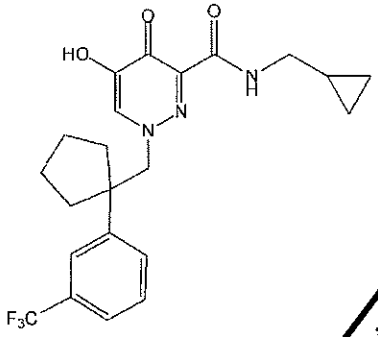
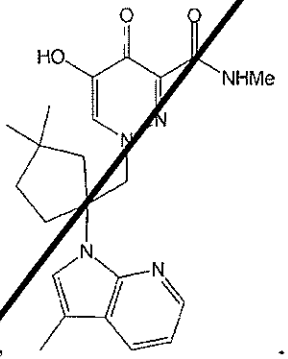
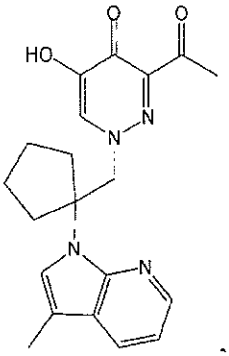
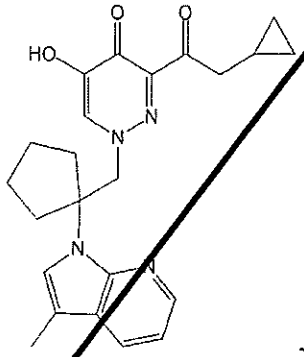
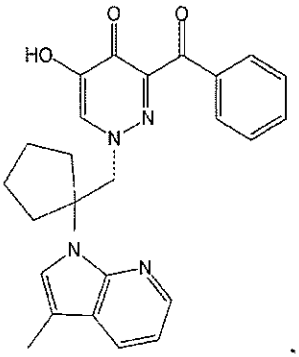
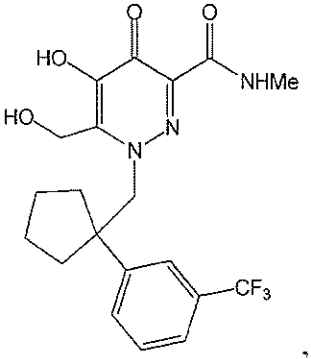


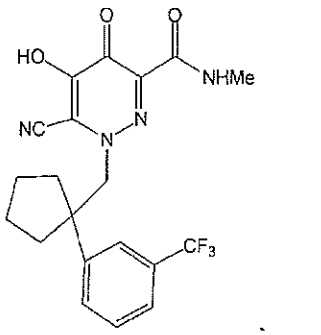
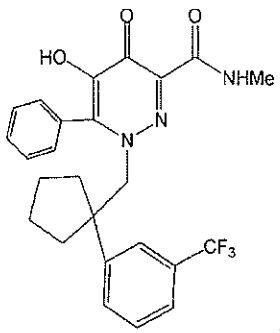
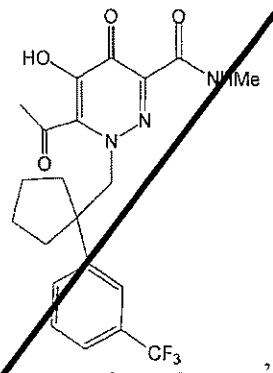
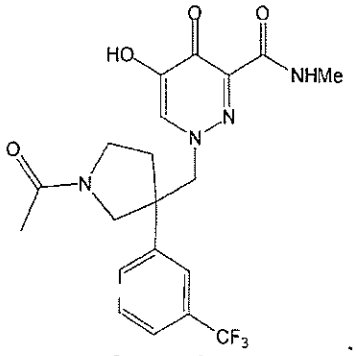
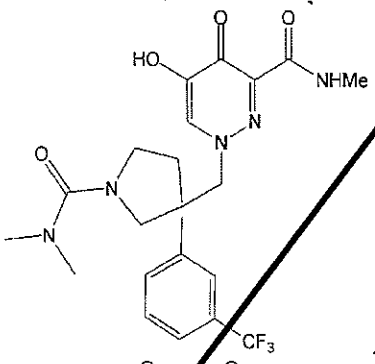
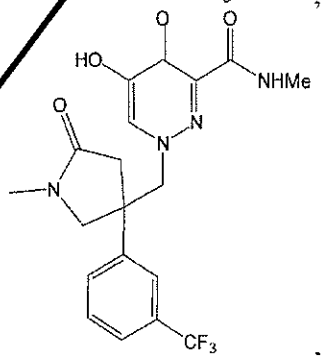
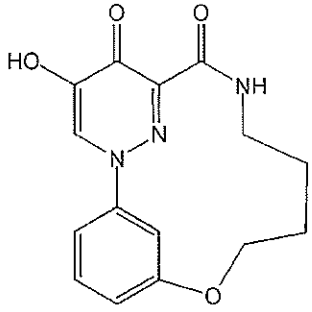
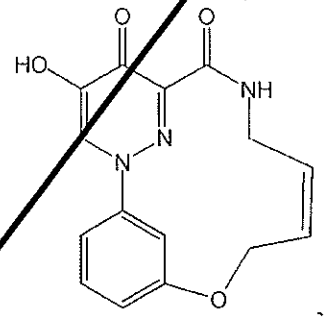
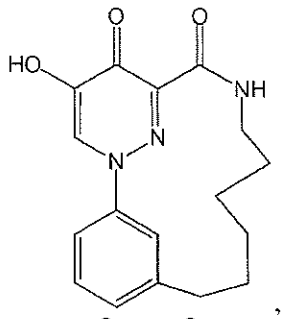
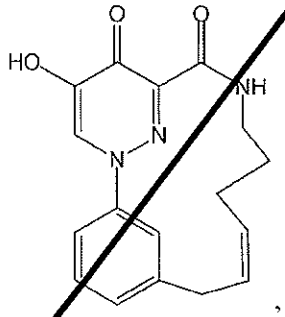
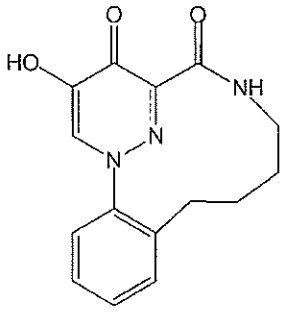
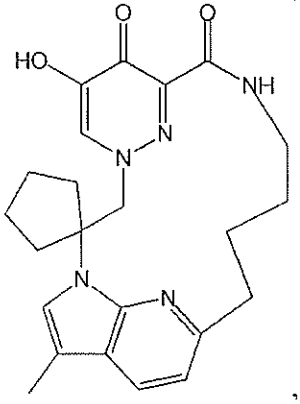


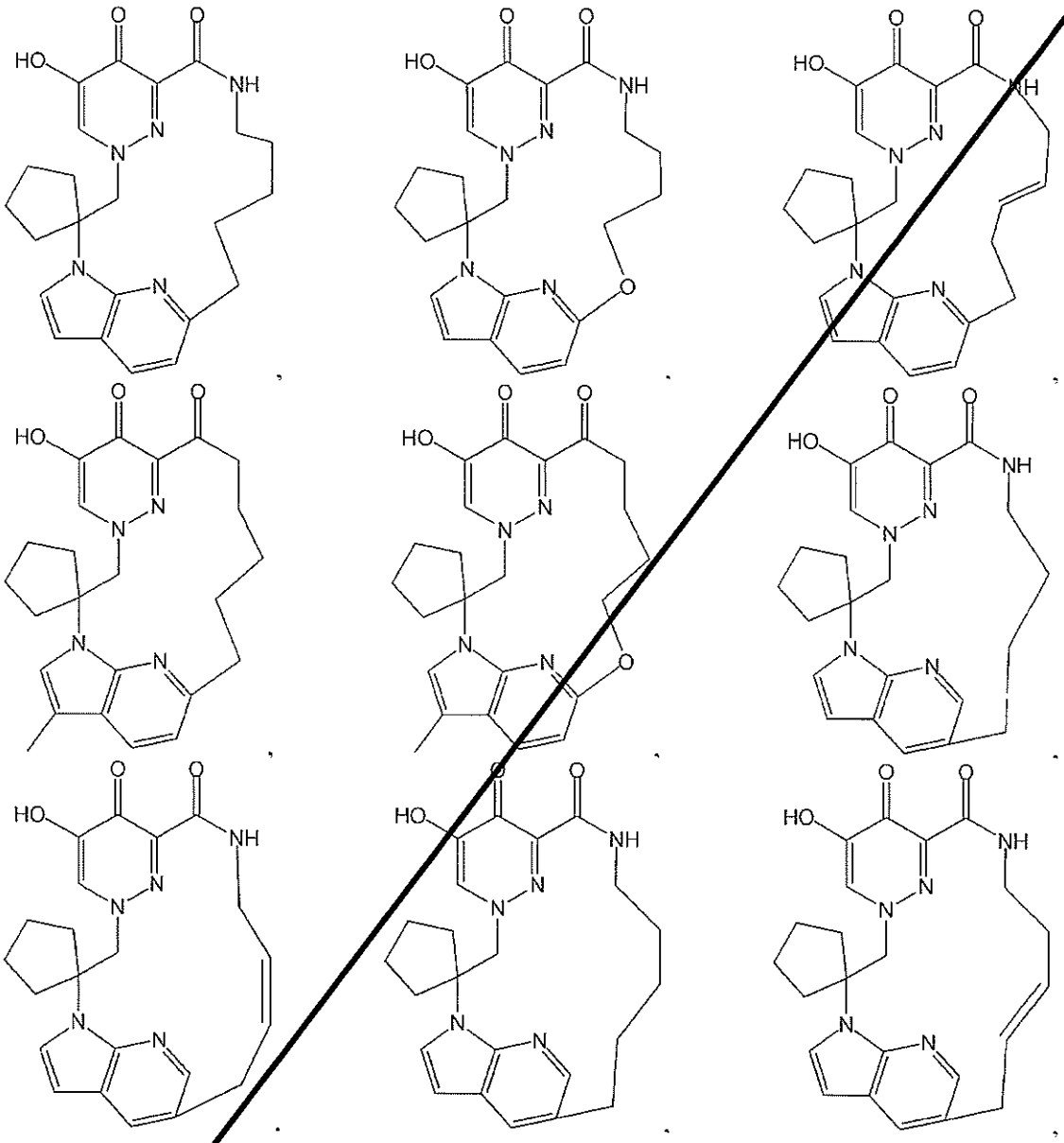













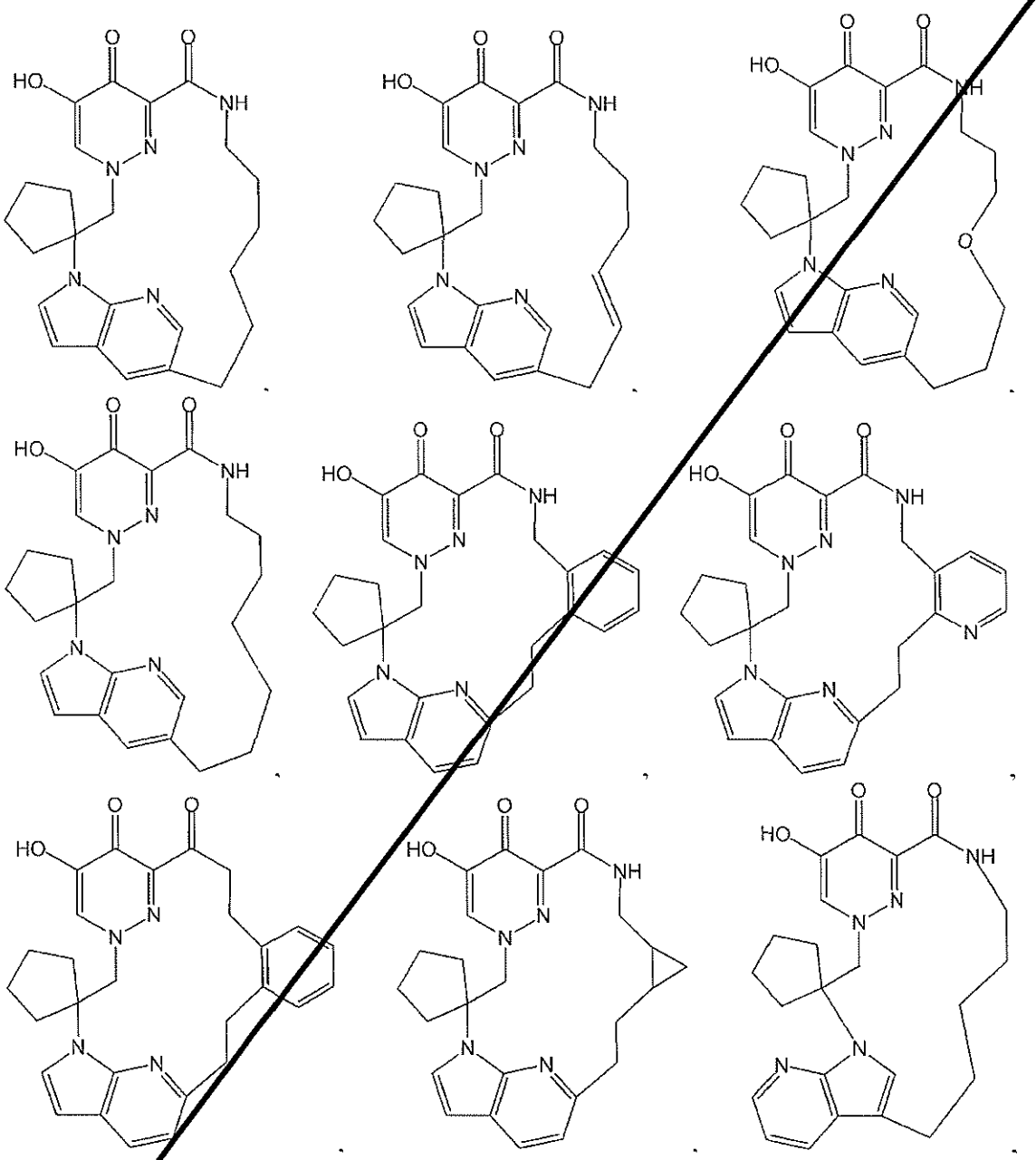


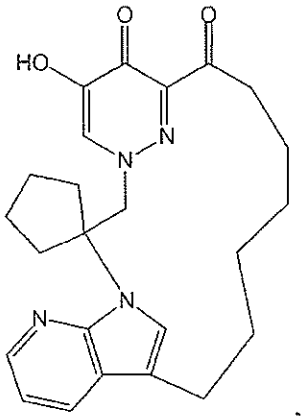
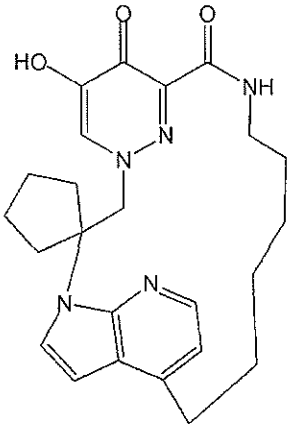
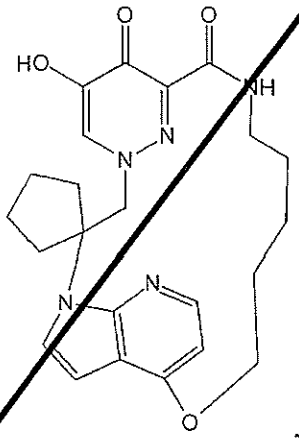
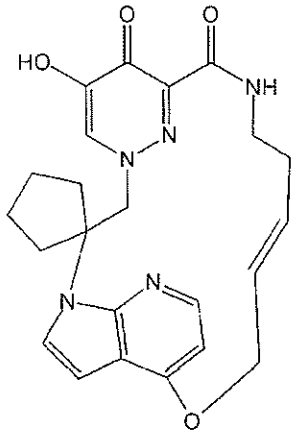
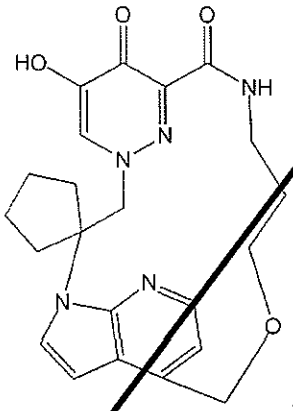


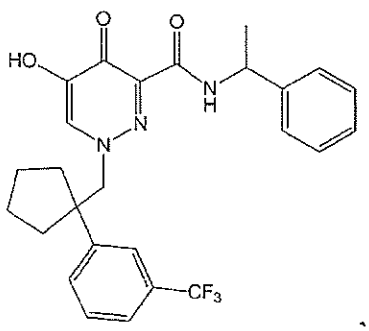
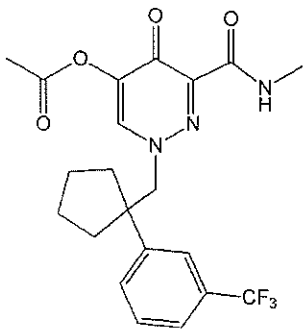
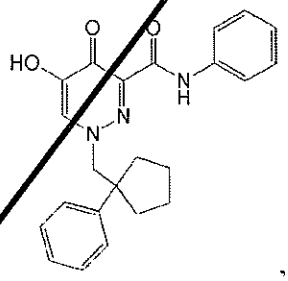
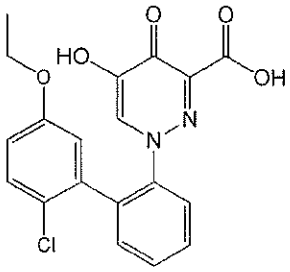
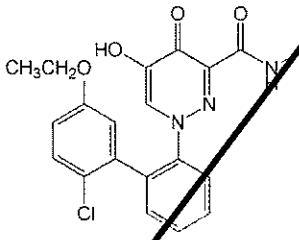
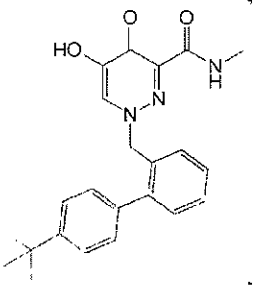
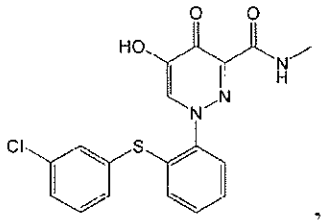
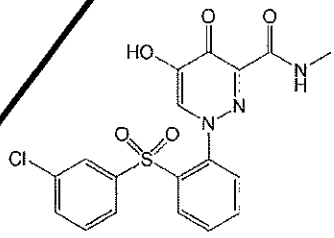
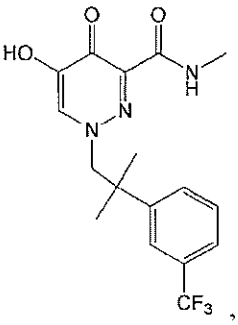
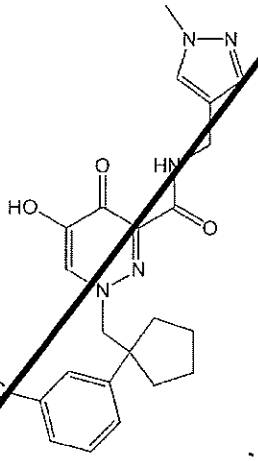
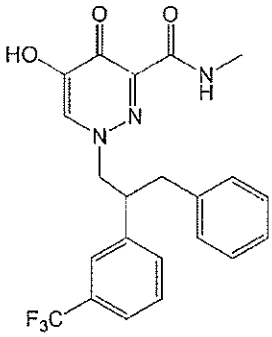
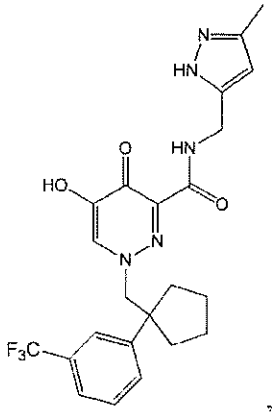


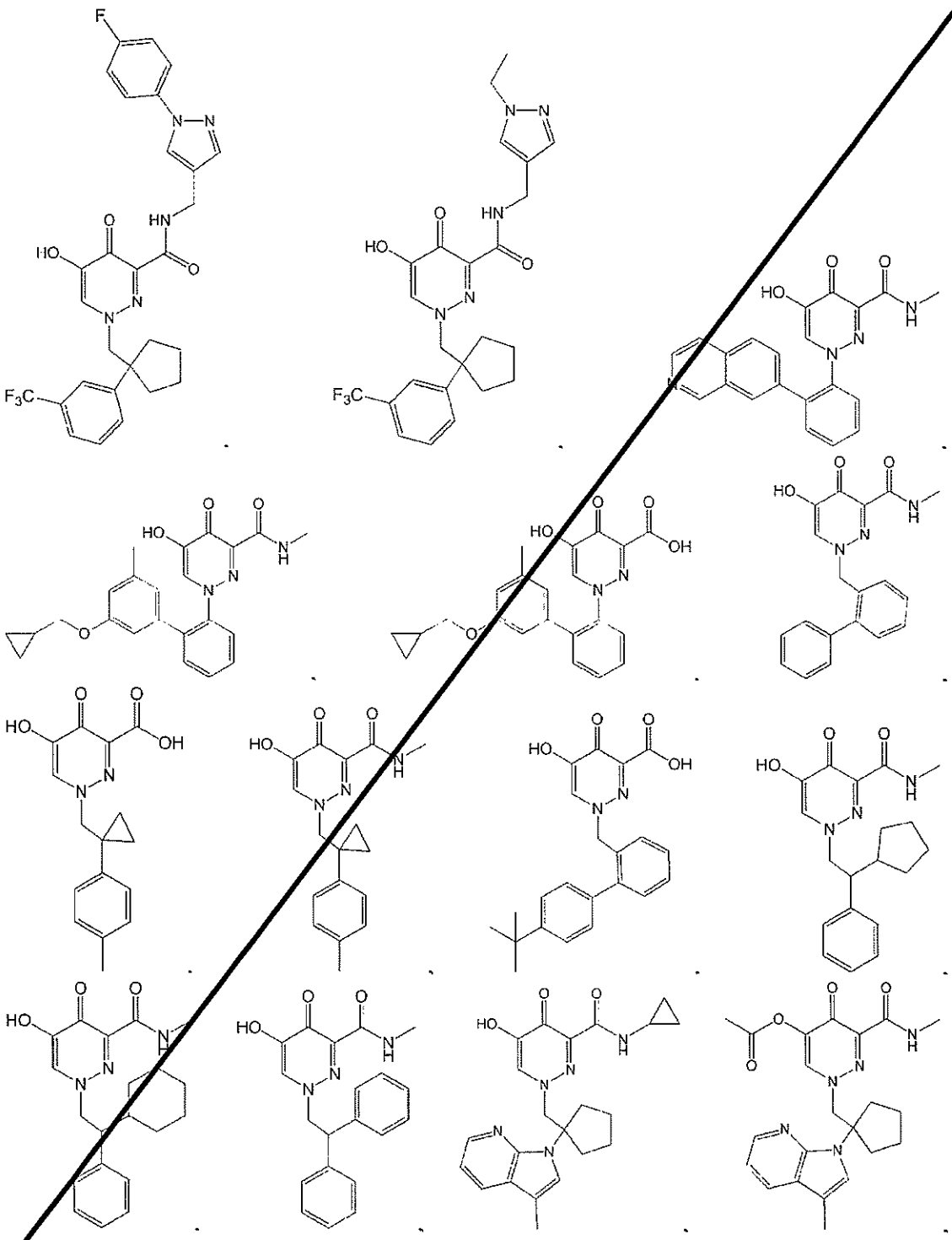


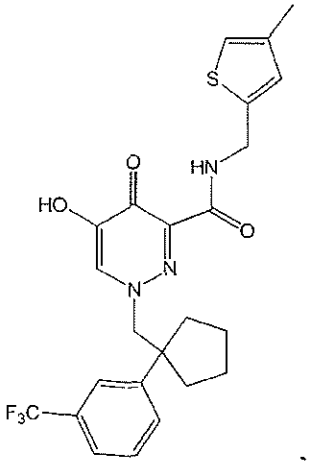






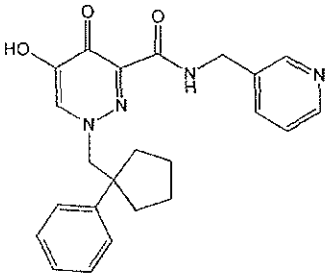
, and , or a pharmaceutically acceptable salt of any of the foregoing.

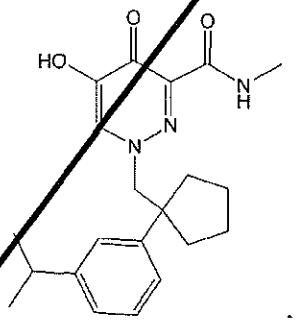
93. The compound of Claim 1, wherein the compound is selected from the group consisting of:

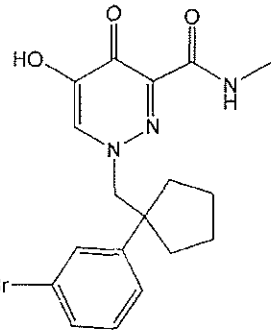













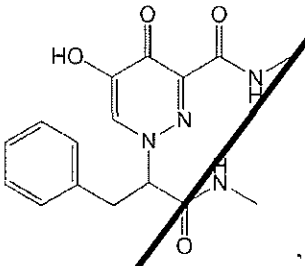


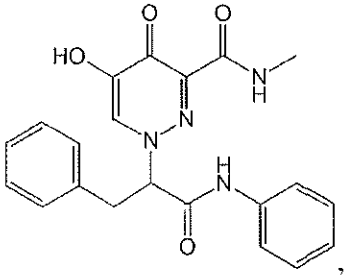


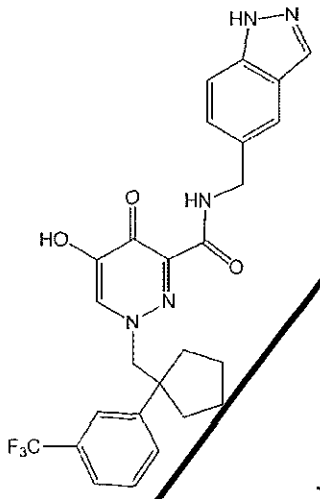


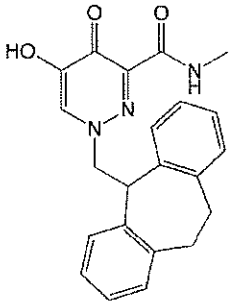


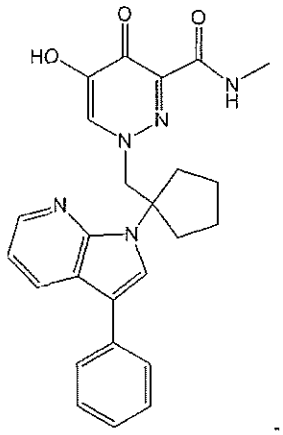


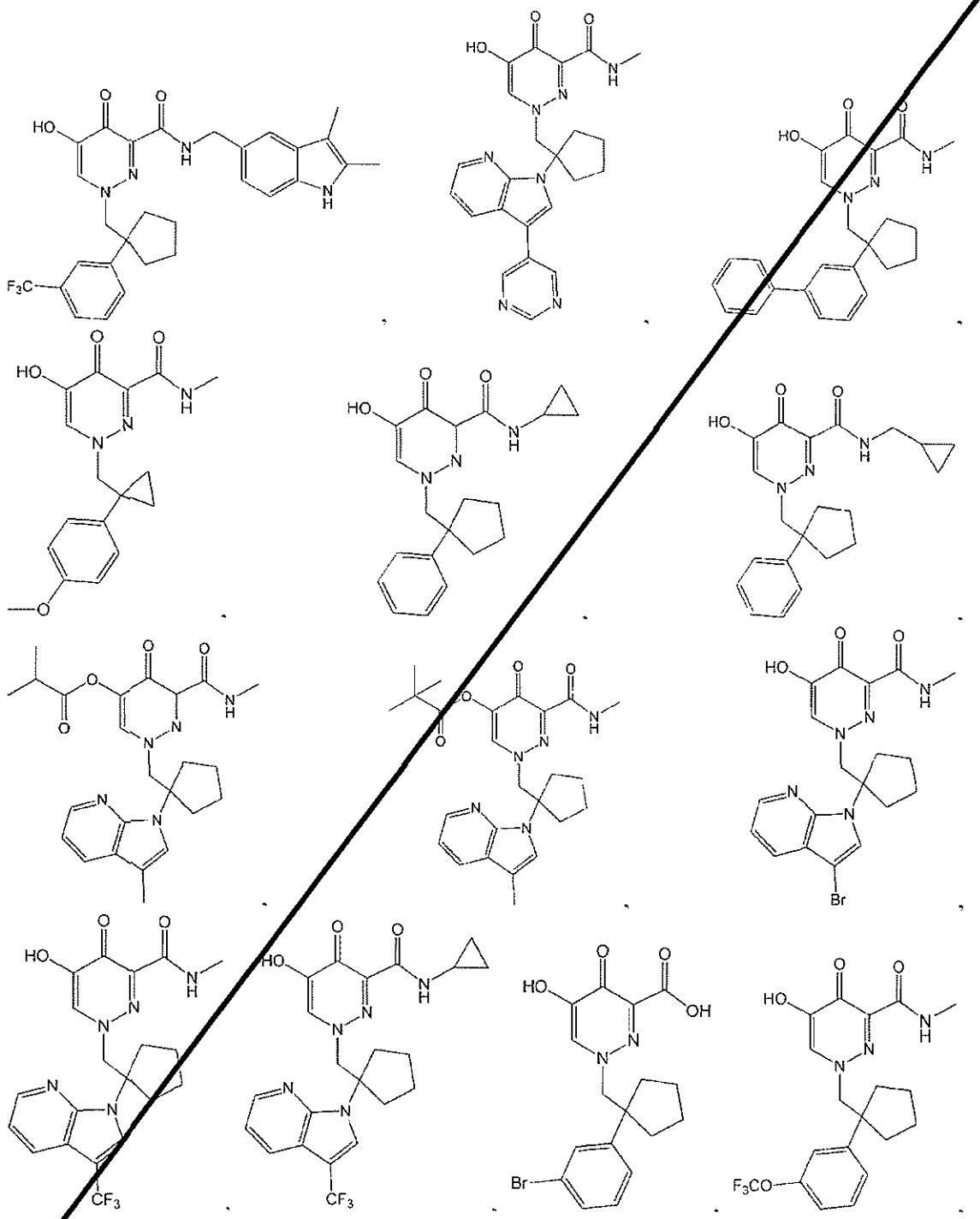


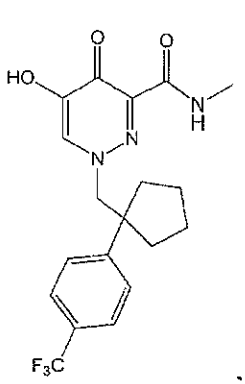
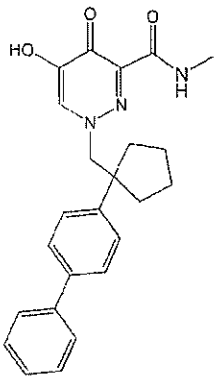
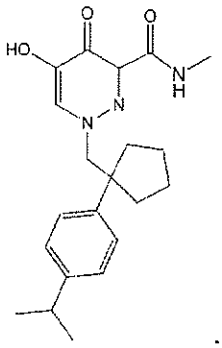
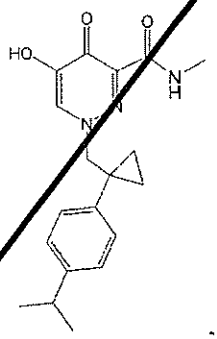
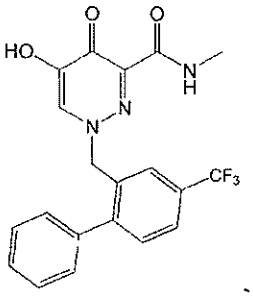
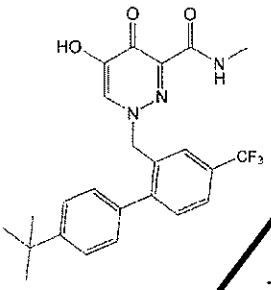
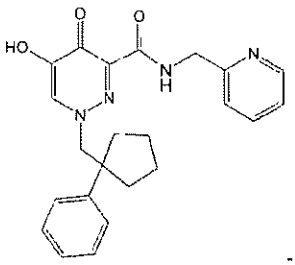
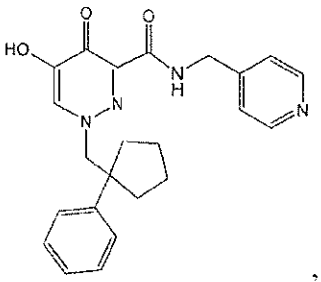
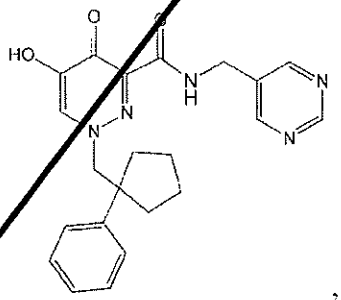
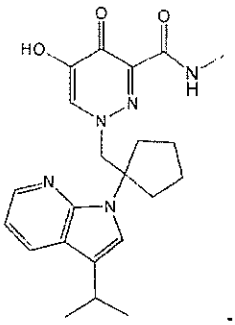
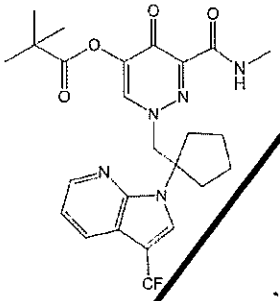
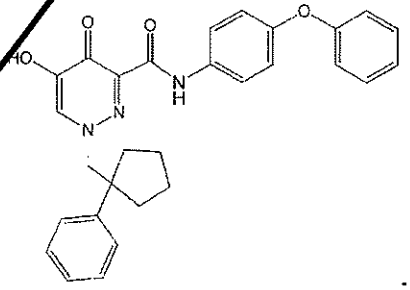
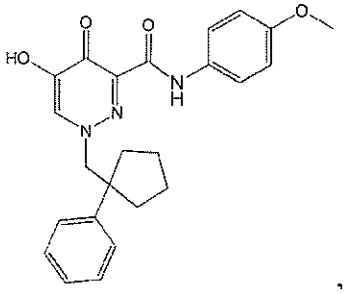


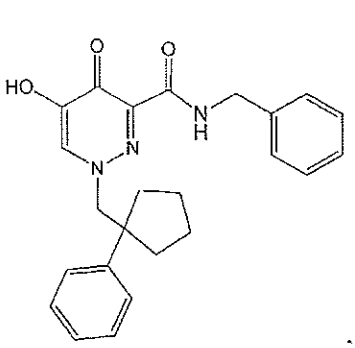
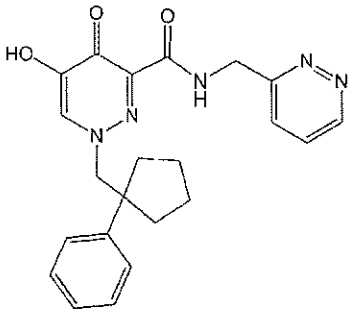
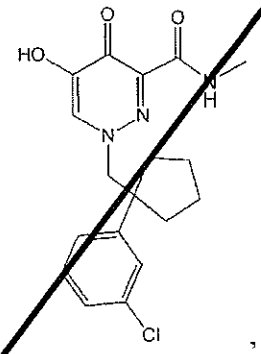
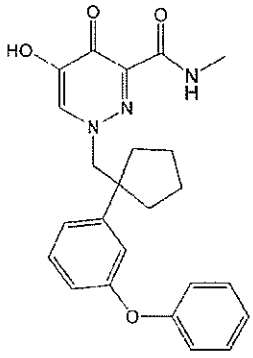
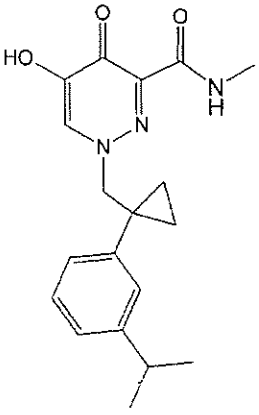
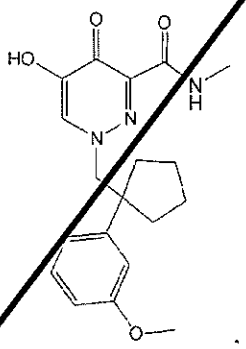
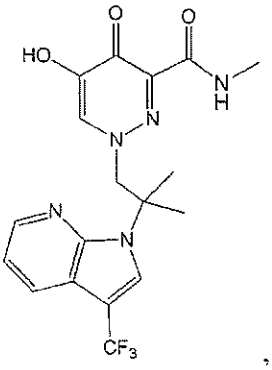
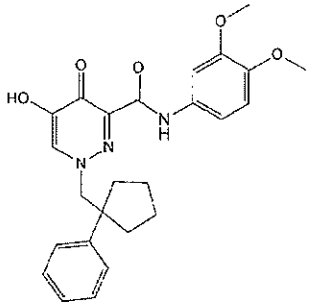
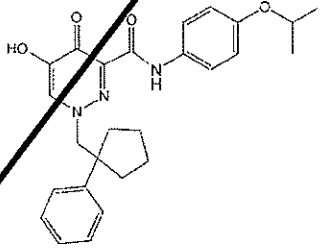
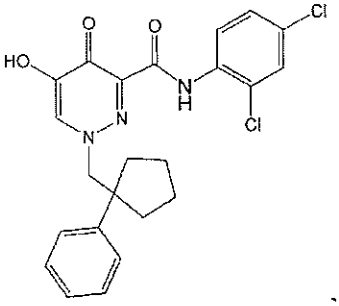
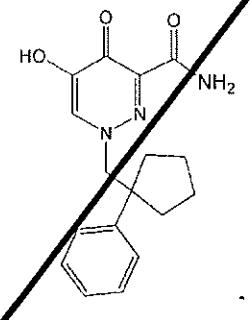
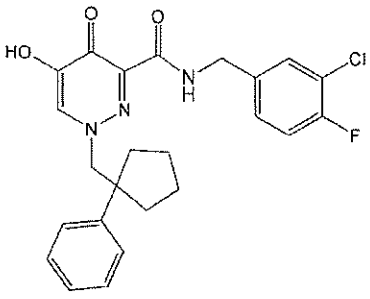
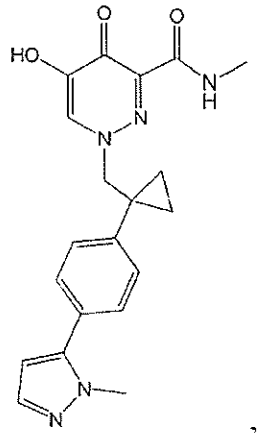


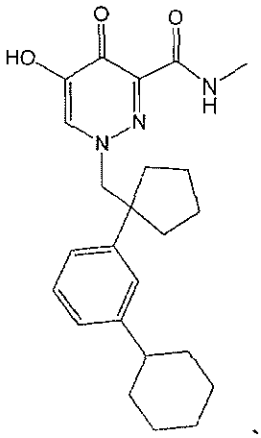
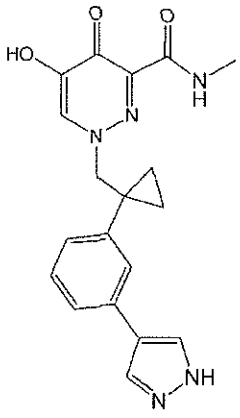
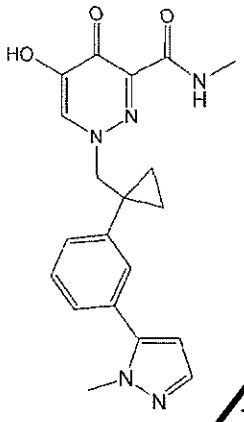
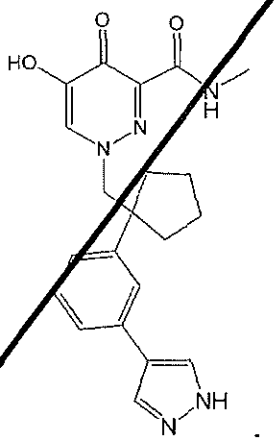
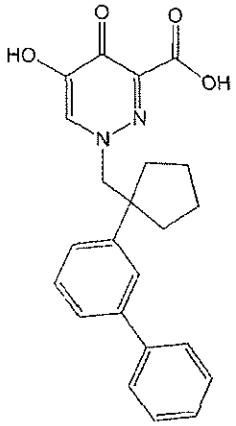
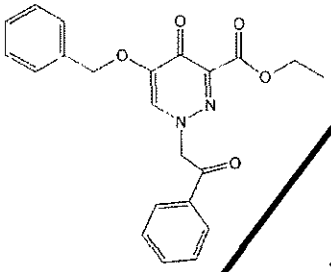
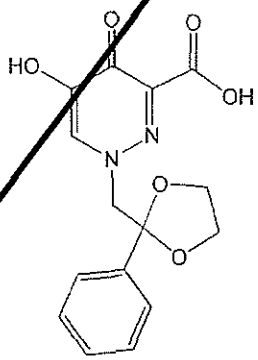
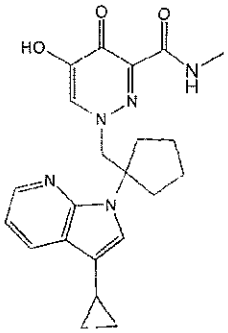
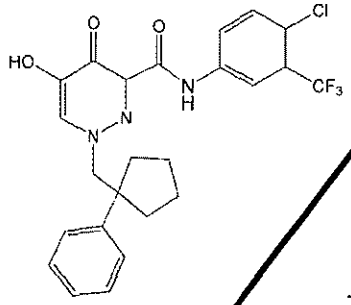
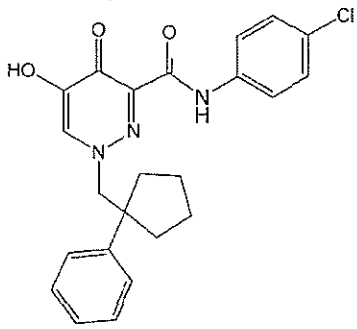
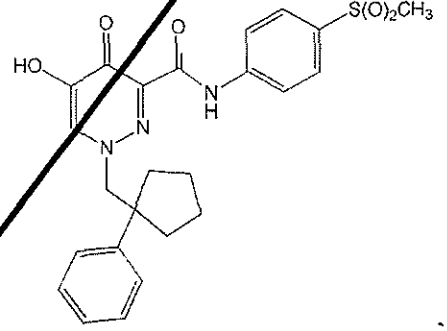
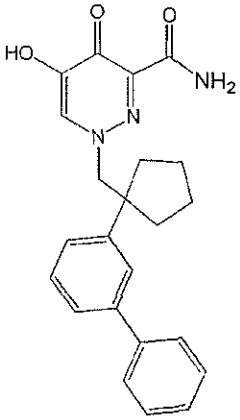
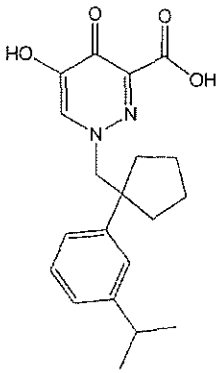


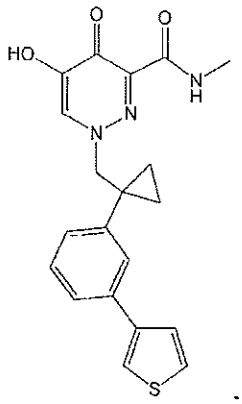
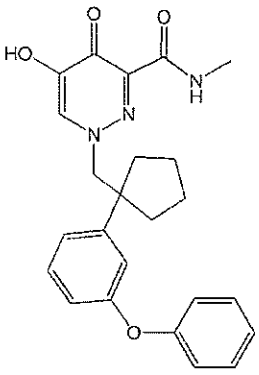
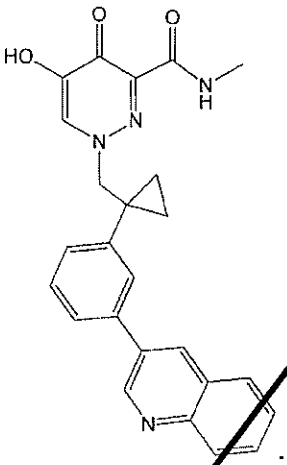
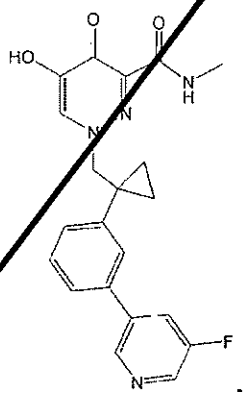
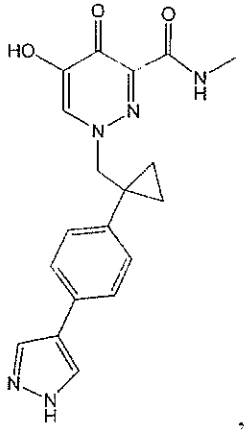
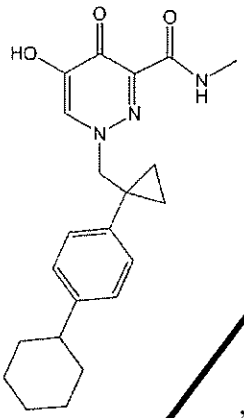
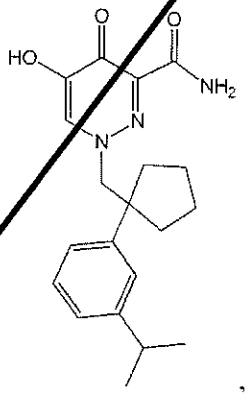
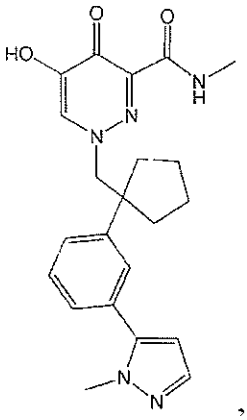
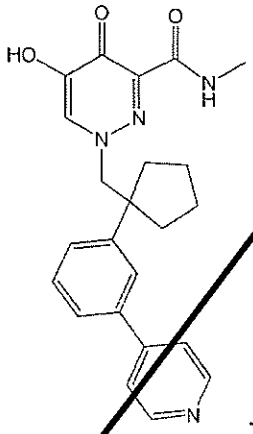
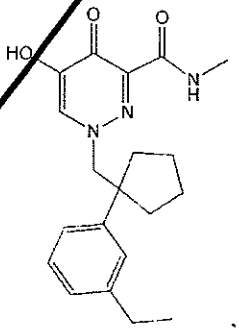
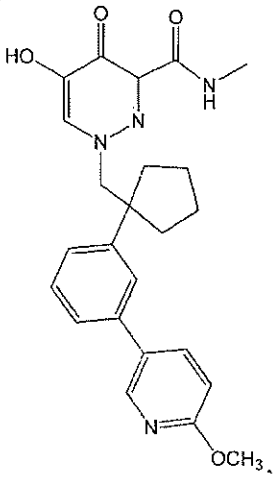
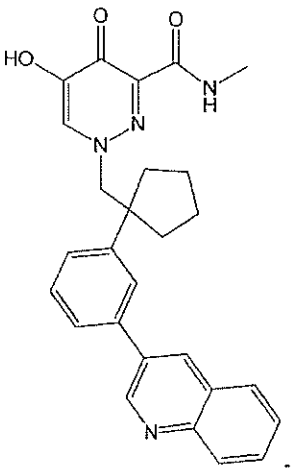


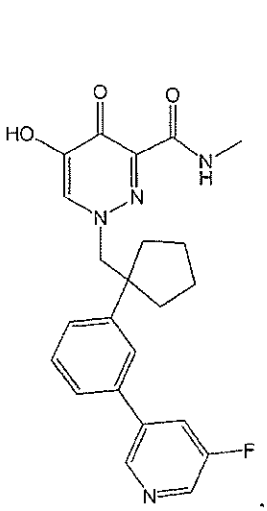


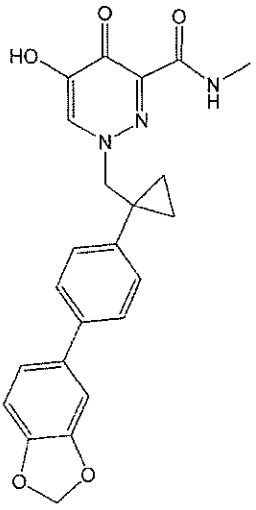














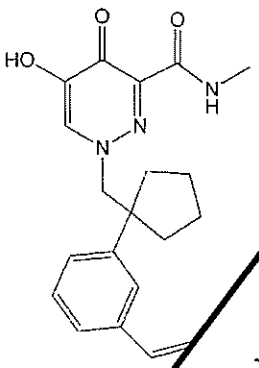














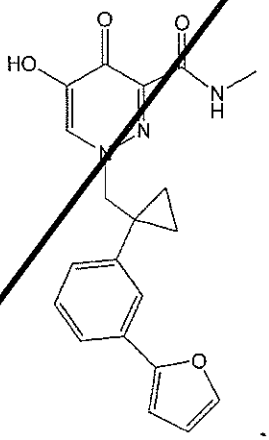














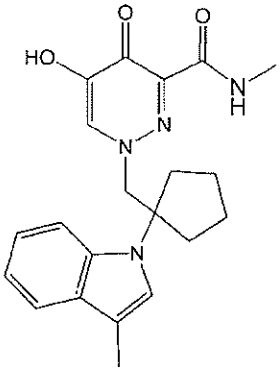













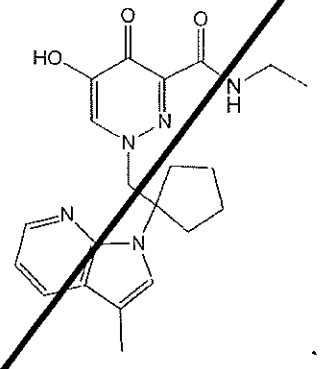


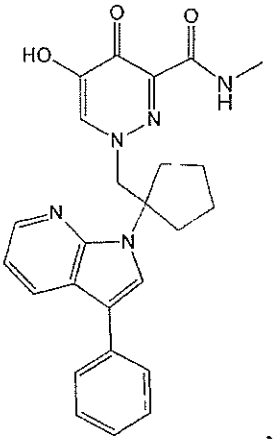


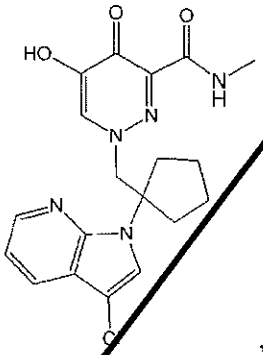


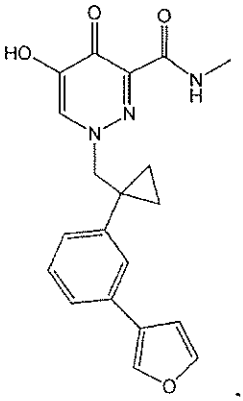


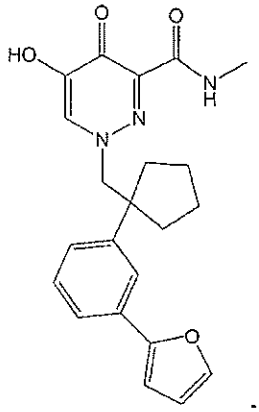


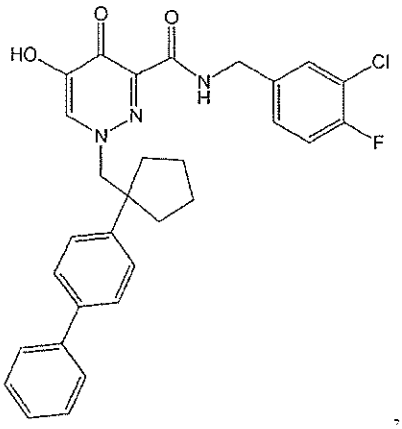


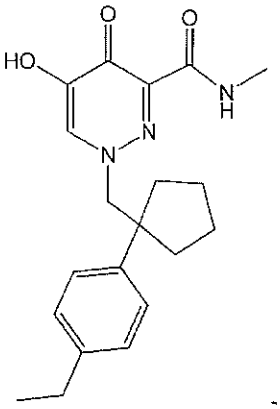


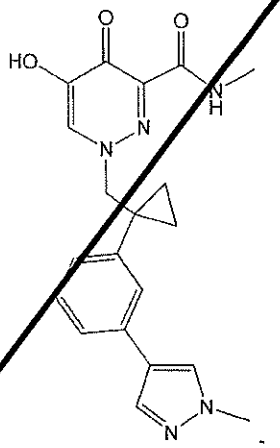


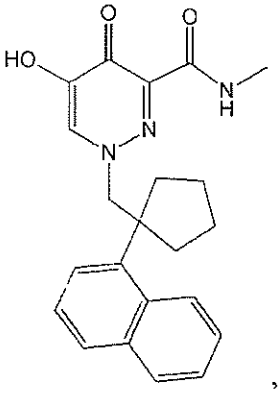


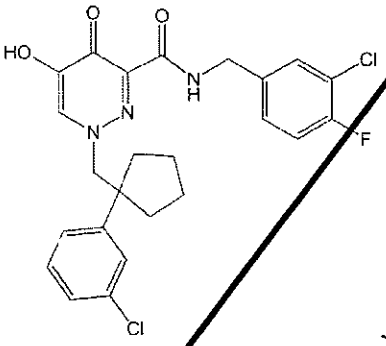


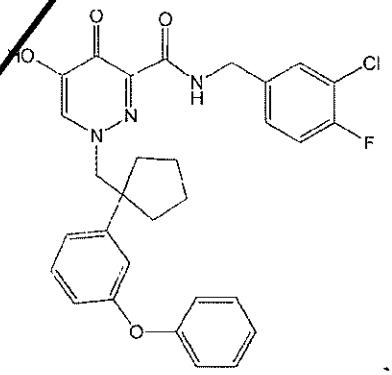


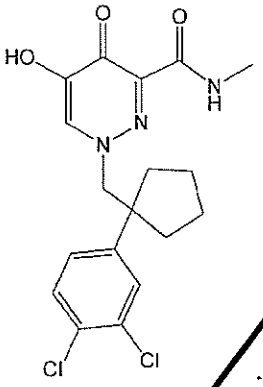


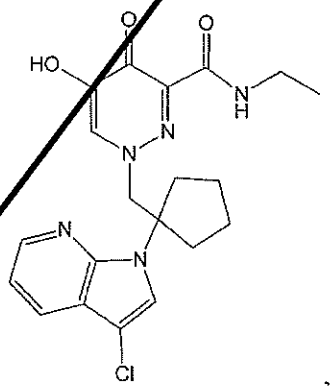


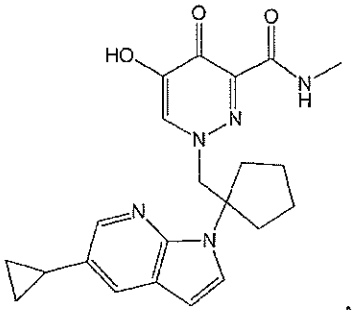


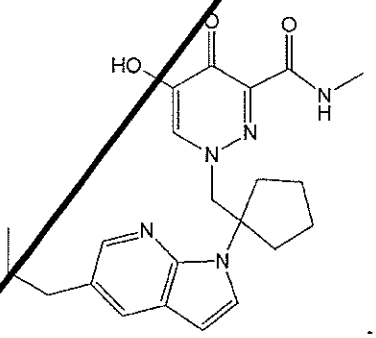


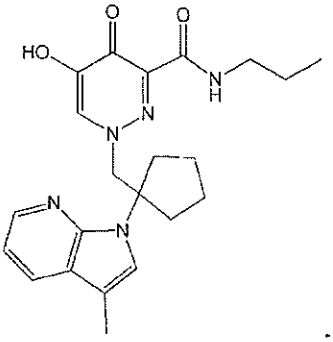


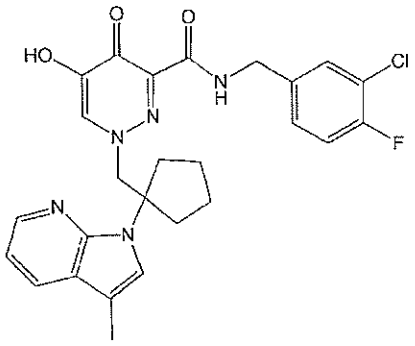


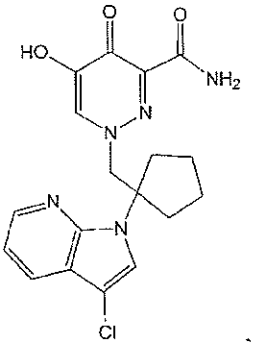


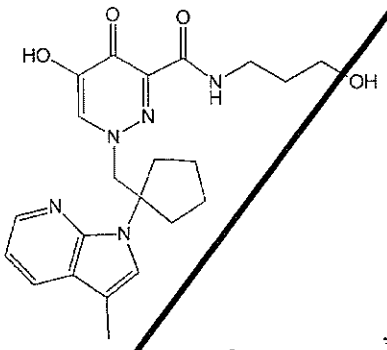


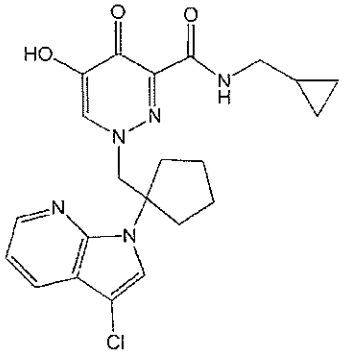


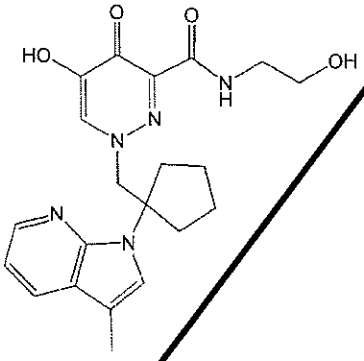


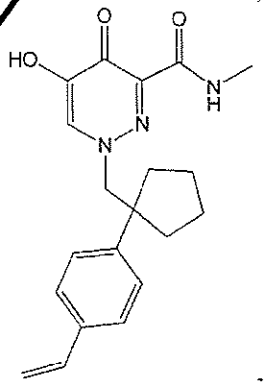


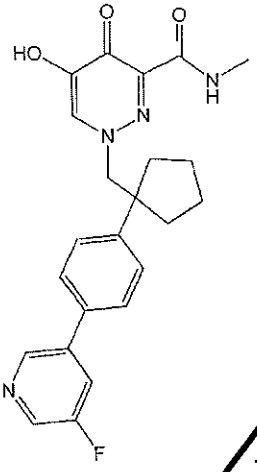


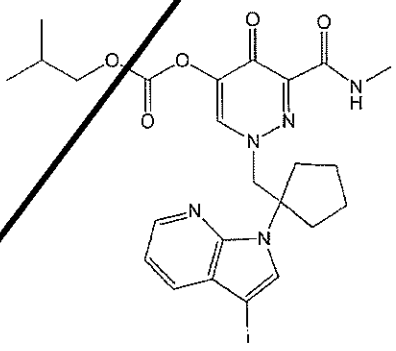


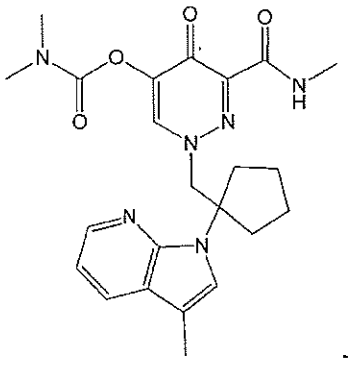


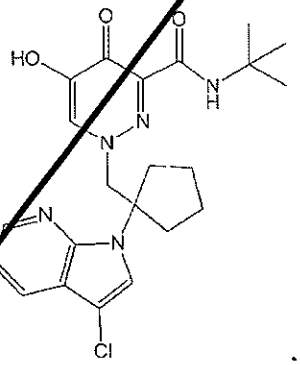


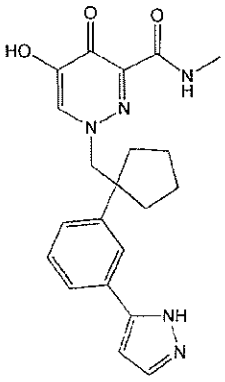


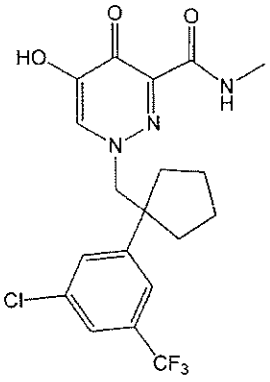


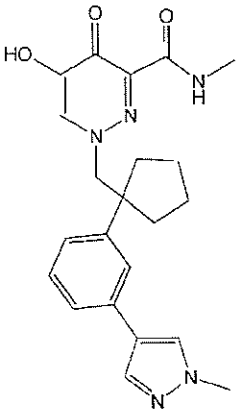


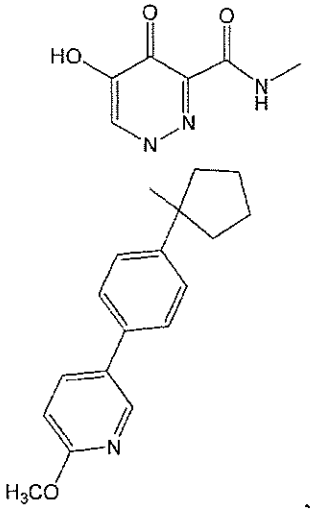


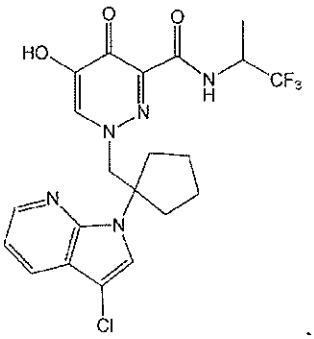


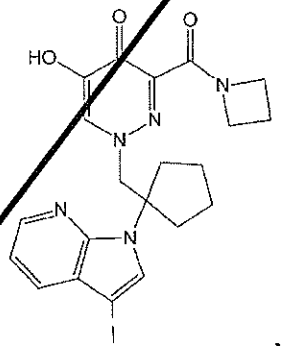


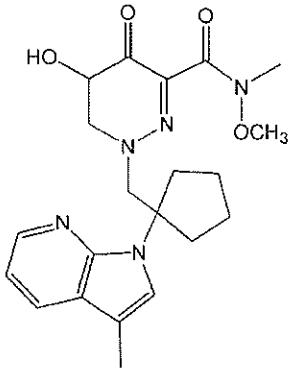


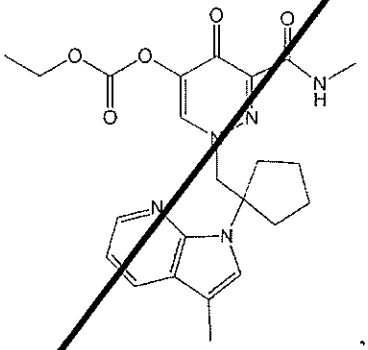


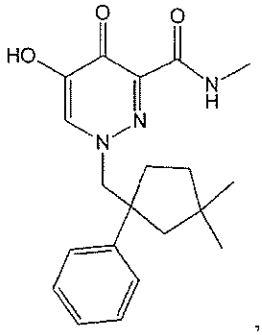


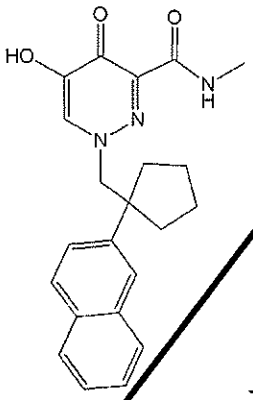


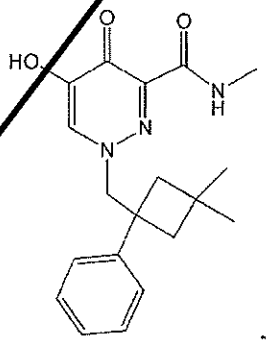


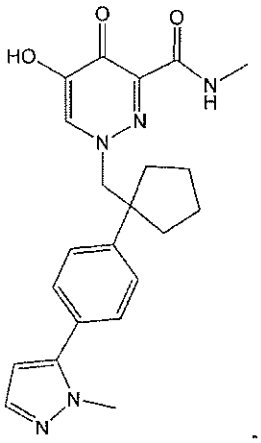


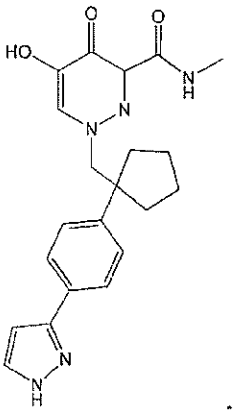


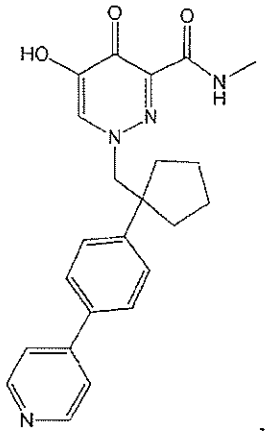


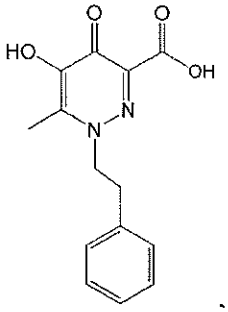


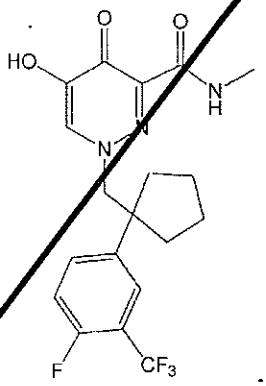


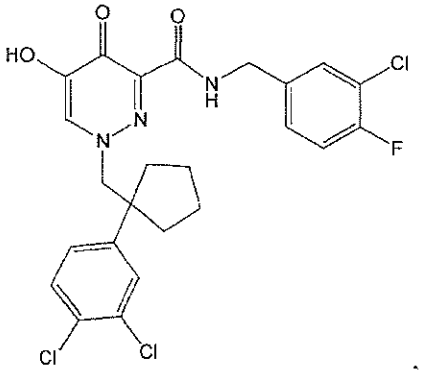


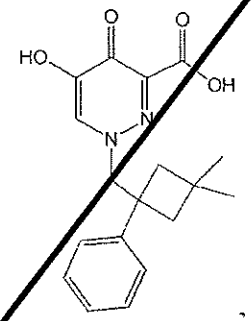


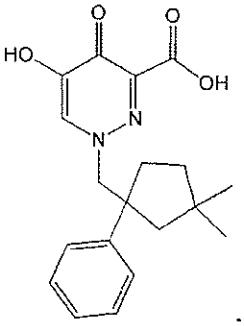


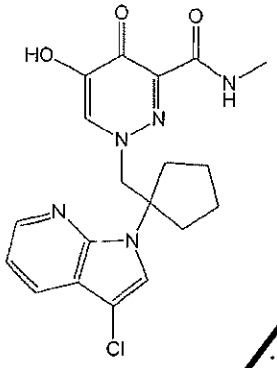


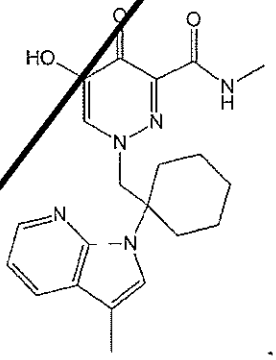


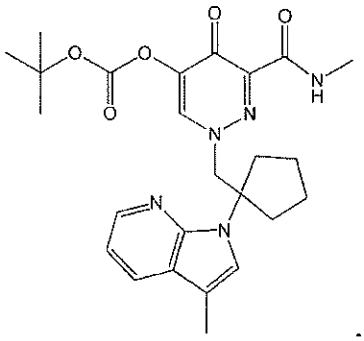


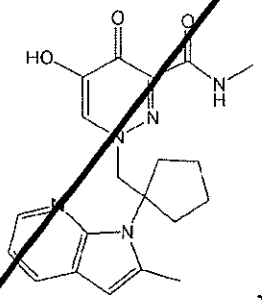


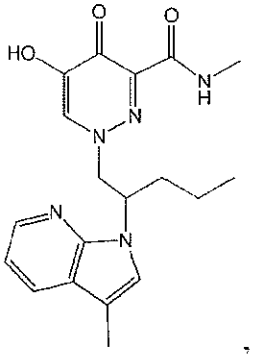


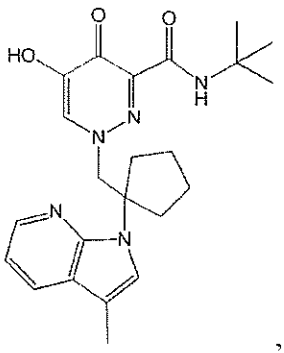


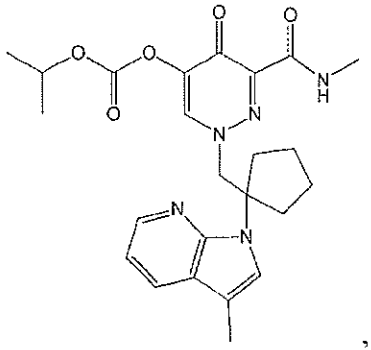


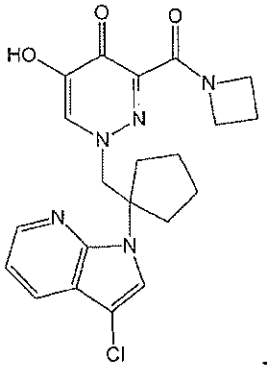


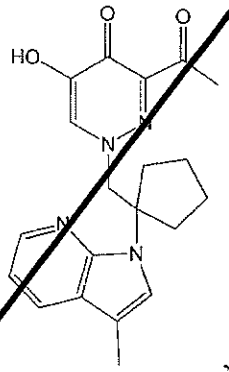


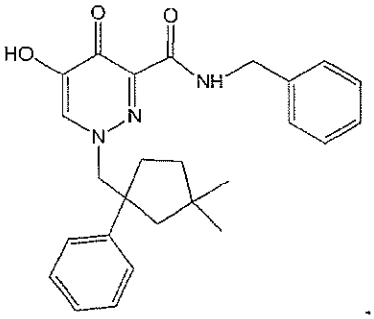


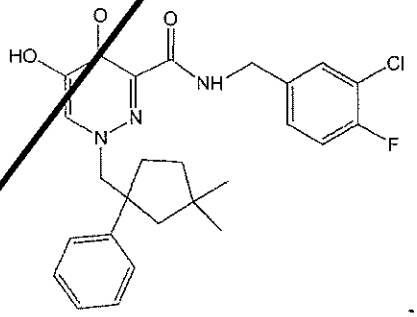


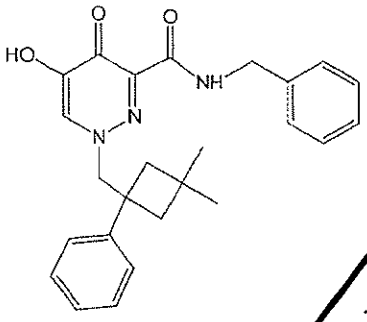


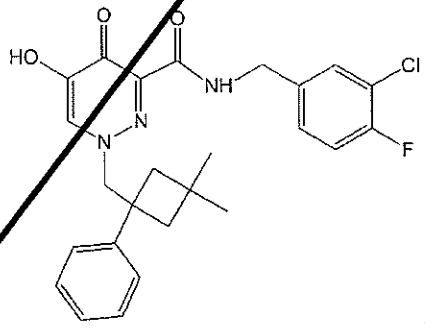


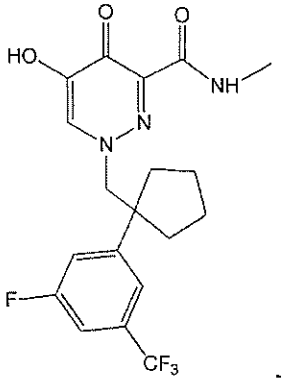


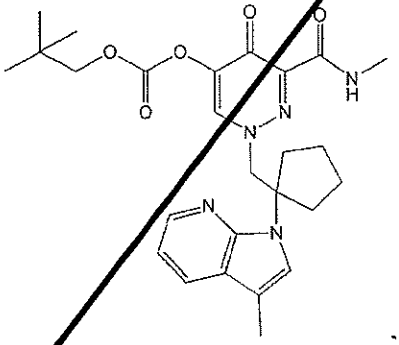


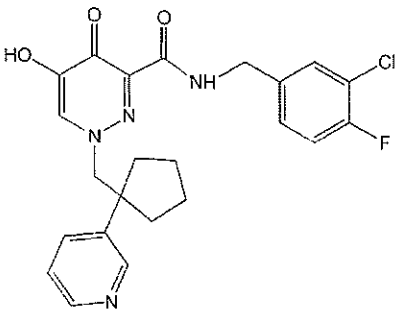


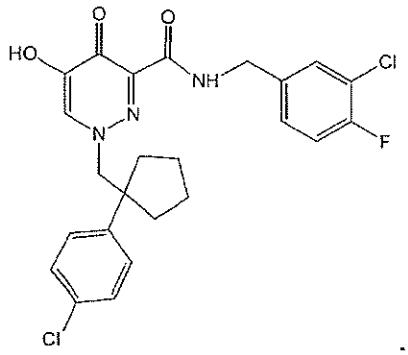


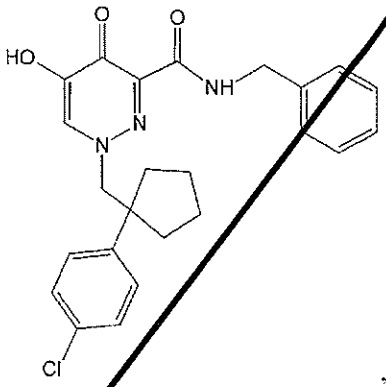


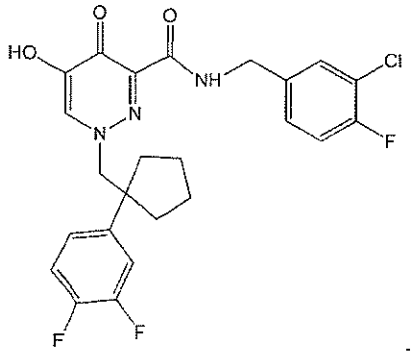


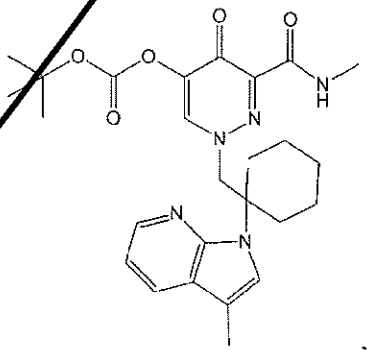


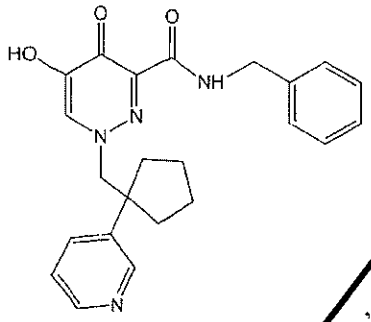


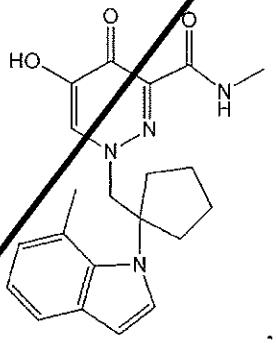


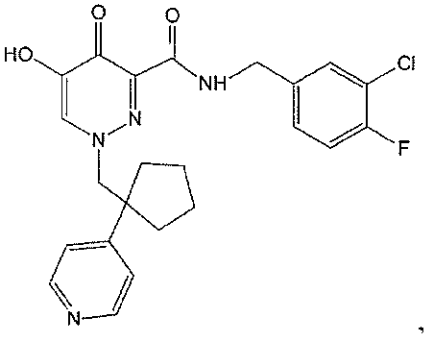


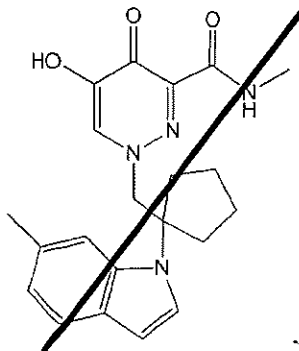


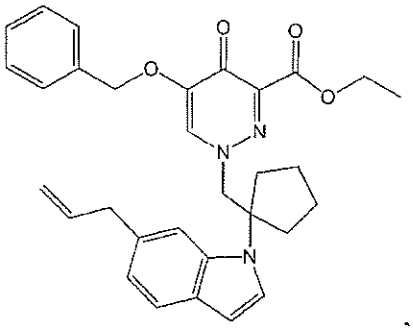


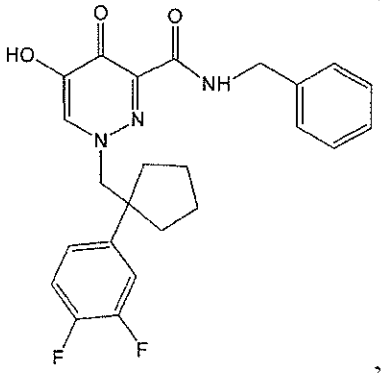


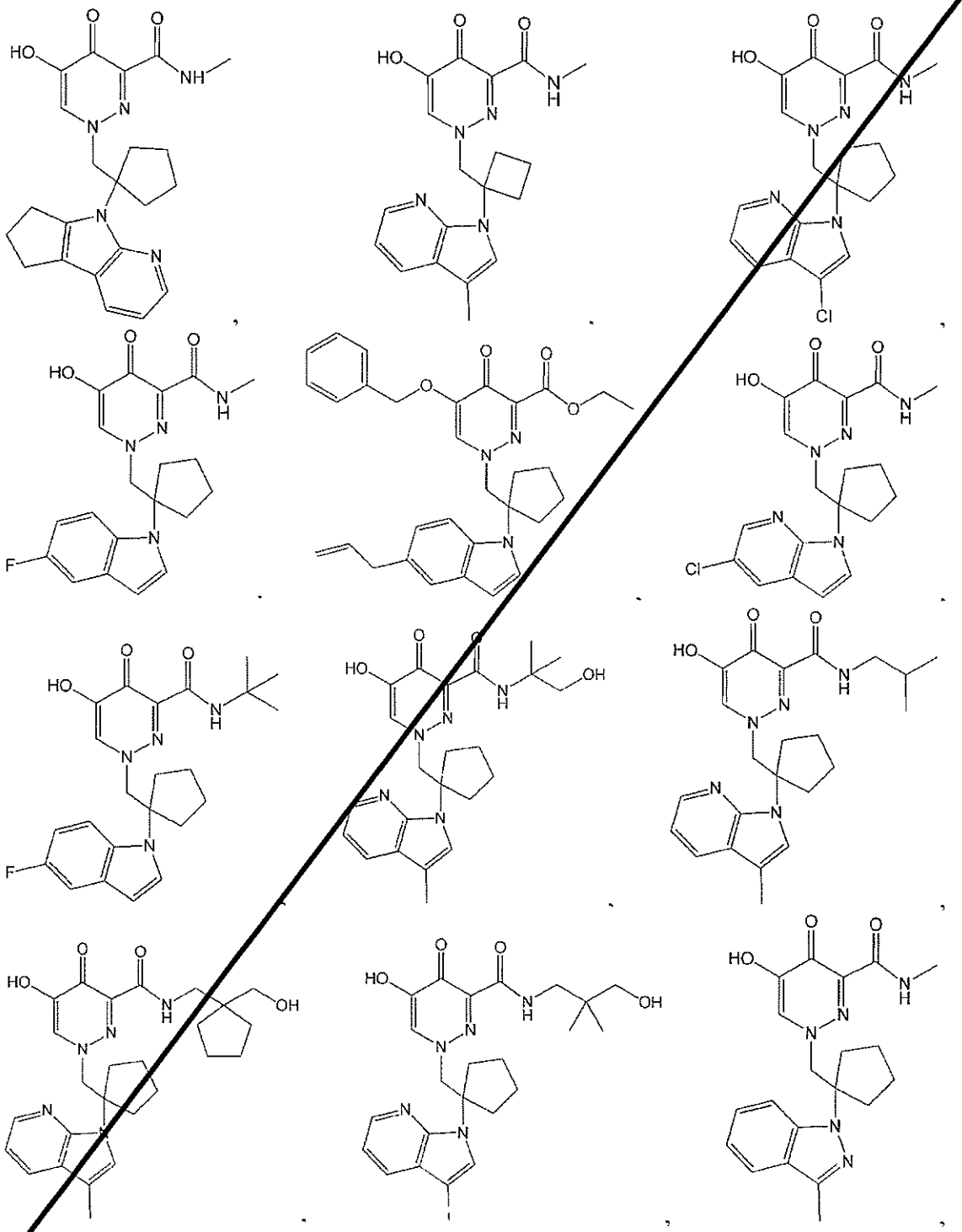


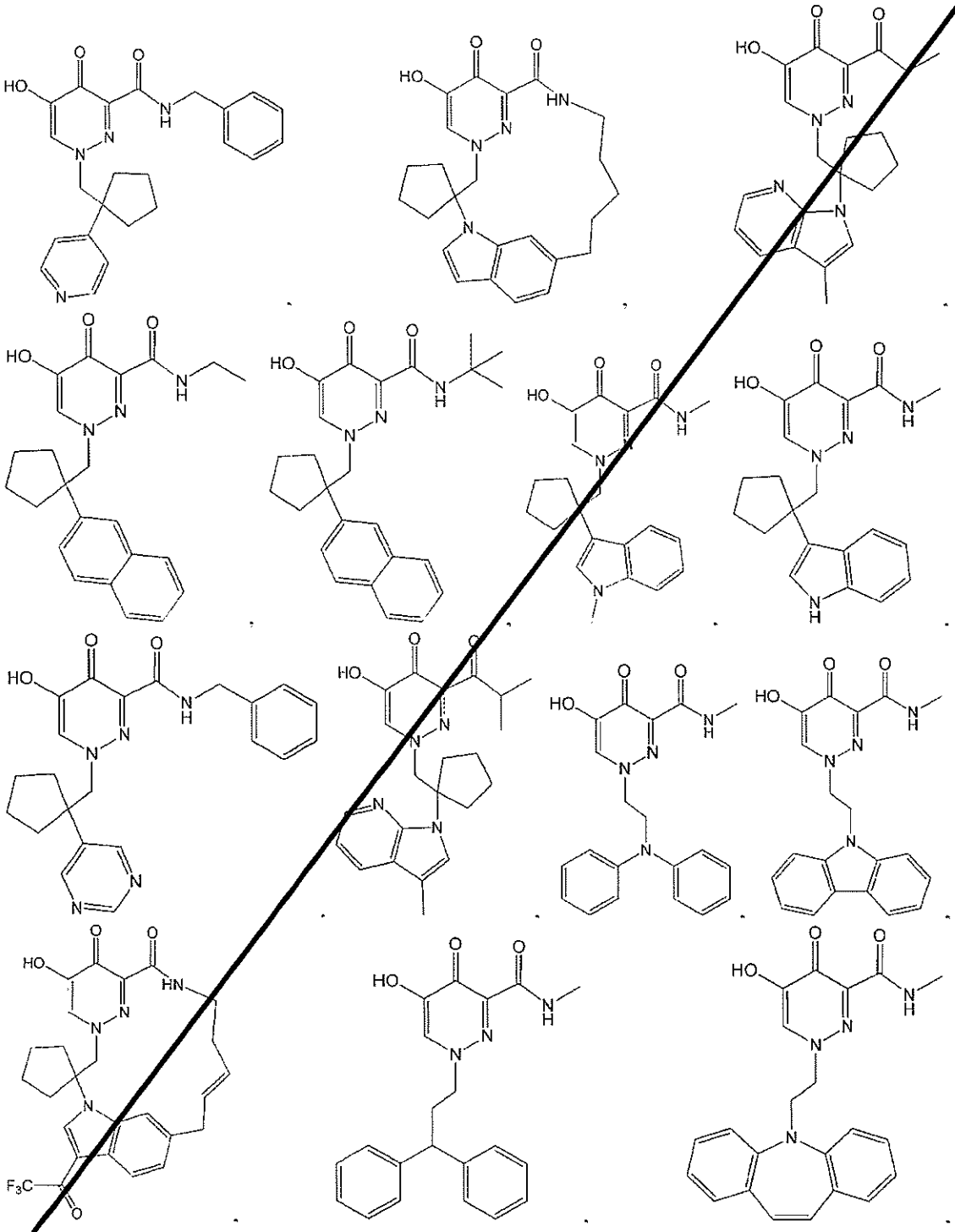


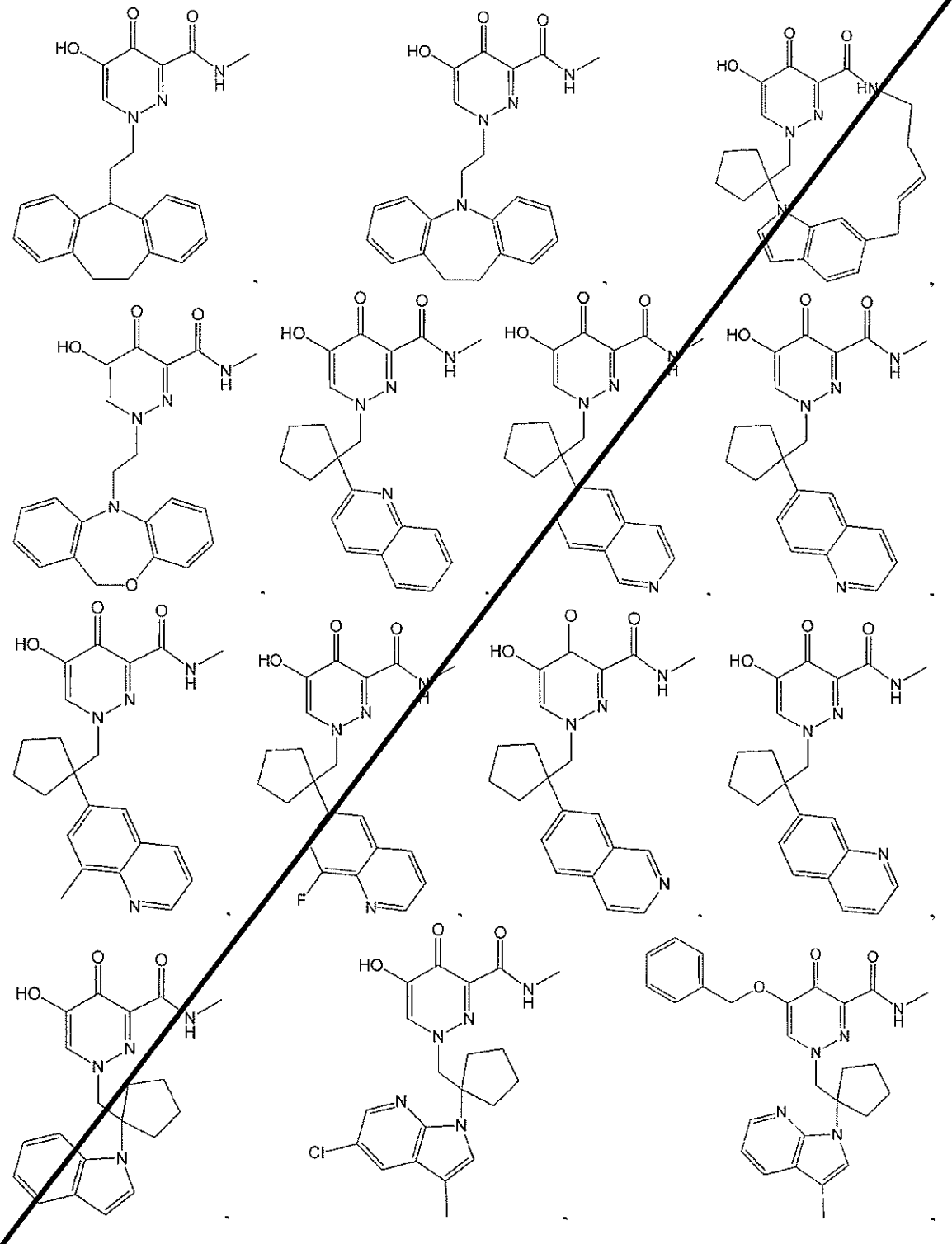


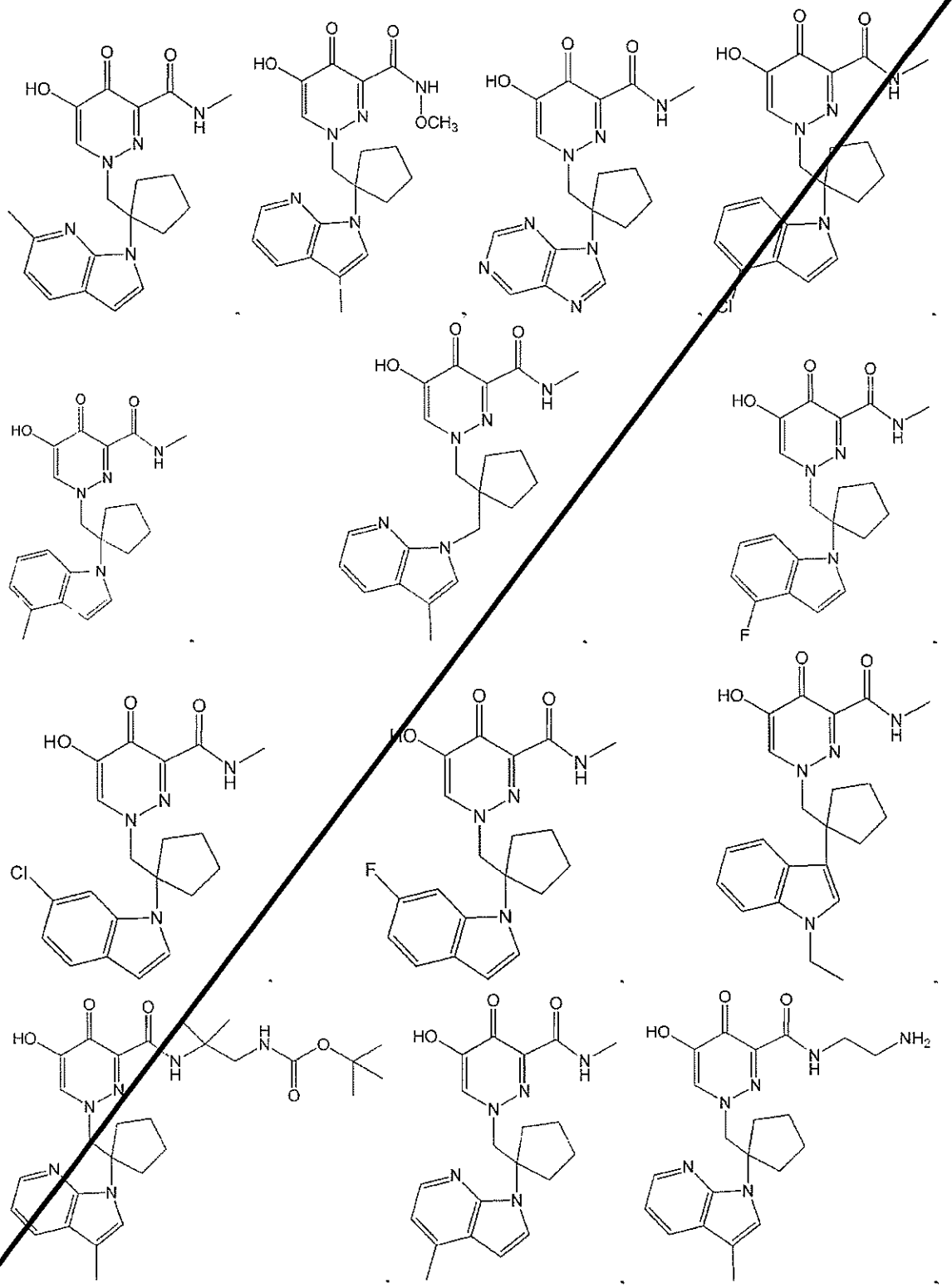


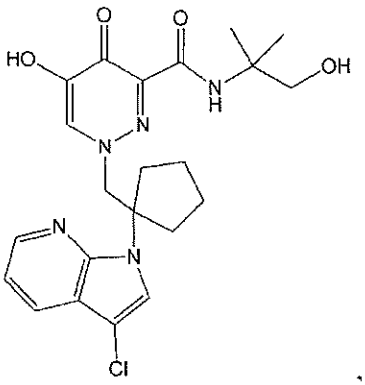


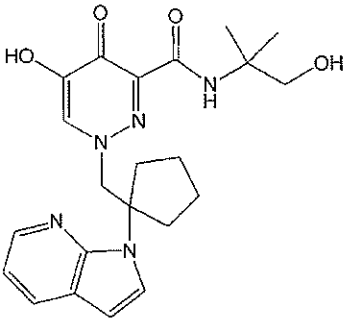


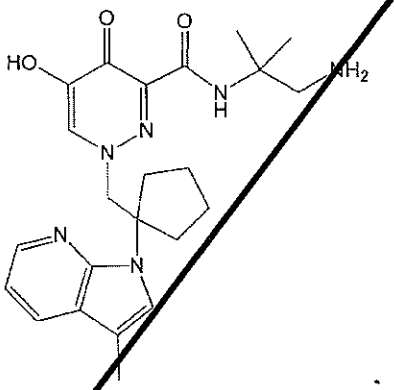


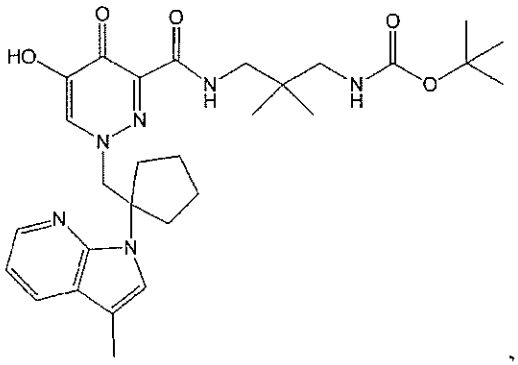


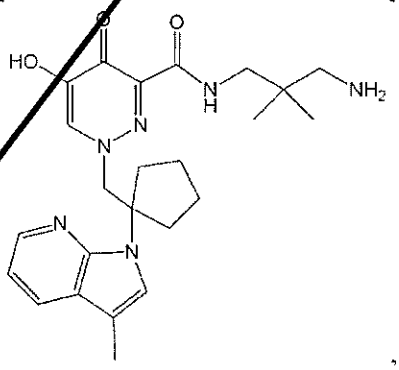


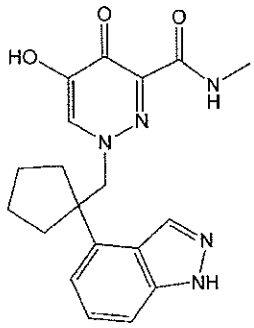


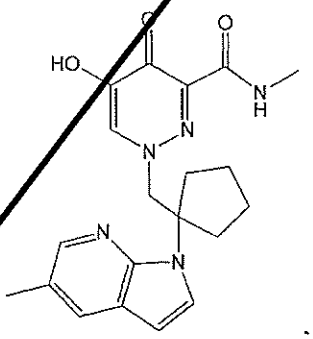


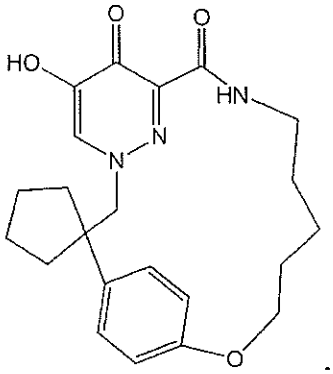


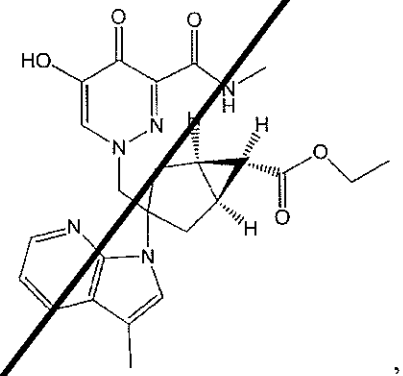


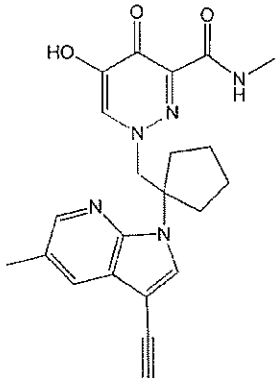


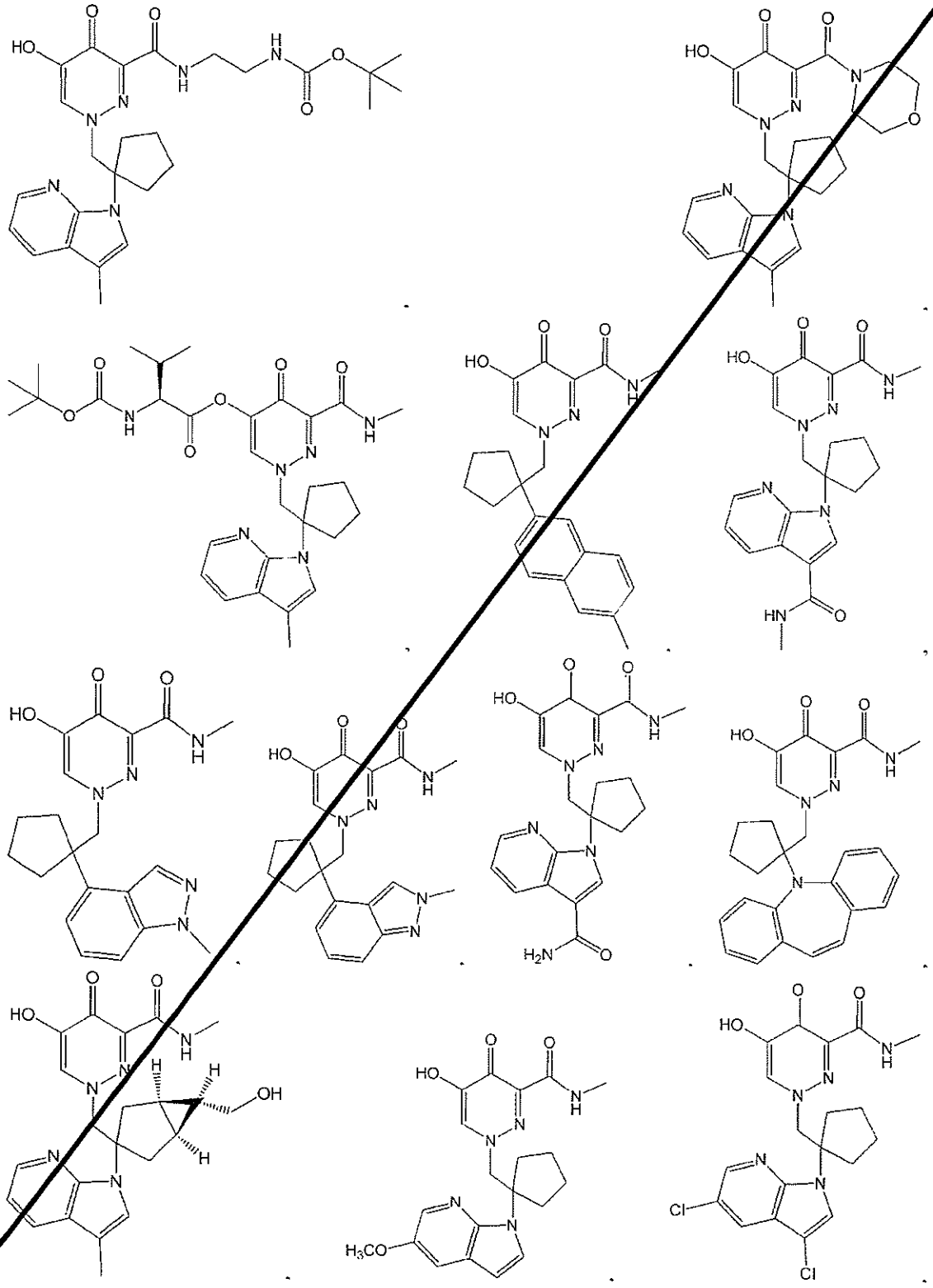


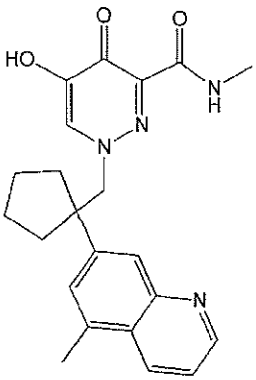
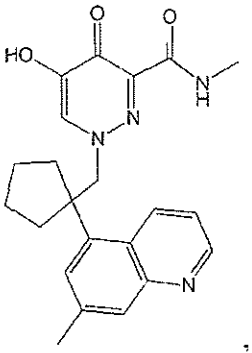
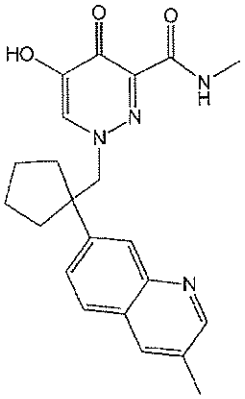
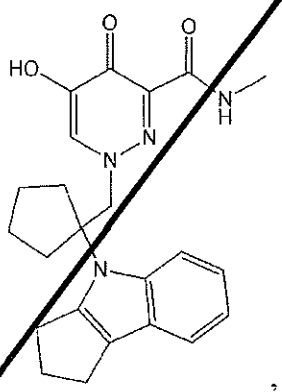
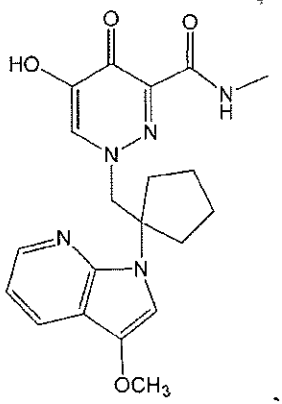
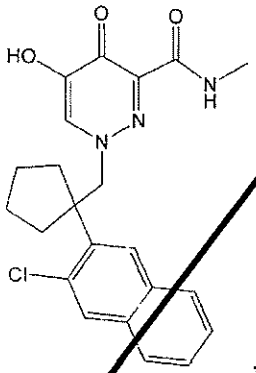
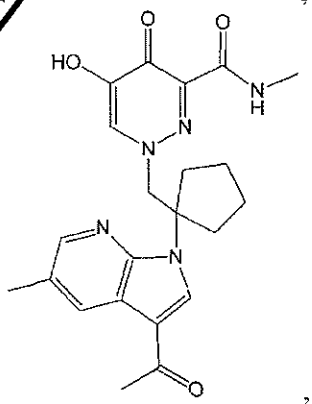
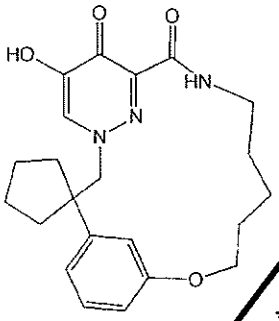
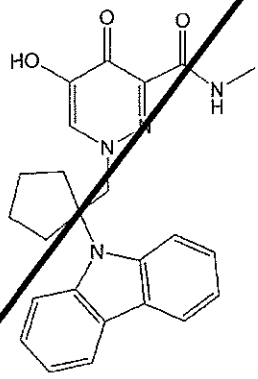
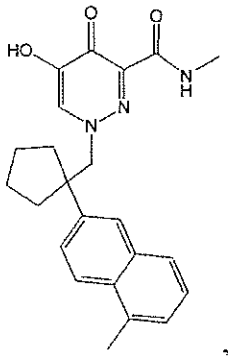
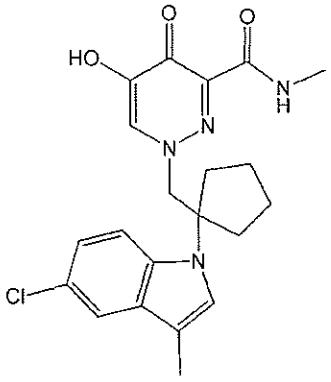
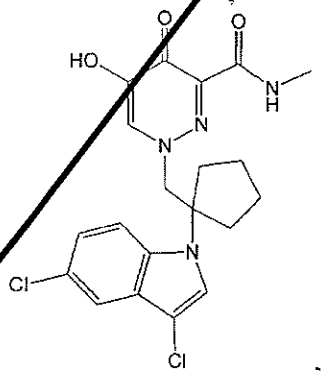






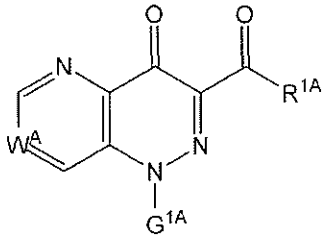





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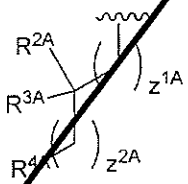
. or a pharmaceutically acceptable salt of any of the foregoing.

94. A compound of Formula (**II**), or a pharmaceutically acceptable salt thereof:



(**II**)

wherein:

G^{1A} is selected from the group consisting of  and R^{5A};

R^{1A} is selected from the group consisting of OR^{6A}, NH_2, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted mono-substituted amine, an optionally substituted di-substituted amine, an optionally substituted heterocyclyl and an optionally substituted N-sulfonamido, or R^{10A};

W^A is -CH- or -N-;

R^{2A} is hydrogen or C_{1-6} alkyl;

R^{3A} is hydrogen or C_{1-6} alkyl;

or R^{2A} and R^{3A} are taken together to form an optionally substituted C_{3-6} cycloalkyl or an optionally substituted 5 to 6 membered heterocyclyl;

R^{4A} is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

R^{5A} is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

R^{6A} is selected from the group consisting of hydrogen, C_{1-6} alkyl, $-C(O)R^{7A}$ and $-C(O)NR^{8A}R^{9A}$;

R^{7A} is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

R^{8A} and R^{9A} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

or R^{8A} and R^{9A} are taken together to form an optionally substituted heterocyclyl;

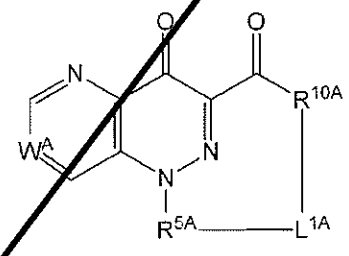
wherein when R^{1A} is R^{10A}, then R^{10A} and R^{4A} are taken together and include L^{1A}, where L^{1A} connects R^{10A} and R^{4A} to form an 11- to 20-membered ring, or wherein when R^{1A} is R^{10A}, then R^{10A} and R^{5A} are taken together and include L^{1A}, where L^{1A} connects R^{1A} and R^{5A} to form an 11- to 20-membered ring;

wherein R^{10A} is optionally substituted $-CH_2-$, optionally substituted -CH=CH-, O (oxygen), S (sulfur), or NR^{11A};

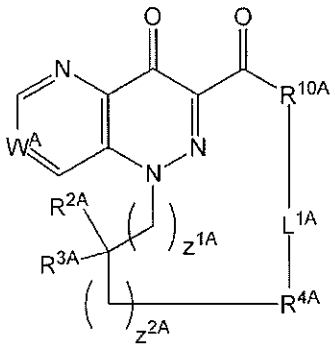
wherein R^{11A} is hydrogen or C_{1-6} alkyl; and

Z^{1A} and Z^{2A} are independently 0, 1, 2, 3 or 4.

95. The compound of Claim 94, having the structure of Formula (**IIc**) or Formula (**IId**), or a pharmaceutically acceptable salt thereof:



(**IIc**) or



(**IId**).

wherein:

L^{1A} is $-L^{2A}-$, or $-L^{3A}-L^{4A}-L^{5A}-$;

L^{2A} is selected from the group consisting of an optionally substituted alkylene, an optionally substituted alkenylene, an optionally substituted heteroalkylene and an optionally substituted heteroalkenylene;

L^{3A} is an optionally substituted C_{1-6} alkylene;

L^{4A} is an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, O (oxygen), S (sulfur), or NR^{11A}; and

L^{5A} is an optionally substituted C_{1-6} alkylene or an optionally substituted heteroalkylene.

96. The compound of Claim 95, wherein L^{2A} is an optionally substituted alkylene.

97. The compound of Claim 95, wherein L^{2A} is an optionally substituted C_{4-7} alkylene.

98. The compound of Claim 95, wherein L^{2A} is an optionally substituted alkenylene.

99. The compound of Claim 95, wherein L^{2A} is an optionally substituted C_{4-7} alkenylene.

100. The compound of Claim 95, wherein L^{2A} is an optionally substituted heteroalkylene.

101. The compound of Claim 100, wherein L^{2A} is an optionally substituted –$(CH_2)_3$-O–, an optionally substituted –$(CH_2)_4$-O–, an optionally substituted -$(CH_2)_5$-O–, an optionally substituted –$(CH_2)_3$-S–, an optionally substituted –$(CH_2)_4$-S–, an optionally substituted -$(CH_2)_5$-S–, an optionally substituted –$(CH_2)_3$-NH–, an optionally substituted –$(CH_2)_4$-NH–, or an optionally substituted -$(CH_2)_5$-NH–.

102. The compound of Claim 100, wherein L^{2A} is an optionally substituted -$(CH_2)_3$-O-, an optionally substituted –$(CH_2)_4$-O–, or an optionally substituted -$(CH_2)_5$-O–.

103. The compound of Claim 95, wherein L^{2A} is optionally substituted heteroalkenylene.

104. The compound of Claim 103, wherein L^{2A} is an optionally substituted -$(CH_2)(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-S–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-S–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-S an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-NH–, an

optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-NH– or an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-NH–.

105. The compound of Claim 103, wherein L^{2A} is an optionally substituted C_3 oxygen containing heteroalkenylene, an optionally substituted C_4 oxygen containing heteroalkenylene, or an optionally substituted C_5 oxygen containing heteroalkenylene.

106. The compound of Claim 95,

wherein:

L^{1A} is $-L^{3A}-L^{4A}-L^{5A}-$;

L^{3A} is an optionally substituted C_{1-4} alkylene;

L^{4A} is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

L^{5A} is an optionally substituted C_{1-4} alkylene.

107. The compound of Claim 95,

wherein:

L^{1A} is $-L^{3A}-L^{4A}-L^{5A}-$;

L^{3A} is an optionally substituted C_{1-4} alkylene;

L^{4A} is O (oxygen), S (sulfur), or NR^{11A}; and

L^{5A} is an optionally substituted C_{1-4} alkylene.

108. The compound of Claim 95,

wherein:

L^{1A} is $-L^{3A}-L^{4A}-L^{5A}-$;

L^{3A} is optionally substituted C_{2-4} alkylene;

L^{4A} is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, O (oxygen), S (sulfur), or NR^{11A}; and

L^{5A} is optionally substituted C_{2-4} alkylene.

109. The compound of any one of Claims 94 or 107-108,

wherein:

R^{1A} is R^{10A} where R^{10A} is NR^{11A}; and

R^{11A} is H (hydrogen).

110. The compound of Claim 94, wherein $\mathbf{R^{1A}}$ is NH_2, an optionally substituted mono-substituted amine or an optionally substituted di-substituted amine.

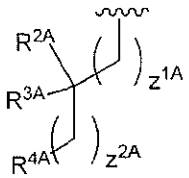
111. The compound of Claim 94, wherein $\mathbf{R^{1A}}$ is an optionally substituted mono-substituted amine.

112. The compound of Claim 94, wherein $\mathbf{R^{1A}}$ is an optionally substituted alkyl.

113. The compound of Claim 94, wherein $\mathbf{R^{1A}}$ is $\mathbf{R^{10A}}$.

114. The compound of Claim 113, wherein $\mathbf{R^{10A}}$ is CH_2.

115. The compound of Claim 113, wherein $\mathbf{R^{10A}}$ is $\mathbf{NR^{11A}}$.

116. The compound of any one of Claims 94-115, wherein $\mathbf{G^{1A}}$ is 

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117. The compound of Claim 116, wherein $\mathbf{R^{2A}}$ and $\mathbf{R^{3A}}$ are taken together to form an optionally substituted C_{3-6} cycloalkyl.

118. The compound of Claim 117, wherein $\mathbf{R^{2A}}$ and $\mathbf{R^{3A}}$ are taken together to form an unsubstituted C_{3-6} cycloalkyl.

119. The compound of Claim 117 or 118, wherein $\mathbf{R^{2A}}$ and $\mathbf{R^{3A}}$ are taken together to form a C_5 cycloalkyl.

120. The compound of any one of Claims 94-119, wherein $\mathbf{R^{4A}}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

121. The compound of any one of Claims 94-119, wherein $\mathbf{R^{4A}}$ is an optionally substituted aryl.

122. The compound of Claim 121, wherein the optionally substituted aryl is an optionally substituted phenyl.

123. The compound of Claim 121, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, aryl, cyano, halogen, haloalkyl and haloalkoxy.

124. The compound of any one of Claims 94-119, wherein $\mathbf{R^{4A}}$ is an optionally substituted heteroaryl.

125. The compound of any one of Claims 94-124, wherein Z^{1A} is 0.

126. The compound of any one of Claims 94-124, wherein Z^{1A} is 1.

127. The compound of any one of Claims 94-126, wherein Z^{2A} is 0.

128. The compound of any one of Claims 94-126, wherein Z^{2A} is 1.

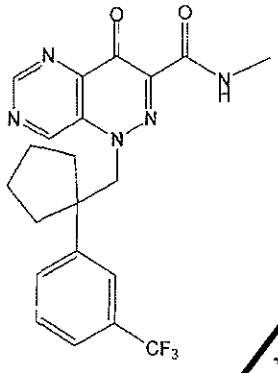
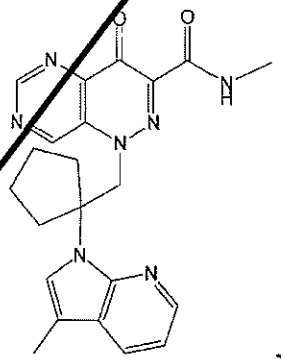
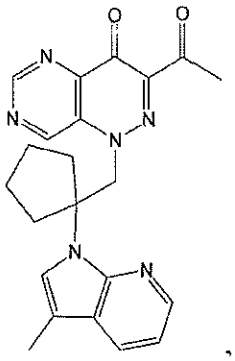
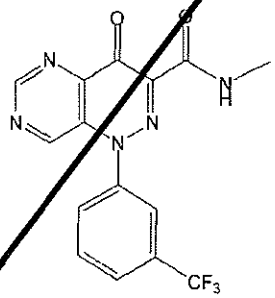
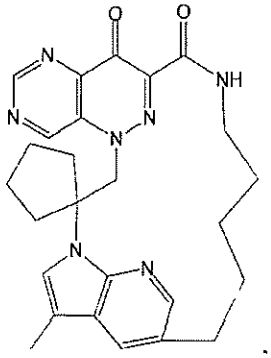
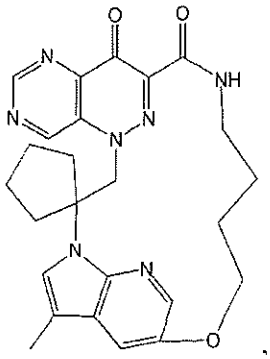
129. The compound of any one of Claims 94-115, wherein G^{1A} is R^{5A}.

130. The compound of Claim 129, wherein R^{5A} is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

131. The compound of Claim 130, wherein R^{5A} is an optionally substituted aryl.

132. The compound of Claim 131, wherein the optionally substituted aryl is an optionally substituted phenyl.

133. The compound of Claim 94, wherein the compound is selected from the group consisting of:


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, and

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or a pharmaceutically acceptable salt of any of the foregoing.

134. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

135. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for ameliorating or treating an orthomyxovirus viral infection.

136. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for inhibiting replication of an orthomyxovirus virus.

137. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for contacting a cell infected with an orthomyxovirus virus.

138. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for ameliorating or treating an orthomyxovirus viral infection in combination with one or more agents comprising administering or contacting a cell with an effective amount of the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

139. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for inhibiting endonuclease activity of an influenza endonuclease.

140. The use of any one of Claims 135-137, wherein the orthomyxovirus viral infection is influenza.

141. The use of Claim 138, wherein the orthomyxovirus viral infection is an influenza virus infection; and wherein the one or more agents is selected from the group consisting of a neuraminidase inhibitor, a M2 protein inhibitor, a polymerase inhibitor, a PB2 inhibitor, amantadine, rimantadine, zanamivir, oseltamivir, peramivir, laninamivir, laninamivir octanoate, favipiravir, fludase, ADS-8902, an immuno-modulator, beraprost,

Neugene®, ribavirin, CAS Reg. No. 1422050-75-6, CAS Reg. No. 1259366-34-1 (VX-787), FluMist Quadrivalent® (MedImmune), Fluarix® Quadrivalent (GlaxoSmithKline), Fluzone® Quadrivalent (Sanofi Pasteur), Flucelvax® (Novartis) and FluBlok® (Protein Sciences).

142. The use of 141, wherein the one or more agents is oseltamivir.

143. The use of any one of Claims 140-141, wherein the influenza is influenza A.

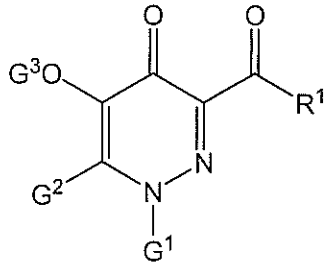
144. The use of any one of Claims 140-141, wherein the influenza is influenza B.

145. The use of any one of Claims 140-141, wherein the influenza is influenza C.

146. The use of any one of Claims 140-141, wherein the influenza is selected from the group consisting of H1N1, H3N2, H5N1 and H7N9.

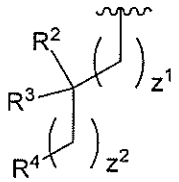
CLAIMS

1. A compound of Formula (**I**), or a pharmaceutically acceptable salt thereof:



(I)

wherein:



$\mathbf{G^1}$ is selected from the group consisting of and $\mathbf{R^5}$;

$\mathbf{G^2}$ is hydrogen, halogen, -CN, an optionally substituted $C_{1\text{-}6}$ alkyl, an optionally substituted aryl, an optionally substituted heteroaryl, $-CH_2OH$, $-CH(\mathbf{Y^1})(OH)$ or $-C(O)\mathbf{Y^1}$,;

$\mathbf{G^3}$ is selected from the group consisting of hydrogen, $-C(O)\mathbf{Y^2}$, $-C(O)O\text{-}\mathbf{Y^2}$, $-(CH_2)\text{-}O(CO)\mathbf{Y^2}$, $-(CH_2)\text{-}O(CO)O\mathbf{Y^2}$, $-(CHCH_3)\text{-}O(CO)\mathbf{Y^2}$, and $-(CHCH_3)\text{-}O(CO)O\mathbf{Y^2}$;

$\mathbf{Y^1}$ and $\mathbf{Y^2}$ are independently an optionally substituted $C_{1\text{-}6}$ alkyl or an optionally substituted aryl;

$\mathbf{R^1}$ is selected from the group consisting of $O\mathbf{R^6}$, NH_2, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted mono-substituted amine, an optionally substituted di-substituted amine, an optionally substituted heterocyclyl, an optionally substituted N-sulfonamido and an optionally substituted alkoxyamine, or $\mathbf{R^{10}}$;

$\mathbf{R^2}$ is hydrogen, $C_{1\text{-}6}$ alkyl, an optionally substituted $C_{3\text{-}6}$ cycloalkyl, an optionally substituted aryl, an optionally substituted aryl($C_{1\text{-}6}$ alkyl) or an optionally substituted C-amido;

$\mathbf{R^3}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

or $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted $C_{3\text{-}6}$ cycloalkyl, an optionally substituted 5 to 6 membered heterocyclyl or =O;

$\mathbf{R^4}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

or $\mathbf{R^4}$ is $\mathbf{A^1R^{A4}R^{B4}}$, wherein $\mathbf{A^1}$ is CH or N; and $\mathbf{R^{A4}}$ and $\mathbf{R^{B4}}$ are each independently an optionally substituted phenyl;

$\mathbf{R^5}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

$\mathbf{R^6}$ is selected from the group consisting of hydrogen, $C_{1\text{-}6}$ alkyl, -C(O)$\mathbf{R^7}$ and -C(O)N$\mathbf{R^8R^9}$;

$\mathbf{R^7}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl($C_{1\text{-}6}$ alkyl), heteroaryl($C_{1\text{-}6}$ alkyl) and heterocyclyl($C_{1\text{-}6}$ alkyl);

$\mathbf{R^8}$ and $\mathbf{R^9}$ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl($C_{1\text{-}6}$ alkyl), heteroaryl($C_{1\text{-}6}$ alkyl) and heterocyclyl($C_{1\text{-}6}$ alkyl);

or $\mathbf{R^8}$ and $\mathbf{R^9}$ are taken together to form an optionally substituted heterocyclyl;

wherein when $\mathbf{R^1}$ is $\mathbf{R^{10}}$, then $\mathbf{R^{10}}$ and $\mathbf{R^4}$ are taken together and include $\mathbf{L^1}$, where $\mathbf{L^1}$ connects $\mathbf{R^{10}}$ and $\mathbf{R^4}$ to form an 11- to 20-membered ring, or wherein when $\mathbf{R^1}$ is $\mathbf{R^{10}}$, then $\mathbf{R^{10}}$ and $\mathbf{R^5}$ are taken together and include $\mathbf{L^1}$, where $\mathbf{L^1}$ connects $\mathbf{R^1}$ and $\mathbf{R^5}$ to form an 11- to 20-membered ring;

wherein $\mathbf{R^{10}}$ is optionally substituted $-CH_2-$, optionally substituted -CH=CH-, O (oxygen), S (sulfur), or N$\mathbf{R^{11}}$;

wherein $\mathbf{R^{11}}$ is hydrogen or $C_{1\text{-}6}$ alkyl; and

$\mathbf{Z^1}$ and $\mathbf{Z^2}$ are independently 0, 1, 2, 3 or 4.

2. The compound of Claim 1,

wherein:

$\mathbf{G^2}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

$\mathbf{G^3}$ is selected from the group consisting of hydrogen, -C(O)$\mathbf{Y^2}$, -C(O)O-$\mathbf{Y^2}$, $-(CH_2)$-O(CO)$\mathbf{Y^2}$, $-(CH_2)$-O(CO)O$\mathbf{Y^2}$, $-(CHCH_3)$-O(CO)$\mathbf{Y^2}$, and $-(CHCH_3)$-O(CO)O$\mathbf{Y^2}$;

$\mathbf{Y^2}$ is $C_{1\text{-}6}$ alkyl;

$\mathbf{R^1}$ is selected from the group consisting of O$\mathbf{R^6}$, NH_2, an optionally substituted mono-substituted amine, an optionally substituted di-substituted amine, an optionally substituted

heterocyclyl and an optionally substituted N-sulfonamido, said optionally substituted mono-substituted amine, optionally substituted di-substituted amine, an optionally substituted heterocyclyl and optionally substituted N-sulfonamido are each optionally substituted with one or more substituents selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, trihalomethanesulfonyl, trihalomethanesulfonamido, an amino, a mono-substituted amino group and a di-substituted amino;

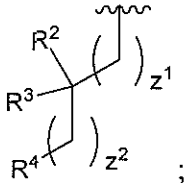
$\mathbf{R^2}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

$\mathbf{R^3}$ is hydrogen or $C_{1\text{-}6}$ alkyl;

or $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted $C_{3\text{-}6}$ cycloalkyl or an optionally substituted 5 to 6 membered heterocyclyl;

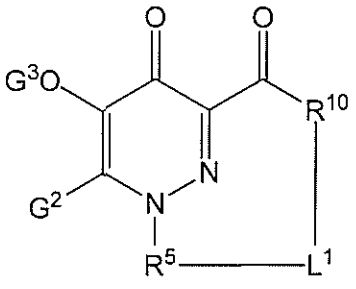
3. The compound of Claim 1,

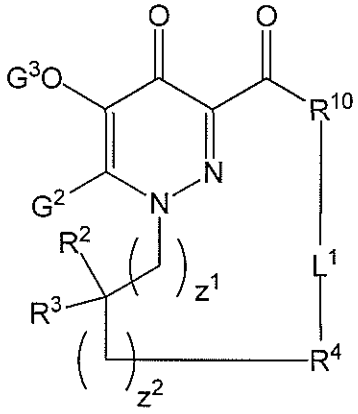
wherein:

$\mathbf{G^1}$ is  ; and

$\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted piperidino or an optionally substituted pyrrolidino.

4. The compound of Claim 1, having the structure of Formula (**Ih**) or Formula (**Ij**), or a pharmaceutically acceptable salt thereof:



(**Ih**) or


(**Ij**),

wherein:

$\mathbf{L^1}$ is $-\mathbf{L^2}-$, or $-\mathbf{L^3}-\mathbf{L^4}-\mathbf{L^5}-$;

$\mathbf{L^2}$ is selected from the group consisting of an optionally substituted alkylene, an optionally substituted alkenylene, an optionally substituted heteroalkylene and an optionally substituted heteroalkenylene;

$\mathbf{L^3}$ is an optionally substituted C_{1-6} alkylene;

$\mathbf{L^4}$ is an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, O (oxygen), S (sulfur), or $N\mathbf{R^{11}}$; and

$\mathbf{L^5}$ is an optionally substituted C_{1-6} alkylene or an optionally substituted heteroalkylene.

5. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted alkylene.

6. The compound of Claim 5, wherein $\mathbf{L^2}$ is an optionally substituted C_{4-7} alkylene.

7. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted alkenylene.

8. The compound of Claim 7, wherein $\mathbf{L^2}$ is an optionally substituted C_{4-7} alkenylene.

9. The compound of Claim 4, wherein $\mathbf{L^2}$ is an optionally substituted heteroalkylene.

10. The compound of Claim 9, wherein $\mathbf{L^2}$ is an optionally substituted $-(CH_2)_3-O-$, an optionally substituted $-(CH_2)_4-O-$, an optionally substituted $-(CH_2)_5-O-$, an optionally substituted $-(CH_2)_3-S-$, an optionally substituted $-(CH_2)_4-S-$, an optionally substituted $-(CH_2)_5-S-$, an optionally substituted $-(CH_2)_3-NH-$, an optionally substituted $-(CH_2)_4-NH-$, or an optionally substituted $-(CH_2)_5-NH-$.

11. The compound of Claim 9, wherein $\mathbf{L^2}$ is an optionally substituted $-(CH_2)_3-O-$, an optionally substituted $-(CH_2)_4-O-$, or an optionally substituted $-(CH_2)_5-O-$.

12. The compound of Claim 4, wherein $\mathbf{L}^2$ is optionally substituted heteroalkenylene.

13. The compound of Claim 12, wherein $\mathbf{L}^2$ is an optionally substituted -$(CH_2)(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-O–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-S–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-S–, an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-S an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)$-NH–, an optionally substituted -$(CH_2)(CH=CH)(CH_2)_2$-NH– or an optionally substituted -$(CH_2)_2(CH=CH)(CH_2)_2$-NH–.

14. The compound of Claim 13, wherein $\mathbf{L}^2$ is an optionally substituted C_3 oxygen containing heteroalkenylene, an optionally substituted C_4 oxygen containing heteroalkenylene, or an optionally substituted C_5 oxygen containing heteroalkenylene.

15. The compound of Claim 4,

wherein:

$\mathbf{L}^1$ is –$\mathbf{L}^3$-$\mathbf{L}^4$-$\mathbf{L}^5$-;

$\mathbf{L}^3$ is an optionally substituted C_{1-4} alkylene;

$\mathbf{L}^4$ is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

$\mathbf{L}^5$ is an optionally substituted C_{1-4} alkylene.

16. The compound of Claim 4,

wherein:

$\mathbf{L}^1$ is –$\mathbf{L}^3$-$\mathbf{L}^4$-$\mathbf{L}^5$-;

$\mathbf{L}^3$ is an optionally substituted C_{1-4} alkylene;

$\mathbf{L}^4$ is O (oxygen), S (sulfur), or N$\mathbf{R}^{11}$; and

$\mathbf{L}^5$ is an optionally substituted C_{1-4} alkylene.

17. The compound of Claim 4,

wherein:

$\mathbf{L}^1$ is –$\mathbf{L}^3$-$\mathbf{L}^4$-$\mathbf{L}^5$-;

$\mathbf{L}^3$ is optionally substituted C_{2-4} alkylene;

$\mathbf{L}^4$ is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, O (oxygen), S (sulfur), or N$\mathbf{R}^{11}$; and

$\mathbf{L}^5$ is optionally substituted C_{2-4} alkylene.

18. The compound of any one of Claims 4 or 16-17,

wherein:

$\mathbf{R^1}$ is $\mathbf{R^{10}}$ where $\mathbf{R^{10}}$ is $N\mathbf{R^{11}}$; and

$\mathbf{R^{11}}$ is H (hydrogen).

19. The compound of Claim 1, wherein $\mathbf{R^1}$ is $O\mathbf{R^6}$.

20. The compound of Claim 19, wherein $\mathbf{R^6}$ is hydrogen.

21. The compound of Claim 19, wherein $\mathbf{R^6}$ is $C_{1\text{-}6}$ alkyl.

22. The compound of Claim 19, wherein $\mathbf{R^6}$ is $-C(O)R^7$.

23. The compound of Claim 19, wherein $\mathbf{R^6}$ is $-C(O)NR^8R^9$.

24. The compound of Claim 1, wherein $\mathbf{R^1}$ is NH_2.

25. The compound of Claim 1, wherein $\mathbf{R^1}$ is an optionally substituted mono-substituted amine.

26. The compound of Claim 1, wherein $\mathbf{R^1}$ is an optionally substituted di-substituted amine.

27. The compound of Claim 1, wherein $\mathbf{R^1}$ is an optionally substituted heterocyclyl.

28. The compound of Claim 27, wherein the heterocyclyl is a 5 to 6 membered heterocyclyl.

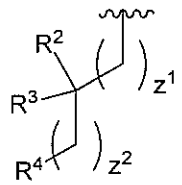
29. The compound of Claim 27 or 28, wherein the heterocyclyl contains at least one nitrogen in the ring and is an N-linked heterocyclyl.

30. The compound of Claim 1, wherein $\mathbf{R^1}$ is an optionally substituted N-sulfonamido.

31. The compound of Claim 1, wherein $\mathbf{R^1}$ is $\mathbf{R^{10}}$.

32. The compound of Claim 1, wherein $\mathbf{R^{10}}$ is CH_2.

33. The compound of Claim 1, wherein $\mathbf{R^{10}}$ is $N\mathbf{R^{11}}$.

34. The compound of any one of Claims 1-18, wherein $\mathbf{G^1}$ is 

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35. The compound of Claim 34, wherein $\mathbf{R^2}$ is hydrogen.

36. The compound of Claim 34, wherein $\mathbf{R^2}$ is $C_{1\text{-}6}$ alkyl.

37. The compound of any one of Claims 34-36, wherein $\mathbf{R^3}$ is hydrogen.

38. The compound of any one of Claims 34-36, wherein $\mathbf{R^3}$ is C_{1-6} alkyl.

39. The compound of Claim 34, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted C_{3-6} cycloalkyl.

40. The compound of Claim 39, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an unsubstituted C_{3-6} cycloalkyl.

41. The compound of Claim 39 or 40, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form a C_5 cycloalkyl.

42. The compound of Claim 34, wherein $\mathbf{R^2}$ and $\mathbf{R^3}$ are taken together to form an optionally substituted 5 to 6 membered heterocyclyl.

43. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

44. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is an optionally substituted aryl.

45. The compound of Claim 44, wherein the optionally substituted aryl is an optionally substituted phenyl.

46. The compound of Claim 45, wherein the optionally substituted phenyl is a substituted phenyl.

47. The compound of Claim 46, wherein the substituted phenyl is a mono-substituted phenyl.

48. The compound of Claim 47, wherein the substituted phenyl is an ortho-substituted phenyl.

49. The compound of Claim 47, wherein the substituted phenyl is a meta-substituted phenyl.

50. The compound of Claim 47, wherein the substituted phenyl is a para-substituted phenyl.

51. The compound of Claim 46, wherein the substituted phenyl is a di-substituted phenyl.

52. The compound of Claim 46, wherein the substituted phenyl is substituted with 3 or more substituents.

53. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is an optionally substituted cycloalkyl.

54. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is an optionally substituted heteroaryl.

55. The compound of any one of Claims 32-42, wherein $\mathbf{R^4}$ is an optionally substituted heterocyclyl.

56. The compound of any one of Claims 32-55, wherein $\mathbf{R^4}$ is substituted with one or more substituents selected from the group consisting of halogen, $C_{1\text{-}6}$ alkyl, alkoxy, aryloxy, haloalkyl, haloalkoxy, hydroxyalkyl, N-sulfonamido, S–sulfonamido, sulfonyl, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, carbonyl, C–carboxy, $-CH_2-$(mono-substituted amine) and CH_2-(di-substituted amine).

57. The compound of Claim 56, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of $C_{1\text{-}6}$ alkyl, alkoxy, aryl, cyano, halogen, haloalkyl and haloalkoxy.

58. The compound of Claim 56, wherein the optionally substituted cycloalkyl is a substituted cycloalkyl substituted with one or more groups selected from the group consisting of $C_{1\text{-}6}$ alkyl, alkoxy, halogen and haloalkyl.

59. The compound of Claim 56, wherein the optionally substituted heterocyclyl is a substituted heterocyclyl substituted with one or more groups selected from the group consisting of $C_{1\text{-}6}$ alkyl, alkoxy, halogen, haloalkyl, aryl($C_{1\text{-}6}$ alkyl) and C-carboxy.

60. The compound of any one of Claims 34-59, wherein $\mathbf{Z^1}$ is 0.

61. The compound of any one of Claims 34-59, wherein $\mathbf{Z^1}$ is 1.

62. The compound of any one of Claims 34-59, wherein $\mathbf{Z^1}$ is 2.

63. The compound of any one of Claims 34-59, wherein $\mathbf{Z^1}$ is 3.

64. The compound of any one of Claims 34-59, wherein $\mathbf{Z^1}$ is 4.

65. The compound of any one of Claims 34-64, wherein $\mathbf{Z^2}$ is 0.

66. The compound of any one of Claims 34-64, wherein $\mathbf{Z^2}$ is 1.

67. The compound of any one of Claims 34-64, wherein $\mathbf{Z^2}$ is 2.

68. The compound of any one of Claims 34-64, wherein $\mathbf{Z^2}$ is 3.

69. The compound of any one of Claims 34-64, wherein $\mathbf{Z^2}$ is 4.

70. The compound of any one of Claims 1-18, wherein $\mathbf{G^1}$ is $\mathbf{R^5}$.

71. The compound of Claim 70, wherein $\mathbf{R^5}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

72. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted aryl.

73. The compound of Claim 72, wherein the optionally substituted aryl is an optionally substituted phenyl.

74. The compound of Claim 73, wherein the optionally substituted phenyl is a substituted phenyl.

75. The compound of Claim 74, wherein the substituted phenyl is a mono-substituted phenyl.

76. The compound of Claim 75, wherein the substituted phenyl is an ortho-substituted phenyl.

77. The compound of Claim 75, wherein the substituted phenyl is a meta-substituted phenyl.

78. The compound of Claim 75, wherein the substituted phenyl is a para-substituted phenyl.

79. The compound of Claim 74, wherein the substituted phenyl is a di-substituted phenyl.

80. The compound of Claim 74, wherein the substituted phenyl is substituted with 3 or more substituents.

81. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted cycloalkyl.

82. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted heteroaryl.

83. The compound of Claim 70, wherein $\mathbf{R^5}$ is an optionally substituted heterocyclyl.

84. The compound of any one of Claims 70-83, wherein $\mathbf{R^5}$ is substituted with one or more substituents selected from the group consisting of halogen, $C_{1\text{-}6}$ alkyl, alkoxy, aryloxy, haloalkyl, haloalkoxy, hydroxyalkyl, N-sulfonamido, S–sulfonamido, sulfonyl, an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted heterocyclyl, carbonyl, C–carboxy, $-CH_2-$(mono-substituted amine) and CH_2-(di-substituted amine).

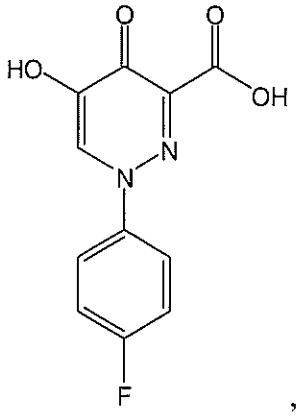
85. The compound of Claim 84, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of $C_{1\text{-}6}$ alkyl, alkoxy, halogen and haloalkyl.

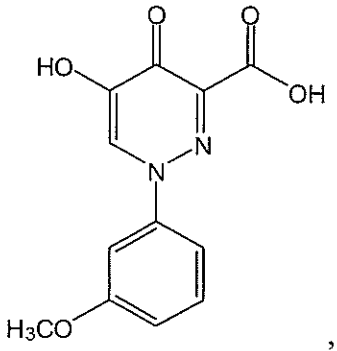
86. The compound of Claim 84, wherein the optionally substituted cycloalkyl is a substituted cycloalkyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen and haloalkyl.

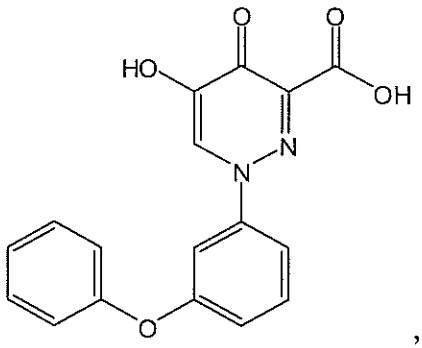
87. The compound of Claim 84, wherein the optionally substituted heterocyclyl is a substituted heterocyclyl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, halogen, haloalkyl, aryl(C_{1-6} alkyl) and C-carboxy.

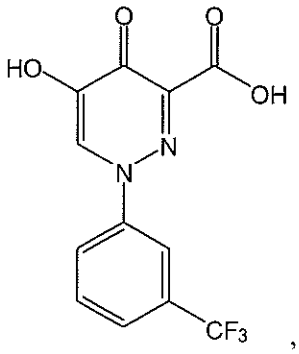
88. The compound of any one of Claims 1-87, wherein $\mathbf{G^3}$ is hydrogen.

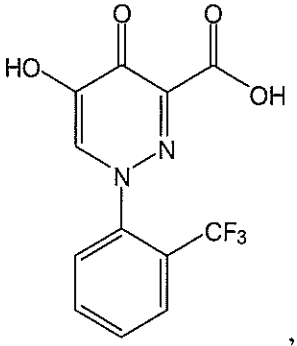
89. The compound of Claim 1, wherein the compound is selected from the group consisting of:

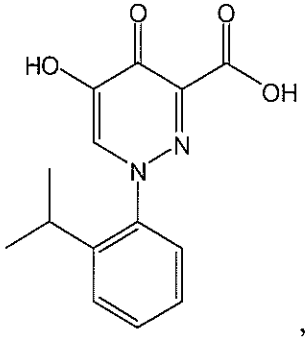


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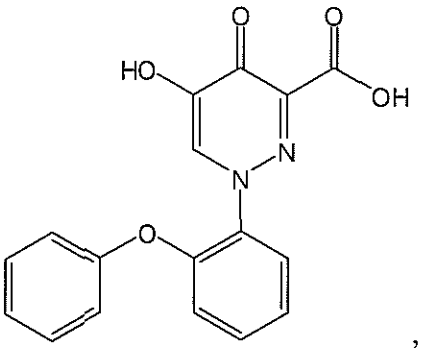
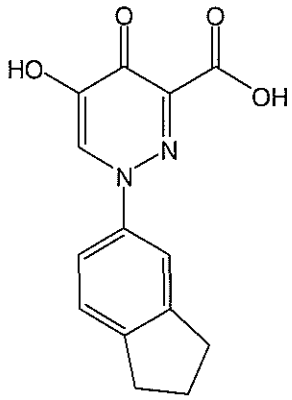
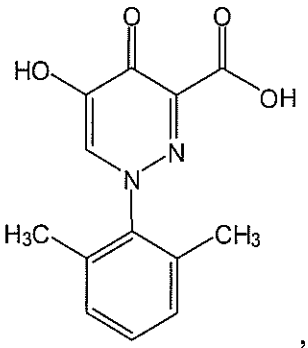
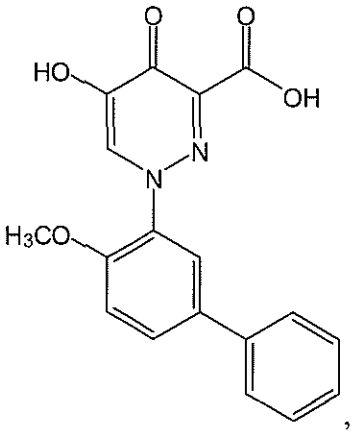
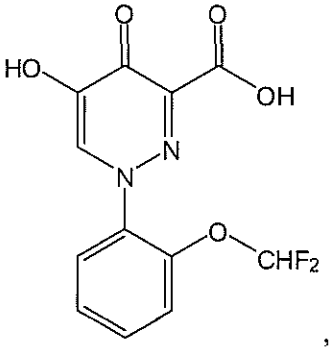
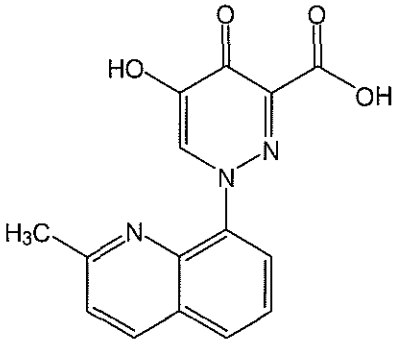
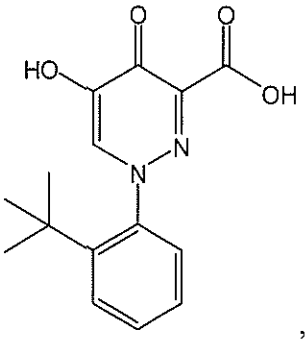
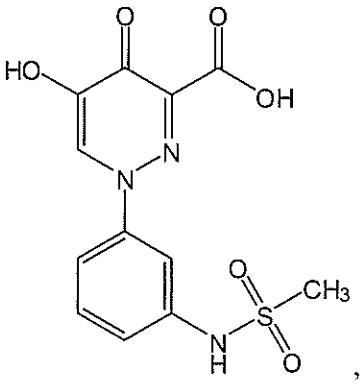
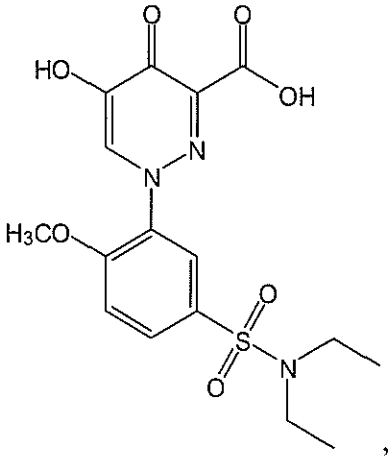
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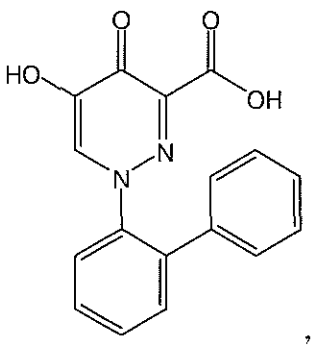
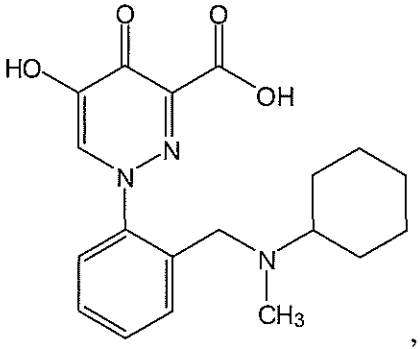
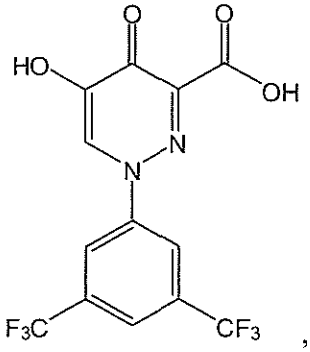
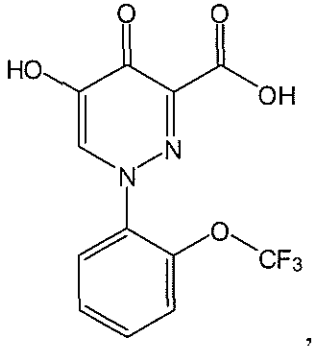
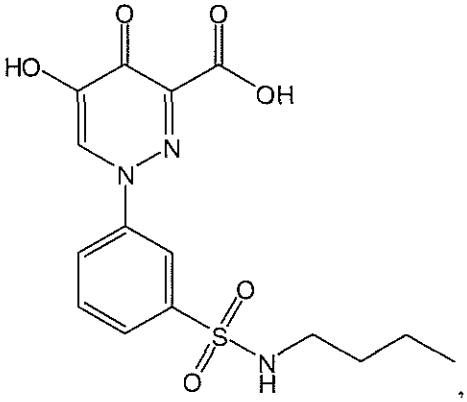
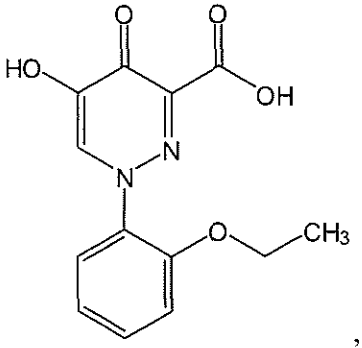
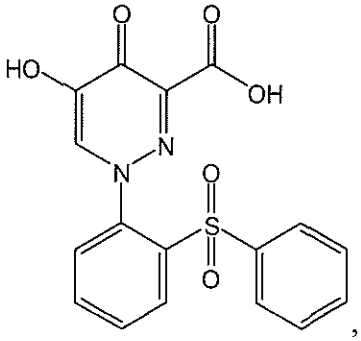
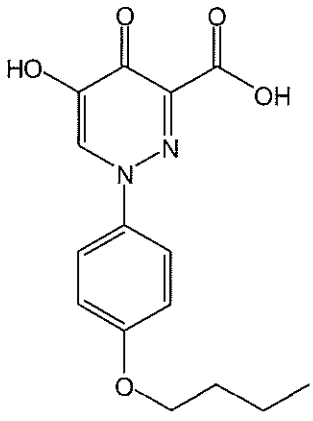
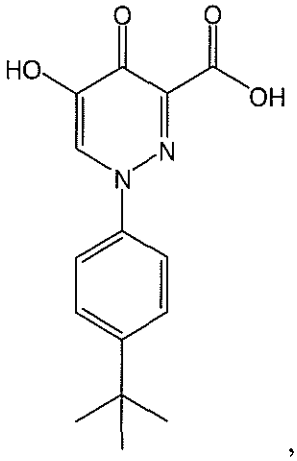
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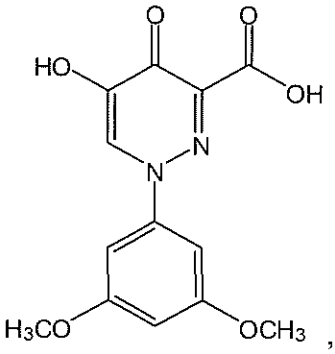
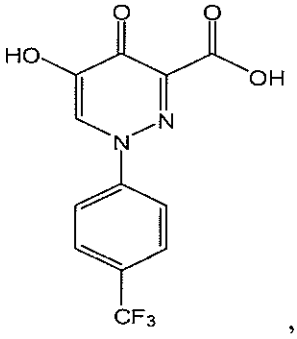
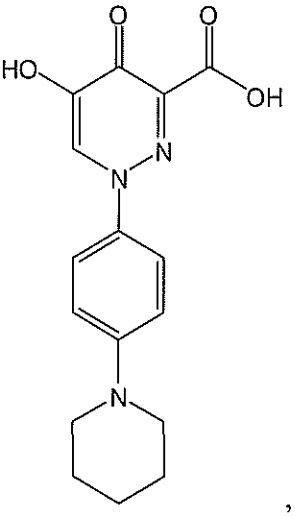
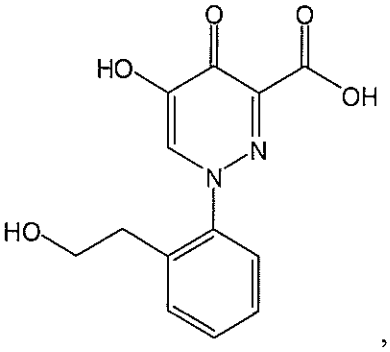
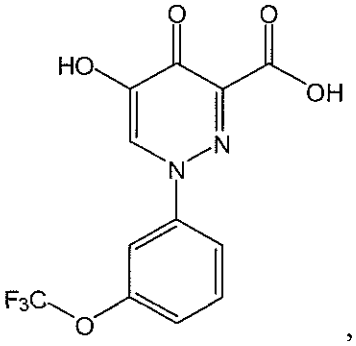
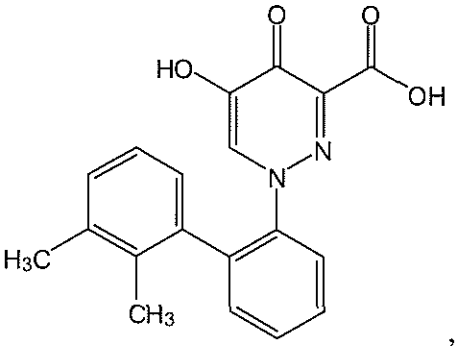
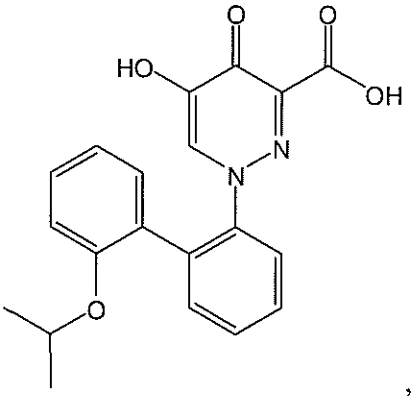
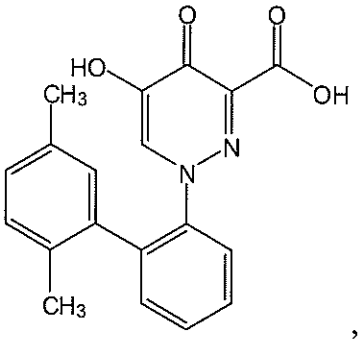
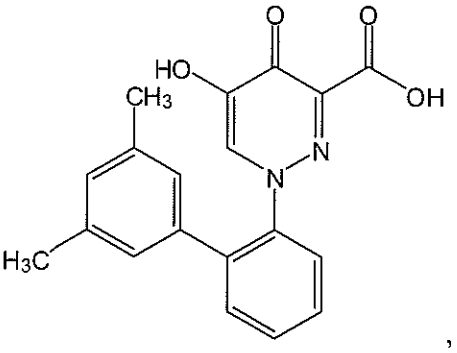
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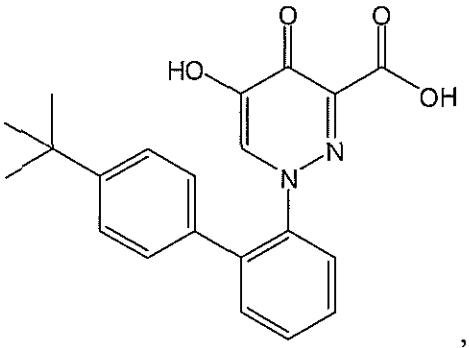
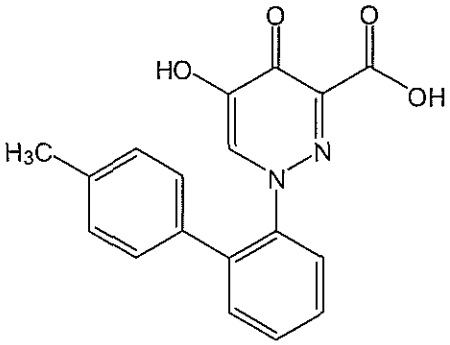
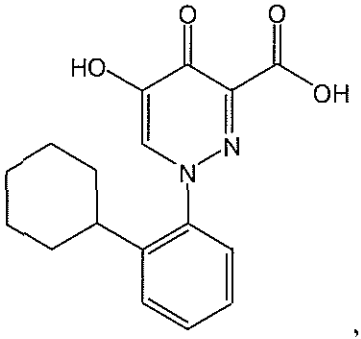
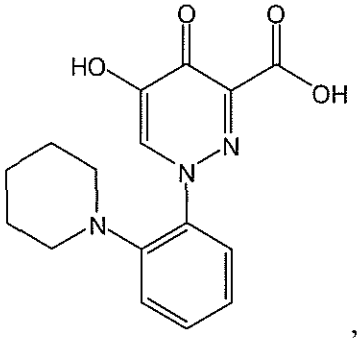
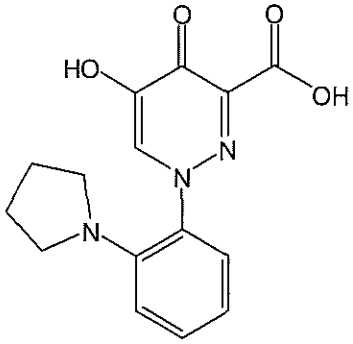
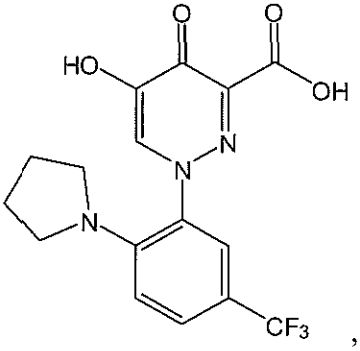
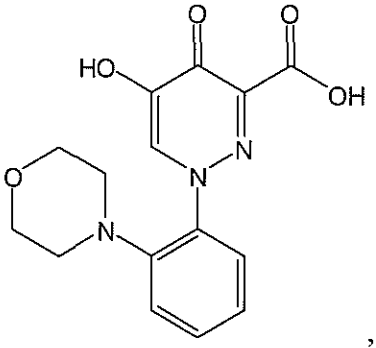
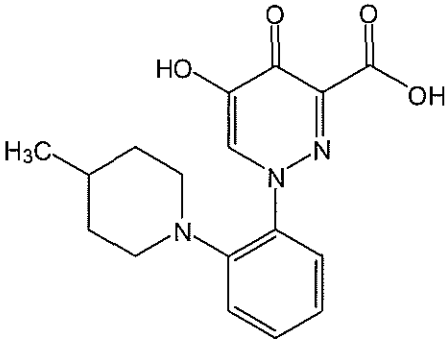
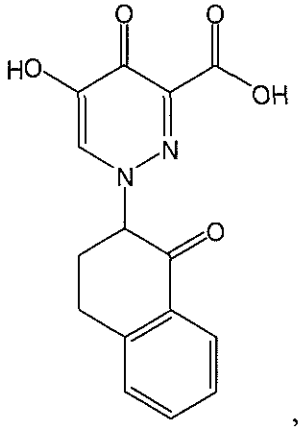
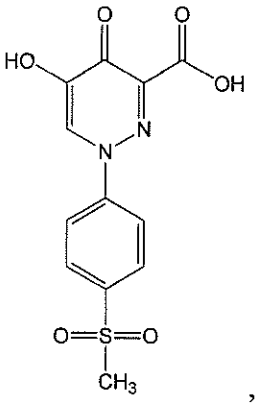
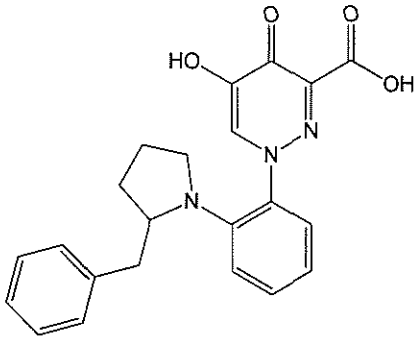
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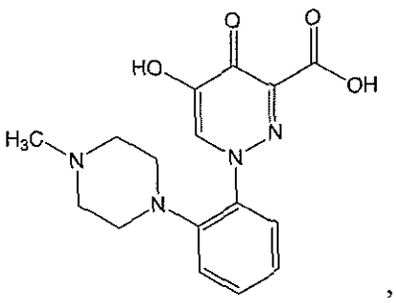
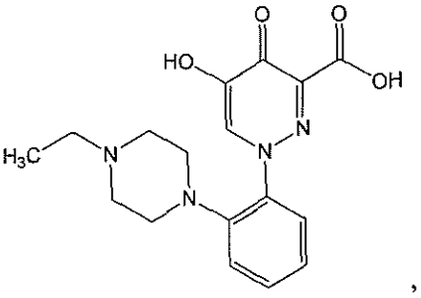
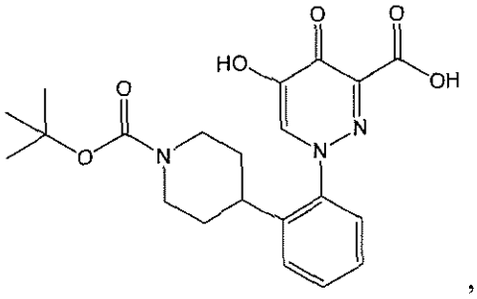
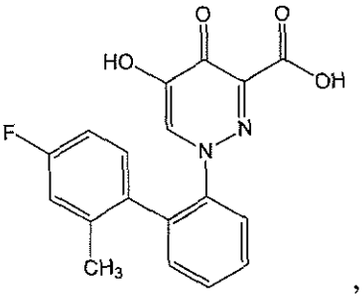
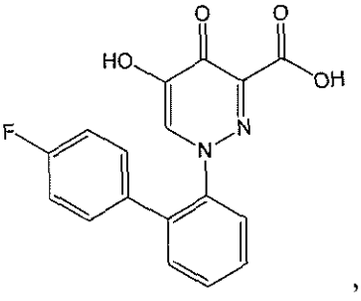
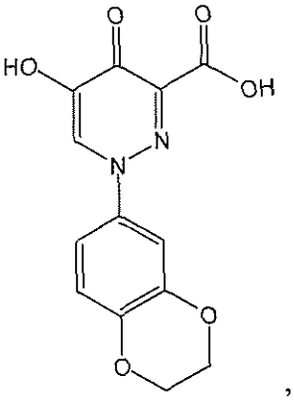
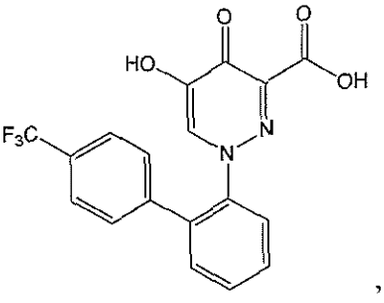
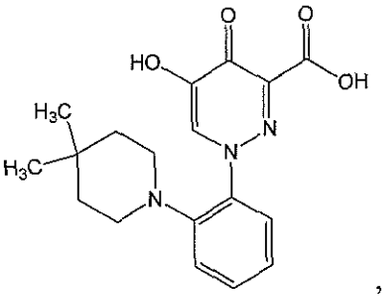
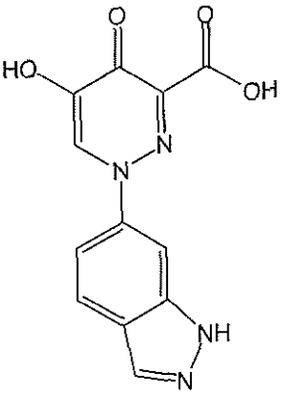
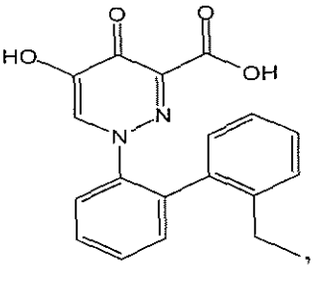
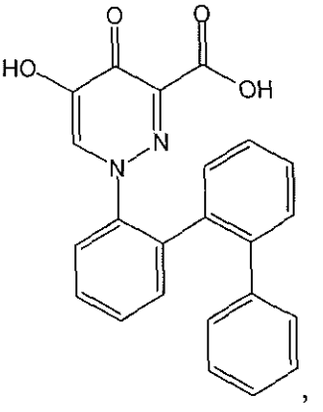
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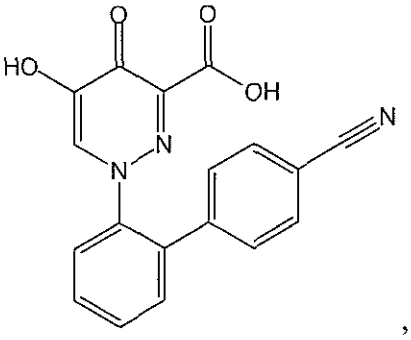
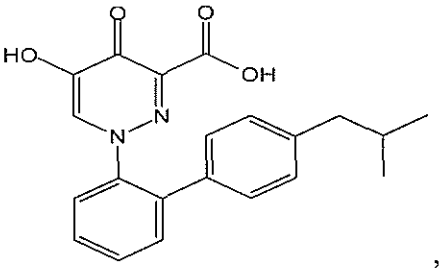
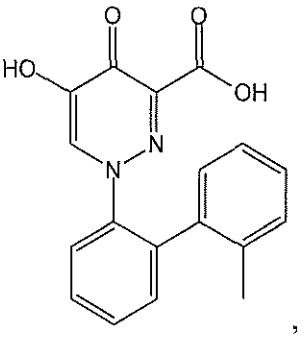
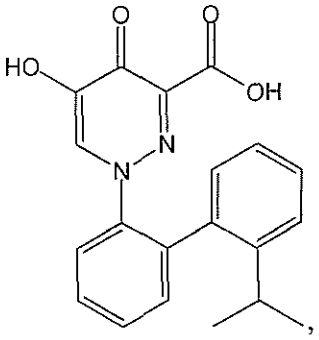
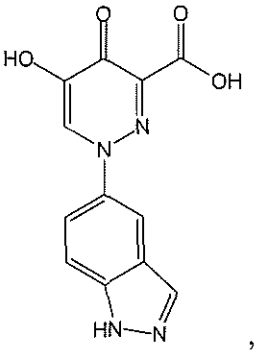
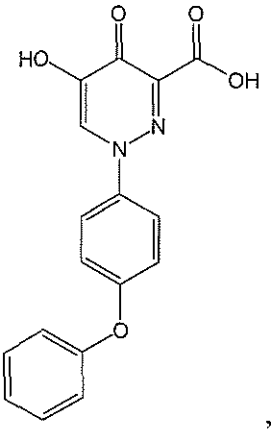
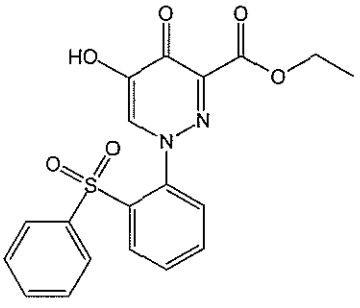
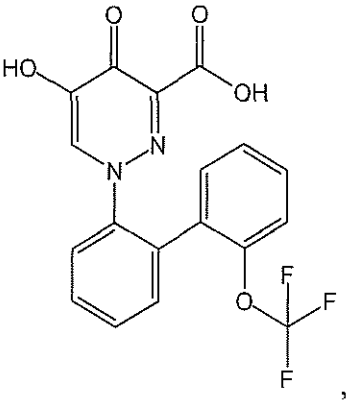

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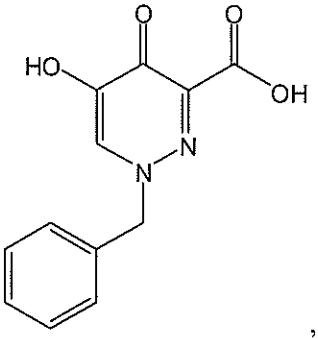
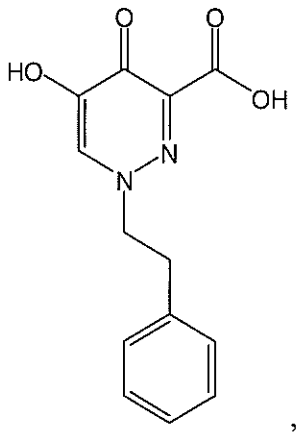
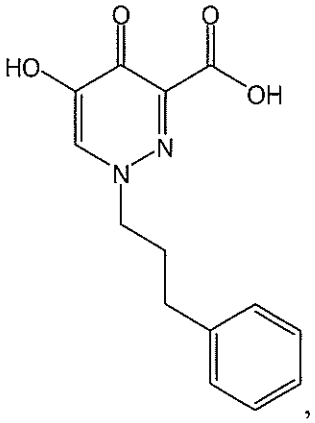
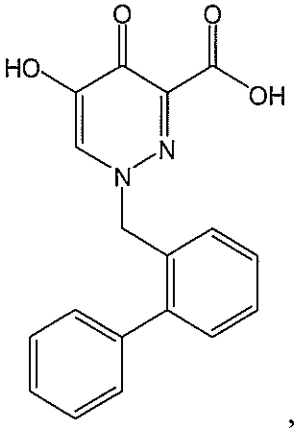
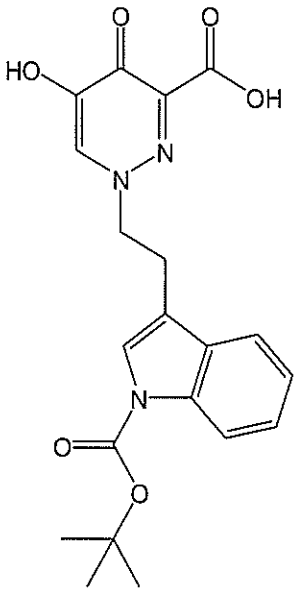
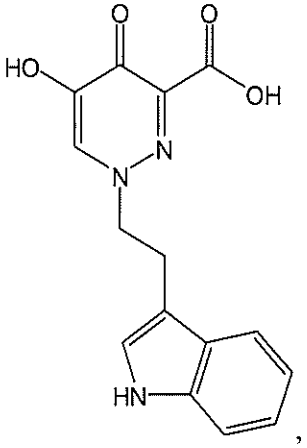
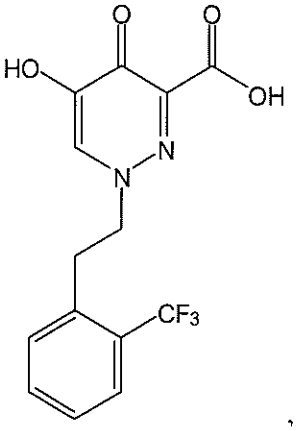
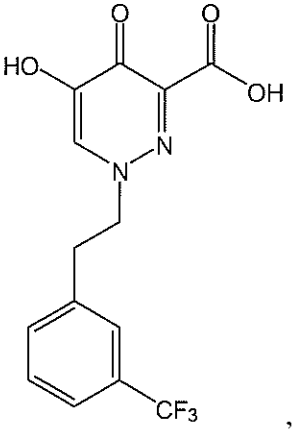
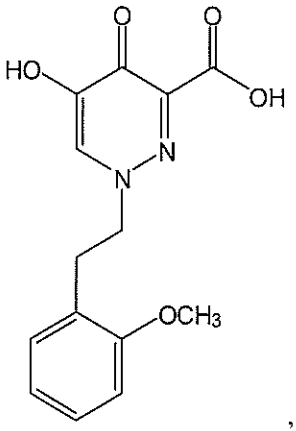
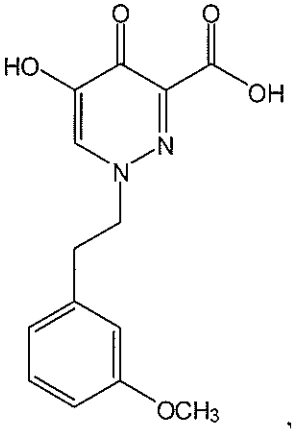

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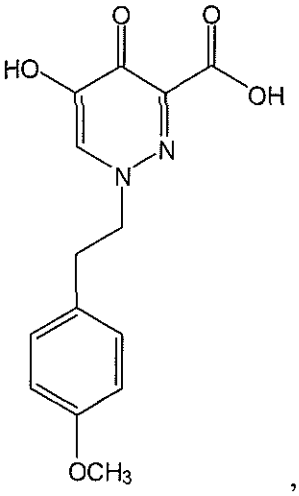
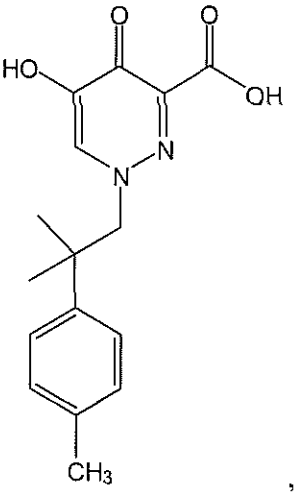
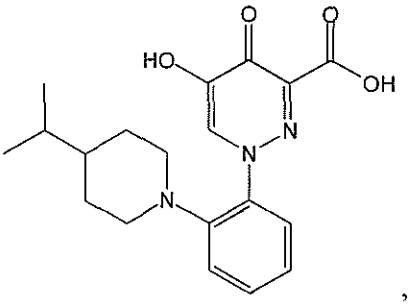
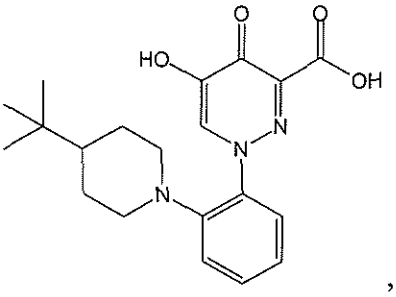
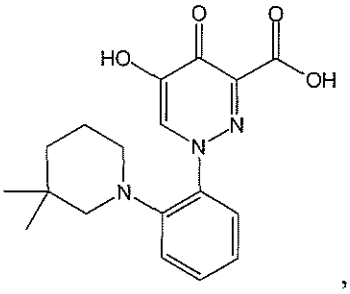
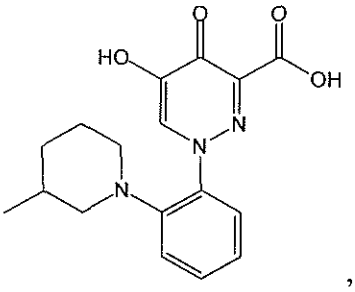
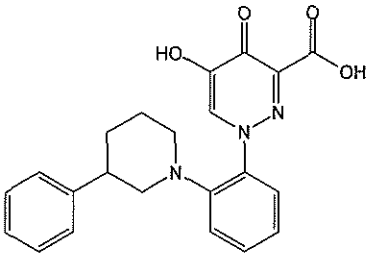
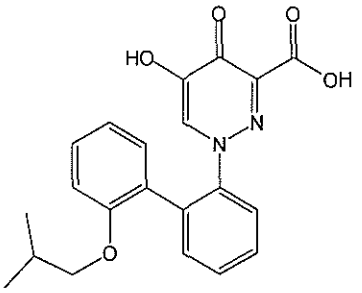
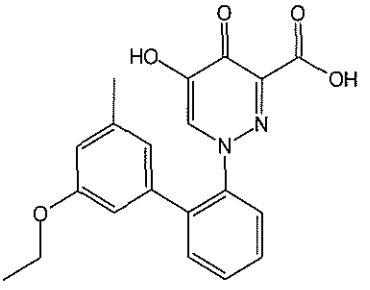
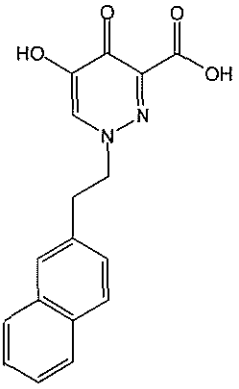
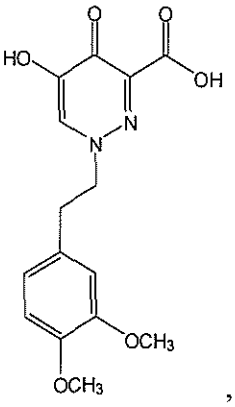

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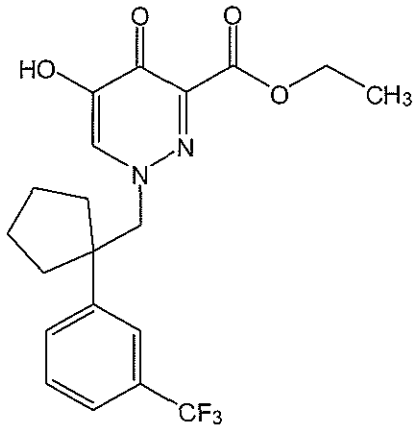
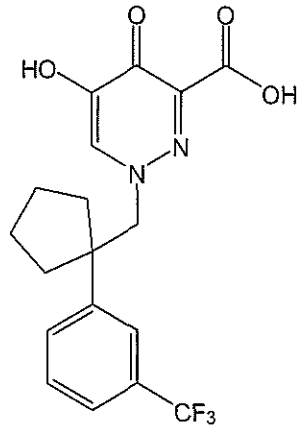
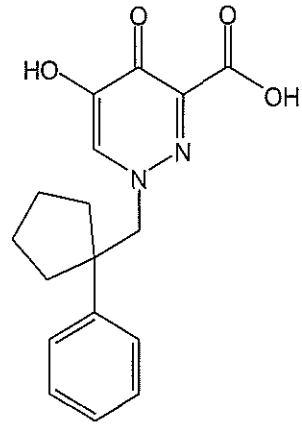
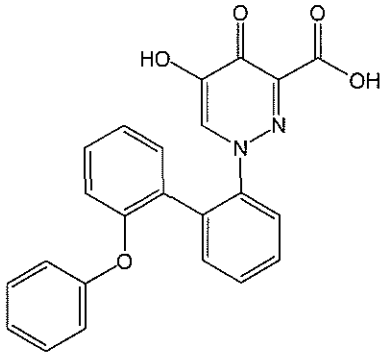
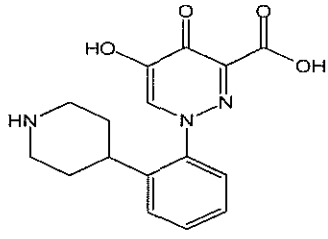
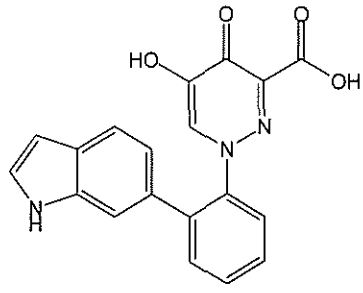
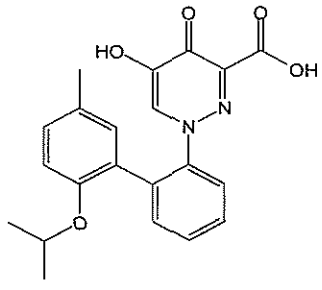
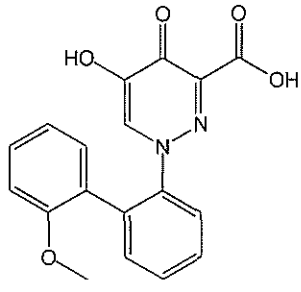
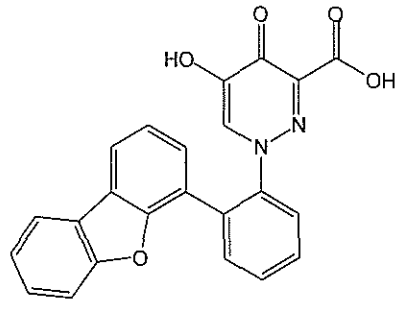
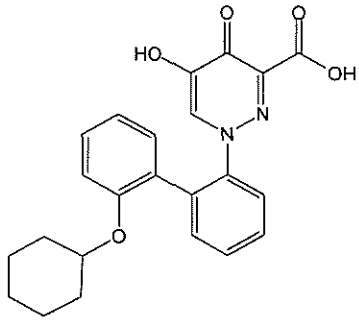
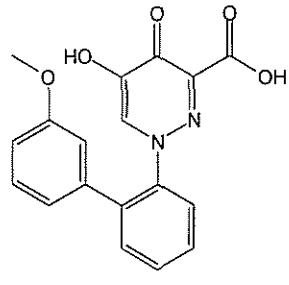
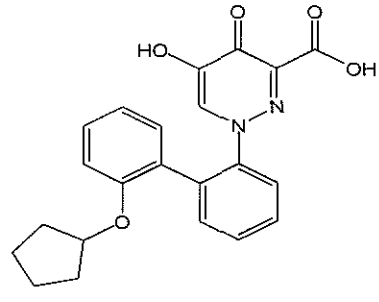

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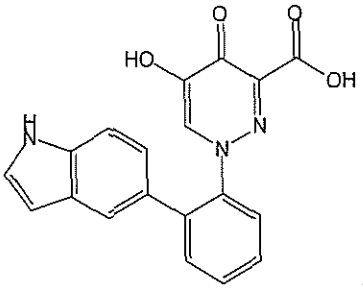
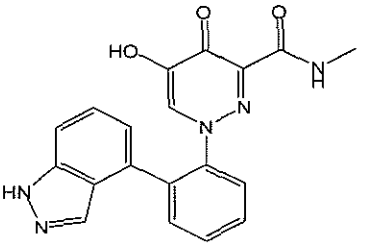
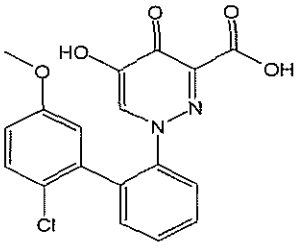
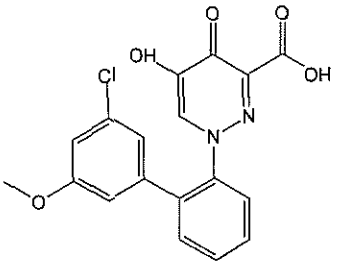
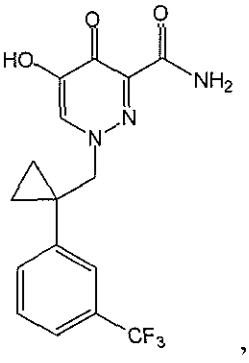
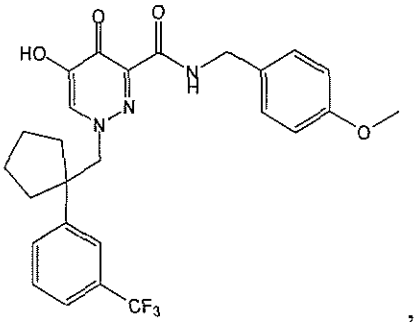
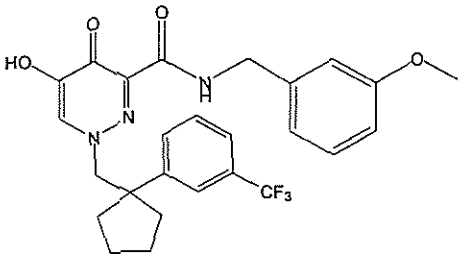
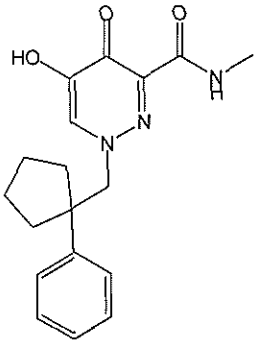
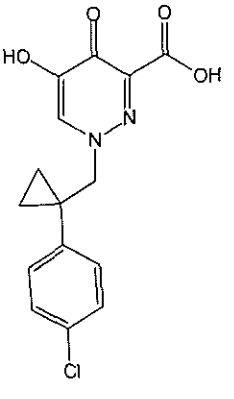
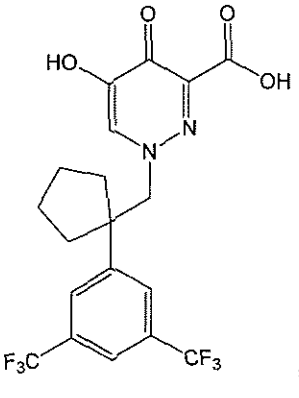
90. The compound of Claim 1, wherein the compound is selected from the group consisting of:


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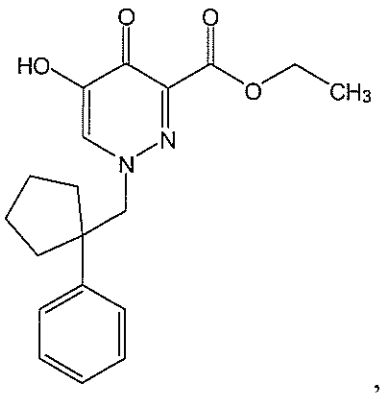
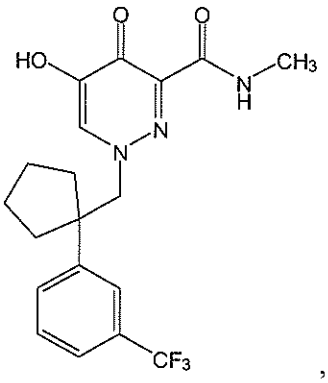
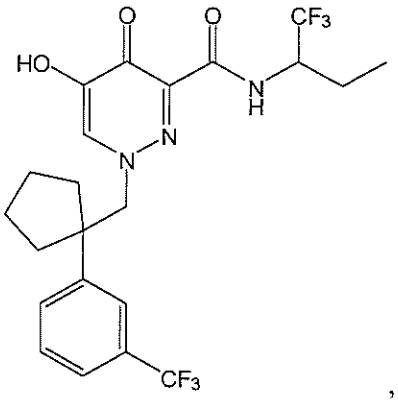
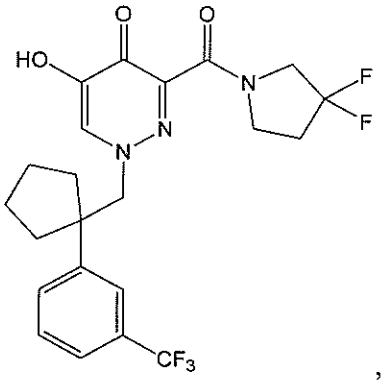
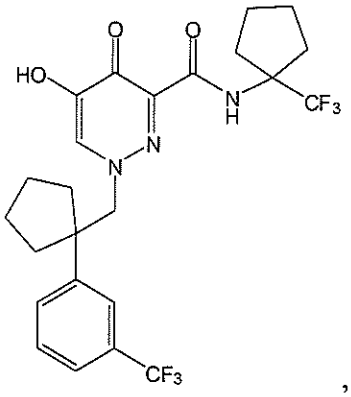
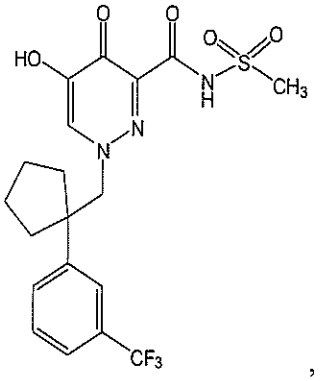
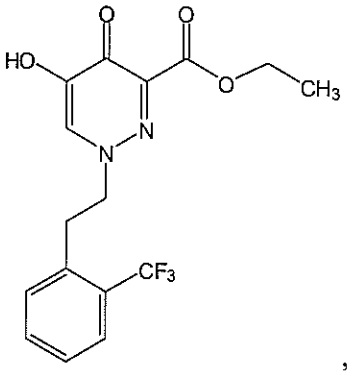
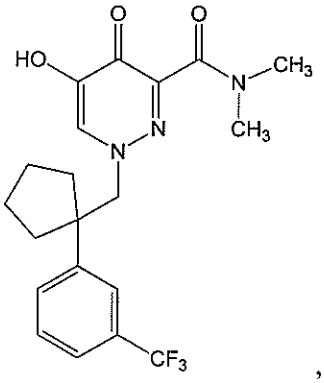
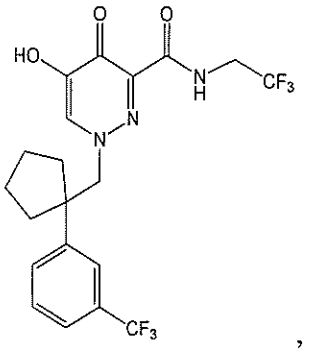

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, or a pharmaceutically acceptable salt of any of the foregoing.

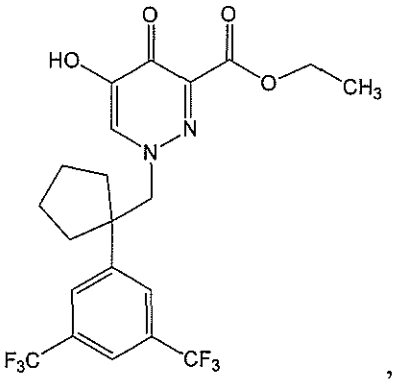
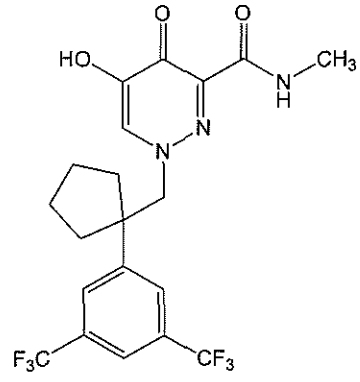
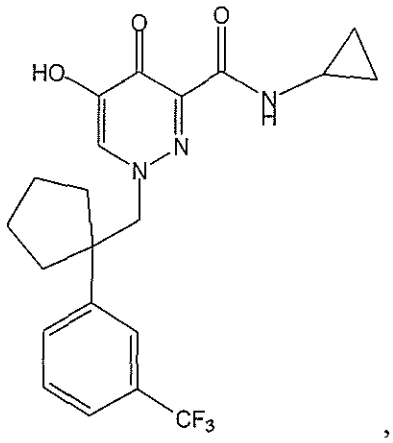
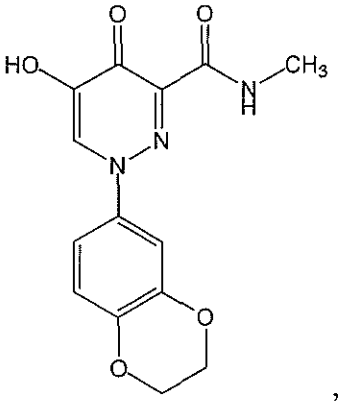
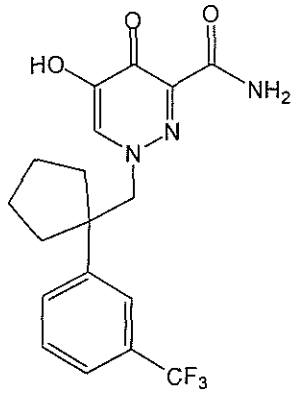
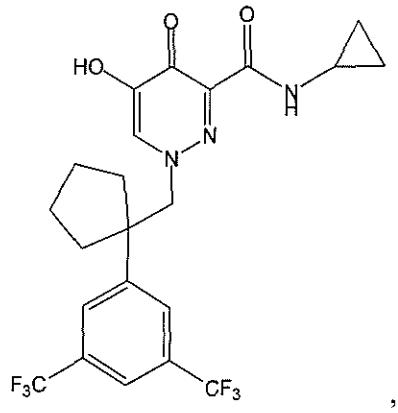
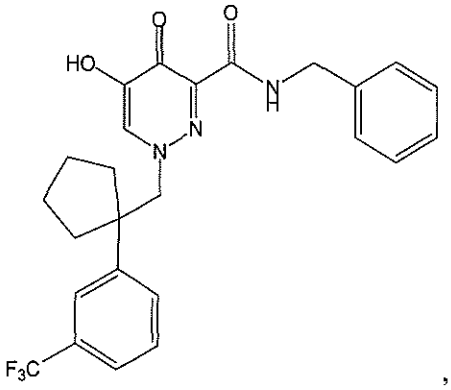
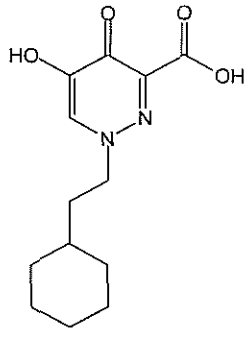
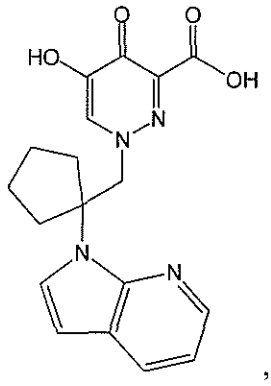
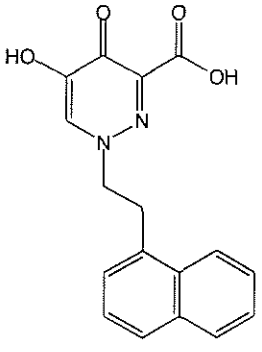
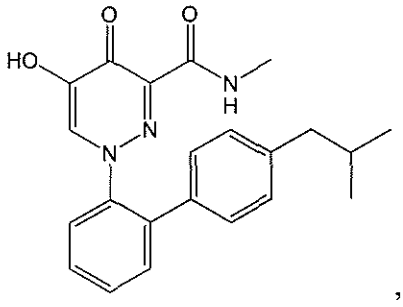
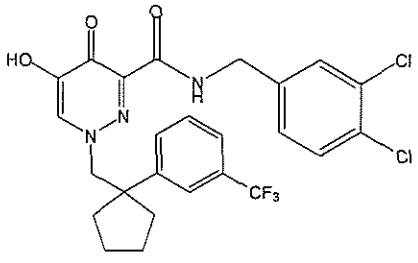
91. The compound of Claim 1, wherein the compound is selected from the group consisting of:

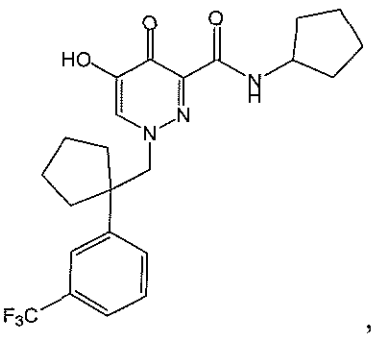
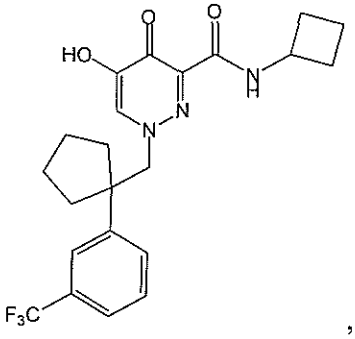
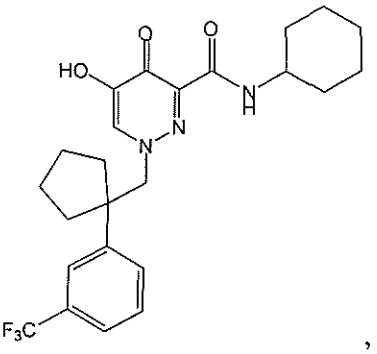
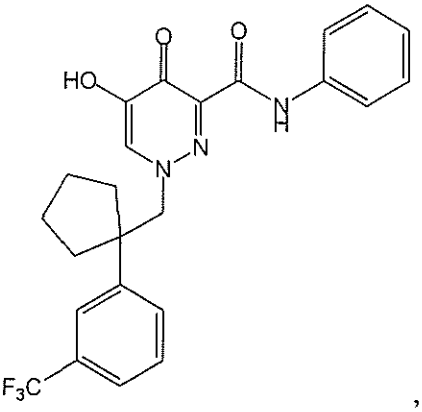
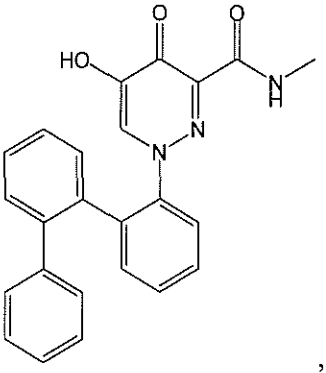
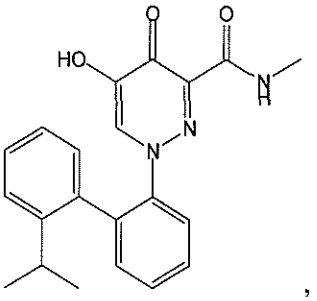
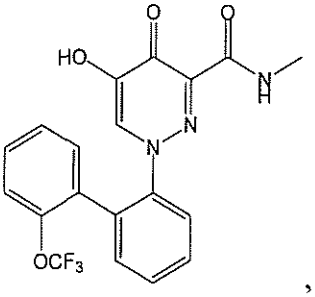
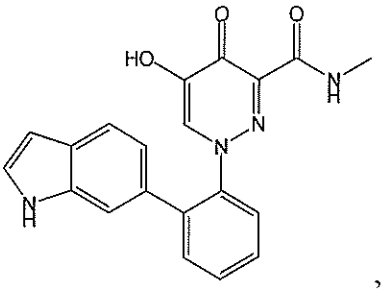
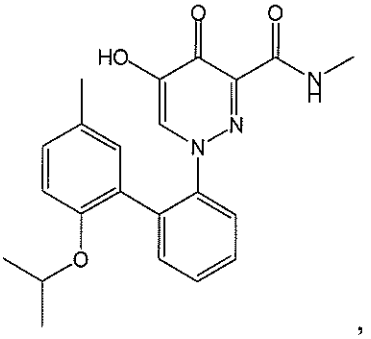
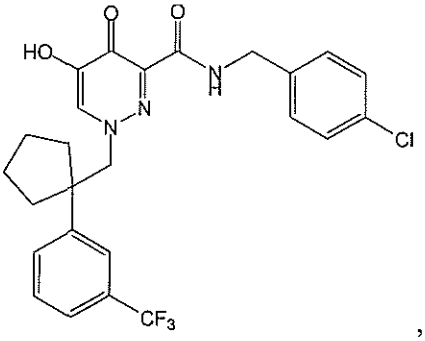
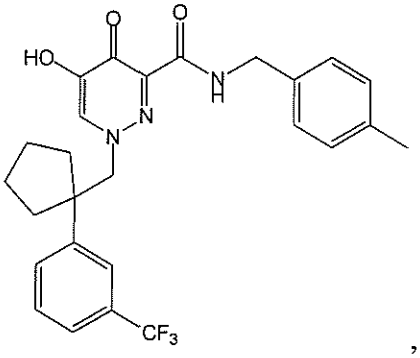
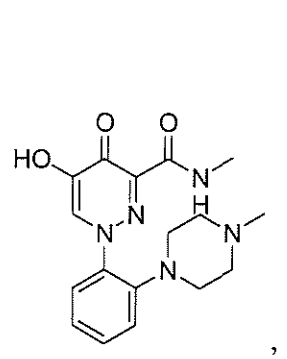

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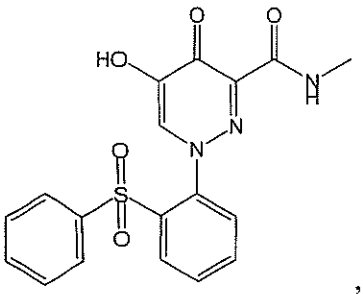
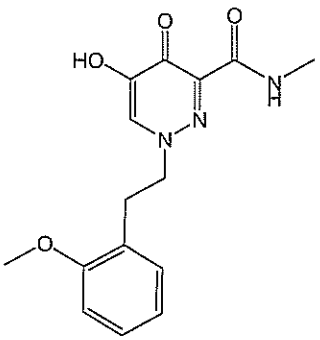
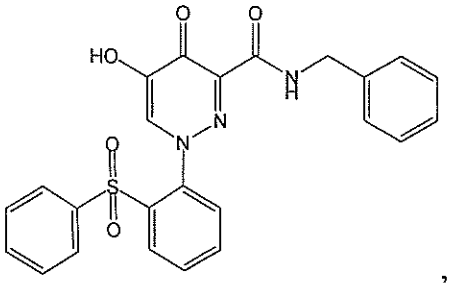
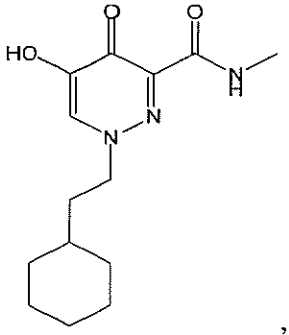
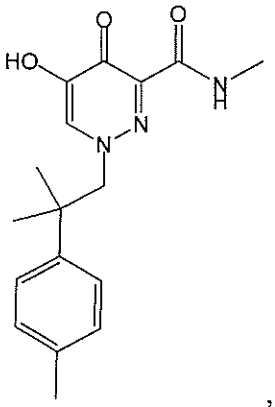
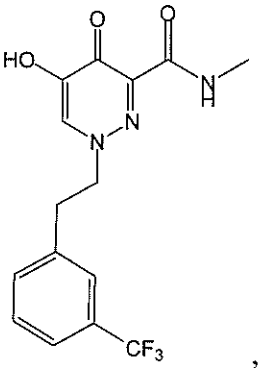
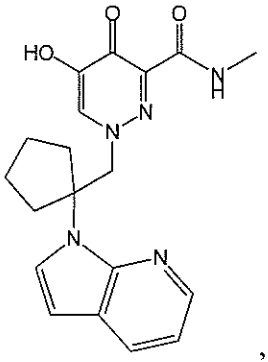
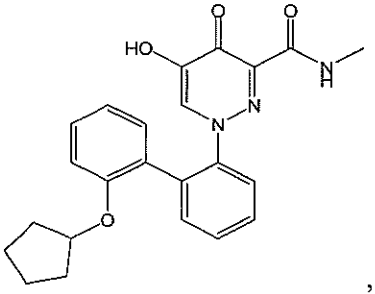
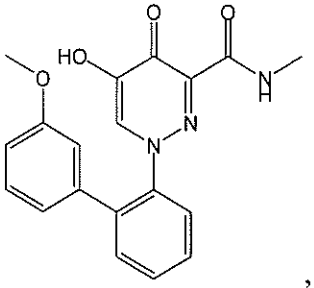
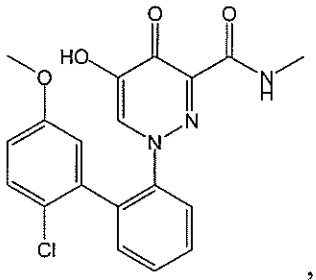
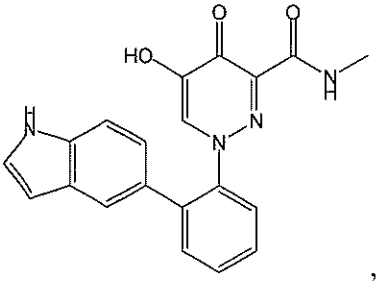
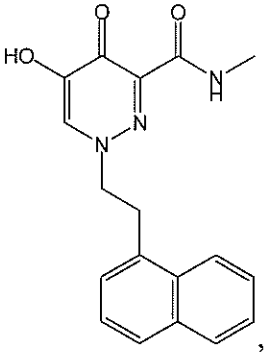
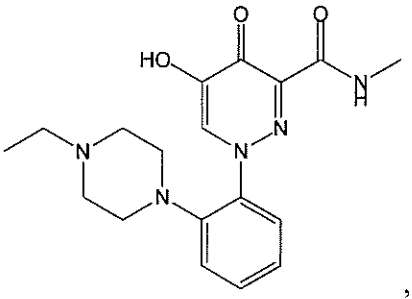

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, or a pharmaceutically acceptable salt of any of the foregoing.

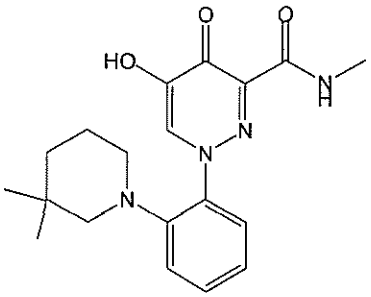
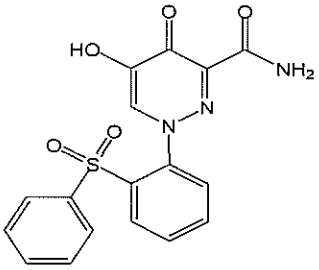
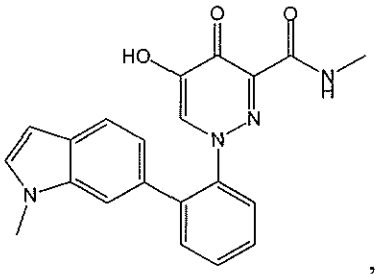
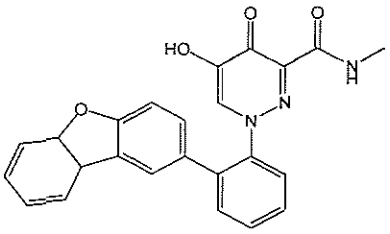
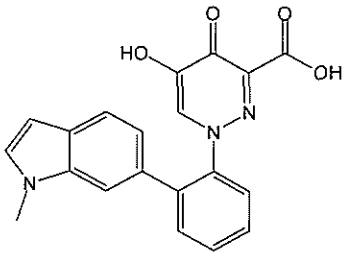
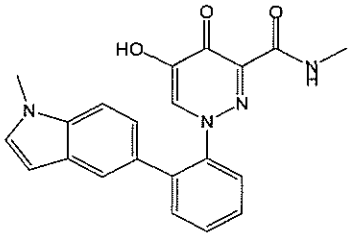
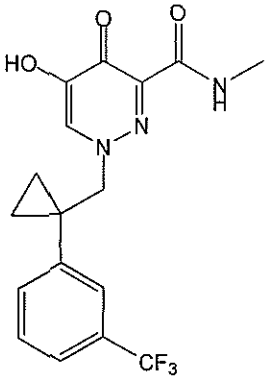
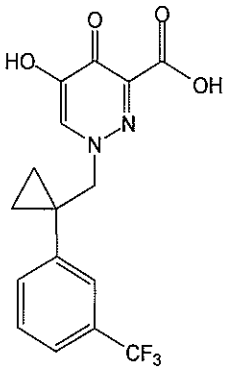
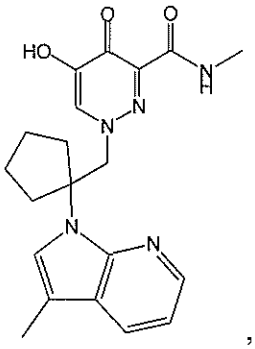
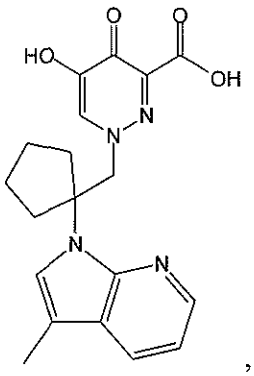
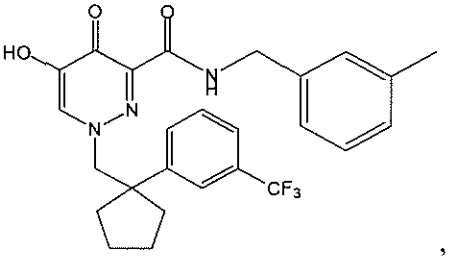
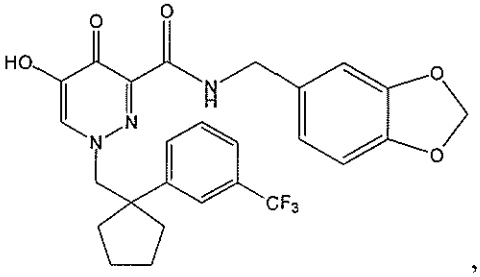
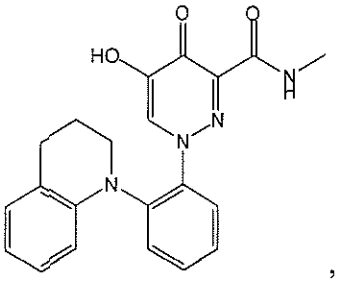
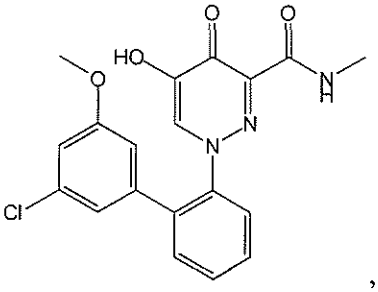
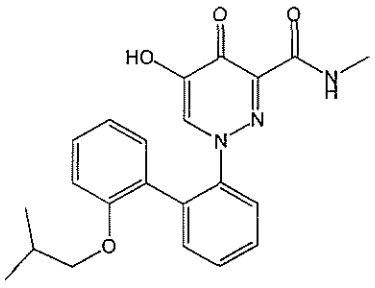
92. The compound of Claim 1, wherein the compound is selected from the group consisting of:

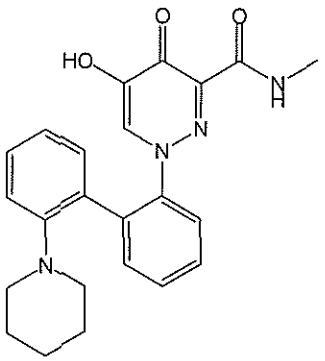
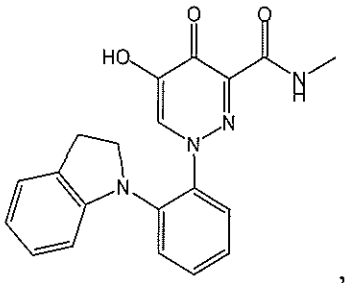
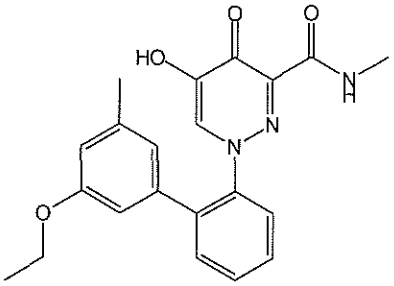
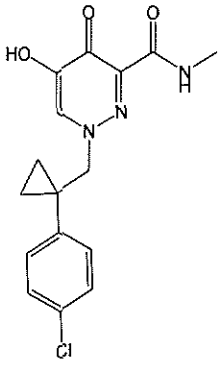
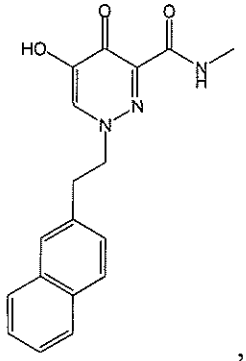
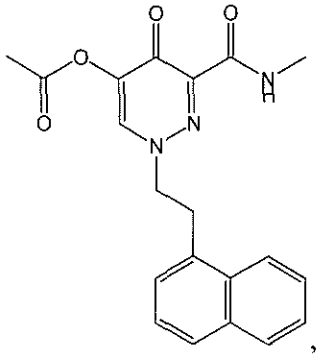
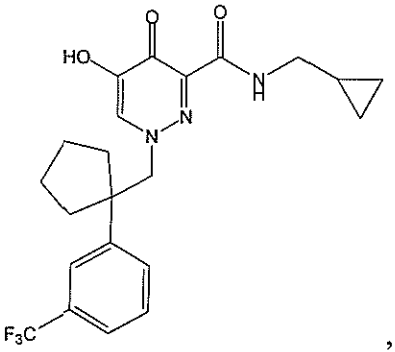
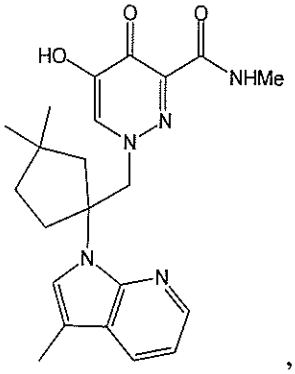
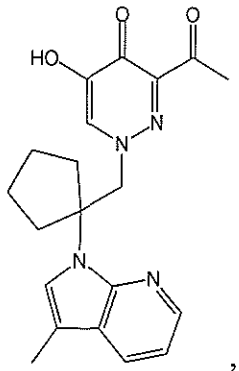
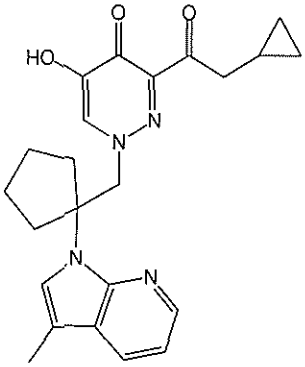
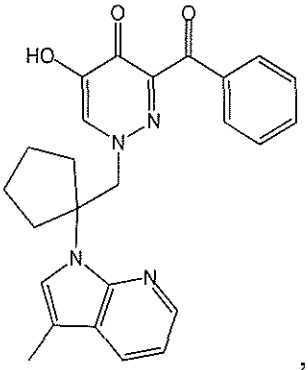
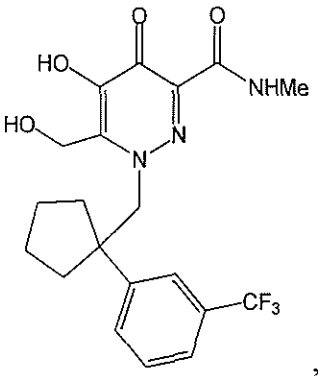

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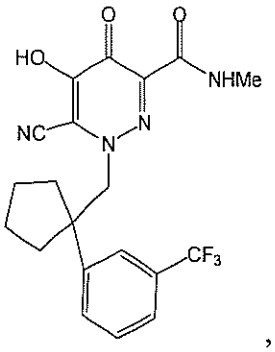
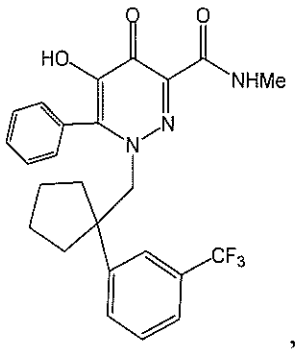
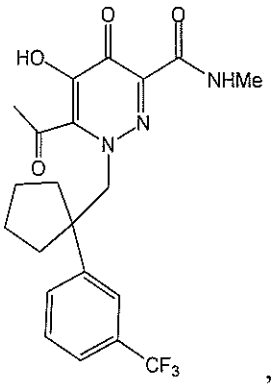
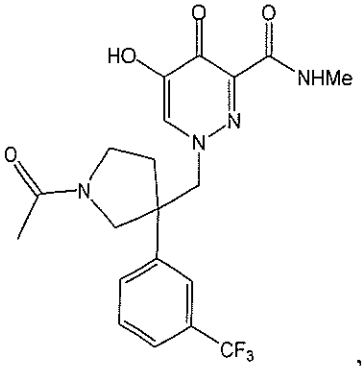
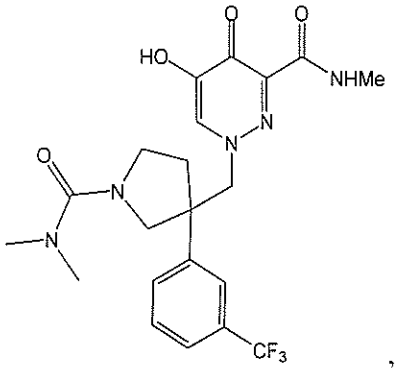
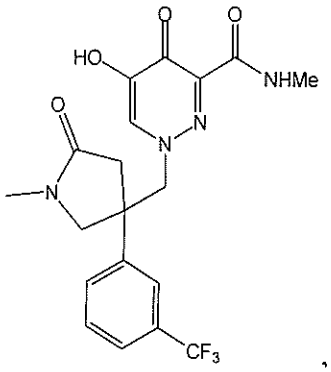
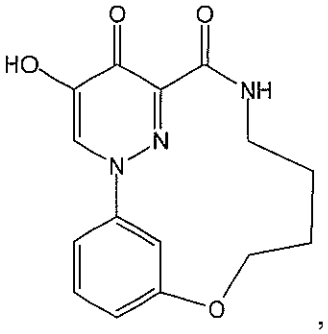
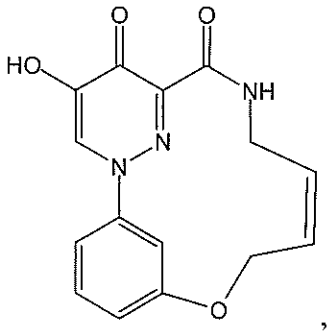
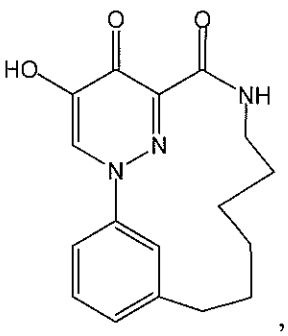
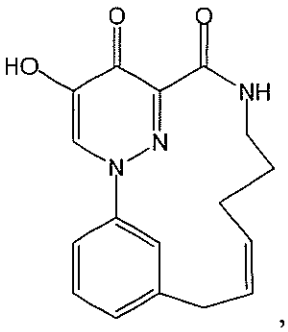
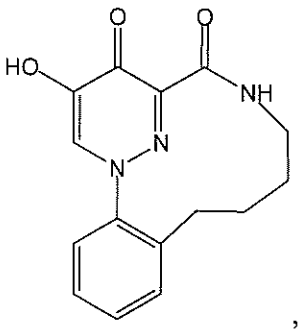
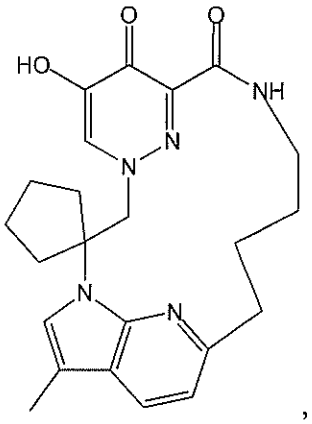

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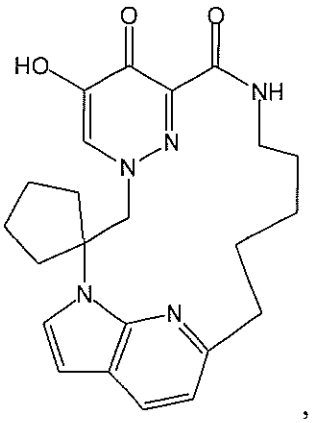
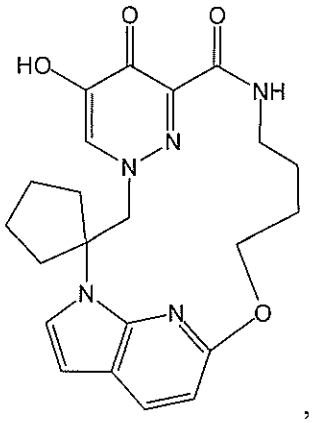
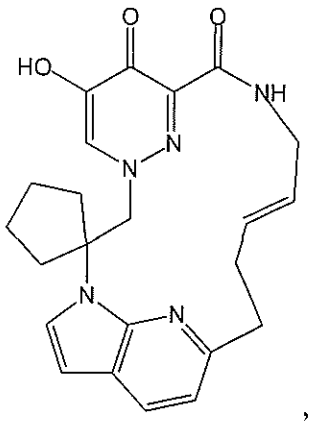
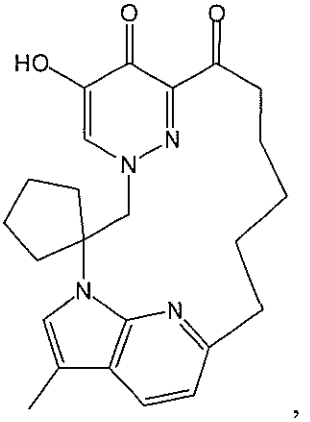
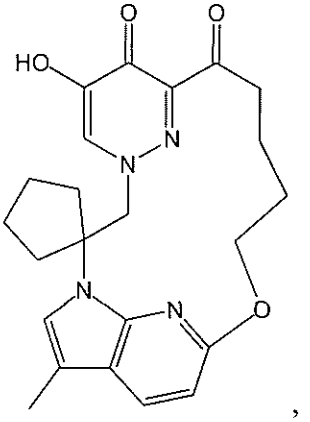
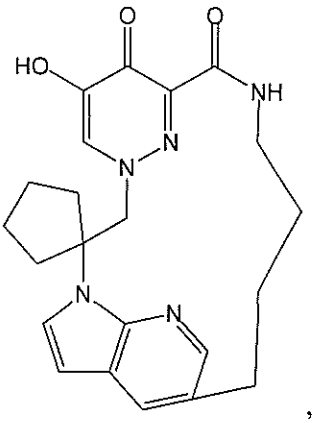
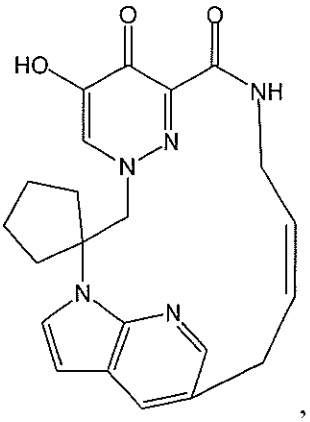
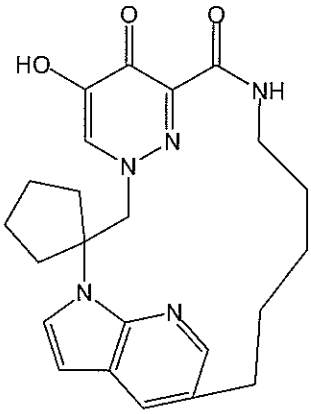
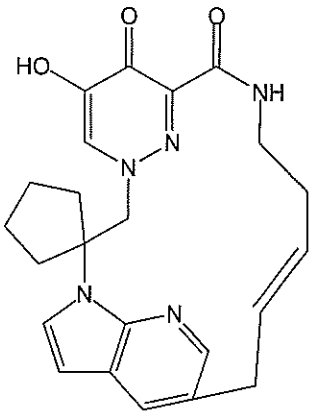

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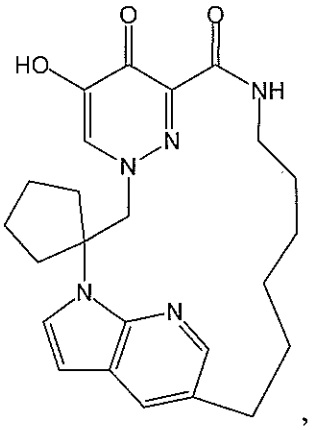
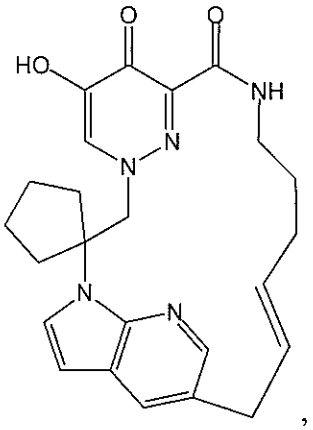
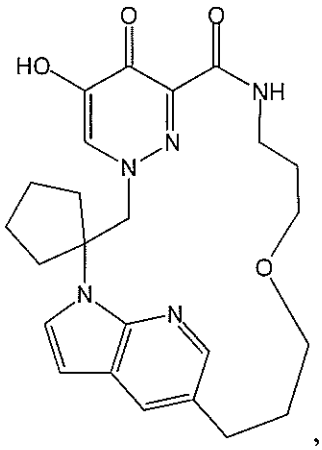
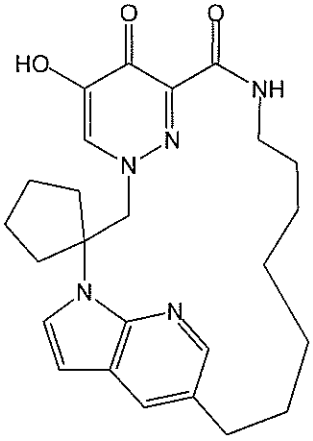
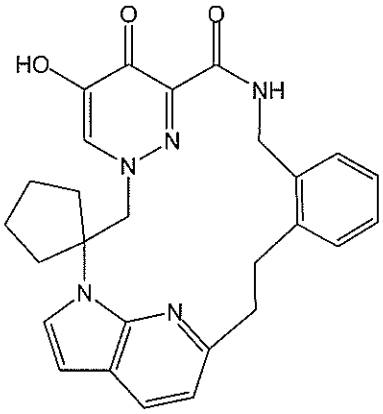
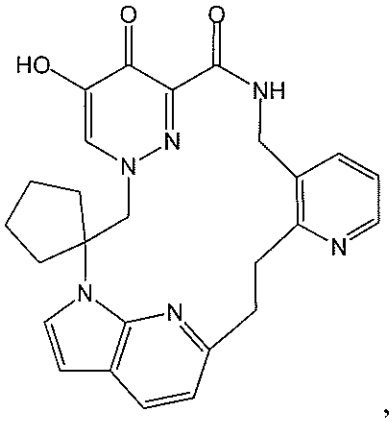
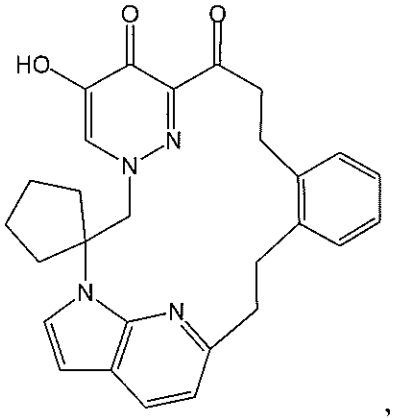
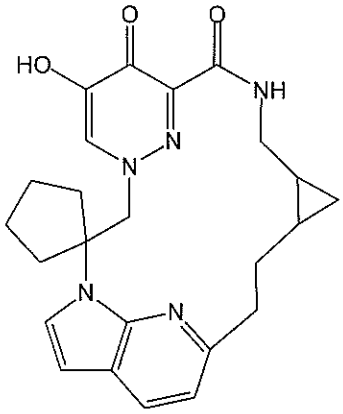
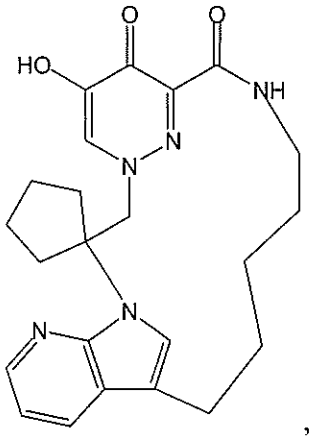

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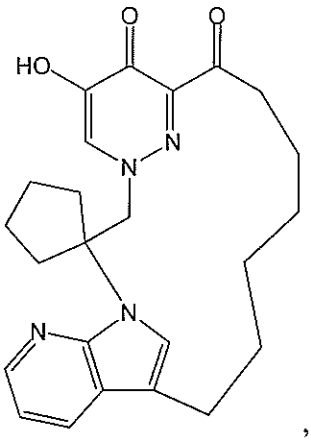
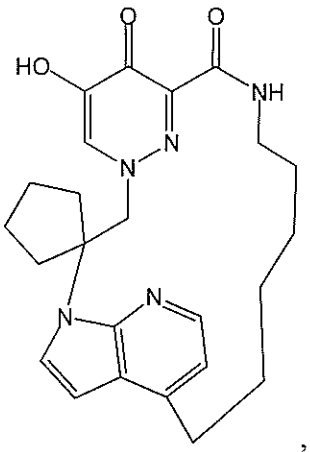
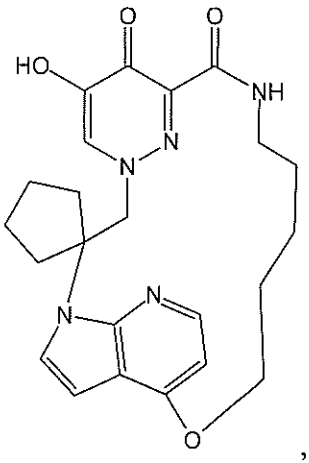
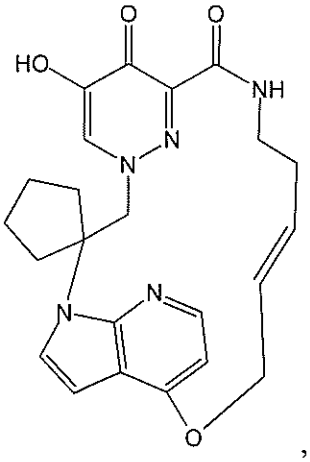
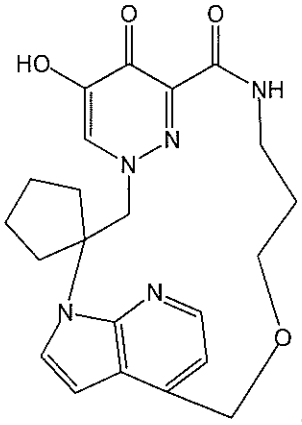

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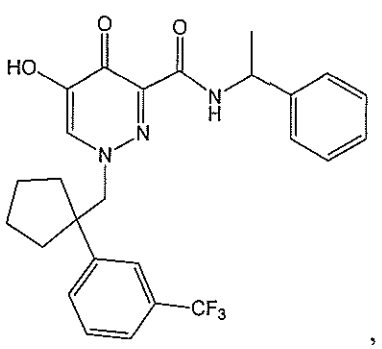
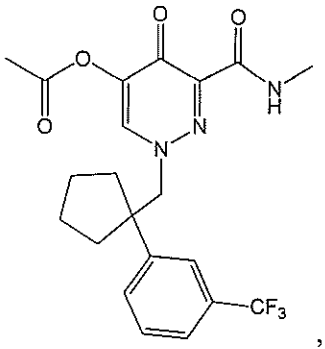
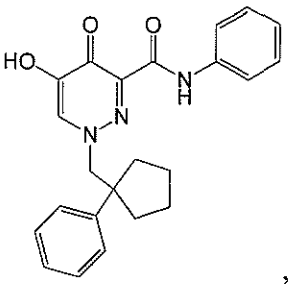
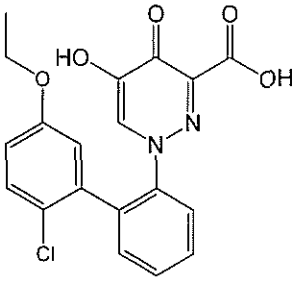
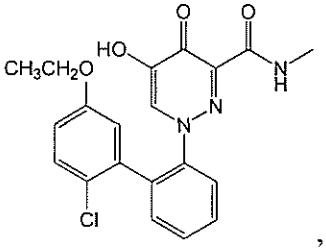
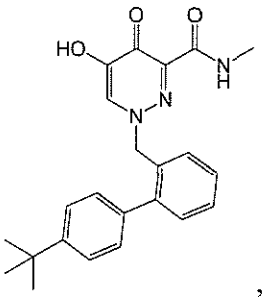
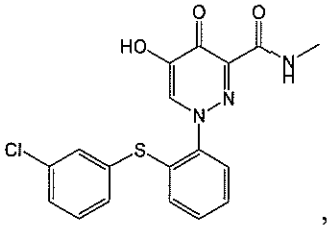
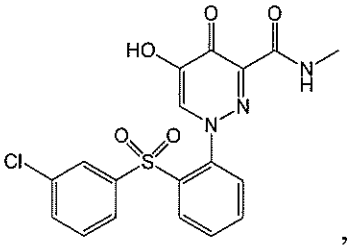
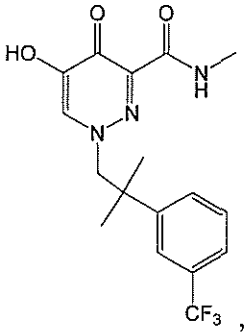

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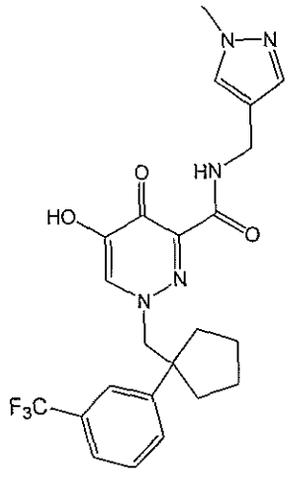
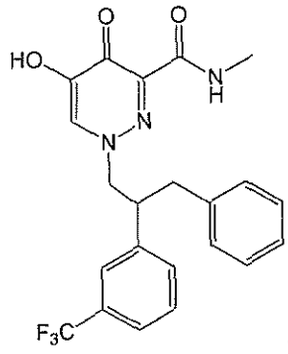
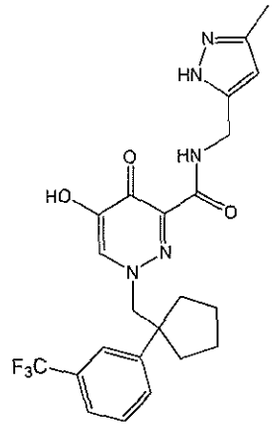
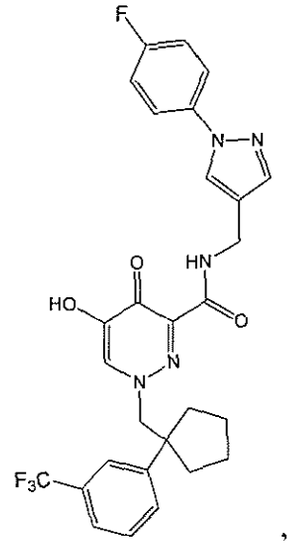
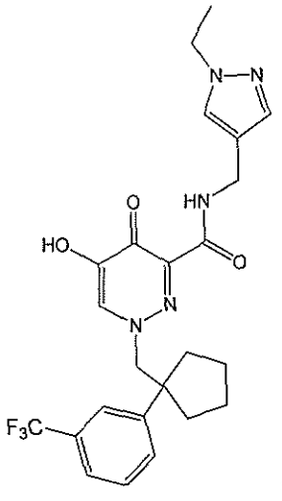
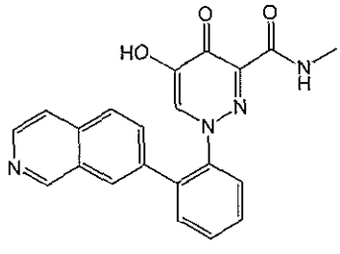
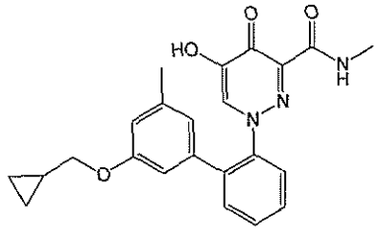
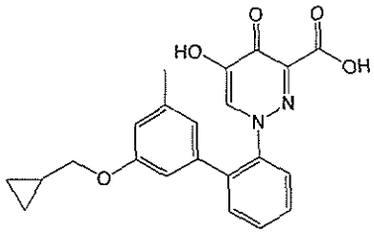
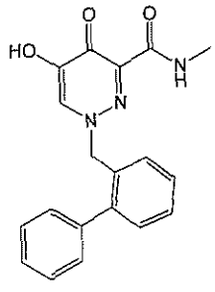
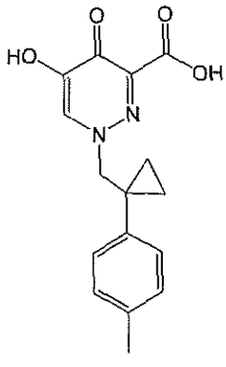
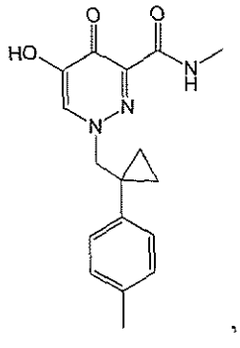

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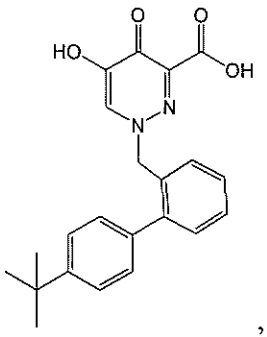
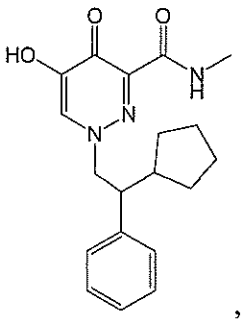
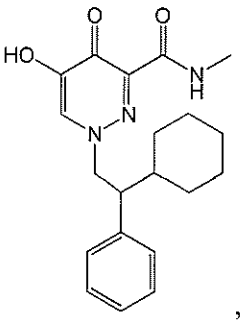
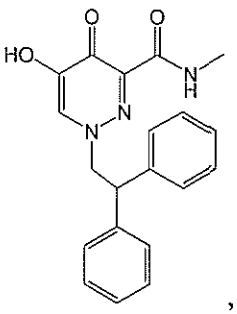
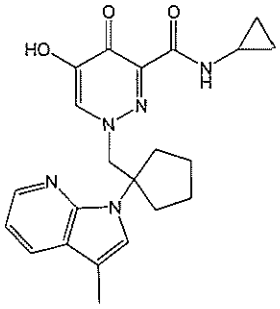
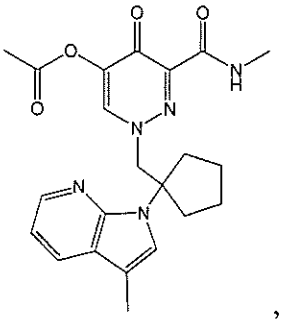
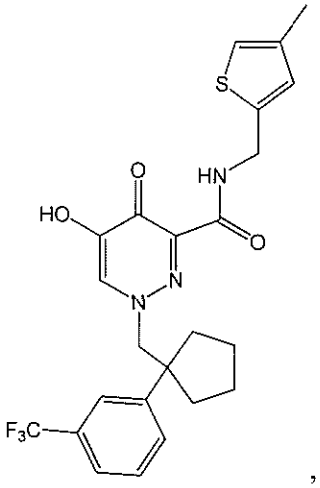
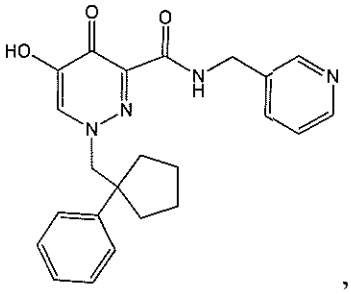
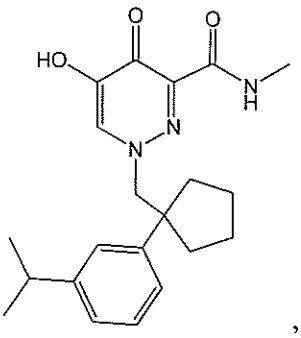
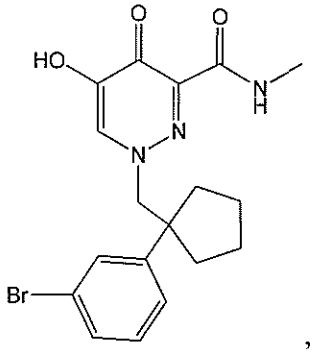

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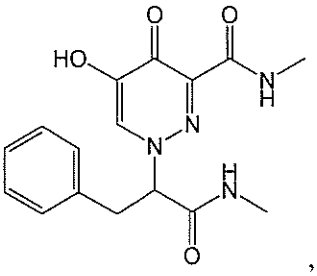
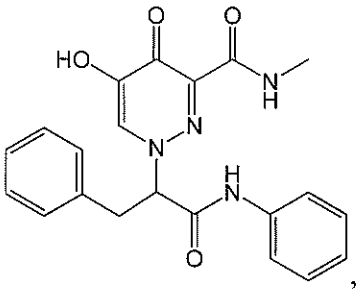
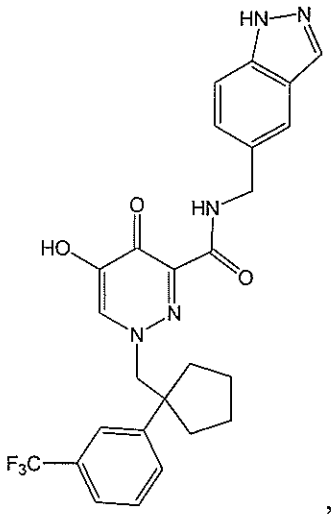
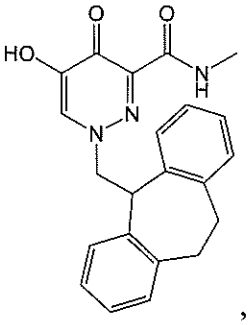
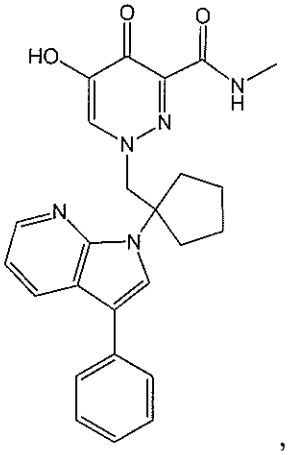
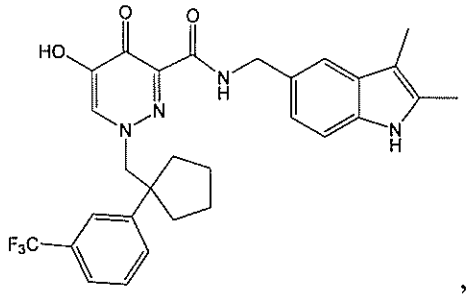
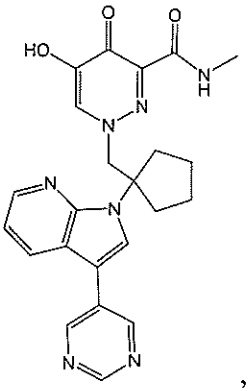
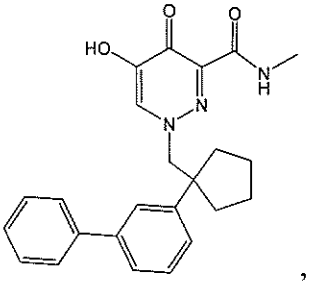
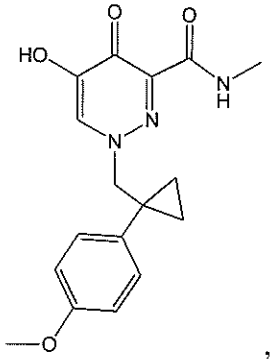
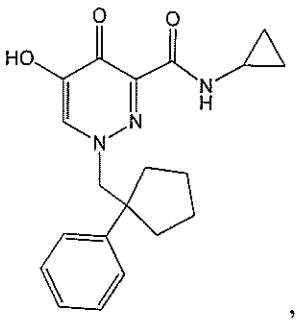

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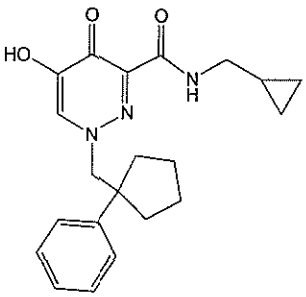
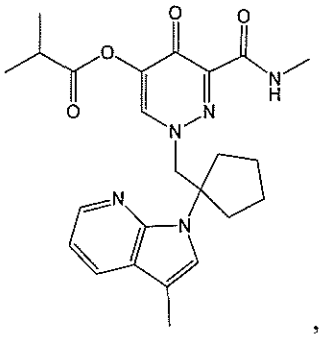
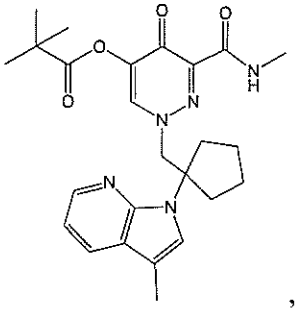
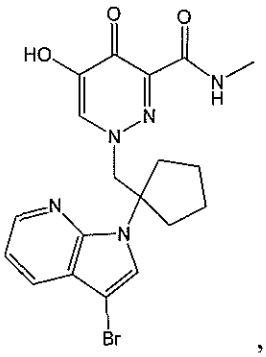
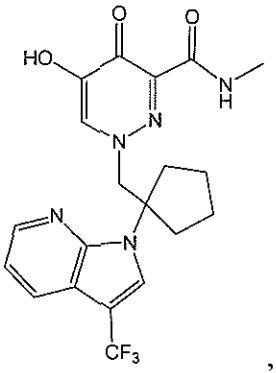
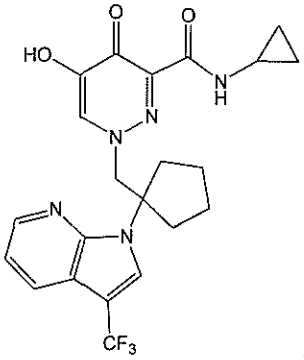
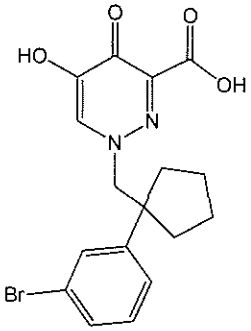
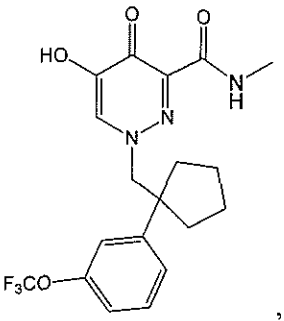
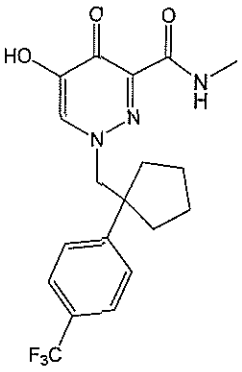
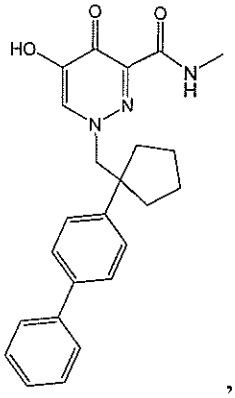
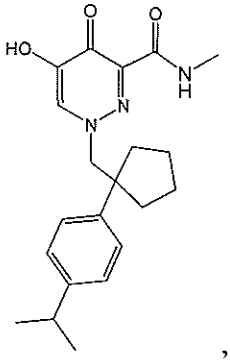
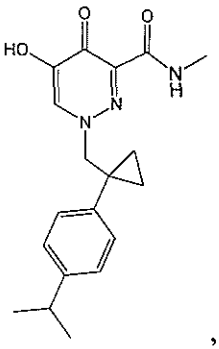
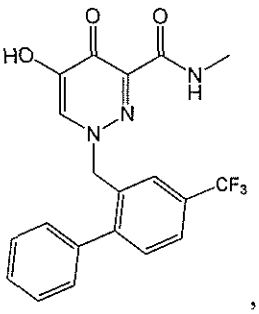
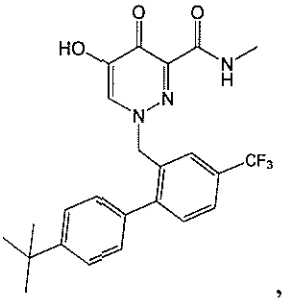
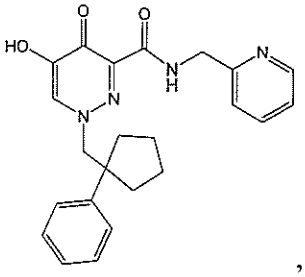
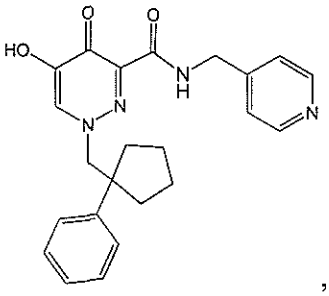
93. The compound of Claim 1, wherein the compound is selected from the group consisting of:

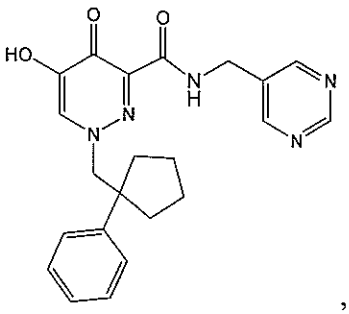
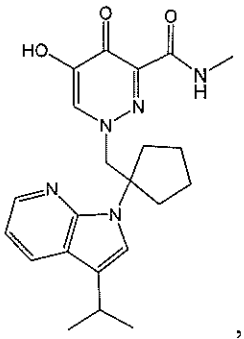
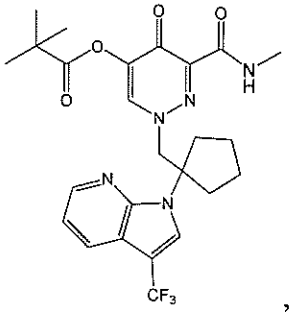
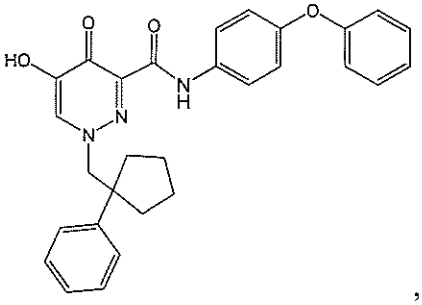
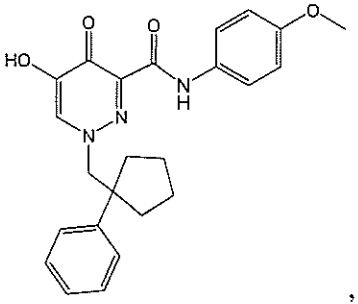
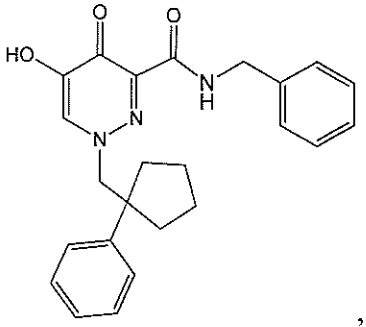
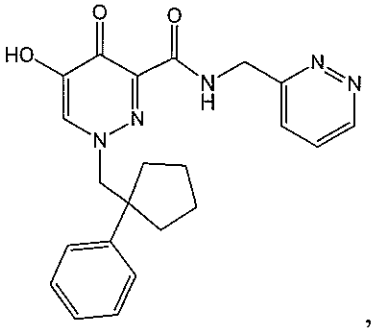
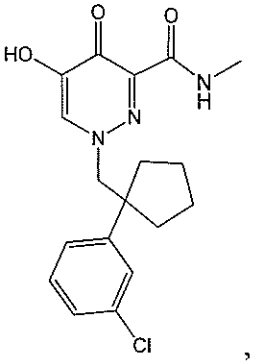
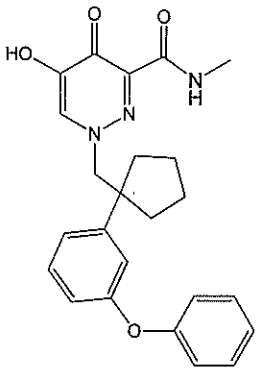
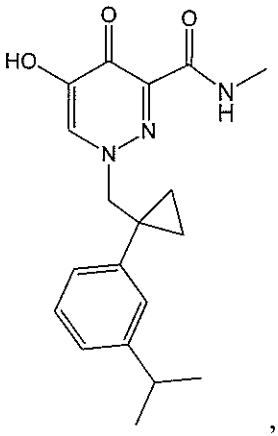
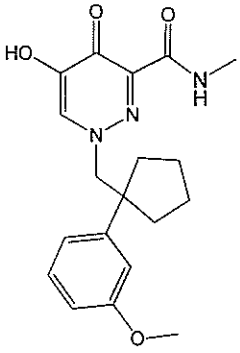
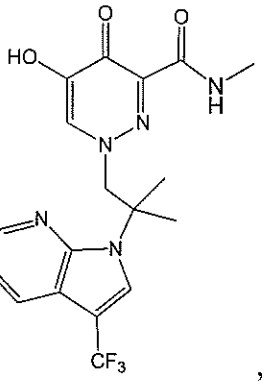
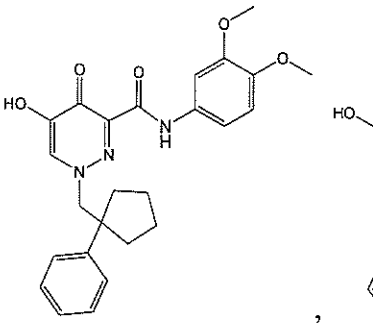
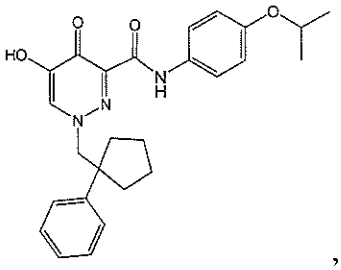

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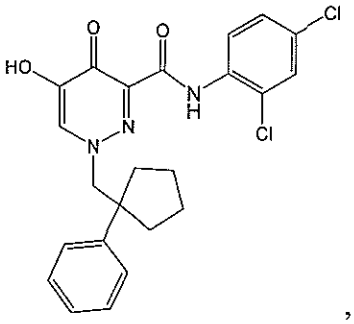
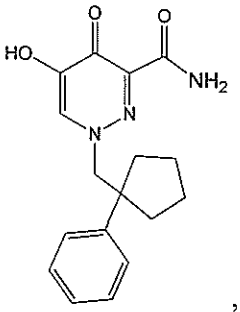
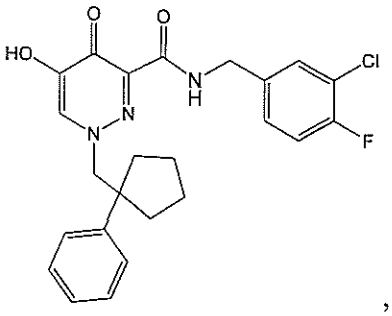
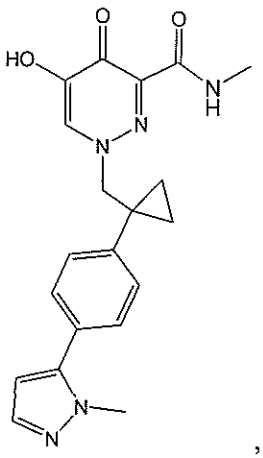
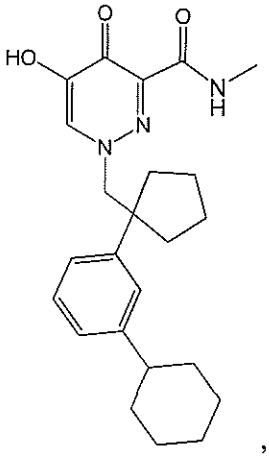
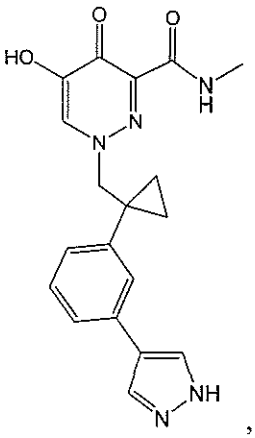
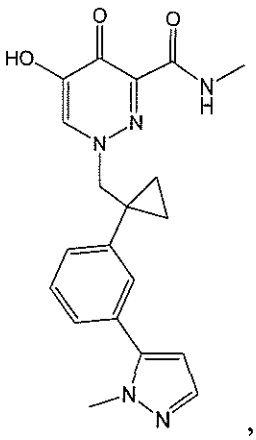
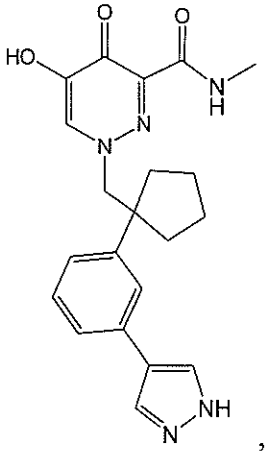
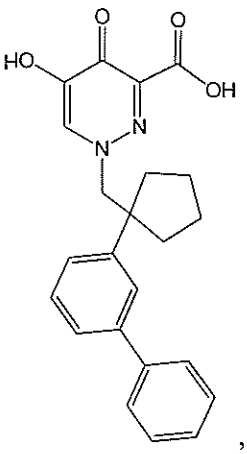
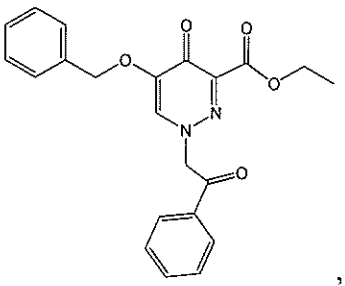
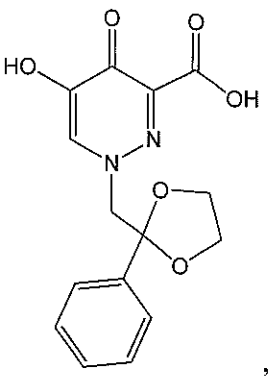
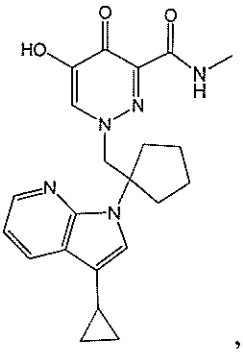
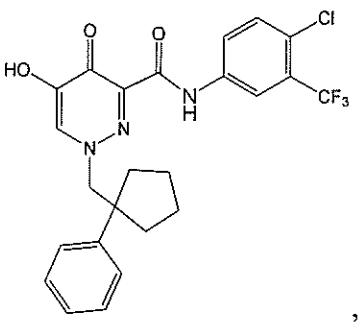
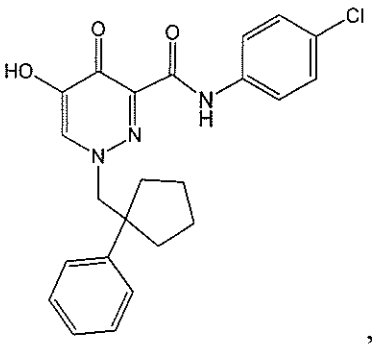

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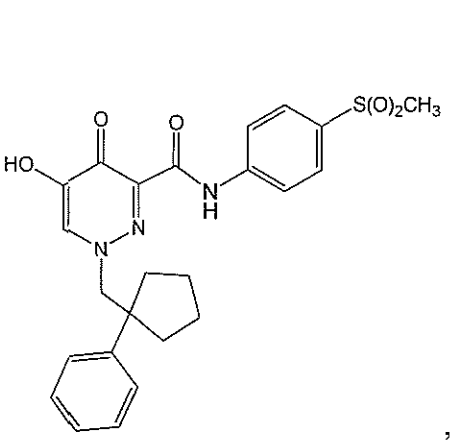
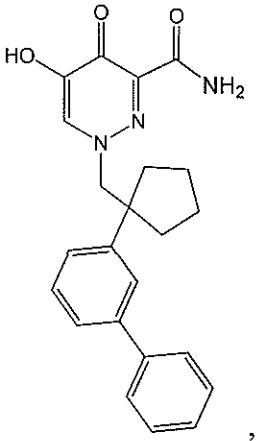
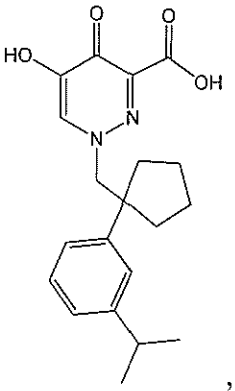
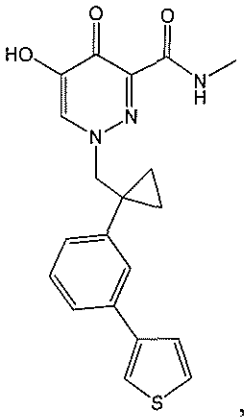
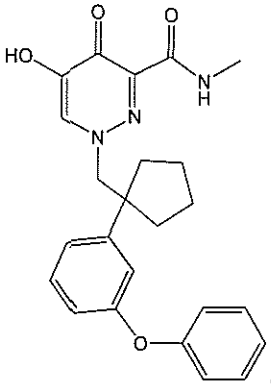
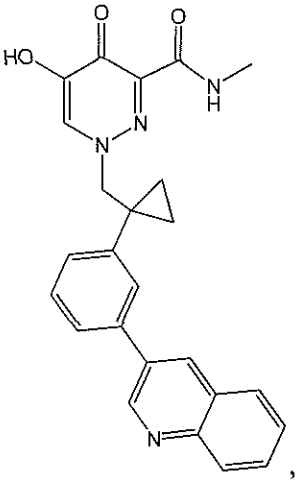
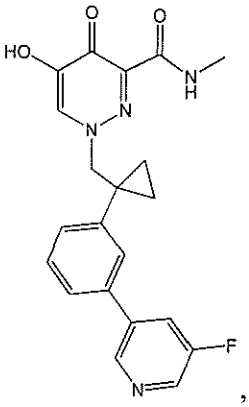
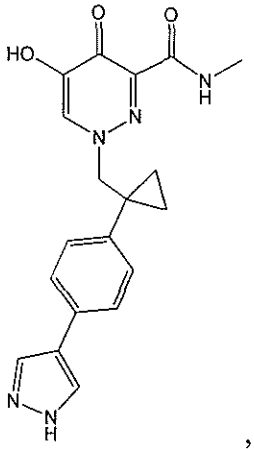
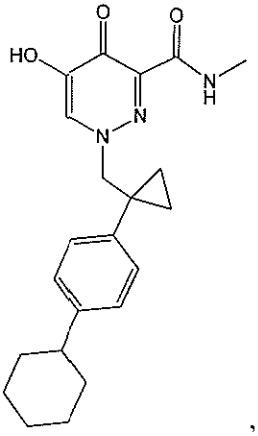
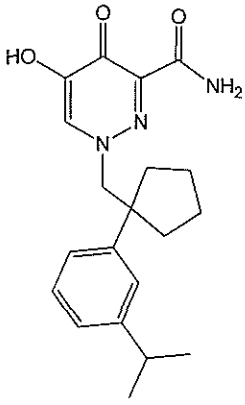
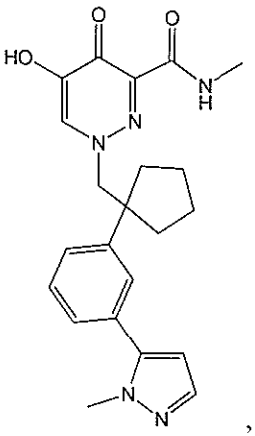
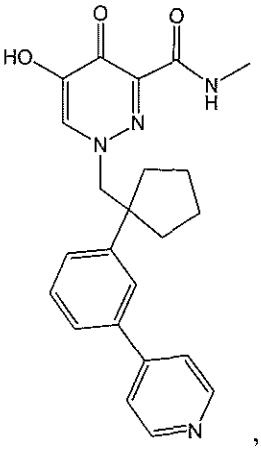

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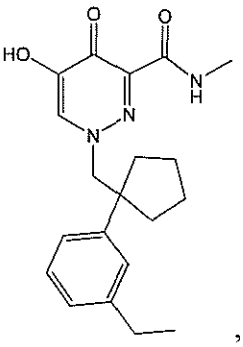
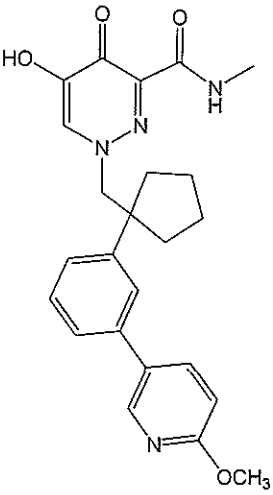
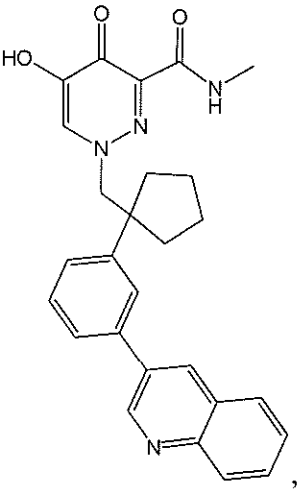
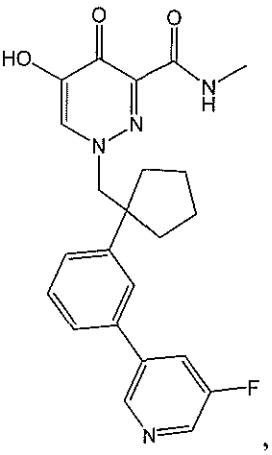
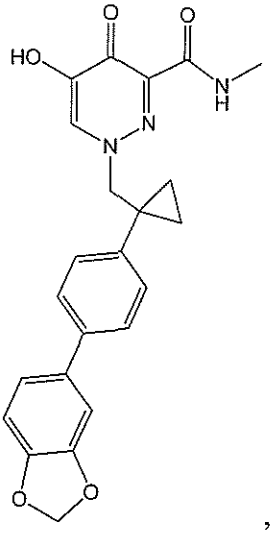
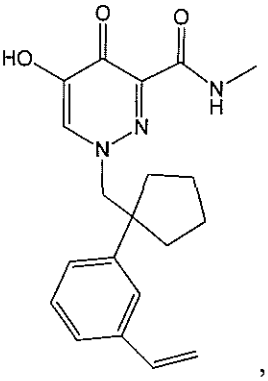
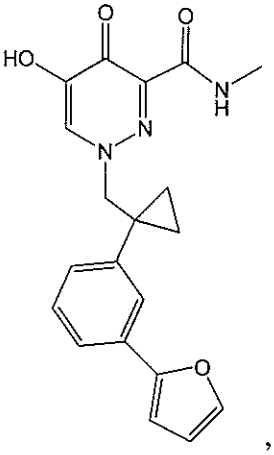
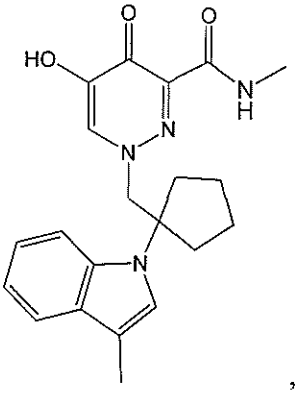
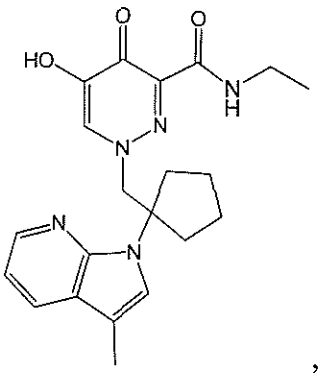
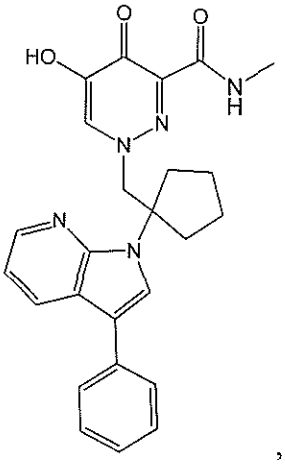
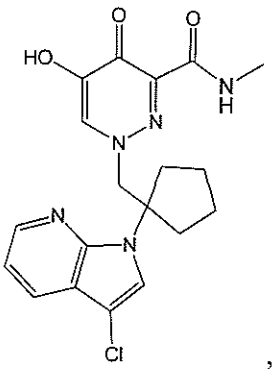
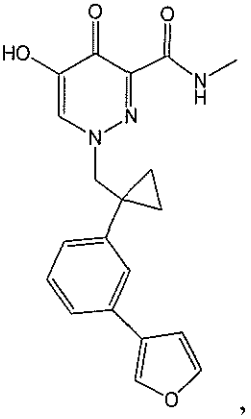

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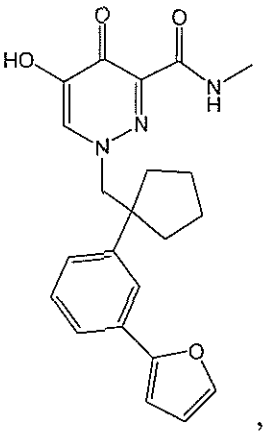
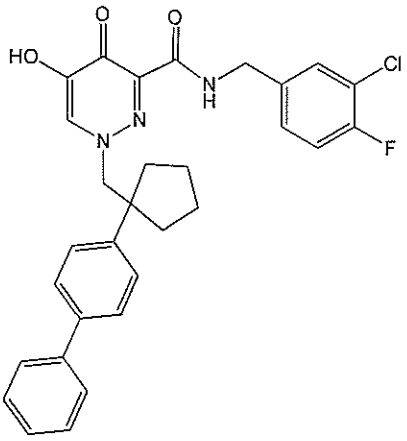
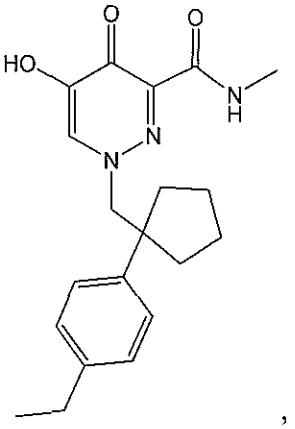
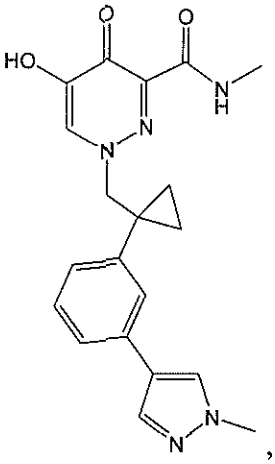
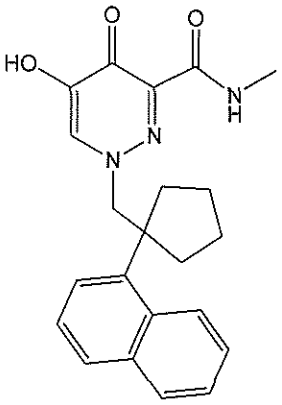
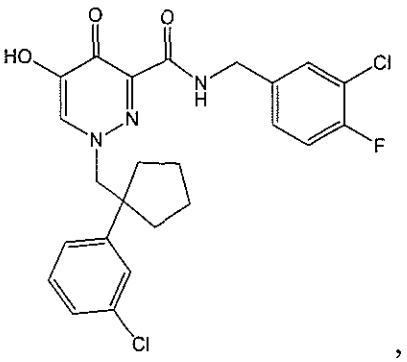
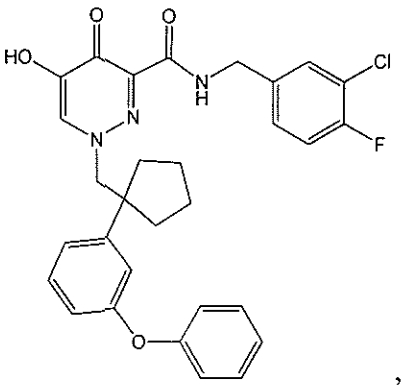
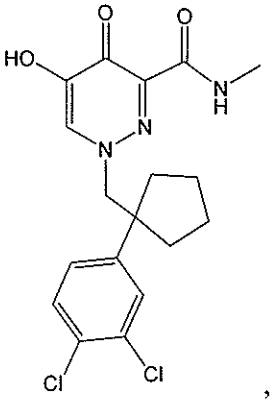
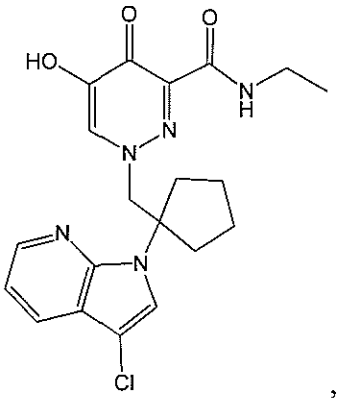

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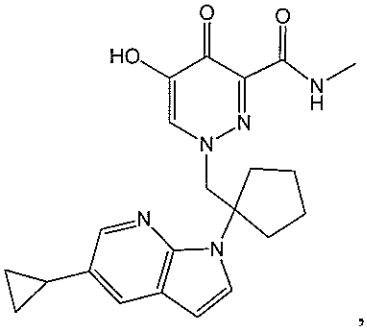
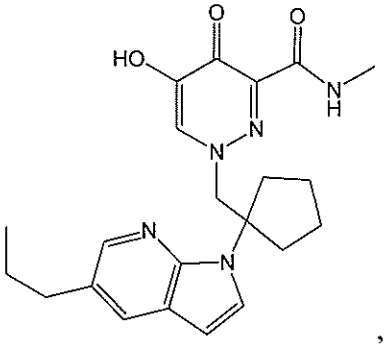
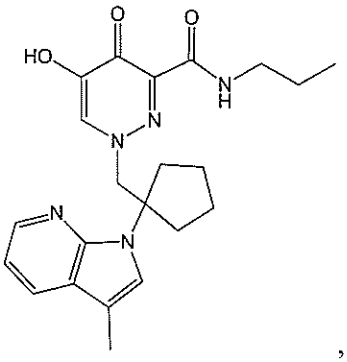
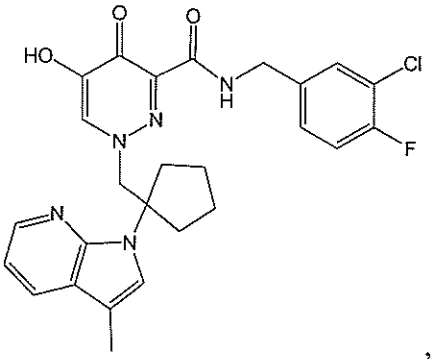
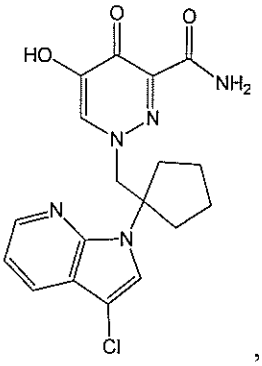
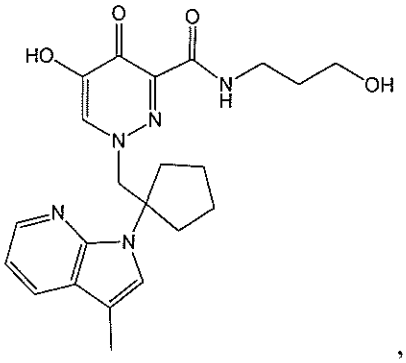
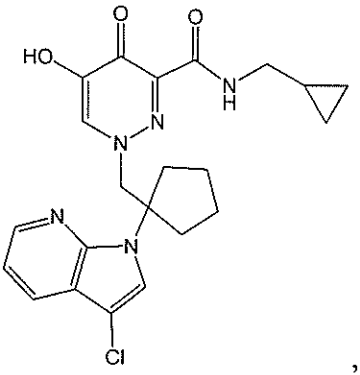
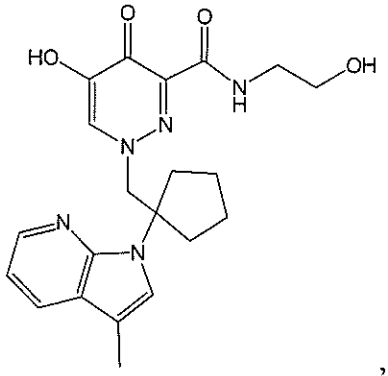
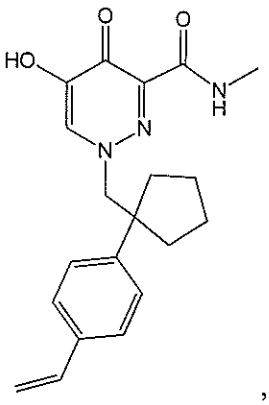
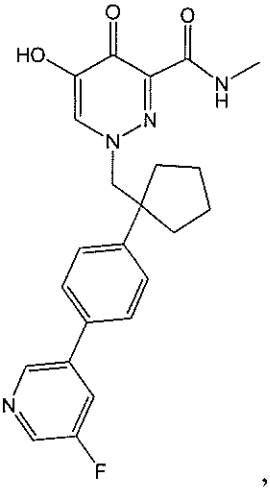
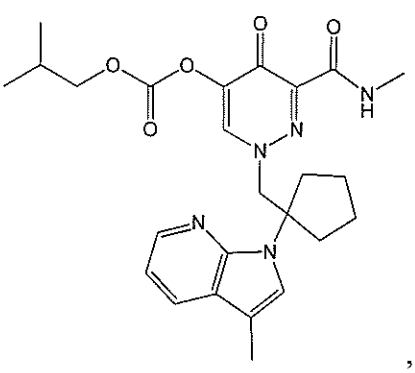
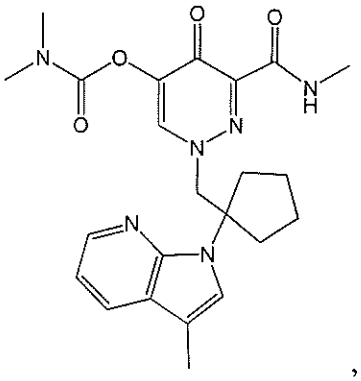

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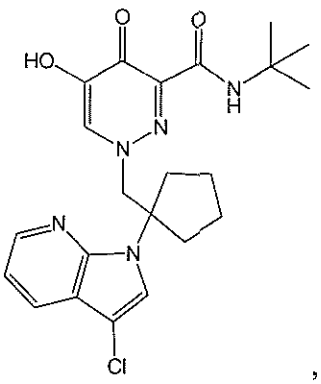
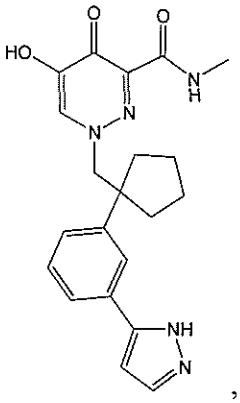
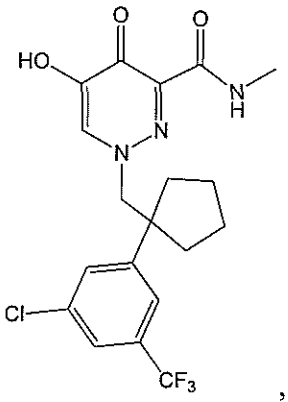
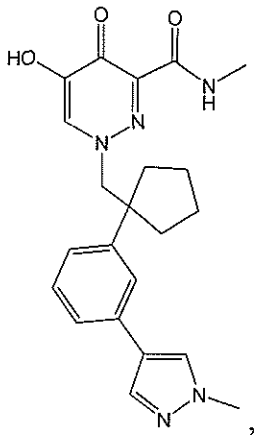
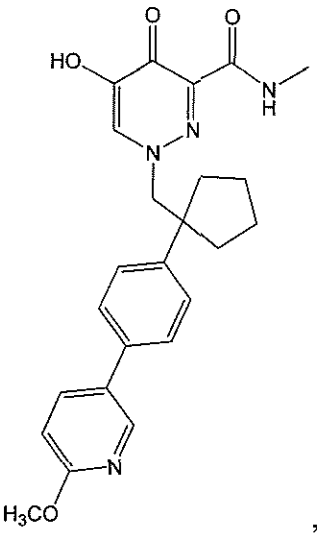
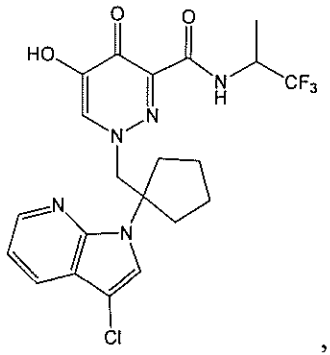
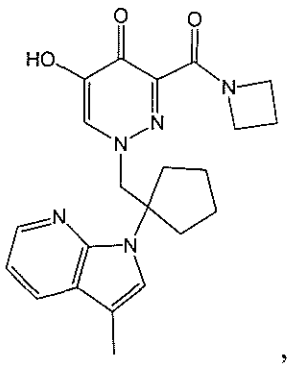
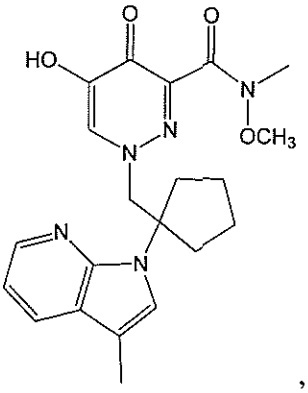
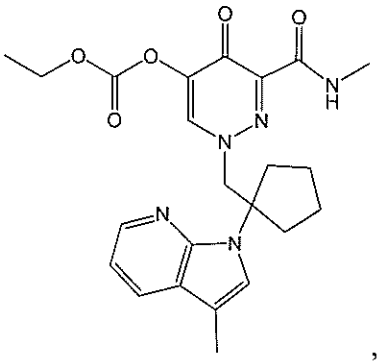
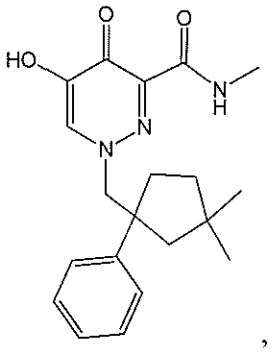

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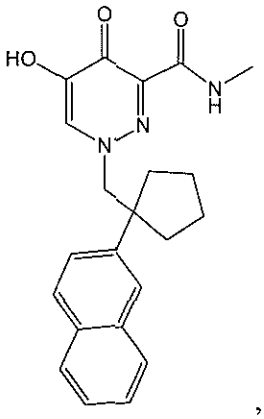
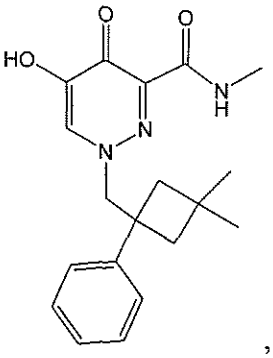
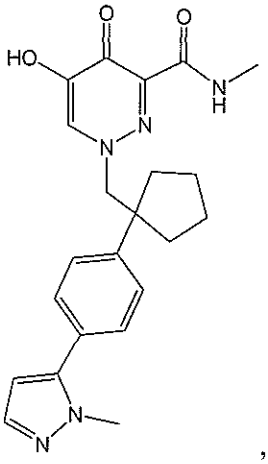
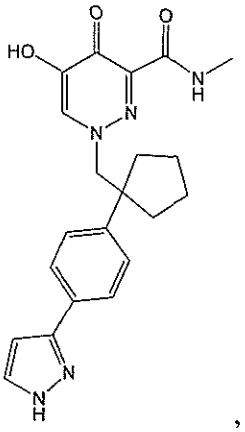
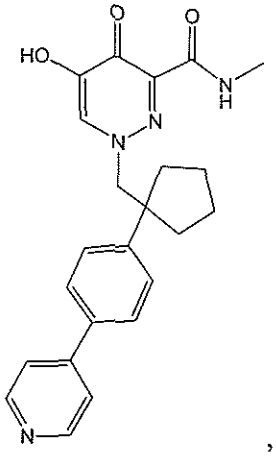
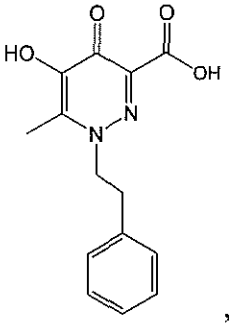
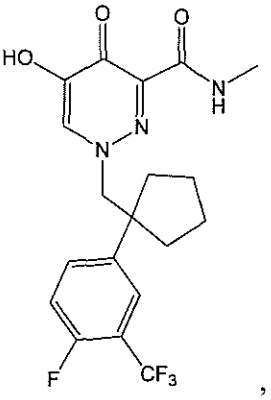
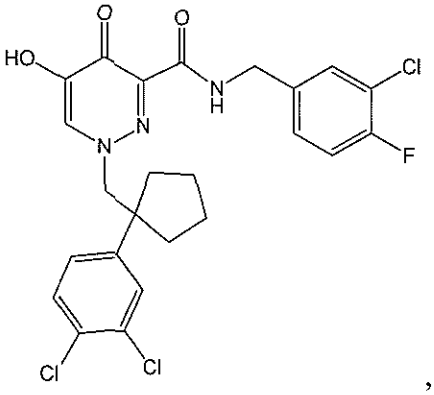
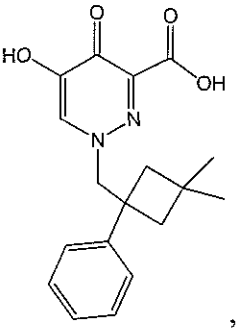
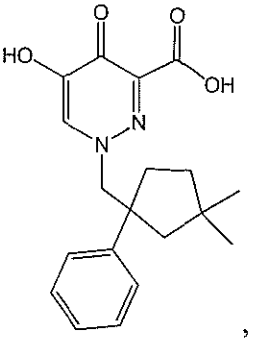

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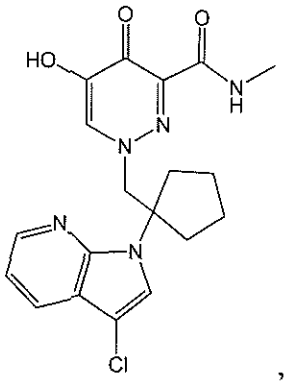
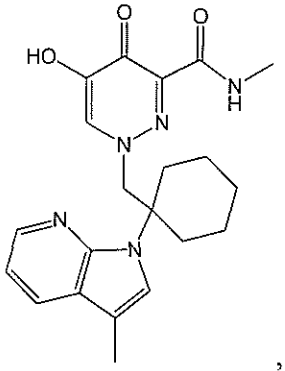
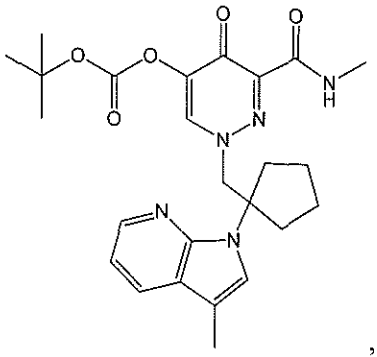
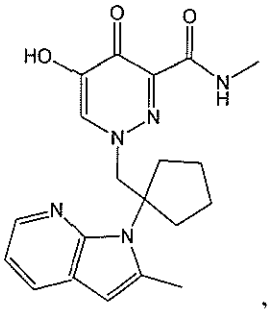
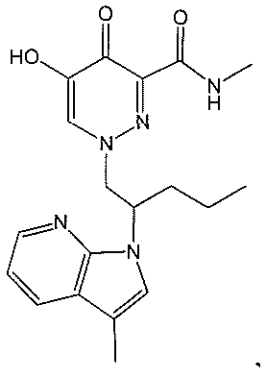
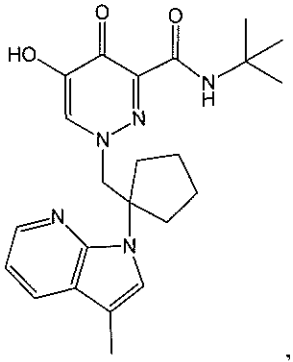
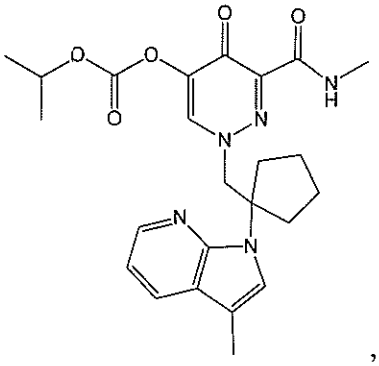
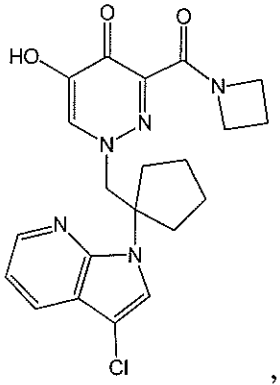
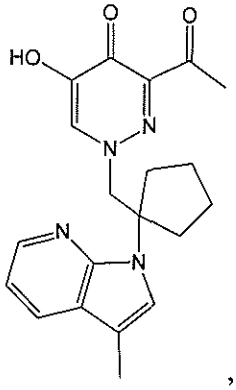
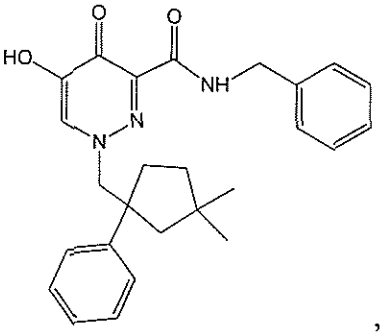
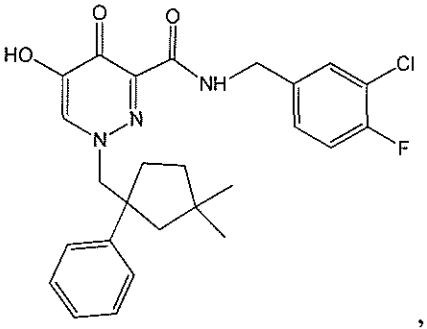
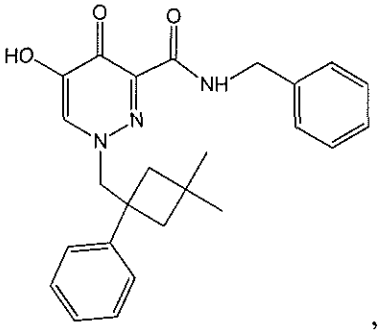

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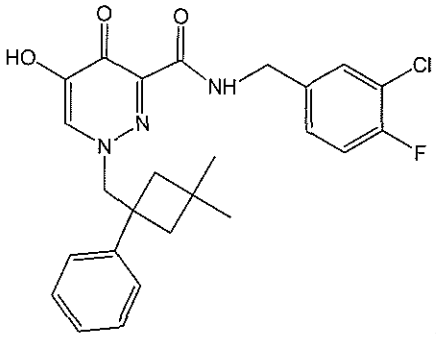
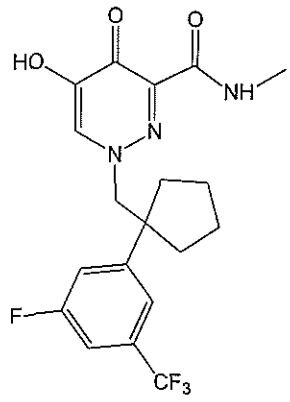
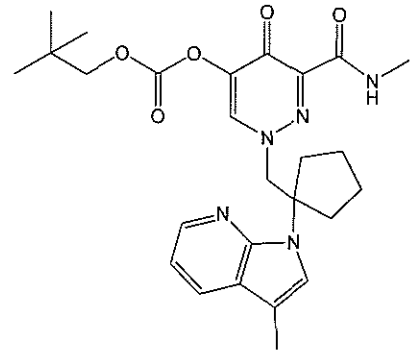
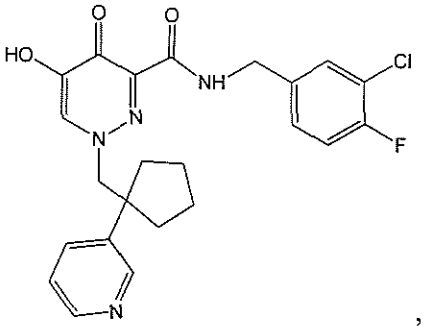
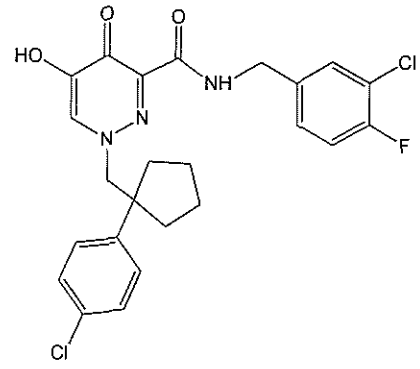
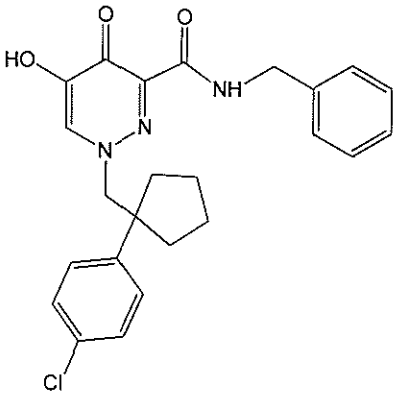
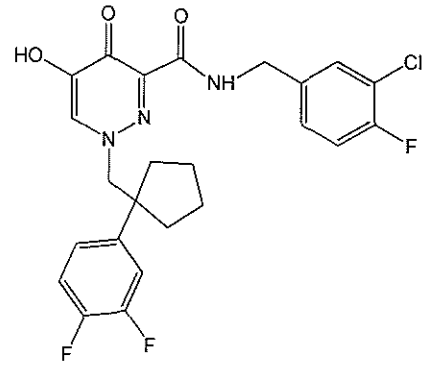
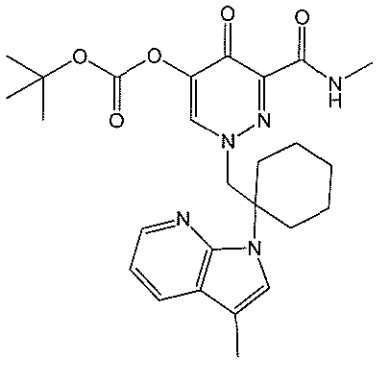
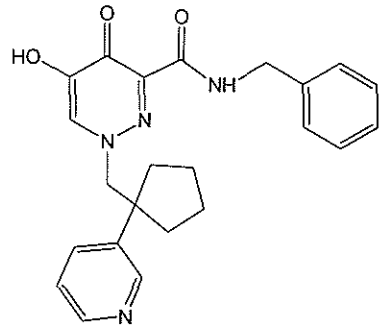
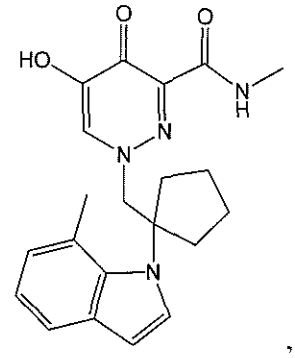

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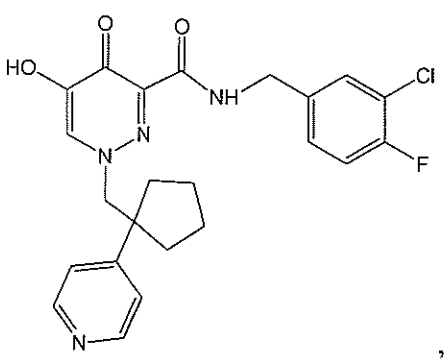
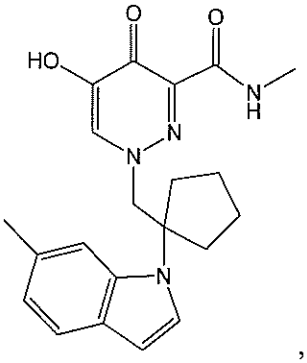
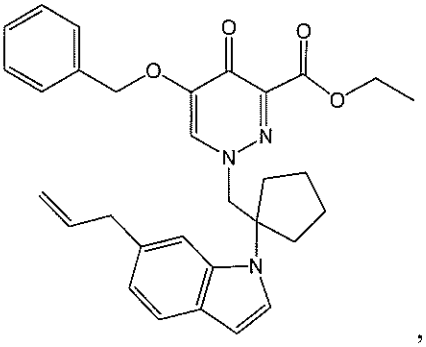
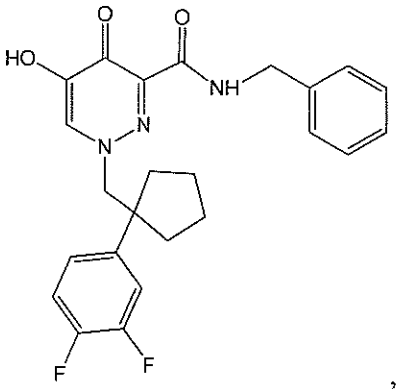
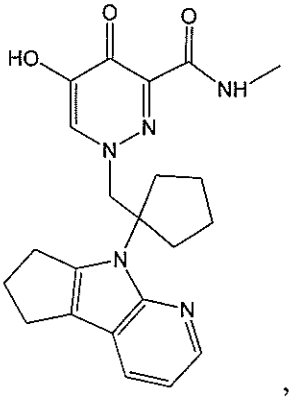
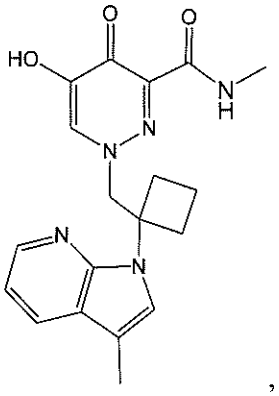
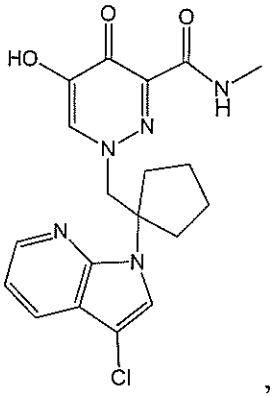
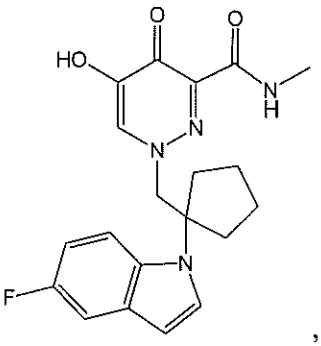
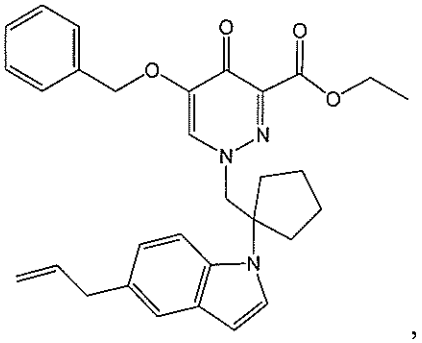
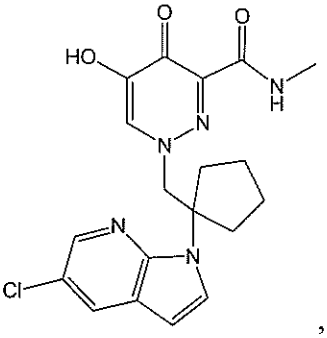
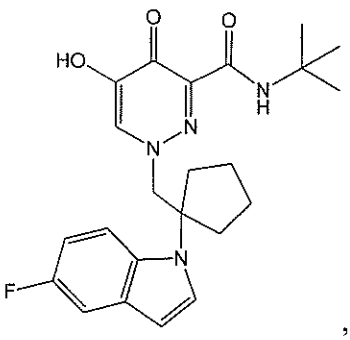
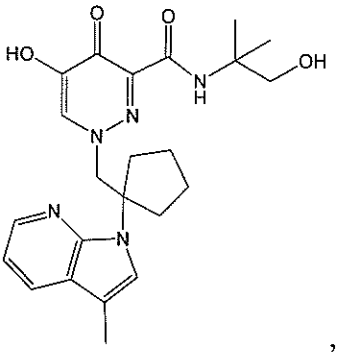

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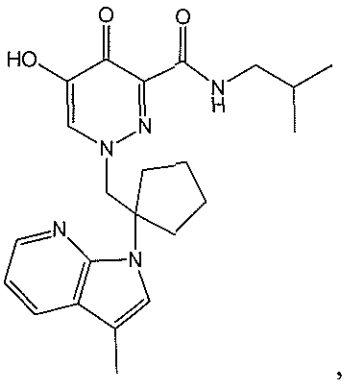
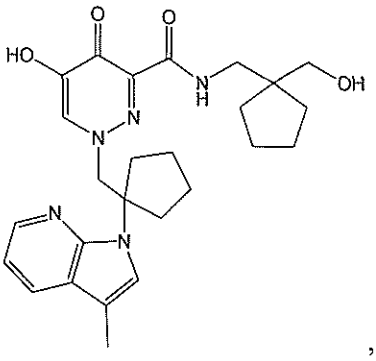
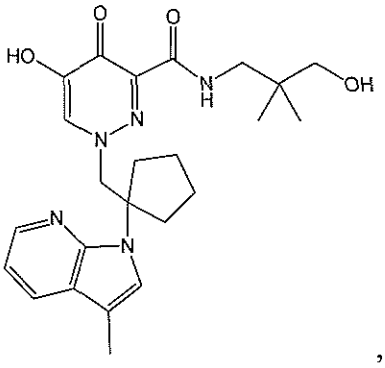
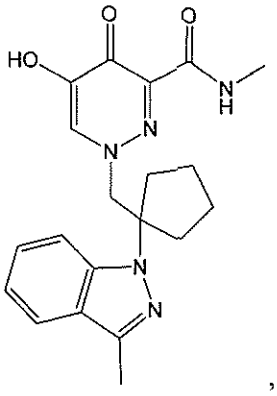
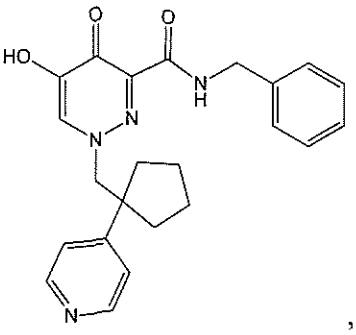
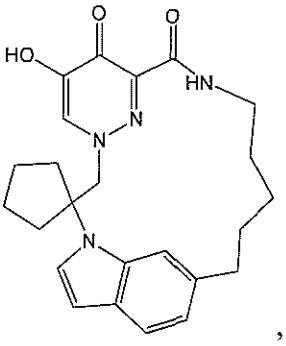
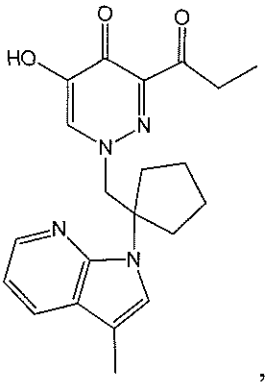
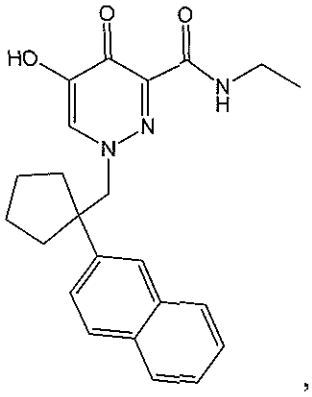
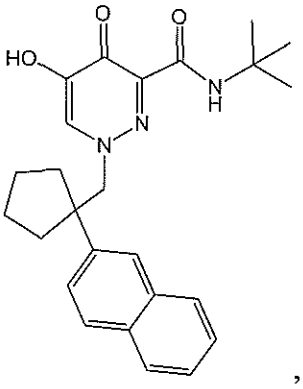
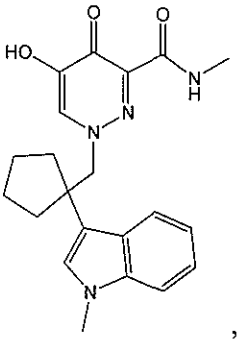
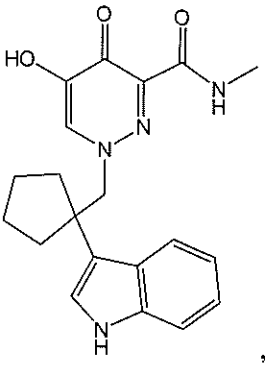
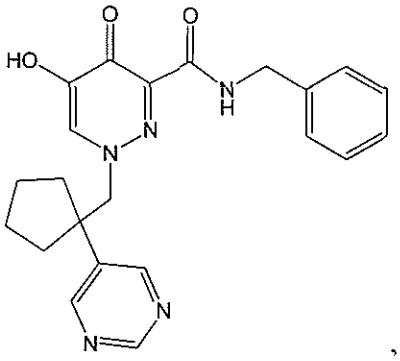
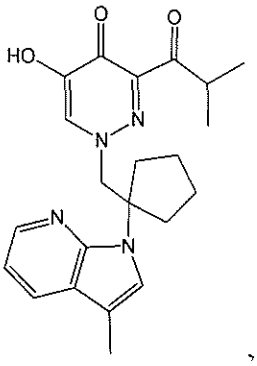
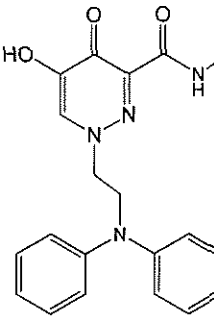

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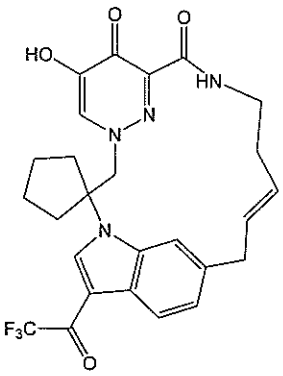
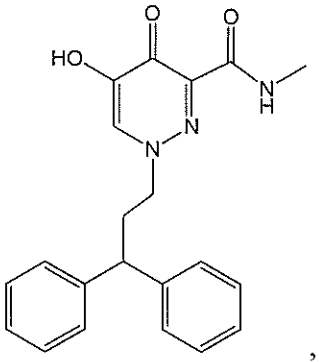
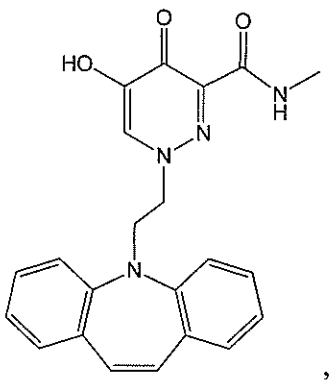
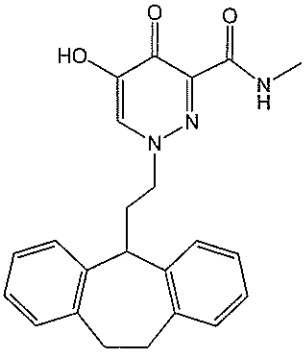
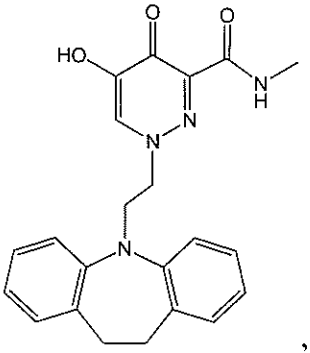
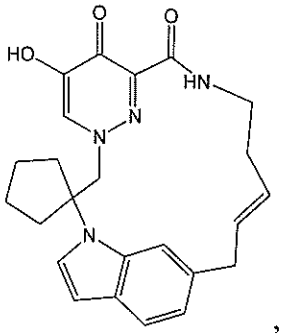
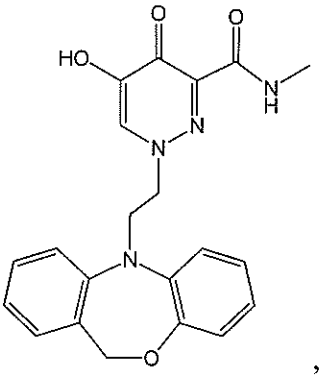
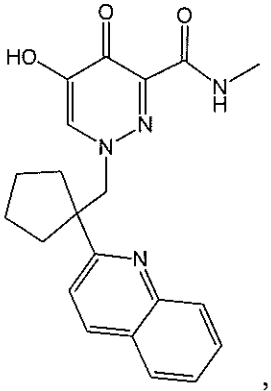
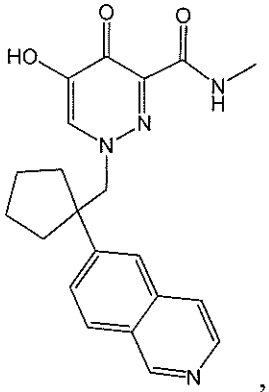
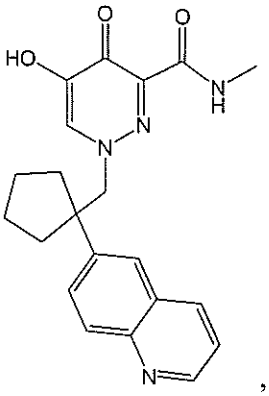
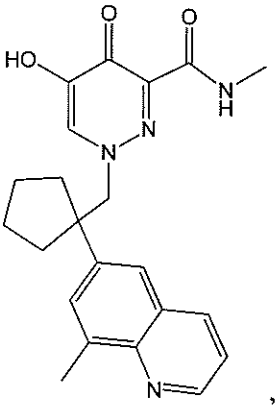
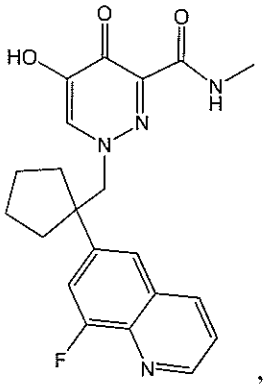
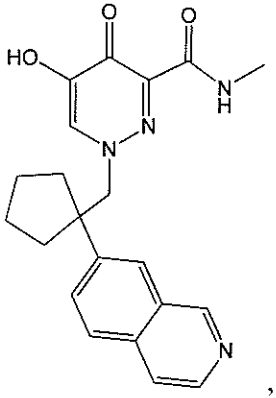
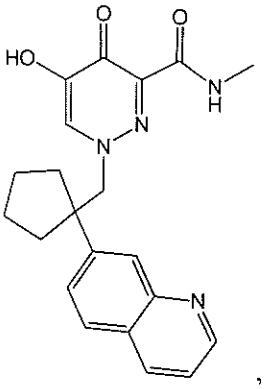

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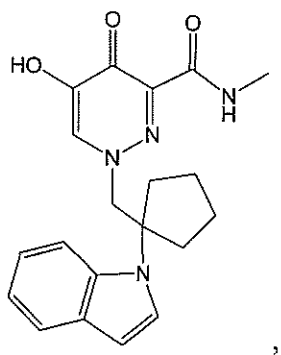
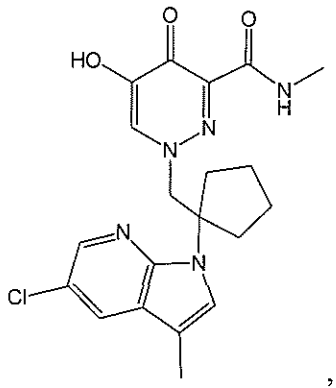
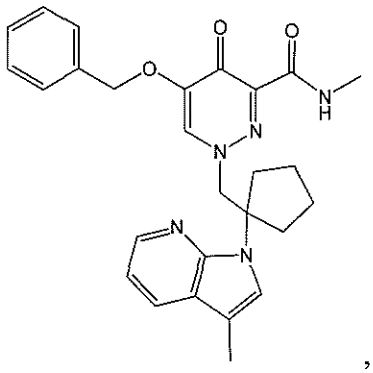
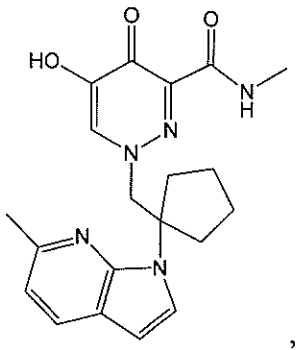
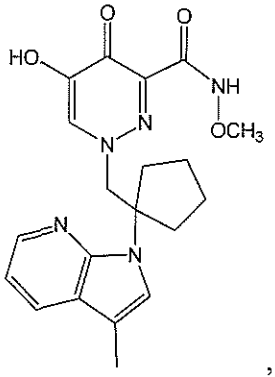
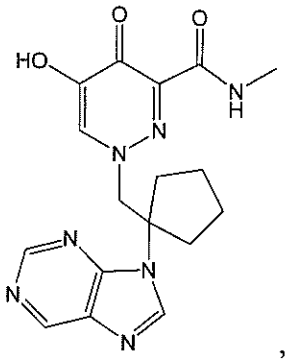
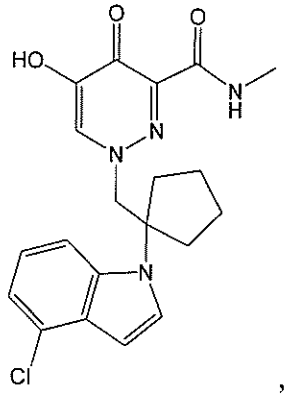
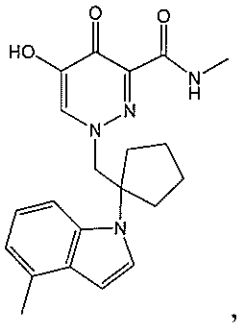
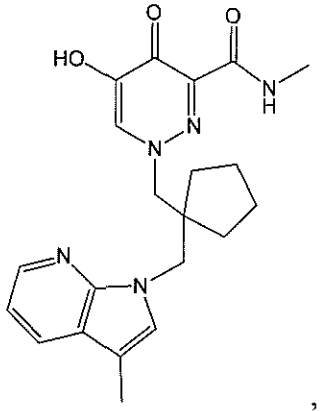
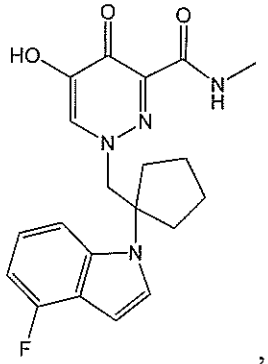
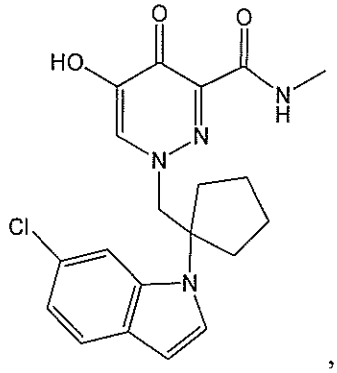
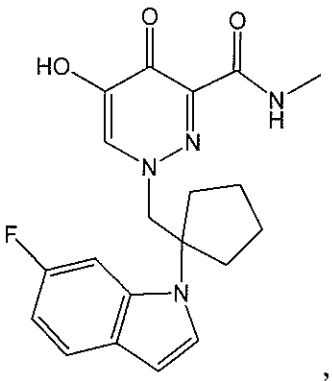
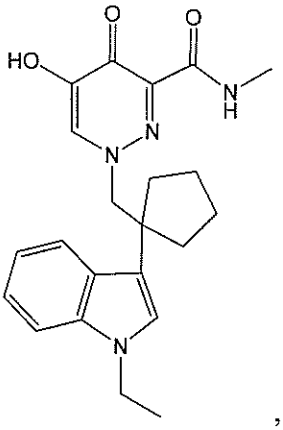
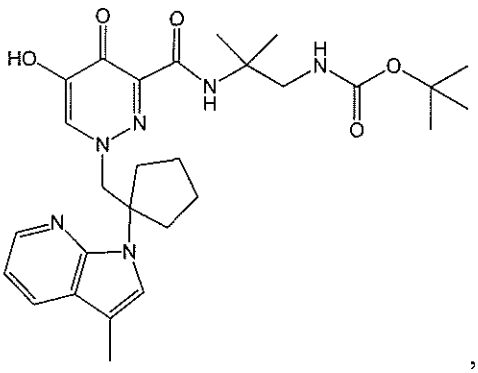

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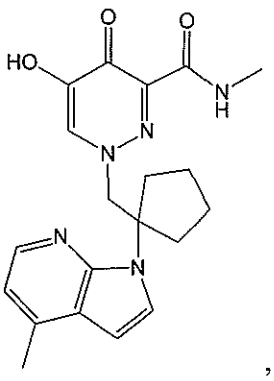
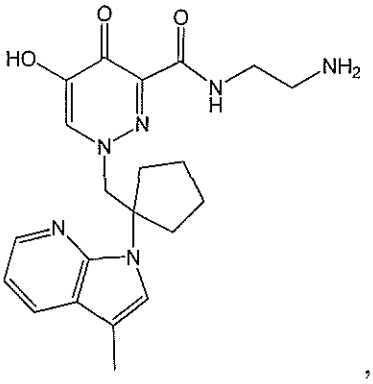
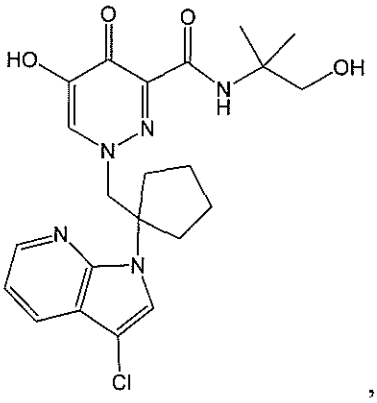
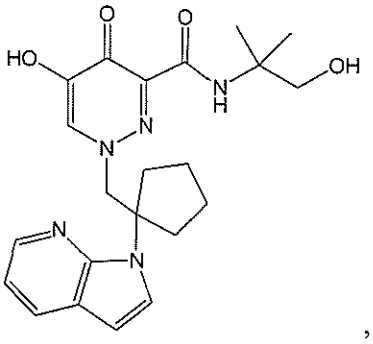
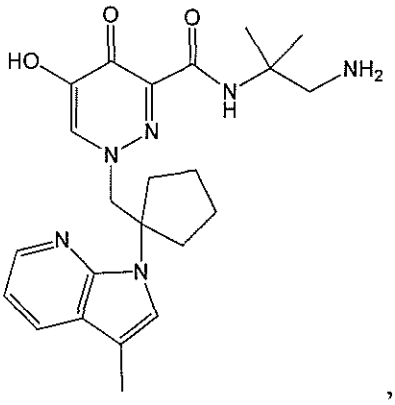
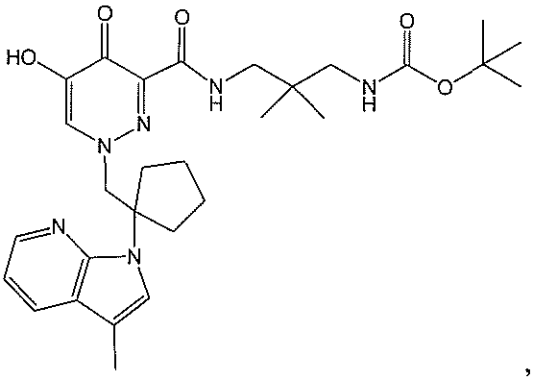
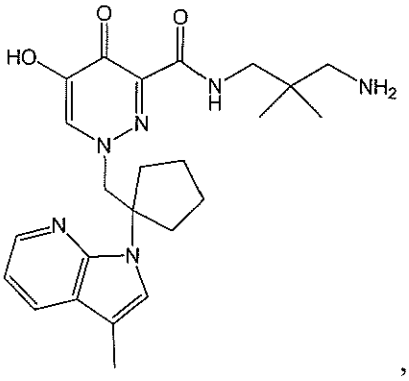
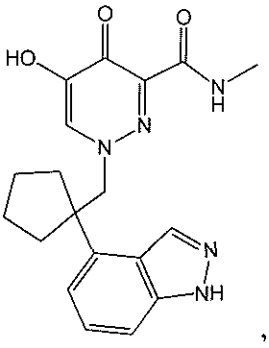
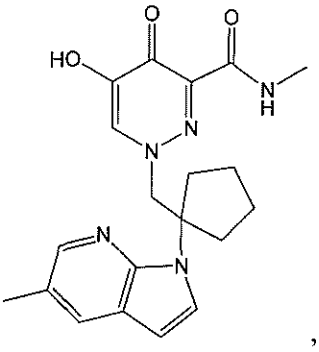
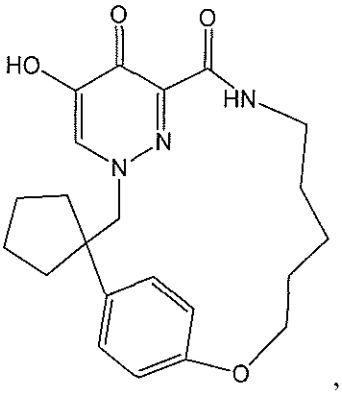

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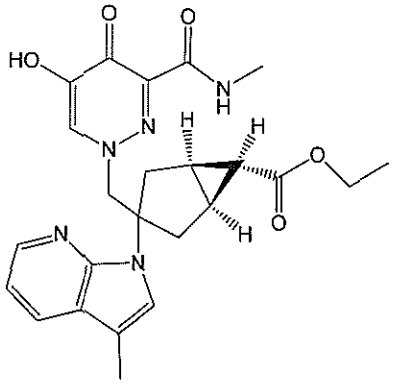
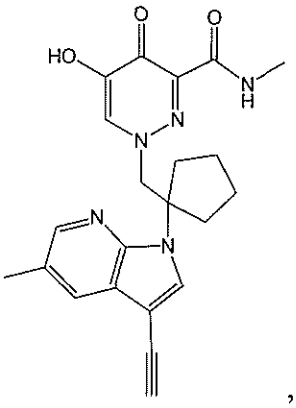
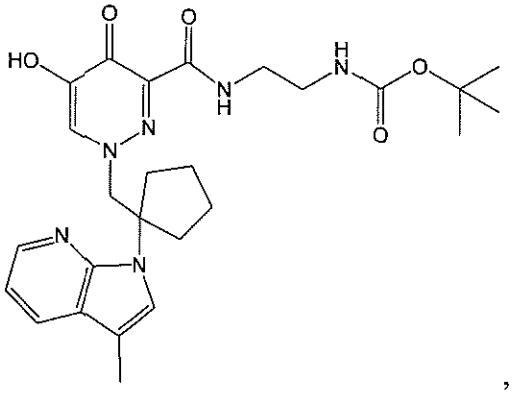
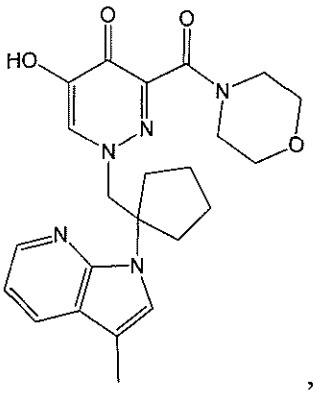
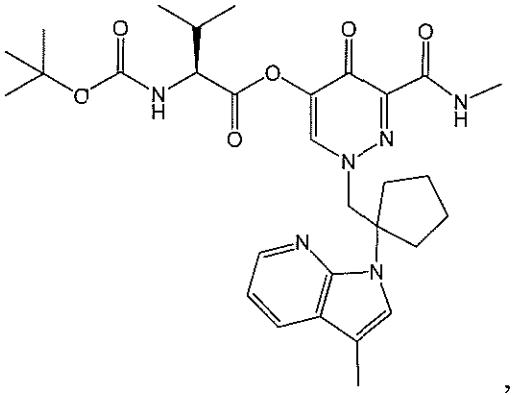
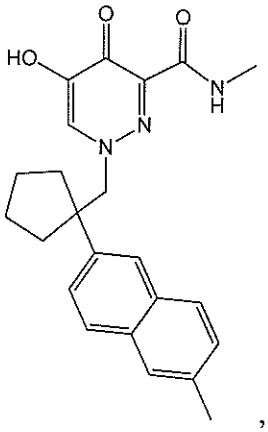
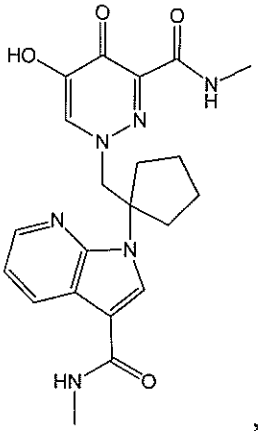
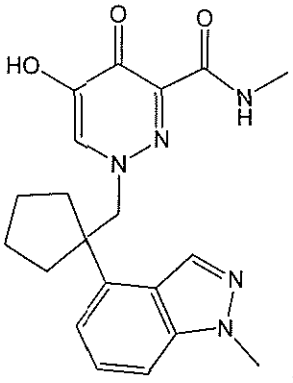
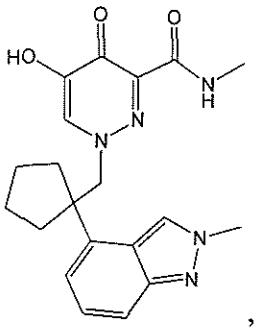
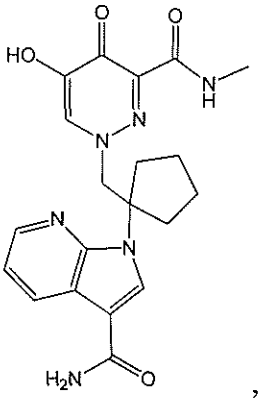
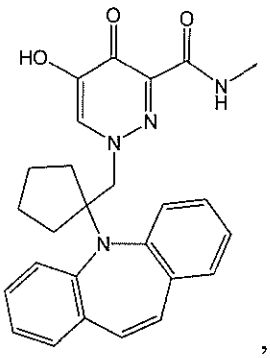

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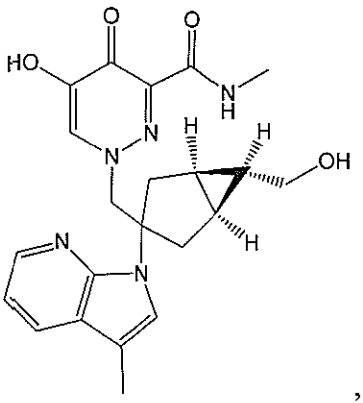
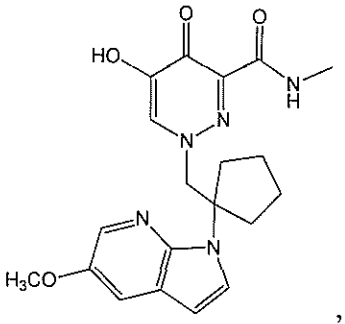
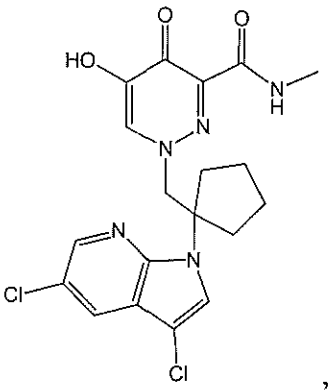
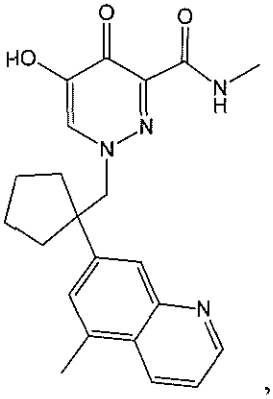
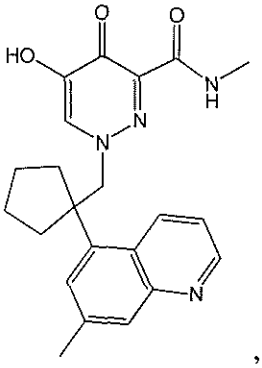
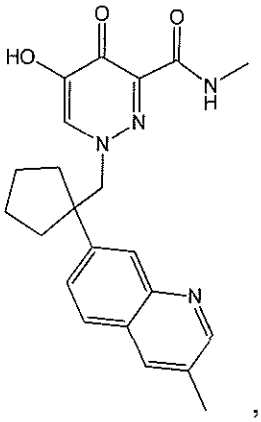
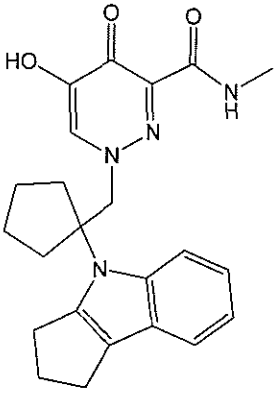
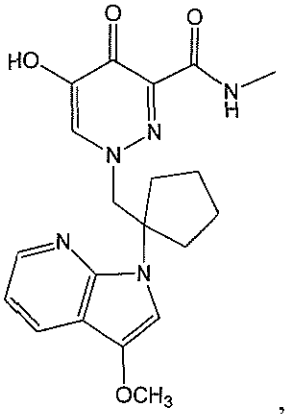
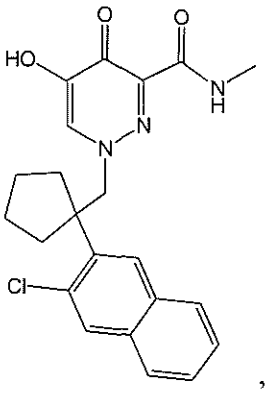
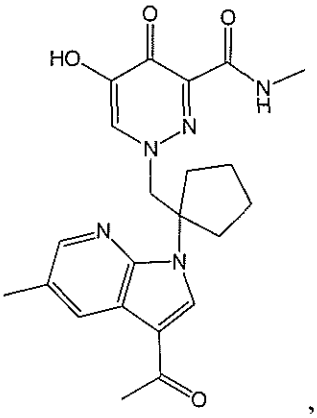
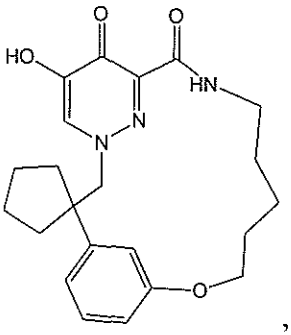
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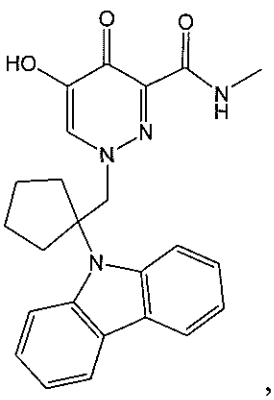
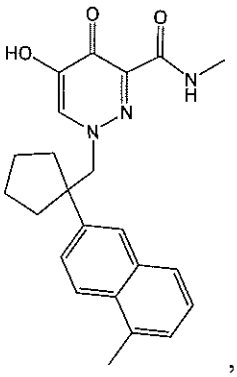
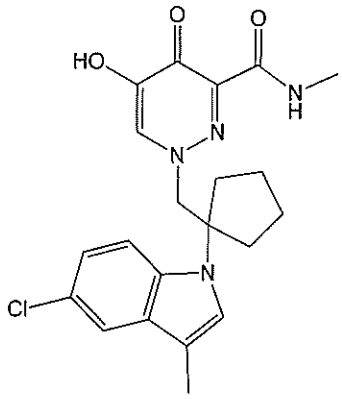
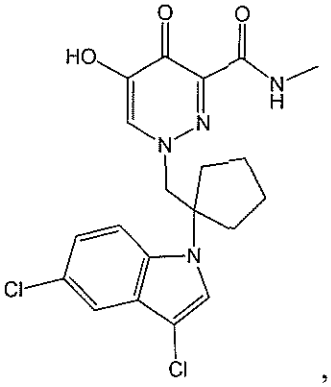

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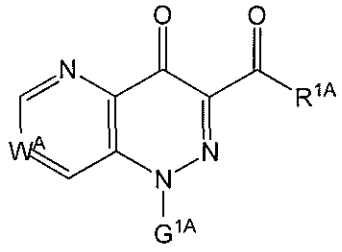

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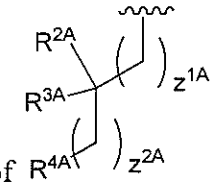

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and

, or a pharmaceutically acceptable salt of any of the foregoing.

94. A compound of Formula (**II**), or a pharmaceutically acceptable salt thereof:



(II)

wherein:



$\mathbf{G^{1A}}$ is selected from the group consisting of and $\mathbf{R^{5A}}$;

$\mathbf{R^{1A}}$ is selected from the group consisting of $O\mathbf{R^{6A}}$, NH_2, an optionally substituted alkyl, an optionally substituted aryl, an optionally substituted mono-substituted amine, an optionally substituted di-substituted amine, an optionally substituted heterocyclyl and an optionally substituted N-sulfonamido, or $\mathbf{R^{10A}}$;

$\mathbf{W^A}$ is -CH- or -N-;

$\mathbf{R}^{2A}$ is hydrogen or C_{1-6} alkyl;

$\mathbf{R}^{3A}$ is hydrogen or C_{1-6} alkyl;

or $\mathbf{R}^{2A}$ and $\mathbf{R}^{3A}$ are taken together to form an optionally substituted C_{3-6} cycloalkyl or an optionally substituted 5 to 6 membered heterocyclyl;

$\mathbf{R}^{4A}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

$\mathbf{R}^{5A}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl;

$\mathbf{R}^{6A}$ is selected from the group consisting of hydrogen, C_{1-6} alkyl, $-C(O)\mathbf{R}^{7A}$ and $-C(O)N\mathbf{R}^{8A}\mathbf{R}^{9A}$;

$\mathbf{R}^{7A}$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

$\mathbf{R}^{8A}$ and $\mathbf{R}^{9A}$ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl) and heterocyclyl(C_{1-6} alkyl);

or $\mathbf{R}^{8A}$ and $\mathbf{R}^{9A}$ are taken together to form an optionally substituted heterocyclyl;

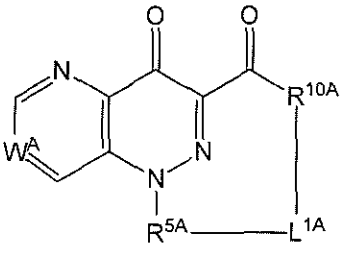
wherein when $\mathbf{R}^{1A}$ is $\mathbf{R}^{10A}$, then $\mathbf{R}^{10A}$ and $\mathbf{R}^{4A}$ are taken together and include $\mathbf{L}^{1A}$, where $\mathbf{L}^{1A}$ connects $\mathbf{R}^{10A}$ and $\mathbf{R}^{4A}$ to form an 11- to 20-membered ring, or wherein when $\mathbf{R}^{1A}$ is $\mathbf{R}^{10A}$, then $\mathbf{R}^{10A}$ and $\mathbf{R}^{5A}$ are taken together and include $\mathbf{L}^{1A}$, where $\mathbf{L}^{1A}$ connects $\mathbf{R}^{1A}$ and $\mathbf{R}^{5A}$ to form an 11- to 20-membered ring;

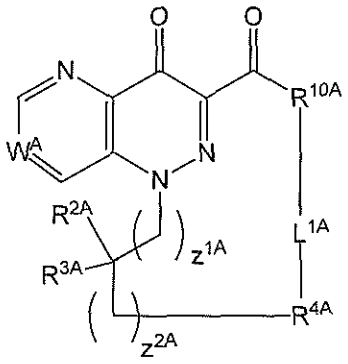
wherein $\mathbf{R}^{10A}$ is optionally substituted $-CH_2-$, optionally substituted -CH=CH-, O (oxygen), S (sulfur), or $N\mathbf{R}^{11A}$;

wherein $\mathbf{R}^{11A}$ is hydrogen or C_{1-6} alkyl; and

$\mathbf{Z}^{1A}$ and $\mathbf{Z}^{2A}$ are independently 0, 1, 2, 3 or 4.

95. The compound of Claim 94, having the structure of Formula (**IIc**) or Formula (**IId**), or a pharmaceutically acceptable salt thereof:



(**IIc**) or


(**IId**),

wherein:

$\mathbf{L}^{1A}$ is $-\mathbf{L}^{2A}-$, or $-\mathbf{L}^{3A}-\mathbf{L}^{4A}-\mathbf{L}^{5A}-$;

$\mathbf{L}^{2A}$ is selected from the group consisting of an optionally substituted alkylene, an optionally substituted alkenylene, an optionally substituted heteroalkylene and an optionally substituted heteroalkenylene;

$\mathbf{L}^{3A}$ is an optionally substituted C_{1-6} alkylene;

$\mathbf{L}^{4A}$ is an optionally substituted cycloalkyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted heterocyclyl, O (oxygen), S (sulfur), or $N\mathbf{R}^{11A}$; and

$\mathbf{L}^{5A}$ is an optionally substituted C_{1-6} alkylene or an optionally substituted heteroalkylene.

96. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is an optionally substituted alkylene.

97. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is an optionally substituted C_{4-7} alkylene.

98. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is an optionally substituted alkenylene.

99. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is an optionally substituted C_{4-7} alkenylene.

100. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is an optionally substituted heteroalkylene.

101. The compound of Claim 100, wherein $\mathbf{L}^{2A}$ is an optionally substituted $-(CH_2)_3-O-$, an optionally substituted $-(CH_2)_4-O-$, an optionally substituted $-(CH_2)_5-O-$, an optionally substituted $-(CH_2)_3-S-$, an optionally substituted $-(CH_2)_4-S-$, an optionally substituted $-(CH_2)_5-S-$, an optionally substituted $-(CH_2)_3-NH-$, an optionally substituted $-(CH_2)_4-NH-$, or an optionally substituted $-(CH_2)_5-NH-$.

102. The compound of Claim 100, wherein $\mathbf{L}^{2A}$ is an optionally substituted -$(CH_2)_3$-O-, an optionally substituted –$(CH_2)_4$-O–, or an optionally substituted -$(CH_2)_5$-O–.

103. The compound of Claim 95, wherein $\mathbf{L}^{2A}$ is optionally substituted heteroalkenylene.

104. The compound of Claim 103, wherein $\mathbf{L}^{2A}$ is an optionally substituted -$(CH_2)(CH{=}CH)(CH_2)$-O–, an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)$-O–, an optionally substituted -$(CH_2)(CH{=}CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)_2$-O–, an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)$-S–, an optionally substituted -$(CH_2)(CH{=}CH)(CH_2)_2$-S–, an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)_2$-S an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)$-NH–, an optionally substituted -$(CH_2)(CH{=}CH)(CH_2)_2$-NH– or an optionally substituted -$(CH_2)_2(CH{=}CH)(CH_2)_2$-NH–.

105. The compound of Claim 103, wherein $\mathbf{L}^{2A}$ is an optionally substituted C_3 oxygen containing heteroalkenylene, an optionally substituted C_4 oxygen containing heteroalkenylene, or an optionally substituted C_5 oxygen containing heteroalkenylene.

106. The compound of Claim 95,

wherein:

$\mathbf{L}^{1A}$ is –$\mathbf{L}^{3A}$-$\mathbf{L}^{4A}$-$\mathbf{L}^{5A}$-;

$\mathbf{L}^{3A}$ is an optionally substituted C_{1-4} alkylene;

$\mathbf{L}^{4A}$ is optionally substituted cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; and

$\mathbf{L}^{5A}$ is an optionally substituted C_{1-4} alkylene.

107. The compound of Claim 95,

wherein:

$\mathbf{L}^{1A}$ is –$\mathbf{L}^{3A}$-$\mathbf{L}^{4A}$-$\mathbf{L}^{5A}$-;

$\mathbf{L}^{3A}$ is an optionally substituted C_{1-4} alkylene;

$\mathbf{L}^{4A}$ is O (oxygen), S (sulfur), or N$\mathbf{R}^{11A}$; and

$\mathbf{L}^{5A}$ is an optionally substituted C_{1-4} alkylene.

108. The compound of Claim 95,

wherein:

$\mathbf{L}^{1A}$ is –$\mathbf{L}^{3A}$-$\mathbf{L}^{4A}$-$\mathbf{L}^{5A}$-;

$\mathbf{L}^{3A}$ is optionally substituted C_{2-4} alkylene;

$\mathbf{L}^{4A}$ is optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocyclyl, O (oxygen), S (sulfur), or $N\mathbf{R}^{11}$; and

$\mathbf{L}^{5A}$ is optionally substituted C_{2-4} alkylene.

109. The compound of any one of Claims 94 or 107-108,

wherein:

$\mathbf{R}^{1A}$ is $\mathbf{R}^{10A}$ where $\mathbf{R}^{10A}$ is $N\mathbf{R}^{11A}$; and

$\mathbf{R}^{11A}$ is H (hydrogen).

110. The compound of Claim 94, wherein $\mathbf{R}^{1A}$ is NH_2, an optionally substituted mono-substituted amine or an optionally substituted di-substituted amine.

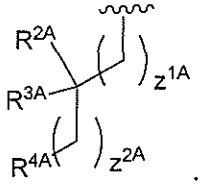
111. The compound of Claim 94, wherein $\mathbf{R}^{1A}$ is an optionally substituted mono-substituted amine.

112. The compound of Claim 94, wherein $\mathbf{R}^{1A}$ is an optionally substituted alkyl.

113. The compound of Claim 94, wherein $\mathbf{R}^{1A}$ is $\mathbf{R}^{10A}$.

114. The compound of Claim 113, wherein $\mathbf{R}^{10A}$ is CH_2.

115. The compound of Claim 113, wherein $\mathbf{R}^{10A}$ is $N\mathbf{R}^{11A}$.

116. The compound of any one of Claims 94-115, wherein $\mathbf{G}^{1A}$ is 

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117. The compound of Claim 116, wherein $\mathbf{R}^{2A}$ and $\mathbf{R}^{3A}$ are taken together to form an optionally substituted C_{3-6} cycloalkyl.

118. The compound of Claim 117, wherein $\mathbf{R}^{2A}$ and $\mathbf{R}^{3A}$ are taken together to form an unsubstituted C_{3-6} cycloalkyl.

119. The compound of Claim 117 or 118, wherein $\mathbf{R}^{2A}$ and $\mathbf{R}^{3A}$ are taken together to form a C_5 cycloalkyl.

120. The compound of any one of Claims 94-119, wherein $\mathbf{R}^{4A}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

121. The compound of any one of Claims 94-119, wherein $\mathbf{R}^{4A}$ is an optionally substituted aryl.

122. The compound of Claim 121, wherein the optionally substituted aryl is an optionally substituted phenyl.

123. The compound of Claim 121, wherein the optionally substituted aryl is a substituted aryl substituted with one or more groups selected from the group consisting of C_{1-6} alkyl, alkoxy, aryl, cyano, halogen, haloalkyl and haloalkoxy.

124. The compound of any one of Claims 94-119, wherein $\mathbf{R^{4A}}$ is an optionally substituted heteroaryl.

125. The compound of any one of Claims 94-124, wherein $\mathbf{Z^{1A}}$ is 0.

126. The compound of any one of Claims 94-124, wherein $\mathbf{Z^{1A}}$ is 1.

127. The compound of any one of Claims 94-126, wherein $\mathbf{Z^{2A}}$ is 0.

128. The compound of any one of Claims 94-126, wherein $\mathbf{Z^{2A}}$ is 1.

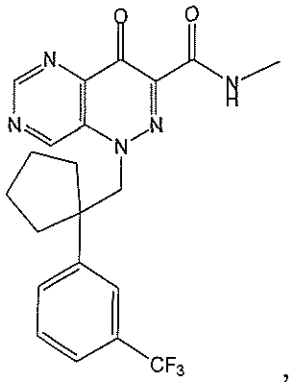
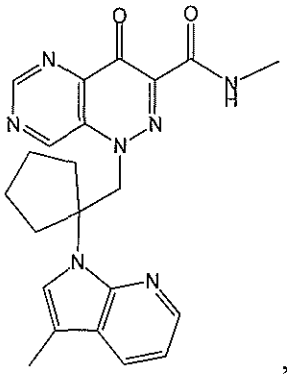
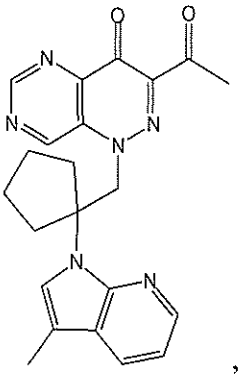
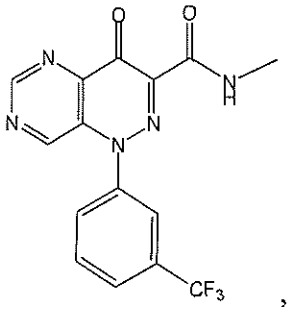
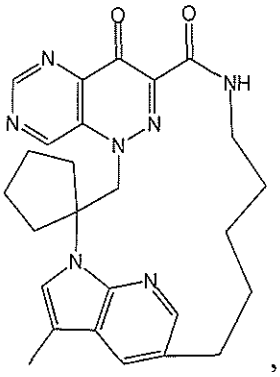
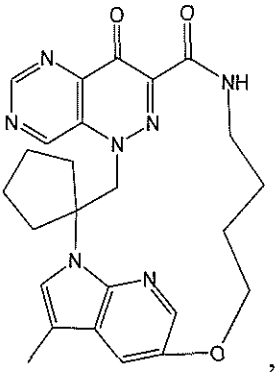
129. The compound of any one of Claims 94-115, wherein $\mathbf{G^{1A}}$ is $\mathbf{R^{5A}}$.

130. The compound of Claim 129, wherein $\mathbf{R^{5A}}$ is selected from the group consisting of an optionally substituted aryl, an optionally substituted heteroaryl and an optionally substituted heterocyclyl.

131. The compound of Claim 130, wherein $\mathbf{R^{5A}}$ is an optionally substituted aryl.

132. The compound of Claim 131, wherein the optionally substituted aryl is an optionally substituted phenyl.

133. The compound of Claim 94, wherein the compound is selected from the group consisting of:


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or a pharmaceutically acceptable salt of any of the foregoing.

134. A pharmaceutical composition comprising an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent, excipient, or combination thereof.

135. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for ameliorating or treating an orthomyxovirus viral infection.

136. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for inhibiting replication of an orthomyxovirus.

137. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for contacting a cell infected with an orthomyxovirus.

138. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the

preparation of a medicament for ameliorating or treating an orthomyxovirus viral infection in combination with one or more agents comprising administering or contacting a cell with an effective amount of the compound, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition.

139. Use of an effective amount of a compound of any one of Claims 1-133, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of Claim 134 in the preparation of a medicament for inhibiting endonuclease activity of an influenza endonuclease.

140. The use of any one of Claims 135-137, wherein the orthomyxovirus is an influenza virus.

141. The use of Claim 138, wherein the orthomyxovirus viral infection is an influenza virus infection; and wherein the one or more agents is selected from the group consisting of a neuraminidase inhibitor, a M2 protein inhibitor, a polymerase inhibitor, a PB2 inhibitor, amantadine, rimantadine, zanamivir, oseltamivir, peramivir, laninamivir, laninamivir octanoate, favipiravir, fludase, ADS-8902, an immuno-modulator, beraprost, Neugene®, ribavirin, CAS Reg. No. 1422050-75-6, CAS Reg. No. 1259366-34-1 (VX-787), FluMist Quadrivalent® (MedImmune), Fluarix® Quadrivalent (GlaxoSmithKline), Fluzone® Quadrivalent (Sanofi Pasteur), Flucelvax® (Novartis) and FluBlok® (Protein Sciences).

142. The use of Claim 141, wherein the one or more agents is oseltamivir.

143. The use of any one of Claims 140-141, wherein the influenza virus is influenza A.

144. The use of any one of Claims 140-141, wherein the influenza virus is influenza B.

145. The use of any one of Claims 140-141, wherein the influenza virus is influenza C.

146. The use of any one of Claims 140-141, wherein the influenza virus is selected from the group consisting of H1N1, H3N2, H5N1 and H7N9.